

1 A Reappraisal: Natural History of Amniote Reproductive Modes In Light of Comparative
2 Evolutionary Genomics

3 Maggs X^{*1}

4 ¹ Richard Gilder Graduate School at The American Museum of Natural History; 200 Central
5 Park West, New York, NY 10024

6 maggs_x@outlook.com; 973-534-9937; ORCID: 0000-0002-6660-7599

7 **Abstract**

8

9 There is a current lack of consensus on the ancestral parity mode, oviparity (egg-laying) and
10 viviparity (live-birth), of amniotes and squamates (snakes and lizards). How transitions between
11 parity modes occur at the genomic level has primary importance on how science conceptualizes
12 the origin of amniotes, and highly variable parity modes in Squamata. Within the context of
13 interdisciplinary literature—medical, poultry science, reproductive biology, and evolutionary
14 biology—I review the genomics and physiology of five broad processes expected to change
15 during transitions between parity modes: eggshell formation, embryonic retention, placentation,
16 calcium transport, and maternal-fetal immune dynamics. Throughout, I offer alternative
17 perspectives and testable hypotheses regarding proximate causes of parity mode evolution in
18 amniotes and squamates. Should viviparity have evolved early in the history of Lepidosauria, I
19 offer the basal cap hypothesis as a proximate explanation. The framework of this hypothesis can
20 be extended to amniotes to infer their ancestral state. I also provide a mechanism through which
21 squamates may reverse back to oviparity without hitting fitness valleys; and make predictions on
22 the directionality of transitions in three reproductively bimodal species. Furthermore, I
23 contextualize the maternal-fetal immune dynamics in light of modern understanding that most
24 embryos are not analogous to allografts (e.g., organ transplants). Overall, this review grounds
25 itself in the historical literature while offering a modern perspective on a subject that has
26 fascinated scientists for centuries—the origin of amniotes. The paper ends with the most realistic
27 option that the first amniote egg was oviparous with extended embryonic retention.
28 *Lampropholis guichenoti* may be an appropriate model for the original amniote egg. The
29 foundations of the framework designed to be applied to squamates can also be applied to test if

30 Testudines are a more suitable model for the origins of amniote. I encourage the scientific
31 community to utilize this manuscript as a resource in future research.

32 *Key Words:* parity modes, amniote origins, squamates, eggshell deposition, embryonic retention,
33 embryonic calcium provisioning, viviparity, maternal-fetal interface, comparative evolutionary
34 genomics, squamates

35

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93 **I. Introduction**

94

95 A reappraisal is needed for the conceptual framework used to research the evolution of
96 oviparity (egg-laying) and viviparity (live-birth) in amniotes (birds, non-avian reptiles, and
97 mammals). Squamates (snakes and lizards) are unique amongst amniotes because they have
98 highly variable parity modes (Figure 1). Beginning with the first phylogenetic analyses on the
99 subject, a warm-blooded scientific disagreement has persisted over the labile nature of
100 evolutionary transitions between parity modes (Blackburn, 1999, 2015; de Fraipont, Clobert &
101 Barbault, 1996; Griffith et al., 2015; Harrington & Reeder, 2017; Lee & Shine, 1998; Pyron,
102 2015; Pyron & Burbrink, 2014; Recknagel et al., 2018, 2021b). A growing number of
103 transcriptomic and genomic studies analyzing the molecular underpinnings of reproductive mode
104 evolution in squamates (e. g., Brandley et al. 2012; Cornetti et al. 2018; Gao et al. 2019; Griffith et al.
105 2016, 2017; Foster et al. 2020, 2022; Recknagel et al. 2021a; Yurchenko et al. 2020; Xie et al. 2022) and
106 recent advances on the ancestral state of amniotes and dinosaurs contribute to this discussion (Jiang et
107 al., 2023; Norell et al., 2020). It is prudent to acknowledge that the relative difficulty of changing
108 phenotypes cannot be determined from morphology alone or unidentified physiological
109 mechanisms. At least theoretically, any phenotypic change could be facilitated by simple
110 genomic changes (e.g., a single nucleotide polymorphism) or any combination of multi-omic
111 changes to any number of loci. As research begins to reveal the molecular networks involved
112 with parity mode evolution, it is important to avoid bias that could be introduced by assumptions
113 on the feasibility of transitions. Through synthesis of modern and historical research on amniote
114 reproduction, this review aims to provide greater context for hypotheses testing ancestral states
115 of parity modes in amniotes and squamates.

116 The earliest estimates predicted that viviparity evolved independently between 90-100
117 times in squamates (Blackburn, 1982, 1985, 1992). These estimates assumed that oviparity was
118 the ancestral state and, based on the theoretical grounds of Dollo's law, that reversals back to
119 oviparity should be exceedingly rare (Blackburn, 1992; Fitch, 1970; Neill, 1964; Tinkle &
120 Gibbons, 1977). An intermediate phenotype of re-evolving an eggshell has been considered as
121 physiologically unviable, preventing reversals (Blackburn, 1995; Griffith et al., 2015). This was
122 demonstrated when experimentally induced extended egg retention in phrynosomatid lizards
123 resulted in adverse embryonic development attributed to impeded gas exchange imposed by the
124 eggshell (Mathies & Andrews, 1999, 2000; Parker & Andrews, 2006). However, this result may
125 be clade-specific.

126 Intermediate phenotypes as fitness valleys assumes 1) eggshells inherently impede gas-
127 exchange and 2) that an eggshell must re-evolve before a reversal back to oviparity is possible
128 (Griffith et al., 2015). Contrarily, eggshells are considered a component of the placenta in
129 viviparous Rough Earth Snakes, *Haldea striatula*, and in viviparous reproductively bimodal
130 European Common Lizards, *Zootoca vivipara* and Yellow-bellied Three-toed Skinks, *Saiphos*
131 *equalis* (Stewart, 2013). Additionally, *Saiphos equalis* is a reproductively bimodal skink that has
132 an oviparous population with incubation times as short as 5 days, thus embryos spend significant
133 time in utero with an eggshell (Smith et al., 2001). Another surprising example of eggshells
134 being compatible with full embryonic development includes a report of a captive tortoise that
135 retained viable eggs until the hatching stage (Kuchling & Hofmeyr, 2022).

136 Several studies predict early origins of viviparity in squamates (Jiang et al., 2023; Pyron
137 & Burbrink, 2014) and reversals back to oviparity (de Fraipont et al., 1996; Fenwick et al., 2011;
138 Harrington & Reeder, 2017; Lee & Shine, 1998; Pyron & Burbrink; Recknagel et al., 2018).

139 *Saiphos equalis* proved the possibility of reversals when a viviparous individual oviposited an
140 egg prior to birthing fully developed young within the same litter (Laird et al., 2019). The
141 unusual absence of an egg-tooth in oviparous Arabian Sand Boas, *Eryx jayakari* (Lynch &
142 Wagner, 2010; Staub & Emberton, 2002) serves as additional biological evidence of a reversal,
143 though this has been challenged (Griffith et al., 2015). Importantly, extended embryonic
144 retention, characteristic of oviparous squamates compared to birds, is viewed as compatible with
145 labile transitions (Jiang et al., 2023). Current expectations are that oviparity may re-evolve more
146 easily in squamate lineages that recently evolved viviparity and which have not lost specific
147 avian eggshell-matrix proteins (Laird et al., 2019; Xie et al., 2022).

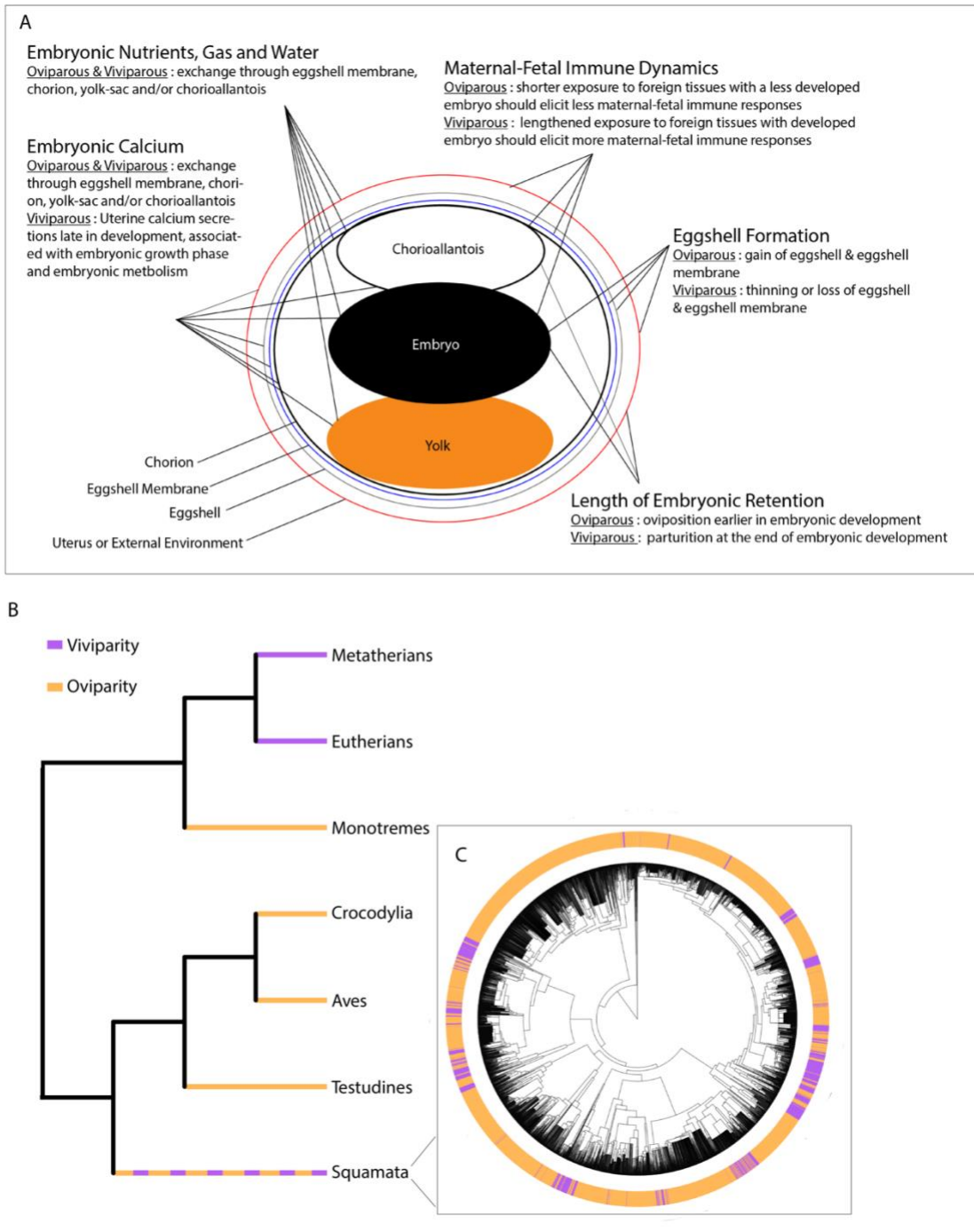
148 Discoveries of viviparity in ancient amniotes are numerous, dating back to the Early
149 Permian (Chuliver, Scanferla & Smith, 2022; Motani et al., 2014; Piñeiro et al., 2012; Jian et al.,
150 2023). A viviparous most recent common ancestor of amniotes is not unreasonable. Most
151 compelling is the report that *Ikechosaurus sp.*, a basal archosauromorph, reached an articulated
152 stage of embryonic development inside of a parchment shelled egg (Jiang et al., 2023). This
153 brings support to the extended embryonic retention model (EER) (Hubrecht, 1910). The EER
154 model postulates that amniote fetal membranes arose through pressure to support exposure to
155 maternal-fetal tissues during extended embryonic retention (see Laurin et al., 2005 for a
156 summary of earlier ancestral reconstructions of EER). It serves as an alternative to the widely
157 accepted model that eggs laid on land prompted the evolution of fetal membranes to retain water
158 with an eggshell that facilitated gas exchange (Romer, 1957). The discovery that hard-shelled
159 eggs most likely evolved three times in dinosaurs, deriving from a soft-shelled ancestor (Norell
160 et al., 2020) is consistent with the EER. As Romer (1957) phrased it “It was the egg which came
161 ashore first; the adult followed”. This is also consistent with EER, which is compatible with both

162 oviparity and viviparity (Laurin, 2005; Mossman 1987). Throughout this review, considering
163 viviparity as the most extreme form of extended embryonic retention, I hope to persuade readers
164 to consider the EER model in a new light. I lay this out through a testable hypothesis on the
165 ancestral eggshell of amniotes and Lepidosaurians that can be extended to amniotes (section III.3), a
166 phylogenetic framework to infer ancestral states based on mechanisms of maternal-embryonic
167 calcium provisioning (section V.2), evolutionary pathways that may support transitions between
168 parity modes (section VII.6 and VII.7), and my consensus on the parity mode of the first amniote
169 (section VII.10).

170 Regardless of disagreements, it is sensible to equate the EER with pre-adaptations of the
171 egg to land. Without substantial amounts of water, converting yolk nutrients to somatic tissue is
172 impossible (Thompson & Speake, 2003). Water is the primary resource provisioned by the
173 mother of viviparous squamates and it is stored in extraembryonic membranes (Lourdais et al.,
174 2015). For example, water and gas exchange are associated with poor chorioallantoic blood flow
175 (Wootton et al., 1977). In oviparous *Saiphos equalis*, a species with extended embryonic
176 retention, the chorioallantois thickens to support embryonic growth in late development (Parker
177 et al., 2010). Thus, if the amniote egg evolved via the EER model, it may have prompted the
178 origin of extraembryonic membranes of amniotes. This translates to an egg washed ashore that
179 has already evolved to withstand dryer environments.

180 Although models that restrict parity mode evolution to be unidirectional (from oviparity
181 to viviparity) are shown to be poor fits for squamates (Pyron & Burbrink; Recknagel et al.,
182 2021b), there is resistance to the proposition that viviparity originated early in Squamata (e.g.
183 Griffith et al., 2015). The most recent ancestral state reconstruction, built from biomineralization
184 and parity mode data across 80 extinct and extant amniotes using a single structured Markov

185 model, inferred viviparity with extended embryonic retention in the first amniotes and in the
186 most recent common ancestor of Lepidosaurs (squamates and sphenodontia) (Jiang et al., 2023).
187 However, maximum parsimony, and alternative maximum likelihood and Bayesian
188 reconstructions did not estimate viviparity in the most recent common ancestor of Lepidosaurs
189 (Jiang et al., 2023). A testable hypothesis regarding a molecular mechanism that may have
190 supported a transition to viviparity at the base of squamates and extended embryonic retention at
191 the base of amniotes will help conclude these decades long debates.



192

193 **Figure 1:** Schematic demonstrating (A) the anticipated processes that change during transitions
 194 between oviparity and viviparity, and the organs associated with those changes. Lines from the
 195 process to different organs indicate the organs expected to be involved with the evolutionary
 196 shift between oviparous and viviparous phenotypes. (B) relationships between major amniote

197 clades and their associated reproductive mode, and (C) the variation of reproductive modes
198 across squamates. The squamate phylogeny is adapted from Pyron et al., (2016) and reproductive
199 modes of squamate species from Pyron & Burbrink (2014).

200

201 The ecological drivers of parity mode evolution are beyond the scope of this review.
202 However, it is generally proposed that viviparity increases protection from adverse
203 environmental conditions (Ma et al., 2018; Pincheira-Donoso et al., 2017), and a general trend
204 that supports this is the higher frequency of viviparous squamates, relative to oviparous,
205 observed at increasing distances from the equator. The cold-climate hypothesis suggests that
206 viviparity is an adaptation to cold climates, and this is generally accepted by the scientific
207 community (e.g. Ma et al., 2018; Zimin et al., 2022). Consistent with the cold-climate
208 hypothesis, a recent study that utilized 65 million years of global paleoclimate data, squamate
209 phylogeny and parity data for over 3,000 taxa showed that persistent, stable cold climates are
210 correlated with transitions to viviparity (Recknagel et al., 2021b). Less focus has been on the
211 adaptive nature of oviparity. Compared to viviparity, oviparity is associated with higher
212 fecundity and lessened maternal investment (Recknagel et al., 2019).

213 With a deep review of interdisciplinary literature across amniotes and associated
214 supplementary materials, I explore genomic and physiological features of gestation and
215 gravidity, including those that could be exploited to support labile shifts, ancestral viviparous
216 states in amniotes and squamates, and those that may facilitate or impede reversals. I propose the
217 framework of the basal cap hypothesis to help elucidate the ancestral parity modes of squamates
218 and amniotes. It details how squamates may have transitioned to viviparity (an extreme form of
219 extended embryonic retention) early in their evolutionary history. After much consideration, I

220 advocate for using squamates as a model to understand the ancestral state of the amniote egg
221 (section VII.8 and VII.9). Future work should consider this thoughtfully and embrace the
222 complexity of the system. I hope this manuscript serves as a foundation for further research on
223 the evolutionary history of the amniote egg and reproductive mode evolution.

224

225 *(1) Terminology*

226 I use the conventional definition of viviparity as retention of eggs until the stage when the
227 embryo is fully developed (Blackburn & Stewart, 2021; van Dyke et al., 2014). Oviparity is
228 defined by eggs that develop outside the mother. I use the terms gravidity and gestation to
229 describe the period of internal retention of the embryo in oviparous and viviparous taxa,
230 respectively. Vertebrate placentas are conventionally defined by apposition of maternal and fetal
231 tissues. It is accepted that all viviparous squamates have a chorioallantoic placenta under this
232 definition (Blackburn & Stewart, 2021; Stewart & Blackburn, 1988). The avian chorioallantoic
233 membrane and mammalian chorioallantoic placenta are homologous (Metcalf & Stock, 1993). I
234 sometimes refer to this organ as the chorioallantoic tissue to describe it for both parity modes.
235 Oviposition refers to the process and act of egg-laying, while parturition refers to the process and
236 act of giving birth to live-young. Parition refers to both oviposition and parturition (Blackburn,
237 1992; Smith, 1975).

238

239 *(1) Main five physiological changes of parity mode transitions*

240 Several physiological features are expected to change during transitions between
241 oviparity and viviparity (Figure 1). I break this down into five physiological features (hereafter
242 Main Five)—1) length of embryonic retention (Murphy & Thompson, 2011; Packard et al.,

243 1977)—only viviparous mothers retain the embryo for the entirety of development; 2) eggshell
244 formation (Heulin et al., 2005; Packard et al., 1977; van Dyke et al., 2014)—viviparous embryos
245 generally do not have an eggshell; 3) placental development for maternal-fetal exchange of
246 required water, gas and/or nutrients (Blackburn, 1992, 2015; Thompson et al., 2000; Thompson
247 & Speake, 2006); 4) embryonic calcium provisioning (Packard et al., 1985; Shadrix et al., 1994;
248 Thompson & Speake, 2006)—sources of embryonic calcium and timing of uterine calcium
249 secretions generally differs between oviparous and viviparous reproduction; 5) maternal-fetal
250 immune dynamics (e.g., Graham et al., 2011; Hendrawan et al., 2017; Foster et al., 2020)—
251 viviparous reproduction is associated with maternal and embryonic exposure to foreign tissues,
252 which is likely to require enhanced regulation of maternal-fetal immune systems.

253

254 **II. Length of Embryonic Retention**

255

256 Viviparous amniotes retain the embryo until it is fully developed, but oviparous amniotes
257 retain the embryo for a fraction of that time. Rather than using precocious hatching and
258 parturition (PH&P), like that of opossums and early viviparous mammals (Wagner et al., 2014),
259 squamates evolve viviparity through extended egg retention (García-Collazo et al., 2012; Shine,
260 1983). Thus, processes affecting the length of embryonic retention are expected to change to
261 support transitions between parity modes (van Dyke et al., 2014).

262

263(1) *Parturition & oviposition*

264 The genes and hormones involved with initiating and ending gestation may provide insights
265 into the tools squamates can co-opt to change the length of embryonic retention during parity

266 mode transitions. Parturition terminates embryonic retention. Parturition can be divided into four
267 parts (Terzidou, 2007; Vannuccini et al., 2016)—quiescence (Phase 0), activation (Phase 1),
268 stimulation (Phase 2) and involution (Phase 3). In eutherian mammals, several processes
269 contribute to the initiation and termination of gestation including inflammation (Challis et al.,
270 2009; Hansen et al., 2017), maternal recognition of pregnancy (MRP), mechanical stretch of
271 uterine tissues (Sooranna et al., 2004; Shynlova et al., 2008), and fluctuating concentrations of
272 corticotropin-releasing hormone, progesterone, and estrogen (Challis et al., 2000; Condon et al.,
273 2004; Shaw & Renfree, 2001).

274

275 (i) *Quiescence & sustained progesterone production in reproductive tissues*

276 Extended embryonic retention could be achieved by triggering mechanisms that extend
277 uterine quiescence, inactivity of the uterus. Inhibition of myometrial contractions through
278 sustained progesterone production supports quiescence across different viviparous amniotes
279 (Bazer, 1992; Casey & MacDonald, 1997; Fergusson & Bradshaw, 1991; Ilicic et al., 2017;
280 Murphy & Thompson, 2011; Putnam et al., 1991; Soloff et al., 2011). The corpus luteum (or
281 plurally called corpora lutea), a transient progesterone-producing organ, produces progesterone
282 during gestation. Extended lifespan of the corpus luteum likely aided the evolution of viviparity
283 in mammals (Amoroso, 1968; Callard et al., 1992; Stouffer & Hennebold, 2015). Thus, early
284 research on squamate viviparity also explored the influence of corpus luteum lifespan. The
285 lifespan of corpora lutea associates with oviparous egg retention and oviposition (Diaz, Alonso-
286 Gomez & Delgado, 1994; Fox & Guillette 1987; Jones & Guillette 1982). Eggshell formation in
287 oviparous Whiptail lizards, *Cnemidophorus uniparens*, is even disrupted by experimental
288 removal of corpora lutea (Cuellar, 1979). The lifespan of corpora lutea do not consistently

289 correlate with length of embryonic retention in viviparous squamates like it does in mammals
290 (Albergotti & Guillette, 2011; Callard et al., 1992).

291 Maternal recognition of pregnancy (MRP) refers to the early signaling of the embryo to
292 prevent luteolysis (Thatcher, Meyer, & Danet-Desnoyers, 1995), degradation of the corpus
293 luteum. Luteolysis occurs in the absence of pregnancy. MRP enables continued progesterone
294 production by the corpus luteum to support uterine quiescence during early gestation. An
295 independent evolution of MRP is reported for Macropodidae, a lineage of marsupial mammals
296 (Freyer, Zeller, & Renfree, 2003), and endometrial recognition of pregnancy is recognized in the
297 opossum (Griffith et al., 2019). MRP has not been explicitly studied in squamates. However,
298 MRP likely happens in squamates, given that corpora lutea do not get degraded in the earliest
299 stages of gravidity/gestation in oviparous or viviparous squamates (Callard et al., 1992;
300 Albergotti & Guillette, 2011).

301 Different genes are signaled by embryos for MRP across mammals. Human chorionic
302 gonadotropin hormone (hCG) establishes MRP (Ross, 1979; Behrman et al., 1993; Duncan,
303 McNeilly, & Illingworth, 1998; Duncan, 2000; Ticconi et al., 2007). In pigs, MRP is
304 hypothesized to be triggered by collaborative signaling of estradiol (E2) and prostaglandins
305 (PGs) (Geisert et al., 2023). Similarly, glycoproteins, estradiol and prostaglandin E2 (PGE2)
306 have been implicated in signaling MRP in horses (Klein & Troedsson, 2011; Klein, 2016). In
307 ruminants, embryonic signaling of IFN- τ establishes MRP (Bazer, 2013; Bazer, Spencer & Ott,
308 1997; Thatcher et al., 1995). During gestation in the uterus of viviparous African Ocellated
309 skinks, *Chalcides ocellatus*, four receptors for interferon alpha, beta, omega, and gamma are
310 differentially expressed but no expression of IFN- τ was detected compared to non-gestational
311 uterine tissue (Brandley et al., 2012). I was unable to find expression patterns of MRP signaling

312 homologs in other squamate reproductive tissues. Should MRP occur in squamates, it may be
313 signaled by genes that are clade-specific, like in mammals. This makes comparatively evaluating
314 the influence of MRP on the evolution of viviparity an interesting avenue for future research.

315 The evolution of viviparous extended embryonic retention may be sufficiently supported by
316 maintenance of chorioallantoic progesterone production coupled with eggshell loss (Griffith,
317 Brandley et al., 2017). This theory may be broadly applicable across amniotes given that the
318 most recent common ancestor of amniotes likely had a chorioallantois with an endocrine
319 function (Griffith, Brandley et al., 2017). Following death of the corpus luteum during gestation,
320 placental progesterone production supports extended embryonic retention in eutherian mammals
321 (Castracane & Goldzieher, 1986; Ellinwood et al., 1989; Nakajima et al., 1991; Rothchild, 2003;
322 Spencer & Bazer, 2004). Viviparous Italian Three-toed Skinks, *Chalcides chalcides*, shift to
323 chorioallantoic progesterone production following degradation of corpora lutea during gestation
324 (Guarino et al., 1998). The placenta of viviparous Southern Snow Skinks, *Carinascincus*
325 *microlepidotus*, produces minimal progesterone but has a strong capacity to convert
326 pregnenolone to progesterone (Girling & Jones, 2003). Whereas all genes involved with a known
327 biosynthesis pathway for progesterone production are expressed in the placenta of horses, *Equus*
328 *caballus*, only some of these genes were detected in the chorioallantois of chickens, *Gallus*
329 *gallus*, viviparous Southern Grass Skinks, *Pseudemoia entrecasteauxii*, and oviparous and
330 viviparous Southeastern Sliders, *Lerista bougainvillii* (Griffith, Brandley et al., 2017). Thus, if
331 chorioallantoic progesterone production has supported multiple origins of viviparity in amniotes,
332 it is not evidenced by a conserved ancestral gene expression pattern for the biosynthesis of
333 progesterone (Griffith, Brandley et al., 2017). Nonetheless, parity trait genes in a reproductively

334 bimodal lizard, *Zootoca vivipara*, are associated with progesterone-binding functions (Recknagel
335 et al., 2021a)—highlighting the role of progesterone in squamate reproduction.

336 Other female reproductive tissues in squamates express genes involved with progesterone
337 biosynthesis—StAR-related lipid transfer domain protein 3 (*StARD3*) and hydroxy-delta-5-
338 steroid dehydrogenase (*HSD3B1*). *STARD3* is significantly upregulated in the uterine tissue
339 during pregnancy in viviparous African Ocellated skinks, *Chalcides ocellatus*, along with
340 significant differential expression of seven paralogs (Brandley et al., 2012). While *StARD3* is
341 expressed during gestation in *Zootoca vivipara*, it is not significant differentially expressed
342 compared to oviparous counterparts; *HSD3B1*, on the other hand, is significantly upregulated
343 during mid-gestation (Recknagel et al., 2021a). Compared to non-gestational samples, *HSD3B1*
344 is significantly upregulated in the uterus during early and late gestation in viviparous individuals
345 of reproductively bimodal *Saiphos equalis* (Foster et al., 2020). Oviparous individuals from the
346 same species did not exhibit this expression pattern (Foster et al., 2020). Activity of *HSD3B1*
347 was detected in the mucosal epithelium of oviparous Eastern Garden Lizards, *Calotes versicolor*
348 (Kumari et al., 1992), and in the uterine glands of oviparous Keeled Indian Mabuya, *Eutropis*
349 *carinata* (Mundkur & Sarkar, 1982). Other genes involved with the biosynthesis of progesterone
350 (e.g., steroidogenic acute regulatory protein or cytochrome-P450-family-11-subfamily-A-
351 polypeptide-1) serve as further candidates for exploring the relationship between organ-specific
352 patterns of progesterone production and the evolution of extended embryonic retention in
353 viviparous squamates.

354 For progesterone to prevent myometrial contractions and support quiescence, there must be
355 progesterone receptors (PGRs) in the uterus (Mesiano et al., 2011; Young et al., 2011). In
356 humans, progesterone responsiveness is related to specific ratios of PGRs, *PR-A* and *PR-B*, in

357 myometrial cells (Young et al., 2011). Minimal research exists on PGR expression in squamate
358 reproductive tissues. One study found that in the uterus of the yolk-sac in viviparous Southern
359 Grass Skinks, *Pseudemoia entrecasteauxii*, one progesterone receptor, *PGRMC2*, is upregulated
360 compared to non-gestational uterine tissue (Griffith et al., 2016); Another progesterone receptor,
361 *PGR*, is downregulated in the uterus of the chorioallantoic placenta and yolk sac placenta
362 compared to non-gestational uterine tissue (Griffith et al., 2016). Downregulation of both *PGR*
363 and *PGRMC2* in the uterus during gestation was detected in viviparous *Chalcides ocellatus*
364 (Brandley et al., 2012). While *PGR* is differentially expressed at mid-gestation in viviparous
365 individuals compared to oviparous, *PGRMC1* and *PGRMC2* are not differentially expressed
366 (Recknagel et al., 2021a). However, admixture mapping revealed three SNPs most highly
367 associated with gestation length in *Zootoca vivipara* are located in close proximity to *PGRMC1*
368 (Recknagel et al, 2021a). Measuring expression of PGRs and their ratios in uteruses of
369 oviparous and viviparous squamates will help elucidate the receptors needed to support
370 progesterone responsiveness in squamate uteruses and their relationship to extended embryonic
371 retention.

372

373 (ii) *Activation & progesterone withdrawal*

374 The activation stage of parturition is marked by the withdrawal, or functional withdrawal, of
375 progesterone leading to an estrogen dominated response during the next state, stimulation
376 (Bakker, Pierce, & Myers, 2017; Fergusson & Bradshaw, 1991). Progesterone may withdraw in
377 response to environmental stimuli in reptiles during parturition (Shine & Guillette, 1988). In
378 mammals, activation is marked by increasing concentrations of corticotropin-releasing hormone
379 and contraction associated proteins (CAPs) including connexin-43, prostaglandins, oxytocin

380 receptors, prostanoid receptors and cell signaling proteins (Bakker et al., 2017; Ilicic et al., 2017;
381 Leadon et al., 1982; Pashen & Allen, 1979; Whittle et al., 2000). Pro-inflammatory cytokines
382 and chemokines, prostaglandin synthase-2 (*COX-2*, also referred to as *PTGS2*), and NF-κB also
383 influence activation in mammals (Christiaens et al., 2008; Lappas et al., 2002; Lappas & Rice,
384 2007; Lindström & Bennett, 2005; Olson, 2003; Terzidou, 2007).

385 Some similar patterns are associated with oviposition in birds. In chickens, *Gallus gallus*,
386 prostaglandin F (PGF) concentrations increase in the hours leading up to oviposition (Takahashi
387 et al., 2004). Experimental injection of oxytocin and arginine vasotocin (AVT), similar
388 neurohypophyseal peptides, revealed that uterine tissues of chickens, *Gallus gallus*, maintain
389 responsiveness to oxytocin but are more sensitive toward arginine vasotocin (Ewy, 1970).

390 Murphy & Thompson (2011) provide a rather exhaustive list of resources on progesterone and
391 estrogen assays across oviparous and viviparous squamates. Future research should consider
392 exploring parallels between mechanisms of activation in mammals and squamates. Any process
393 that can trigger or stall activation should lead to extended embryonic retention.

394

395 (iii) *Stimulation & electrical gradients, inflammation, and hormonal regulation*

396 Mechanical stretch, electrical gradients, inflammatory processes, and hormonal regulation
397 contribute to stimulation, the phase when contractions, cervical ripening and dilation occur.
398 Stimulation involves contributions from maternal and fetal tissues. As early as 460 BC there was
399 uncertainty over the proportional influence of mother or fetus on the initiation of parturition.
400 Hippocrates proposed that the fetus initiates parturition by pushing its feet on the fundus of the
401 uterus. Although the reality is not so cartoonish, mechanical stretch of the uterus from the

402 growing embryo plays a role in parturition (Lefebvre et al., 1995; Tamizian & Arulkumaran,
403 2004; Wray et al., 2015).

404 Physical stretching of the uterus causes an influx of calcium and sodium, altering the action
405 potential and enabling contractions (Kao & McCullough, 1975). Calcium further activates
406 voltage gated calcium channels on myometrial cell membranes, enhancing the influx of calcium
407 ions, mediating the force and speed of myometrial contractility (Arrowsmith & Wray, 2014;
408 Wray et al., 2015). The influence of uterine overdistention on partition in birds and non-avian
409 reptiles has not yet been examined, to my knowledge. However, differentially expressed genes
410 functionally enriched the GO term for “voltage-gated calcium channel activity” in uterine tissues
411 during gravidity and gestation in *Saiphos equalis* (Foster et al., 2020). A uterine response to
412 overdistention is among the many possible explanations for this. It may be important to consider
413 the influence of uterine overdistention on squamate parity mode transitions, because should
414 bioelectrical responses to uterine overdistention be a common feature of vertebrate parturition,
415 lessened distention may be a hurdle to reverse back to oviparity. Uterine overdistention may
416 influence parturition by triggering an “inflammatory pulse” that activates further myometrial
417 contractility, which leads to preterm birth in primates (Adams Waldorf et al., 2015).

418 During parturition, there is an influx of uterine and embryonic pro-inflammatory genes and
419 immune cells (Adams Waldorf et al., 2015; Charpigny et al., 2003; Mesiano et al., 2002; Park et
420 al., 2005). Uterine contractions in humans involve actions of prostaglandins (PGs), oxytocin,
421 corticotropin-releasing hormone, cytokines, and neutrophils (Adams Waldorf et al., 2015; De
422 Rensis et al., 2012; Olson & Hertelendy, 1983; Park et al., 2005; Sykes et al., 2014; Terzidou,
423 2007).

424 The cycling concentrations of a neuropeptide, corticotropin-releasing hormone (CRH),
425 supports parturition in humans. This has been compared to a biological clock that is initiated at
426 early stages of gestation (Lockwood, 2004; McLean & Smith, 2001). Increased production of
427 CRH facilitates parturition by interacting with CRH receptors, CRH-R1 and CRH-R2, which are
428 suggested to promote myometrial relaxation or contractility, respectively (Hillhouse &
429 Grammatopoulos, 2001). Altered regulation, phenotype or function of hormones that function as
430 biological clocks, like CRH, may have a particularly strong influence on evolutionary changes to
431 length of embryonic retention, a trait inherently related to time.

432 Placental CRH production has only been identified in primates thus far (Challis et al., 2005;
433 Emanuel et al., 1994; Florio et al., 2002; Hillhouse & Grammatopoulos, 2001; Karteris et al.,
434 1998; Mendelson, 2009; Robinson et al., 1989). Placental CRH production may, therefore, be
435 unique to primates. However, the amino acid sequence of CRH is highly conserved in vertebrates
436 (Noy et al., 2017), indicating there is a possibility for shared function across diverse taxa. Like
437 CRH cycling in mammals, timely fluctuations of AVT stimulates uterine contractions, enables
438 oviposition in birds, turtles, and lizards (Ewy, 1970; Fergusson & Bradshaw, 1991; Guillette Jr &
439 Jones, 1980; Jones et al., 1987; Rzasa, 1978; Wu et al., 2019).

440 Prostaglandin E₂ (PGE₂) and prostaglandin F_{2α} (PGF_{2α}) influence, respectively, uterine
441 contractions and cervical relaxation for partition across many amniotes including humans, *Homo*
442 *sapiens* (Terzidou, 2007), domestic pigs (De Rensis et al. 2012), domestic chickens (Hertelendy
443 et al., 1974; Olson et al., 1986), and Loggerhead Sea turtles (Guillette et al., 1991). Injections of
444 PGF_{2α} and PGE₂ induce parturition in viviparous Yarrow's Spiny lizards, *Sceloporus jarrovi*, and
445 Raukawa geckos, *Woodworthia maculatus* (Cree & Guillette, 1991; Guillette et al., 1992).
446 However, no injected dosages of PGF_{2α} or PGE₂ induced oviposition in oviparous Collard

447 lizards, *Crotaphytus collaris*, Eastern Fence lizards, *Sceloporus undulatus*, Six-lined
448 racerunners, *Aspidoscelis sexlineatus*, or Striped Plateau lizards, *Sceloporus virgatus* (Guillette et
449 al., 1991). It is interesting that injections of $\text{PGF}_{2\alpha}$ and PGE_2 induced parturition in viviparous
450 lizards but did not induce oviposition in oviparous lizards studied. Given this, it is plausible that
451 regulatory or functional changes to $\text{PGF}_{2\alpha}$ and/or PGE_2 in squamates could facilitate changes to
452 the length of embryonic retention to support transitions between reproductive modes. However,
453 induction of parturition with $\text{PGF}_{2\alpha}$ in viviparous *Woodworthia maculatus* only worked with
454 pre-treatment of β -adrenoceptor (Cree & Guillette, 1991).

455 $\text{PGF}_{2\alpha}$ decreases progesterone concentrations during stimulation (De Rensis et al., 2012). In
456 humans, biosynthesis of PGs is driven largely by the enzyme cyclooxygenase (*COX*)-2 rather
457 than *COX-1* (i.e., prostaglandin synthase-2 and -1) (Slater et al., 1995, 1999). This helps
458 maintain the decreased progesterone/estrogen ratio of stimulation. In ovariectomized viviparous
459 Garter snakes, *Thamnophis*, increased estrogen stimulated thickness of uterine epithelial cells
460 and glandular activity, whereas administration of progesterone had little influence on uterine
461 histology (Mead et al., 1981). Uterine pig models revealed that estrogen stimulates involuntary
462 contraction and relaxation (peristalsis) of the uterus (Mueller et al., 2006).

463 The softening of the cervix is important during the stimulation stage of parturition. A
464 hormone related to insulin, *relaxin*, promotes myometrial softening in humans, *Homo sapiens*,
465 domestic pigs, and turtles (Mercado-Simmen et al., 1982; Sorbera et al., 1988; Weiss &
466 Goldsmith, 2001). The cervix also gets softer by actions of PGE_2 . PGE_2 activates pro-
467 inflammatory cytokines, interleukin (IL)-8 and tumor necrosis factor (TNF)- α , which activates
468 the collagenases and matrix metalloproteinases for cervical softening (Bakker et al., 2017). This
469 causes a positive feedback loop between IL-8 and PGE_2 synthesis (Denison et al., 1998;

470 Denison, Calder & Kelly, 1999; Terzidou, 2007; Li et al., 2010). Upregulated of IL-8 is also
471 promoted by the protein complex NF- κ B during parturition in humans (Elliott, 2001). Similar
472 patterns were observed during parturition in mice and baboons (Mendelson & Condon, 2005;
473 Mendelson, 2009).

474 A few studies focus on the role of cytokines on squamate reproduction but not explicitly
475 during oviposition or parturition (Hendrawan et al., 2017; Paulesu et al., 1995, 2005, 2008).
476 Some studies detected expression of cytokines during late gestation (Foster et al., 2020; Gao et
477 al., 2019; Recknagel et al., 2021a). TNF- α related activity was only detected at this time in
478 viviparous Tussock Cool-skinks, *Pseudemoia entrecasteauxii*, which were found to
479 downregulate TNF- α induced proteins (*TNFAIP6* and *TNFAIP8L2*) in the ‘uterus of the
480 chorioallantoic placenta’ and *TNFAIP6*, *TNFAIP1*, and *TNFAIP2* in the ‘uterus of the yolk-sac
481 placenta’ compared to not gestational uterine tissues (Griffith et al., 2016). Activity of TNF- α in
482 reproductive tissues during gestation in viviparous Italian Three-toed skinks, *Chalcides*
483 *chalcides*, and reproductively bimodal European common lizards, *Zootoca vivipara*, was
484 associated with maternal-fetal immune dynamics (Paulesu et al., 1995, 2005, 2008; Hendrawan
485 et al., 2017).

486 Altered expression or phenotype of contractility agonists, oxytocin receptors and estrogen
487 receptors, and contractility antagonists, progesterone receptors and β -adrenergic receptors
488 (Ravanos et al., 2015) may also change the length of embryonic retention to support transitions
489 between parity modes. Differences in length of embryonic retention in oviparous and viviparous
490 agamas, *Phrynocephalus przewalskii* and *Phrynocephalus vlangalii*, appears to be driven by
491 regulatory differences of prostaglandins, *COX-2*, an AVT receptor (*MTR*), β -adrenergic receptors,
492 and estrogen receptors. During oviposition, *P. przewalskii*, exhibited the following: promotion of

493 contractions through downregulation of β -adrenergic receptor (*ADRB2*), and upregulation of
494 *COX-2* and prostaglandin, and absent (potentially lost) expression of two estrogen receptors
495 (*ESR1* and *ESR2*) and the AVT receptor, *MTR* (Gao et al., 2019). During the stage of gestation
496 corresponding to oviposition, viviparous sister-species, *P. vlangalii*, exhibited the following
497 alternate pattern: inhibition of contractions caused by upregulation of *ADRB2* and
498 downregulation of two estrogen receptors (*ESR1*, *ESR2*), *MTR*, *COX-2*, and prostaglandin (Gao
499 et al., 2019). Some viviparous squamates, *Saiphos equalis*, *Chalcides ocellatus*, and *Pseudemoia*
500 *entrecasteauxii*, share some of these expression patterns (*COX-2*, *MTR*, and *ADRB*, respectively)
501 thought to be involved with extended embryonic retention in viviparous *P. vlangalii* (Brandley et
502 al., 2012; Foster et al., 2020; Gao et al., 2019; Griffith et al., 2016); and *ADRB2* is upregulated at
503 mid-gestation in viviparous *Zootoca vivipara* compared to oviparous counterpart (Recknagel et
504 al., 2021a). Overexpressed genes in viviparous uterine tissues of *Zootoca vivipara* also
505 functionally enriched pathways for beta 1 and beta 2 adrenergic receptor signaling pathways
506 (Recknagel et al., 2021a). This study, which compared uterine expression profiles during
507 gestation across viviparous species of squamates, rodents, canines, ungulates, and humans,
508 concluded that shared regulatory networks are recruited to support viviparity (Reckangel et al.,
509 2021a).

510 Recently, in humans, the only Classical Major Histocompatibility Antigen (C-MHC)
511 expressed by trophoblasts (specialized placental cells) was associated with parturition when it
512 was discovered that HLA-C is significantly increased during laboring term and preterm placentas
513 compared to non-laboring placentas (Hackmon et al., 2017). The authors suggested a mechanism
514 where fetal HLA-C open conformers on the placenta provoke inflammation of maternal tissues,
515 leading to parturition (Hackmon et al., 2017). Expression of MHC alloantigens, foreign antigens

516 to the host, by fetal cells is also associated with parturition in cows and horses (Benedictusa,
517 Koets & Ruttena, 2015; Davies et al., 2004; Joosten et al., 1991; Rapacz-Leonard et al., 2018).
518 Around one month prior to parturition in cows, endometrial epithelium thins and eventually
519 disappears completely, putting the antigen-presenting trophoblasts (Adams et al., 2007) in
520 contact with maternal connective tissue of the endometrium (Podhalicz-Dzięgielewska et al.,
521 2000). Fetal MHC alloantigens are proposed to promote the loosening of maternal and fetal
522 tissues (Benedictusa et al., 2015). MHC molecules are expressed during gestation in some
523 squamates (Murphy, Thompson & Belov, 2009) but their role in oviposition or parturition has
524 not yet been considered to my knowledge. Identifying the presence or absence of MHC
525 alloantigens on embryonic tissues before and during parition across more diverse taxa may
526 reveal how ubiquitous the influence of embryonic MHC molecules is on this.

527 Involution (phase 3) occurs after the embryo(s) is released. In eutherian involution, the
528 placenta detaches, and the uterus shrinks. This is supported by actions of prostaglandins
529 (Husslein, 1984) and oxytocin (Terzidou, 2007). It seems unlikely for processes of involution to
530 be related to evolutionary changes to the length of embryonic retention.

531

532 (2) *Unique qualities of oviposition & parturition in Sauropsids*

533 The physiology of avian oviposition is dependent on a circadian schedule (Williams, 2012).
534 A general model of an “open period”, when eggs are laid are separated by “laying gaps”
535 (Williams, 2012). Chicken ovulation and oviposition cycles leave an 8-hour open period where
536 luteinizing hormone (LH) and progesterone surge, initiating ovulation and continuing the cycle.
537 At the extreme, the ancient murrelet, *Synthliboramphus antiquus*, oviposits a two-egg clutch on
538 seven-day intervals (Williams, 2012). Longer laying intervals have been associated with longer

539 intervals between initiation of yolk development (Astheimer & Grau, 1990). Differing from
540 birds, oviparous squamates retain eggs longer than the ovarian cycle (Tinkle & Gibbons, 1977).
541 This suggests that oviparous squamates may rely on different molecular mechanisms to support
542 oviposition than birds.

543 Non-avian reptiles are unique in that they are the only ectothermic amniotes. This makes
544 them uniquely reliant on temperature for embryonic retention and associated embryonic
545 signaling to indicate the stage of embryonic development. Additionally unique, gemales are the
546 heterogametic sex in several squamates, leading some research to suggest chromosome linkage
547 evolution may increase the speed of evolution in genes associated with gestation length
548 (Recknagel et al., 2021a). Admixture mapping, made possible by the natural hybridization of
549 oviparous and viviparous populations of *Zootoca vivipara*, revealed 439 candidate genes
550 associated with embryonic retention (Recknagel et al., 2021a). Eleven of these genes were also
551 associated with eggshell traits (Recknagel et al., 2021a)—underscoring the pleiotropic roles of
552 some genes putatively involved in squamate parity mode evolution.

553

554(3) *Pre-term birth & embryonic retention mechanisms*

555 The literature on pre-term birth may be a fruitful avenue of research to inform understanding
556 on the evolutionary genomics of embryonic retention length. Slower increases of CRH (Ellis et
557 al., 2002) and higher expression of Neurokinin B, for example, are associated with pre-term birth
558 in humans (Torricelli et al., 2007). Injections of RU486, a progesterone receptor (PGR)
559 antagonist, promoted pre-term labor in rhesus macaques but the progression of physiological
560 activity differed from normal parturition (Haluska et al., 1987). Examining homologs of genes
561 involved with human pre-term birth in squamates may provide further candidates for genes that

562 could impact the length of embryonic retention in squamates. Some evolutionary studies are
563 taking implications of pre-term birth into account. For example, a comparative evolutionary
564 transcriptomics study across therians, monotremes, squamates, and an amphibian recently
565 associated *HAND2* with preterm birth in Eutherian mammals (Marinić et al., 2021).

566 In humans, pregnancy loss from infection follows distorted ratios of immune factors at the
567 maternal-fetal interface (Arenas-Hernandez et al., 2016; Chaturvedi et al., 2015; Chattopadhyay
568 et al., 2010). Future research on the evolution of lengthened embryonic retention to support
569 viviparity may benefit from exploring ratios of immune cells in the uterus and embryonic tissues
570 during term and pre-term pregnancy in squamates. I direct researchers to the literature on the
571 reptile immune system and immune cell ratios at the maternal fetal interface during term and pre-
572 term mammalian pregnancy for further exploration (Yang et al., 2019; Zimmerman, 2010, 2020).

573

574(4) *Discussion & future directions—embryonic retention and parity mode evolution*

575 The physiological processes involved with the start of gestation (maternal recognition of
576 pregnancy) and the end of gestation (partition) in birds and mammals provide insights into the
577 genes and hormones squamates may co-opt to alter length of embryonic retention during
578 transitions between parity modes. Unsurprisingly, hormones like estrogen and progesterone, play
579 important roles in partition across amniotes. Further processes to be examined in squamates
580 include signaling of homologous genes for MRP, placental progesterone production, novel
581 pathways for biosynthesis of progesterone, the role of beta 1 and beta 2 adrenergic receptor
582 signaling pathways, fluctuating ratios of progesterone receptors, the lifespan of the corpus
583 luteum across a broader range of taxa, production and circulation of homologs for AVT and
584 CRH or other similarly structured genes, expression of fetal alloantigens and inflammatory

585 cytokines in utero, and the influence of uterine overdistention on contractions. Regarding
586 squamate parity mode transitions, the role of uterine overdistention in mammalian parturition
587 suggests a lack of uterine overdistention may be one hurdle for reversals back to oviparity.
588 Understanding the evolutionary physiology and genomics of embryonic retention in oviparous
589 and viviparous squamates will benefit from focused attention on reproductively bimodal species
590 (Whittington et al., 2022) and from genomics/physiological research across more taxa that vary
591 in reproductive modes.

592

593 **III. Eggshell Formation**

594

595 Oviparous amniotic embryos develop within an eggshell that is at least partially
596 mineralized, whereas viviparous embryos generally do not. Primarily, the eggshell serves as
597 physical protection and calcium reserve (Stewart & Ecaj 2010; Stewart et al., 2009). The
598 eggshell matrix contains immune properties and pores that enable gas exchange and water uptake
599 (Packard et al., 1982). Evolutionary transitions between parity modes therefore requires changes
600 to the process of eggshell formation. The history of research on the evolutionary morphology of
601 the amniote egg is important for future comparative research (Blackburn & Stewart, 2021). Some
602 have suggested that the amniote eggshell originated multiple times (Aoki, 1993).

603 Birds have hard calcareous eggshells. Other than two lineages of geckos with hard shells,
604 oviparous squamates have parchment-shelled eggs with a thin layer of calcium deposits on the
605 outer surface of the shell membrane (Blackburn & Stewart, 2021; Choi et al., 2018).
606 Monotremata (egg-laying mammals) have an eggshell but far less has been documented about its
607 structure compared to other amniotes (Legendre et al., 2022). The structure and physiological

608 mechanisms involved with eggshell calcification are most well resolved in birds (Choi et al.,
609 2018; Francesch et al., 1997; Jonchère et al., 2010, 2012; Rose-Martel, Du, & Hincke, 2012).
610 Eggshell deposition in tuatara and squamates differs dramatically (Choi et al., 2018). Viviparous
611 squamates lack an eggshell, absorb the eggshell during gestation, or have a thin layer of calcium
612 deposits.

613 The earliest records of amniote eggshells have features characteristics of Archelosaur
614 eggshells, including the mammillary layer (Stein et al., 2019; Legendre et al., 2022). Recent
615 reconstructions are consistent with a thin eggshell in ancestral dinosaurs (Norell et al., 2020;
616 Stein et al., 2019). It is important to consider that the semi-rigid shells of Lepidosaur and
617 testudines are not homologous (Legendre et al., 2022); the microstructure of Archelosauria
618 (birds, crocodiles, turtles and dinosaurs) and Lepidosaur eggshells are remarkably different (Choi
619 et al., 2018); and recent reconstructions of the composition and ultrastructure of dinosaur
620 eggshells revealed that calcified hard eggshell of dinosaurs originated three times (Norell et al.,
621 2020). In the remainder of this section, I consider how structural, mineral,
622 genomic/transcriptomic, and proteomic information on amniote eggshells can inform scientific
623 understanding of the ancestral eggshell of amniotes and Lepidosaur.

624 The genetic drivers of eggshell formation are not resolved in squamates. Two oviparous
625 lizards, *Lerista bougainvillii* and *Lampropholis guichenoti*, differentially express either zero or
626 two genes, respectively, in utero in non-gravid vs gravid comparisons (Griffith et al., 2016).
627 However, this study only measured gene expression at one developmental stage, making it
628 difficult to infer if regulatory changes influence eggshell formation. Nonetheless, oviparous
629 *Saiphos equalis* and *Phrynocephalus przewalskii* have extensive differential expression during
630 gravidity (Foster et al., 2020; Gao et al 2019). It is interesting to see drastically different uterine

631 gene expression profiles associated with oviparity, given that shared genes are recruited to the
632 uterus to support viviparity across diverse amniotes (Recknagel et al., 2021a). Under the
633 assumption that conserved traits should be accompanied with more similar gene expression
634 profiles than convergent traits, uterine gene expression profiles in themselves currently reveal
635 more conserved regulatory networks in utero for squamate viviparity than oviparity.

636 Some genetically determined traits are known to be evolutionarily labile in squamates, like
637 venom and limb reduction (Camaiti et al., 2021; Sites et al., 2011). In *Saiphos equalis*, shell
638 characteristics of facultatively partitioned oviparous and viviparous embryos are similar, leading
639 authors to infer that both parity modes utilize the same machinery to produce egg coverings
640 (Laird et al., 2019). In this species, environmental influences on gestation length, rather than
641 genetic influences on eggshell thickness, may play a more dominant role in parity mode
642 evolution (Laird et al., 2019). In *Zootoca vivipara*, Recknagel et al. (2021a) identified 38
643 candidate genes associated with eggshell traits and concluded that the genetic architecture of
644 eggshell traits is simpler than that of gestation length.

645

646 (1) Mineral composition of eggshells

647 The different mineral compositions of eggshells across amniotes may provide insight into the
648 differing physiological conditions and evolutionary histories under which they are formed (Table
649 1). Taxa use a polymorph of calcium carbonate—calcite, aragonite or vaterite—to develop the
650 eggshell (Hincke et al., 2012). Amorphous calcium carbonate (ACC) is a transient non-
651 crystalline precursor phase of calcite and aragonite that is important for many calcification
652 processes in invertebrates (Hincke et al., 2012). It was recently shown to control avian eggshell
653 mineralization (Rodríguez-Navarro et al., 2015).

654 In birds, the organic components of uterine fluid promote the formation of calcite
 655 (Hernández-Hernández, Gomez-Morales et al., 2008; Hernández-Hernández, Rodriguez, et al.,
 656 2008; Hernández-Hernández, Vidal et al., 2008). Most amniotes use this polymorph (Hernández-
 657 Hernández, Gomez-Morales et al., 2008; Hernández-Hernández, Rodriguez, et al., 2008;
 658 Legendre et al., 2022). However, turtle eggshells are predominately developed with aragonite
 659 (Choi et al., 2022; Mikhailov, 1997). The eggshell of most squamates consists of an inner fibrous
 660 protein layer overlain by calcium carbonate that can be a single layer or scattered crystals (Choi
 661 et al., 2018; Packard & DeMarco, 1991; Stewart et al., 2010).

662 There are differing accounts on the microstructure of monotreme eggshells, however
 663 conceptus coats include three layers including zona pellucida, mocooid coat and shell coat
 664 (Frankenberg & Renfree, 2018). Further studies are needed test for secondary homology.
 665 Monotreme shells are described as proteinaceous, permeable, and flexible (Hughes, 1984).
 666 Marsupials lack an eggshell but have an eggshell coat, similar to that of monotremes
 667 (Frankenberg & Renfree, 2018), that is secreted by the epithelial cells and endometrial glands
 668 early on in embryonic development prior to implantation (Roberts et al., 1994; Roberts & Breed,
 669 1996). Upon hatching of the shell coat and attachment of the embryo, a cooperative
 670 inflammatory response ensues (Stadtmauer et al., 2020a, 2020b).

671 **Table 1.** Amniote Eggshell Ultrastructures

Taxon	Eggshell ultrastructure
Testudoid	Radial aragonite with organic core at base
Crocodiloid	Tabular, arranged in wedges of calcite with no organic core
Squamate	Two types: <ul style="list-style-type: none"> • rigid-shelled eggs with well-developed crystalline layer (dibamid and gekkonid lizards). Stem-like crystals grow downward making for a rigid shell • flexible-shelled eggs with parchment-like shell of fibrils overlaid with little thin crystal caps or no crystalline material (other squamates)
Ornithoid (avian)	Calcite with a clear boundary between lower and upper parts. Mammillary layer defines the lower portion of the shell, with calcite crystals that radiate upwards
Monotreme	Distensible, permeable and highly proteinaceous

672 Note: Adapted from Choi et al., (2018); Frankenberg & Renfree, (2018); Hallman & Griebeler, (2015); Hincke et
673 al., (2012); Trauth & Fagerberg, (1984)

674

675

676 (2) *Uterine glands & the evolution of parity modes*

677 Eggshell formation occurs in the uterus where the uterine glands secrete precursors of the
678 eggshell (Girling, 2002; Guillette, Fox & Palmer, 1989; Jonchère et al., 2010; Nys et al., 2004;
679 Picariello et al., 1989; Stewart & Ecaj, 2010). Uterine glands are critical for gravidity/gestation
680 in both oviparous and viviparous amniotes (Braz et al., 2018; Burton et al., 2002; Cooke et al.,
681 2013). For example, in humans, uterine glands provide histiotrophic nutrition to the early
682 embryo (Burton et al., 2002). In reptiles, precursors for the proteinaceous eggshell membrane are
683 secreted by the uterine glands (Corso, Delitala & Carcupino, 2000; Heulin et al., 2005; Palmer et
684 al., 1993). Calcium secretion can also involve uterine epithelial cells (Herbert, Thompson &
685 Lindsay, 2006; Thompson et al., 2007). Uterine epithelium of the soft-shelled turtle, *Lissemys*
686 *punctata punctata*, and the eastern collard skink, *Chrotaphytus collaris* stain positive for calcium
687 (Guillette et al., 1989; Sarkar et al., 1995).

688 Viviparous squamates have an absent or reduced eggshell membrane to facilitate gas
689 exchange (Blackburn, 1993; Braz et al., 2018) Some squamates are encased in the thin
690 membrane through the entirety of development like the viviparous lizard, *Zootoca vivipara*
691 (Heulin, 1989). Others have the membrane only in the early stages of embryonic development
692 like in garter snakes *Thamnophis radix* and *T. sirtalis* (Blackburn & Lorenz, 2003). Calcium
693 deposits are detected on the outer surface of the membrane throughout development in other
694 viviparous lizards (Stewart et al., 2013).

695 Reduced number or size of eggshell glands leads to reduced eggshell membrane thickness in
696 viviparous squamates. In chickens, variation in size, spacing, and neutron density of eggshell
697 glands may also be important for eggshell structure (Guillette & Jones, 1985). In the

698 reproductively bimodal Yellow-bellied three toed skink, *Saiphos equalis*, the density of eggshell
699 glands plays a role in eggshell thickness (Stewart et al., 2010). In the reproductively bimodal
700 lizard, *Zootoca vivipara*, viviparous individuals have a uterine glandular layer that is less
701 developed during the stage of eggshell formation compared to oviparous individuals (Heulin et
702 al., 2005). Additionally, in *Lerista fragilis*, which lays eggs that hatch within just hours of
703 oviposition, the uterus contains very few mucosal glands (Guillette, 1992). In the fence lizard,
704 *Sceloporus a. aeneus*, the irregular surface of the eggshell was attributed to the irregular spacing
705 of shell glands (Guillette & Jones, 1985). In an oviparous gecko, *Hemidactylus turcicus*, their
706 eggshell glands have loosely packed secretory granules that produce a hard, calcareous shell
707 (Girling et al., 1998). In a comparison of oviparous and viviparous water snakes from the genus
708 *Helicops*, viviparous embryos have thinner shell membranes which associated with reduced size
709 of eggshell glands (Braz et al., 2018). In an oviparous gecko, *Saltuarius wyberba*, their secretory
710 granules are tightly packed, and their shell is soft and parchmentlike (Girling et al., 1998). In a
711 viviparous relative, *Hoplodactylus maculatus*, there are far fewer eggshell glands, and where
712 there are glands, the secretory granules are smaller and more electron dense (Girling, Cree &
713 Guillette, 1997; Girling, Cree & Guillette, 1998). Smaller eggshell gland size during or after
714 vitellogenesis is also found in other viviparous squamates compared to oviparous counterparts
715 (Braz et al., 2018; Gao et al., 2019; Heulin et al., 2005). To my knowledge, in monotremes the
716 relationship between eggshell thickness and shell gland size, density or compaction of secretory
717 granules has not been explored.

718 In the oviparous Przewalski's toadhead agama lizard, *Phrynocephalus przewalskii*, 148 genes
719 are highly expressed in the uterus during the stage of eggshell gland development (Gao et al.,
720 2019). Only three of these are highly expressed in *P. vlangalii*, a viviparous close relative at this

721 time, suggesting differences in oviparous and viviparous eggshell gland development requires
722 regulatory changes to dozens of genes (Gao et al., 2019). In the opossum, a marsupial,
723 proliferation of uterine glands is not induced by the conceptus (Griffith et al., 2019).

724

725 (3) *Evolutionary implications of the physiology of eggshell formation*

726 Presumably because of the influence it has on food production, the process of eggshell
727 formation has been studied most extensively in chickens (Hincke et al., 2012). The avian
728 eggshell is formed in a cell-free environment, and it is the fastest calcifying process known to
729 biology (Hincke et al., 2012; Rodríguez-Navarro et al., 2015). During eggshell formation in
730 birds, uterine fluid containing a supersaturation of ionized calcium and bicarbonate ions
731 surrounds the egg (Nys et al., 1991). Transport of calcium in the uterus correlates with plasma
732 membrane Ca^{2+} -ATPase (*PMCA*) activity and with concentrations of calbindin-D28K within
733 shell gland epithelial cells (Herbert et al., 2006; Wasserman et al., 1991). This leads to the
734 spontaneous precipitation of calcium carbonate into calcite (Hincke et al., 2012). In the
735 oviparous lizard, *Lampropholis guichenoti*, immunofluorescence microscopy revealed activity of
736 *PMCA* in the uterus at the time of eggshell calcification (Thompson et al., 2007).

737 Eggshell formation begins with the eggshell membrane. Two unciliated cell types in the
738 uterus contribute to eggshell membrane formation in a viviparous skink, *Chalcides ocellatus*
739 *tiligugu* (Corso et al., 2000). One secretes sulfated glycosaminoglycans to form the inner shell
740 membrane, and the other which secretes acidic glycoproteins to form the outer layers (Corso et
741 al., 2000). Simple alveolar glands in the lamina propria secrete collagen fibers (Corso et al.,
742 2000). Inhibition of fiber formation or cross-linking, typically caused by aminopropionitrile or a

743 copper deficiency, causes distorted formations of the eggshell membrane in birds (Arias et al.,
744 1997; Chowdhury & Davis, 1995; Hincke et al., 2012).

745 In characteristic Archelosaur eggshells (Choi et al., 2018; Legendre et al., 2022), organic
746 aggregates are deposited onto the shell membrane creating mammillary knobs, which are absent
747 in Lepidosaur shells (Choi et al., 2018). Mammillary knobs are a distinct layer between the outer
748 eggshell membrane and the calcified shell matrix layer (Hamilton, 1986). Part of the mammillary
749 knobs, called basal caps, are embedded into the outer eggshell membrane fibers (Tyler, 1965).
750 Mammillary knobs serve as regions of crystal initiation where ACC is deposited (Gautron et al.,
751 2021) and converted into calcite crystals with no intermediate phase (Rodríguez-Navarro et al.,
752 2015). Cones are formed that radiate in all upward directions, extending up to the shell matrix
753 layer (Tyler, 1965). Despite the direct relationship between mammillary knobs and calcium
754 carbonate crystallization (Rao et al., 2015), the protein comprising mammillary knobs remains
755 uncharacterized. A keratan sulfate (KS)-proteoglycan, “mammillan”, has been implicated in the
756 composition of mammillary knobs (Fernandez et al., 2001; Hincke et al., 2012). Any given
757 proteoglycan is a product of multiple coding genes and biosynthesis of KS-proteoglycans is non-
758 trivial (Caterson & Melrose, 2018; Funderburgh, 2002; Iozzo et al., 2015). However,
759 investigations into the keratan sulfate proteoglycan proposed as “mammillan” and identifying its
760 Properties that Facilitate Calcium Deposition (P-FCD) has far reaching implications given that
761 KS-proteoglycans are proving to be important players in neurological and cancer research
762 (Leiphrakpam et al., 2019). The role of homologs of “mammillan” in eggshell formation in
763 squamates may reveal more about the evolutionary history of the eggshell in amniotes.

764 Parsimony would suggest that all oviparous amniotes shared an ancestral process of
765 eggshell formation. In Archelosaurs, the process of eggshell formation relies on mammillary

766 knobs and upward growth of calcite, as described above. In Lepidosaur eggshells, which have
767 substantially less calcite growth, calcium is deposited on the surface of the eggshell membrane
768 and, in the case of gekkonids and the tuatara, crystal growth proceeds inward toward the center
769 (Choi et al., 2018). The strikingly divergent structure and directionality of eggshell formation
770 between Archelosauria and Lepidosauria suggests that the dissimilar processes of eggshell
771 formation are a result of genetic drift (e.g. Schiffman & Ralph, 2022), selection for specific
772 eggshell traits, or, in the case of an early origin of viviparity in Amniotes (Jiang et al., 2023)
773 and/or Lepidosauria (Pyron & Burbrink, 2014), eggshells are a derived convergent trait.

774 Hypothetically, if a version of the avian eggshell was the microstructure for basal
775 Lepidosauria, loss of mammillary knobs and their basal caps should have prevented calcium
776 deposition since mammillary knobs are the site at which calcium carbonate spontaneously
777 precipitates into calcite in Archelosaurs. Given that embryonic signaling supports at least two
778 main differences between oviparous and viviparous squamates—the timing of calcium secretions
779 and the length of embryonic retention (Griffith et al., 2015, 2017; Stewart & Ecy, 2010)—the
780 loss of mammillary knobs/basal caps may have supported an early origin of viviparity in
781 squamates. It would have theoretically facilitated 1) an early loss of the eggshell, 2) enhanced
782 contact between maternal and embryonic tissues and 3) enhanced signaling from the embryo to
783 support both altered timing of calcium secretions and hormonal signaling for extended
784 embryonic retention. This potential mechanism for an early origin of viviparity in squamates is
785 proposed here, for the first time, as the basal cap hypothesis. When mammillary knobs originated
786 is of paramount importance to the basal cap hypothesis, and inferences that can be gained from
787 applying it to the evolution of oviparity and viviparity in amniotes. If a version of the avian
788 eggshell was the ancestral microstructure of oviparous amniotes, the loss of basal caps could

789 result in a rapid loss of the eggshell and thus a relatively fast transition to viviparity or extended
790 embryonic retention.

791 Extending to the ancestral state of amniotes (e.g. Jiang et al., 2023; Laurin, 2005; Romero,
792 1957), absence of functional “mammillan” with P-FCD in squamates and mammals would be
793 consistent with a derived state of calcified eggshells in Archelosaurs. Absence of functional
794 “mammillan” with P-FCD exclusively in Lepidosaurians would be consistent with the basal cap
795 hypothesis. Presence of functional “mammillan” with P-FCD across Amniota would be
796 consistent with the conventional understanding that the amniote egg evolved to prevent
797 desiccation and enable gas exchange following oviposition of eggs on land (Romero, 1957).
798 Overall, identifying the evolutionary trajectories of the biosynthetic pathway of “mammillan”
799 across amniotes is likely to create a better picture of the evolution of the amniote egg.

800 New recommendations for estimating ancestral microstructure of amniote eggshells have
801 recently been put forth, which abandons the traditional classification of hard/soft/semi-rigid
802 shells (Legendre et al., 2022). Including the structure of eggshell membranes in viviparous
803 squamates (e.g. Corso et al., 2000) would also improve phylogenetic reconstructions of the
804 amniote eggshell.

805 Several pieces of biological evidence lend themselves to an early origin of viviparity in
806 Lepidosaurians and the basal cap hypothesis including—the lack of homology between the semi-
807 rigid shells of testudines and Lepidosaurians (Legendre et al., 2022), the later stage of embryonic
808 development when eggs are commonly oviposited in squamates (Blackburn, 1995), and the more
809 predominant reliance on yolk calcium rather than eggshell calcium in squamates compared to
810 Archelosaurs (Packard, 1994; Stewart & Ecyay 2010). Viviparity in the most recent common
811 ancestor of Lepidosaurians may provide clear evolutionary insights on these phenomena.

812 Other features of eggshells are also worth consideration. In chickens, ovotransferrin is
813 present in the eggshell membrane and basal cap-layer (Gautron, Hincke, Panhéleux et al., 2001).
814 Ovotransferrin promotes the development of elongated crystals (Gautron, Hincke, Panhéleux et
815 al., 2001). The resulting shell matrix is made up of the crystal layer and cuticle (Hamilton, 1986).
816 On the inner portion of the avian eggshell, it is unclear what prevents growing crystalized cones
817 from extending into the inner membrane or the albumen. Collagen type X has been implicated
818 (Arias et al., 1993, 1997; Hincke et al., 2012). The role of collagen type X in creating a boundary
819 that prevents calcite from passing through the eggshell membrane could inform squamate
820 eggshells deposition (as discussed, they deposit calcium only on the outer surface, or crystals
821 grow inward). The only non-avian eggshell matrix protein, pelovaterin, was identified in the soft-
822 shell turtle (Lakshminarayanan et al., 2005).

823 Over 500 proteins are found in the chicken eggshell matrix (Mann, Maček, & Olsen, 2006;
824 Mikšík et al., 2007, 2010). Ovocleidin-116 (*OC-116*), ovocalyxin-36 (*OCX-36* or *BPIFB4*),
825 ovocalyxin-21 (*OCX-21*), and ovocleidin-17 (*OC-17*) are important for avian eggshell formation
826 (Hernández-Hernández, Gomez-Morales et al., 2008; Jonchère et al., 2010; Tian et al., 2010).
827 *OC-116*, *OC-36*, *OCX-21*, and *OC-17* are some of the most differentially expressed genes during
828 eggshell calcification in chickens (Gautron et al., 2007; Hincke et al., 1999, 2012; Jonchère et al.,
829 2010). Ovocalyxin-21 may serve as a chaperone protein along with the protein endoplasmin
830 (ENPL) to facilitate proper folding of the avian eggshell matrix (Jonchère et al., 2010). In birds,
831 *OC-17* is concentrated in the inner mammillary cone layer, it interacts strongly with ACC, and it
832 is implicated in early stages of biomineralization of the eggshell (Gautron et al., 2021).

833 Originally considered avian-specific, several homologs of avian eggshell matrix proteins
834 have now been identified in non-avian reptiles and mammals (Le Roy et al., 2021). A recent

835 study found a significantly reduced number of intact avian eggshell matrix proteins in viviparous
836 squamates compared to oviparous squamates, a pattern that was especially apparent in snakes
837 (Xie et al., 2022). This study also found that *OC-17* was only absent in viviparous squamates but
838 was always present in the oviparous species in the dataset (Xie et al., 2022). Due to this, and the
839 central role of *OC-17* in avian eggshell formation in birds, they ascribe losing intact *OC17* with
840 the prevention of reversals back to oviparity (Xie et al., 2022). However, given that *OC-17* is
841 implicated in initiation of mineralization in the mammillary cone layer, which is absent in
842 squamates, the necessity of *OC-17* for squamates eggshell formation requires further
843 investigation. Other genes, like osteopontin (*OPN* or *SPPI*), also play a central role in
844 biomineralization of the avian eggshell and should be investigated in squamates.

845 *OCX-36* and other bactericidal/permeability-increasing (BPI) family B proteins (also called
846 *LPLUNCs*) are now thought to have a common origin in vertebrates with multiple duplication
847 events (Gautron et al., 2007; Tian et al., 2010). Orthologs of *OCX-36* are found in Archelosauria
848 and Monotremata (Le Roy et al., 2021). In birds, *OCX-36* plays a role in innate immune
849 responses and is found in high concentrations in the inner eggshell membrane (Gautron et al.,
850 2007, 2011; Tian et al., 2010).

851 *OC-116* is homologous to mammalian *MEPE*, which plays a role in bone and teeth
852 mineralization (Bardet et al., 2010a, 2010b). In birds, *OC-116* influences shell thickness, elastic
853 modulus, and egg shape (Le Roy et al., 2021). *OC-116* was identified in a crocodile, *Crocodylus*
854 *siamensis*, proteome (Le Roy et al., 2021; Mikšík et al., 2018). Synteny analysis across seven
855 turtle species and platypus (*Ornithorhynchus anatinus*) revealed absence of *MEPE/OC116* (Le
856 Roy et al., 2021). Other genes and lncRNAs are purported to be important for the quality of
857 eggshell formation in hens—*FGF14*, *COL25A1*, *GPX8*, and several members of the solute

858 carrier protein (*SLC*) gene family (Yang et al., 2020). Research into lncRNAs activity in
859 squamate reproductive tissues during embryonic development represents another valuable track
860 for research.

861 Various evolutionary genomics studies have revealed squamate-specific candidates for shell
862 formation (e.g. Recknagel et al., 2021a; Gao et al., 2020). Some of these candidates span the
863 major clades of amniotes. Seven of the genes expressed during eggshell gland development in
864 *Phrynocephalus przewalskii*—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*, *RRBP1* and
865 *TRAMI*—are purported to be important for eggshell calcification in chickens (Brionne et al.,
866 2014). Given this overlap across species that diverged over 300 million years ago (Shen et al.,
867 2011), these are excellent candidates for further exploration.

868 A functional genomics study harnessed hybridizations of oviparous and viviparous
869 individuals of *Zootoca vivipara* to reveal 17 SNPs and 38 genes associated with eggshell traits
870 (Recknagel et al., 2021a). These genes enriched terms related to cell communication and the
871 immune system, while differentially expressed gene during gravidity enriched pathways for
872 transforming growth factor (Recknagel et al., 2021a). The three loci with the strongest
873 association with eggshell traits mapped closely to *LG MN*, *LYPLA1*, and *CRTCI* (Recknagel et
874 al., 2021a). The association of these genes with eggshell traits is particularly interesting. *LG MN*,
875 for example, is involved with the cadherin pathway. Cadherins have an established role in
876 squamate reproduction. In squamates, previous literature discusses how cadherins influence
877 embryonic attachment in viviparous taxa (Wu et al., 2011). *LG MN* is also differentially
878 expressed across many viviparous squamates and mammals (Recknagel et al., 2021a). Thus,
879 *LG MN*, appears to support both oviparous and viviparous gestation in different ways. There are a
880 number of ways to approach exploring how *LG MN* may support both maternal-fetal

881 interconnectivity (viviparous individuals) and eggshell formation (oviparous individuals). Cell-
882 to-cell communication analysis using single cell data on uteruses of a reproductively bimodal
883 species would enable researchers to identify different interaction networks of *LGMN* and
884 associated cells in oviparous vs viviparous individuals.

885 During gravidity in *Saiphos equalis* two GO terms associated with calcium homeostasis are
886 enriched by the set of upregulated genes (Foster et al., 2020). However, most of these genes are
887 associated with regular cellular responses to calcium and even those associated with calcium
888 transport are upregulated in both early and late stages of gravidity (Foster et al., 2020). Their role
889 in eggshell formation in this uniquely labile species is therefore ambiguous.

890 In oviparous individuals of another reproductively bimodal skink, *Lerista bougainvillii*, only
891 two genes are significantly differentially expressed in the gravid uterine tissue compared to non-
892 gravid uterine tissue (Griffith et al., 2016). No genes are differentially expressed in the gravid
893 uterine tissue of the oviparous garden skink, *Lampropholis guichenoti*, compared to non-gravid
894 uterine tissue (Griffith et al., 2016). The genes involved in the shelling process in these species
895 may not involve changes in expression from the non-gravid state. The dissimilarity in uterine
896 gene expression profiles across lizards during gravidity suggests there may be multiple ways
897 oviparous squamates shell their eggs. Given the variation already observed, the eggshell
898 deposition in squamates should be considered in a phylogenetic context and under the different
899 evolutionary history inferred by ancestral state reconstructions (Harrington & Reeder, 2017;
900 Pyron & Burbrink, 2014). Supplementary table 1 compares candidate genes associated with
901 eggshell formation and shell gland development in squamates to that of birds.

902

903 (4) *Pleiotropy of genes and proteins involved with eggshell formation*

904 Substantial pleiotropy of genes involved with eggshell formation would imply that regardless
905 of parity mode, taxa have innately conserved toolkits that can be readily exploited to form an
906 eggshell for oviparous gestation. In addition to the candidate genes associated with both
907 gestation length and eggshell traits in *Zootoca vivipara* (Reckagel et al., 2021a), several genes
908 associated with eggshell deposition have pleiotropic effects within species or have different
909 effects in oviparous vs. viviparous amniotes. Osteopontin (*SPP1* or *OPN*) is found in bone and
910 kidneys, and transports calcium to other tissues in the body (Pines et al., 1995). It plays an
911 important role in calcium carbonate biomineralization of the avian eggshell (Gautron et al.,
912 2021). It is highly expressed in the chicken uterus during calcification (Jonchère et al., 2010) but
913 supports pregnancy recognition and implantation in sheep (Bazer et al., 2011). Improper
914 functioning of *SPP1* in the uterus leads to cracked and abnormal shells in birds (Arazi et al.,
915 2009; Hincke et al., 2008).

916 When expressed in the uterus, some bone morphogenic protein-coding genes (*BMPs*) aid
917 eggshell calcification (Jonchère et al., 2010). *BMPs* are part of the *TGF- β* superfamily and are
918 involved with the formation of new cartilage and bone, and with biomineralization in corals and
919 mollusks (Canalis et al., 2003; Lelong et al., 2000; Zoccola et al., 2009). Chordin (*CHRD*) is an
920 antagonist of the *BMP* pathway. *BMP*-binding endothelial regulatory protein (*BMPER*) and
921 *CHRD* are expressed in the chicken uterus during the stage of eggshell calcification (Jonchère et
922 al. 2010). Regulation of *BMPs* by *CHRD* is essential for early embryogenesis and adult
923 homoeostasis.

924 *BMPER* and seven *BMPs* are expressed during gestation in *Chalcides ocellatus*, a viviparous
925 skink (Brandley et al., 2012). Most of these are upregulated (Brandley et al. 2012). *BMP* genes
926 are expressed during both gravidity and non-gravidity in oviparous *Lerista bougainvillii* and

927 *Lampropholis guichenoti* (Griffith et al., 2016). *BMP2* is upregulated in oviparous late gestation
928 compared to viviparous late gestation in the reproductively bimodal lizard, *Saiphos equalis*
929 (Foster et al., 2020).

930 Differential expression of *BMPR1B* is associated with differences in eggshell quality in
931 chickens (Yang et al., 2020). Another study associated stage-specific high-expression of
932 *BMPR1B* with the stage corresponding to extended embryonic retention and placentation in
933 *Phrynocephalus vlangalii* (Gao et al., 2019). They identified a co-expression network of highly
934 expressed genes, including *BMPR1B*, that they associated with placentation (Gao et al., 2019).
935 *BMPR1B* also reaches significant levels of differential expression in uterine tissues of other
936 gestating viviparous lizards, *Chalcides ocellatus* and *Pseudemoia entrecasteauxii*, compared to
937 non-gestational uterine tissue (Brandley et al., 2012; Griffith et al., 2016). Receptors for *BMPs*
938 are also expressed in the uterus during gestation in other viviparous lizards, *Phrynocephalus*
939 *vlangalii* and *Pseudemoia entrecasteauxii* (Gao et al., 2019; Griffith et al., 2016). Perhaps
940 unsurprisingly, *BMPR1B* is also differentially expressed in the uterus of viviparous *Zootoca*
941 *vivipara* compared to oviparous individuals during gestation.

942 The potential role of these genes in squamate eggshell formation remains unclear. *BMPs*
943 influence on dorsal-ventral axis patterning during early embryogenesis and growth of skeletal
944 structures in post-natal tissues (Medeiros & Crump, 2012). It may be difficult to disentangle their
945 roles in embryonic development, placental development, and eggshell deposition. Future
946 research on them may inform scientific understanding of parity mode evolution.

947 *SLIT* genes are purported to be involved with folding the eggshell matrix in chickens
948 (Jonchère et al., 2010). The *SLIT2* gene functions across birds and mammals in diverse organs,
949 and encodes a protein that provides a structural framework for protein-protein interactions

950 (Jonchère et al., 2010; Marillat et al., 2002). In a functional genomics study, *SLIT2* was
951 identified as an important gene for eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).
952 *SLIT2* is among the 50 most downregulated genes in the uterus during pregnancy in the
953 viviparous African ocellated skink, *Chalcides ocellatus*, compared to non-pregnancy (Brandley
954 et al., 2012). However, in the uterus of the yolk-sac placenta in the viviparous skink, *Pseudemoia*
955 *entrecasteauxii*, *SLIT2* is upregulated compared to non-reproductive uterine tissue (Griffith et al.,
956 2016). *SLIT3* is differentially expressed during the stage of placentation in the viviparous agama
957 lizard, *Phrynocephalus vlangalii* (Gao et al., 2019). *SLIT* genes also play a role in axonal
958 pathfinding and neuronal migration in rats (Marillat et al., 2002). *SLIT2* was associated with
959 reproduction in humans (Chen, Chu et al., 2015).

960 Podocalyxin (*PODXL*) is a sialoprotein associated with eggshell calcification in chickens
961 (Jonchère et al., 2010). In the viviparous Qinghai toad-headed agama lizard, *Phrynocephalus*
962 *vlangalii*, a weighted gene correlation network analysis associated *PODXL* with uterine
963 structural changes (Gao et al., 2019). The gene may play a role in placentation in these species
964 given that it was also differentially expressed in the uterus during the stage of placentation (Gao
965 et al., 2019). Interestingly, *PODXL* is downregulated in the uterus of the yolk-sac placenta in
966 another viviparous skink, *Pseudemoia entrecasteauxii* (Griffith et al., 2016). Based on its role in
967 chickens and *P. vlangalii*, *PODXL* is a good candidate for further research on the molecular
968 evolution of eggshell formation and placentation in squamates.

969

970 (5) Eggshell formation termination

971 When eggshell formation is terminated, the egg is still bathed in the supersaturated
972 calcium and bicarbonate ion fluid (Hincke et al., 2012). Some component(s) of the terminal

973 uterine fluid may prevent precipitation of calcium carbonate (Gautron, Hincke & Nys, 1997),
974 such as phosphate anions (Lin & Singer, 2005). The presence of phosphorous in the superficial
975 layers of the chicken shell suggest it may be a factor preventing the deposition of calcite crystals
976 in the terminal stage. Additionally, the high concentration of *OCX-32* in the outer eggshell and
977 cuticle, suggest that the gene may inhibit proteinaceous crystal growth in the terminal stage of
978 eggshell calcification (Gautron, Hincke, Mann et al., 2001). It is informative to viviparous
979 reproduction and consistent with the basal cap hypothesis that exposure to precursors of the
980 eggshell does not necessitate eggshell deposition. The influence of phosphate anions and *OCX-*
981 *32* on inhibition of calcium carbonate precipitation on the eggshell membrane of viviparous
982 squamate embryos has not been examined to my knowledge.

983

984 *(6) Rotating the egg for eggshell formation*

985 Oviparous amniotes rotate the egg for calcium formation and viviparous mammals rotate the
986 embryos for parturition. One hurdle to reversing back to oviparity may be re-evolving rotation of
987 the egg for shell formation early in gravidity (Griffith et al., 2015). Given the complex
988 musculature of the uterus across taxa, that allows for multidirectional force for parturition and
989 eggshell formation, it is difficult to determine the degree of difficulty for re-evolving appropriate
990 timing of egg-rotation. Cadherins and hormonal signaling support embryonic attachment (Wu et
991 al., 2011; Biazik et al., 2012), which can prevent rotation of the egg. Oviparous taxa lack
992 embryonic attachment, enabling the uterus to rotate the egg for eggshell formation. This rotation
993 does not happen until later in gestation for eutherian mammals when, for example, the embryo
994 detaches and cadherins become less concentrated (Wu et al., 2011). Perhaps a candidate gene for
995 studying this is, a cadherin *CDH5*, the only gene that is differentially expressed in all viviparous

996 squamates studied thus far studied (Recknagel et al., 2021a). Genes that enrich the GO term for
997 “voltage-gated calcium channel activity” are also useful candidates for investigating uterine
998 rotation associated with eggshell formation because voltage-gated calcium channels effect the
999 action potential of cells and can cause muscle contractions.

1000

1001 (7) Discussion & future directions—eggshell formation and parity mode evolution

1002 The process of eggshell formation is more resolved in birds compared to non-avian reptiles
1003 and monotremes (Choi et al., 2018; Frankenberg & Renfree 2018). I described some overlaps
1004 gleaned from the literature which prove as curious candidates for further research
1005 (Supplementary Table 1). Of particular interest are avian eggshell matrix proteins (Alföldi et al.,
1006 2011; Le Roy et al., 2021; Tian et al., 2010; Xie et al., 2022), genes with biomineralizations
1007 functions, candidate genes associated with eggshell traits in *Zootoca vivipara* (Recknagel et al.,
1008 2021a), and the homologs for avian eggshell matrix proteins identified in the *Anolis carolinensis*
1009 genome (Alföldi et al., 2011; Tian et al., 2010). Additionally, genes purported to be important for
1010 eggshell calcification in chickens associated with eggshell gland formation in an oviparous
1011 lizard, *Phrynocephalus przewalskii*, are relevant—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*,
1012 *RRBPI* and *TRAMI* (Brionne et al., 2014; Gao et al., 2019). Overlaps between the genes
1013 associated with gestation length and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a)
1014 hint at genes that could potentially evolve to innately effect multiple traits relevant to parity
1015 mode transitions. The basal cap hypothesis also offers a simple evolutionary mechanism to
1016 investigate the evolutionary history of amniote parity mode evolution (see section III.3).
1017 Alternatives to the basal cap hypothesis are that dissimilar eggshells and eggshell deposition

1018 processes evolved through selective pressure, genetic drift, or both. Fortunately, the basal cap
1019 hypothesis can be utilized to ascertain the likelihood of this.

1020

1021 **IV. Placentation & Transport of Embryonic Water, Gas, and Nutrients**

1022

1023 The evolutionary pressures on fluid allocation, gas exchange and nutrient transport should
1024 differ between oviparous and viviparous taxa because their sources of all or some of these
1025 resources differ (Blackburn, 1992; Bonnet et al., 2001; Bonnet, Naulleau & Shine, 2017; van
1026 Dyke et al., 2014). In viviparity, maternal gas and water are accessed through the chorioallantois,
1027 which is especially important in the latter half of development (van Dyke et al., 2014; Carter,
1028 2012). Nutrients can be available from the yolk, maternal transfer, or both yolk and maternal
1029 transfer.

1030 While viviparity is associated with shared patterns of uterine gene expression during amniote
1031 gestation (Recknagel et al., 2021a), the same does not occur in viviparous amniote placentas
1032 (Foster et al., 2022). Instead, different genes that serve similar functions are recruited to the
1033 placenta across independent origins of viviparity (Foster et al., 2022). Additionally, where other
1034 amniotes can rely on the albumen for fluid allocation, squamates lack an albumen (Blackburn &
1035 Stewart, 2021). The eggshells of various squamates supports uptake of water from the
1036 environment (Blackburn & Stewart, 2021). The evolutionary implications of this have not been
1037 documented to my knowledge.

1038

1039 *(1) Anatomy & methods of water, gas & nutrient provisioning*

1040 The embryonic membranes regulate embryonic fluid transport, nutrient supply, respiration,
1041 immunity, and waste (Brace, 1997; Burton & Tullett, 1985; Ferner & Mess, 2011; Packard &
1042 Packard, 1980). Fluids are important for the developing embryo because they prevent desiccation
1043 and compression (Ferner & Mess, 2011; Packard & Packard, 1980). Over-abundance or under
1044 abundance of embryonic sac fluids leads to reproductive failure (Chamberlain et al., 1984;
1045 Fedakâr et al., 2016; Hadi, Hodson & Strickland, 1994; Mercer et al., 1984). Water is the
1046 predominant resource provisioned from the mother in most viviparous squamates (Lourdais et
1047 al., 2015).

1048 Oxygen flux in embryonic mammals is largely determined by oxygen-diffusing capacity of
1049 the placenta, the rates of blood flow in the umbilical and uterine arteries, and the oxygen
1050 capacities and affinities of fetal and maternal blood (Carter, 2009). Reptilian and mammalian
1051 blood vessels differ in basic characteristics such as capillary density, capillary surface, and
1052 oxygen diffusion gradients (Pough, 1980). Oviparous taxa regulate gas exchange through pores
1053 in their eggshells.

1054 Patterns of embryonic nutrient exchange can be broadly categorized into lecithotrophy,
1055 obtaining nutrients from the yolk, and placentrophy or matrotrophy, obtaining nutrients from the
1056 mother. Taxa belonging to Archelosauridae are lecithotrophic. The ancestral state of mammals
1057 was most likely oviparous matrotrophy that later evolved into viviparous matrotrophy in therians
1058 (Blackburn, 2005). The ancestral state of reptiles was likely lecithotrophy (Blackburn, 2005).
1059 Most viviparous squamates are lecithotrophic, some are lecithotrophic and matrotrophic, and a
1060 few have specializations for substantial matrotrophy (e.g. Blackburn, 2015a, Blackburn, 1985b;
1061 Stewart & Thompson, 1993; Thompson, Stewart et al., 1999; van Dyke et al., 2014). Even in
1062 lecithotrophic viviparous squamates some degree of organic or inorganic nutrients pass through

1063 the chorioallantoic placenta (Blackburn, 2005; Swain & Jones, 1997, 2000; Stewart & Eday,
1064 2010; Thompson, Stewart et al., 1999; Thompson & Speake, 2002). Reversals may be most
1065 unlikely in lineages that have specialized placentas for substantial nutrient exchange because
1066 they would need to re-evolve lecithotrophy. Highly matrotrophic squamates are extremely rare
1067 (Blackburn, 2015a).

1068

1069 *(2) Evolutionary history of yolk-sac formation and yolk processing*

1070 Vitellogenesis is the process of yolk formation in the oocyte, providing the embryo with a
1071 valuable source of nutrients, primarily through the accumulation of precursor proteins to yolk,
1072 vitellogenins. Vitellogenin is produced in the liver, called hepatic vitellogenesis, and transported
1073 to the maturing ovum (Ho, 1987). Vitellogenins were lost in all mammals except monotremes
1074 (Brawand, Wahli & Kaessmann, 2008). They are a primary source of nutrition for other
1075 amniotes. Functionally similar to vitellogenin, caseins have persisted in all mammalian milks
1076 (Brawand et al., 2008). Active functioning of the yolk sac is restricted to the first trimester in
1077 placental mammals, and it is postulated to provide nutrients to the embryo (Kuzima et al., 2023).
1078 The detection of glycodelin in the yolk sac epithelium also supports this (Burton et al., 2002). In
1079 the yolk-sac of bats, dogs, and non-human primates the mesoderm derived layer is absorptive
1080 and may transfer substances from the exocoelomic cavity where the yolk sac is located (Enders
1081 et al., 1976; Freyer & Renfree, 2009; King & Wilson, 1983; Lee et al., 1983).

1082 The morphology of the yolk-sac and process of vitellogenesis differs between birds and non-
1083 avian reptiles. In birds, during the process of meroblastic cleavage, the zygote's cells divide
1084 while the yolk component does not. The yolk forms a large, fluid, non-cellularized mass
1085 surrounded by the extraembryonic yolk sac. The formation of the yolk-sac placenta in birds has

1086 the following pattern—first the bilaminar omphalopleure forms and then trilaminar
1087 omphalopleure; blood vessels move into folds of the extraembryonic endoderm, becoming
1088 stratified epithelium; the folds carrying the blood vessels reach the peripheral regions of the yolk
1089 only and the center of the yolk mass remains uncellularized (Starck, 2021). Intensive
1090 development of hemopoietic tissue surrounding the blood vessels during most of embryonic
1091 development, thus far, appears to be unique to birds (Starck, 2021). Compared to non-avian
1092 sauropsids, the unique pattern of yolk processing in birds facilitates faster embryonic
1093 development (Blackburn, 2021).

1094 The yolk sac characteristic of non-avian reptilian eggs serves as a model for the transition
1095 between the egg of anamniotes and amniotes (Blackburn, 2020). A series of recent papers,
1096 covering species of snakes, lizards, crocodiles, and turtles, indicate that these taxa utilize similar
1097 developmental pathways of yolk-sac formation and yolk processing that differs from birds
1098 (Blackburn, 2020, 2021; Blackburn et al., 2019; Elinson et al., 2014; Elinson & Stewart 2014;
1099 Stinnett et al., 2011). Across these taxa, a bilaminar/trilaminar omphalopleure overgrows the
1100 yolk mass, and the yolk mass gets invaded by proliferating endodermal cells that phagocytose
1101 the yolk material. These cells form clumps, progressively filling the yolk mass. Small blood
1102 vessels derived from yolk sac vasculature invade the yolk sac cavity and the endodermal cells
1103 arrange in monolayers around these vessels, forming “spaghetti bands” (Blackburn, 2021). The
1104 yolk sac of *Pantherophis guttatus* is one suitable model for studying the transition of the yolk-
1105 sac from anamniotes to amniotes (Elinson & Stewart, 2014; Elinson et al., 2014).

1106 A major difference between non-avian reptilian yolk-sac formation is the morphology and
1107 extent of vascularization and cellularization in the yolk sac cavity (Starck, 2021). Birds have a
1108 yolk-sac with absorptive endodermal lining that digests nutrients and send them into blood

1109 circulation (Starck, 2021) whereas snakes, lizards, turtles, and crocodylians have a yolk sac that
1110 becomes invaded by endodermal cells that proliferate and phagocytose yolk material (Blackburn,
1111 2021). In these taxa, yolk material becomes cellularized, digested, and transported by vitelline
1112 vessels to the developing embryo (Blackburn, 2021). Factors involved with cellularization of the
1113 yolk-sac are proposed to include cell cycle regulators and structural proteins (Elinson et al.,
1114 2014). Generation of these cells are suspected to be reliant on processes of angiogenesis and are
1115 likely transcriptionally active (Elinson et al., 2014). Few transcriptomic profiles of yolk-sac
1116 placentas in reptiles have been documented to my knowledge (Griffith et al., 2016). Significant
1117 overlaps in the yolk-sac transcriptomes of human, mice, and chicken—including apolipoproteins
1118 and SLC transporters—however, suggest functional conservation (Cindrova-Davies et al., 2017).

1119 As discussed in a previous section, progesterone inhibits myometrial contractility, but it also
1120 inhibits estrogen-induced hepatic vitellogenin synthesis (Custodia-Lora, Novillo, & Callard,
1121 2004; Callard et al., 1992). Variable progesterone concentrations in circulation throughout
1122 gestation in viviparous squamates may reflect a trade-off to allow estrogen expression to support
1123 hepatic vitellogenin synthesis during embryonic development, thus supporting nutrient
1124 provisioning during the lengthened embryonic retention. Although hepatic vitellogenesis usually
1125 ceases during gestation, vitellogenin synthesis and mother-to-embryo transfer was detected in
1126 one viviparous fish, *Xenotoca eiseni*, during gestation (Iida et al., 2019). Future research should
1127 consider the timing of vitellogenin synthesis throughout the reproductive cycle in gestating and
1128 non-gestating viviparous squamates to investigate this further.

1129

1130 (3) *Evolutionary history of placentrophy in mammals & squamates*

1131 Traditionally, it was thought that placentrophy evolved after viviparity in squamates
1132 (Packard, Tracy, & Roth, 1977; Shine & Bull, 1979). Further research demonstrated that
1133 placentrophy and viviparity evolved simultaneously (incipient matrotrophy) in mammals and
1134 may have in squamates (Blackburn, 1985, 1992, 2005, 2006; Stewart & Eday, 2010). The
1135 incipient matrotrophy model relies on evidence that 1) uterine provisioning of nutrients predates
1136 the origin of viviparity (Blackburn 1985, 1992, 2006), 2) uterine and embryonic tissues have a
1137 close anatomical and physiological association in viviparous taxa and 3) some degree of
1138 placental transfer of organic or inorganic molecules occurs in viviparous taxa (Stewart & Eday,
1139 2010). In squamates, the potential for both incipient matrotrophy and evolution of placentrophy
1140 after viviparity is supported (Stewart & Eday, 2010). Facultative placental nutrient provisioning
1141 and incipient matrotrophy may have driven the evolution of squamates with substantial
1142 matrotrophic nutrient provisioning (Stewart, 2020; Swain & Jones, 2000).

1143 Placentation and implantation are not homologous in mammals compared to squamates
1144 (Griffith, van Dyke & Thompson, 2013). Several placental specializations for gas and nutrient
1145 exchange are unique to mammals including erosion of the uterine mucosa, extensively invasive
1146 implantation, hemochorial contact, retention of a vascularized choriovitelline membrane, and
1147 countercurrent patterns of blood flow (Blackburn, 2005). This enables extensive exchange of
1148 nutrients in addition to water and gas. The vast majority of viviparous squamates have the most
1149 superficial type of chorioallantoic placenta called epitheliochorial placenta (Blackburn, 1993).

1150 Nutrient provisioning through placentrophy is obligate for embryonic development in only
1151 five lineages of squamates, all of which are scincid lizards (Blackburn, 2000; Flemming &
1152 Blackburn, 2003; Ramírez-Pinilla et al., 2011; van Dyke et al., 2014). *Pseudemoia*
1153 *pagenstecheri*, a lizard with a highly specialized placenta, out-performs lecithotrophic oviparous

1154 close relatives in the relative amount of nutrients it transfers to the embryo (Stewart et al., 2009).
1155 *Pseudemoia entrecasteauxii* is a moderately matrotrophic viviparous skink, with roughly half of
1156 embryonic nutrient uptake from the yolk and half through a specialized cyto-epitheliochorial
1157 placenta (Adams et al., 2005; Speake et al., 2004; Stewart & Thompson, 1993, 2009).

1158 Specializations of the chorioallantoic placenta for nutrient provisioning in some squamates
1159 include elaborate specializations for uterine secretion and absorption, including placentomes,
1160 chorionic areolae, hypertrophied uterine mucosa, and chorionic epithelia modified for absorption
1161 (Blackburn, 2005). In squamates, specializations for gas exchange across the chorioallantoic
1162 placenta include decreased diffusion distance between maternal and fetal capillaries, uterine
1163 vascularity, shell membrane deterioration, and modifications of both fetal and maternal blood
1164 properties (Blackburn, 1998, 2005; Blackburn & Lorenz, 2003; Blackburn & Vitt, 2002).

1165 Mammalian placenta-specific genes have deep origins in vertebrates (Rawn & Cross, 2008).
1166 Placentation to support viviparity likely employs genes that are ancestral to the chorioallantois.
1167 However, one study that looked at placentation and gene expression across a small sample of
1168 divergent amniotes found only one gene with a placentrophy-specific pattern of gene expression,
1169 *DIO3* (Griffith, Brandley et al., 2017). In mammals, *DIO3* is an imprinted gene and
1170 preferentially paternally expressed. The authors suggest that the gene may increase offspring
1171 resource uptake during pregnancy in the horse and a viviparous lizard, *Pseudemoia*
1172 *entrecasteauxii*, where it is recruited to the placenta (Griffith, Brandley et al., 2017).

1173

1174 (4) Genes involved with embryonic water, gas, and nutrient transport

1175 Water transport in animals is regulated by a family of molecular water channels called
1176 aquaporins (AQs or AQPs) (Borgnia et al., 1999). In humans, *AQP1*, *AQP3*, *AQP4*, *AQP8* and

1177 *AQP9* are found in the placenta but further research is needed to understand how these influence
1178 water fluxes between maternal and fetal tissues (Damiano, 2011). Transcriptomic analysis on
1179 uterine tissue of the gestating, viviparous skink, *Chalcides ocellatus*, reveal differential
1180 expression of *AQP1*, *AQP3*, *AQP5*, *AQP6*, *AQP8*, *AQP9* and *AQP11* when compared to non-
1181 gestating uteruses (Brandley et al., 2012). In birds, *AQP1* is expressed in the chorioallantoic
1182 membrane, and it is suggested to influence angiogenesis throughout embryonic development
1183 (Ribatti et al., 2002). In a viviparous lizard, *Pseudemoia entrecasteauxii*, *AQP8* and *AQP9* were
1184 more highly expressed in the chorioallantoic placenta compared to the yolk-sac placenta (Griffith
1185 et al., 2016). During gestation in both oviparous and viviparous populations of the reproductively
1186 bimodal skink, *Saiphos equalis*, several genes involved with water homeostasis are upregulated
1187 in the uterus including *AQP1*, *AQP3* and *AQP12B* (Foster et al., 2020). In uteruses of *Saiphos*
1188 *equalis*, *AQP5* and *AQP8* are upregulated during oviparous late gestation compared to viviparous
1189 late gestation. In sheep, *AQP3* is differentially expressed during gestation, where it serves a dual
1190 role of water transport to the embryo and fetal urea export (Johnston et al., 2000). This is similar
1191 to the function of *AQP9* in humans (Damiano, 2011). Immunocytochemistry reveals that *AQP1*
1192 and *AQP3* are expressed in the uterus of the highly placentrophic South American scincid lizard,
1193 *Mabuya sp.* (Wooding et al., 2010). In *Zootoca vivipara*, *AQP9* is upregulated at midgestation
1194 (Recknagel et al., 2021a).

1195 Some molecules are implicated in the regulation of aquaporins including insulin (INS),
1196 human chorionic gonadotropin (HcG), cyclic adenosine monophosphate (cAMP) and cystic
1197 fibrosis transmembrane conductance regulator (CFTR) (Damiano, 2011). Genes predicted to be
1198 involved with reproduction in *Anolis carolinensis* are enriched for the GO term for cAMP-
1199 mediated signaling (Alföldi, Di Palma, et al., 2011). Further comparative research should be

1200 done to elucidate the functional differences of aquaporins in oviparous and viviparous amniotes
1201 and how they relate to the differing conditions under which these embryos develop.

1202 Genes involved embryonic oxygen transport precede the origin of amniotes. Hemoproteins
1203 arose in evolutionary history well before they were used for placental oxygen transfer (Hardison
1204 1998). In mammals, adult (Alpha: HBA; Beta: HBB, HBD) and embryonic hemoglobins (Alpha:
1205 HBZ, HBA; Beta: HBE, HBG, and HBH) are involved with oxygen transport (Carter, 2012).
1206 Some of these are unique to eutherian mammals following a series of duplication events (Opazo
1207 et al., 2008). However, fetal hemoglobins are found in turtles, lizards, and snakes (Pough, 1980).
1208 HBA, HBB and HBM are all significantly downregulated in the uterine tissue of the viviparous
1209 African Ocellated Skink, *Chalcides ocellatus*, during gestation compared to non-gestation
1210 (Brandley et al., 2012). The oxygen demands of reptile embryos are relatively low until stage 30,
1211 when most oviparous taxa oviposit (Shine & Thompson, 2006). In viviparous and oviparous
1212 species with long egg retention, embryonic demand for maternal provision of oxygen and
1213 removal of CO₂ increases at this stage.

1214 Improper water, gas and nutrient exchange can occur due to poor chorioallantoic blood flow
1215 (Wootton et al., 1977). Thus, viviparous taxa require greater degrees of vascularization and
1216 vasodilation to facilitate enhanced requirements for maternal resources compared to oviparous
1217 taxa. Rather than increasing the size of the placenta, increasingly dense blood vessels can support
1218 fetal growth without compromising space for embryonic growth as occurs in some pigs (Ford,
1219 1997; Vonnahme et al., 2002). Embryonic vascularization and vasodilation are dependent on
1220 signals from the endoderm (Jin et al., 2005; Vokes & Krieg, 2002; Wilt, 1965). In oviparous
1221 individuals of *Saiphos equalis*, populations with extended egg retention, there is expansion of the
1222 uterine vascular bed and thickening of the chorioallantoic tissue that supports increased

1223 embryonic growth in the later portion of oviparous gravidity (Parker et al., 2010). In the
1224 viviparous scincid lizard, *Eulamprus quoyii*, angiogenesis, the formation of new blood vessels,
1225 and expansion of the vessel-dense elliptical area of the uterus is associated with supporting
1226 increased embryonic oxygen demand (Murphy et al., 2010).

1227 Several protein-coding genes are known to be involved with angiogenesis, vascularization,
1228 and vasodilation in utero. One study that examined expression patterns across chickens
1229 (oviparous), horses (viviparous), two viviparous squamates, and one oviparous squamate found
1230 that no examined genes for angiogenesis showed a viviparity-specific expression pattern
1231 (Griffith, Brandley et al., 2017). However, other than the chicken, the only oviparous taxa
1232 included in this study was a reproductively bimodal skink, *Lerista bougainvillii* (Griffith,
1233 Brandley et al., 2017). Alternatively, differential gene expression analyses on oviparous and
1234 viviparous individuals of *Zootoca vivipara*, revealed pathways for angiogenesis enriched in
1235 viviparous female reproductive tissues; and pathways for angiogenesis were enriched across
1236 genes under divergent selection in oviparous and viviparous *Z. vivipara* individuals.

1237 In the uterine tissue of gestating viviparous skinks and rats, several genes for angiogenesis
1238 are upregulated—*EPASI*, *HIF1A* and *VEGFA* (Brandley et al., 2012; Whittington et al., 2015,
1239 2017). Other proteins involved in vascularization and vasodilation in utero include members of
1240 the vascular endothelial growth factor (*VEGF*) gene family, VEGF receptors (*VEGFRs*),
1241 placental growth factor (*PGF*) and nitric oxide synthase (*NOS*) (Blomberg et al., 2010; Chen,
1242 Wang et al., 2015; Gilbert, 2010; Reynolds et al., 2006; Risau, 1997; Torry et al., 2003;
1243 Vonnahme et al., 2001). In *Saiphos equalis*, different homologs of *NOS* experience different
1244 patterns of gene expression across the oviparous and viviparous stages of gestation/gravidity
1245 (Foster et al., 2020). One homolog of *NOS* is upregulated during oviparous late gestation, and

1246 another is upregulated during viviparous late gestation (Foster et al., 2020). Several genes
1247 involved with angiogenesis and vascular morphogenesis are downregulated in the pre-
1248 implantation uterus of a marsupial, the Fat Tailed Dunnart, *Sminthopsis crassicaudata*—
1249 *ADGRA2, ADGRB2, ANGPTL1, EPHB4, ISM1, PDZRN3, RHOJ, TNMD,* and *VEGFD*
1250 (Whittington et al., 2018).

1251 In humans, immune factors are also responsible for increasing embryonic blood supply.
1252 Embryonic non-classical MHC class I molecule, HLA-G, and uterine natural killer (uNK) cells
1253 support increased embryonic blood supply (Moffett & Loke, 2006; Rajagopalan et al., 2006). A
1254 similar pattern of utilizing immune properties to support embryonic blood supply has not been
1255 yet identified in squamates.

1256 Lipids are a main energy source for embryos. Lipoprotein lipase (LPL) is an important
1257 enzyme in lipid transport. LPL is significantly expressed on the syncytiotrophoblasts, specialized
1258 placental cells, of humans (Lindegaard et al., 2005) and the endometrium of cows (Forde et al.,
1259 2011), and pigs (Ramsay et al., 1991), where it plays a role in lipid mobilization. A viviparous
1260 lizard, *Pseudemoia entrecasteauxii*, increases capacity for lipid transport toward the end of
1261 pregnancy (Griffith, van Dyke & Thompson, 2013). The uterine tissue of the yolk-sac placenta in
1262 this species had significantly higher expression of LPL than the uterine tissues of the
1263 chorioallantoic placenta (Griffith, van Dyke & Thompson, 2013), leading the authors to suggest
1264 that the yolk-sac placenta is the major site of lipid transport. LPL expression was not detected
1265 during pregnancy in the viviparous skink, *Chalcides ocellatus* (Blackburn, 1992; Brandley et al.,
1266 2012). Instead, lipid transport may be facilitated by fatty acid binding proteins in this species
1267 (Chmurzyńska, 2006; Brandley et al., 2012). These are also active on mammalian placenta
1268 (Haggarty, 2002).

1269 Apolipoproteins are also suitable candidates for transport of fatty acids, cholesterol, and
1270 phospholipids. Five of these (*APOA1*, *APOA2*, *APOA4*, *APOE*, and *APOM*) and *APOA1BP* are
1271 significantly upregulated in the pregnant uterus of the viviparous skink, *Chalcides ocellatus*
1272 (Brandley et al., 2012). *APOA1BP* is also upregulated in the uterus of the chorioallantoic
1273 placenta and yolk-sac placenta compared to non-gestational uterine tissues in *Pseudemoia*
1274 *entrecaeauxii* (Griffith et al., 2016). Additionally, upregulation of 136 genes that encode solute
1275 carrier proteins (SLCs) in the pregnant uterus of *Chalcides ocellatus* are associated with
1276 transport of inorganic ions, metals, glucose, amino acids, peptides, fatty acids, and carboxylic
1277 acids (Brandley et al., 2012).

1278 Supply of amino acids is required for embryonic development. SLCs have important
1279 transport functions, including the transport of amino acids, and thus they are considered to be
1280 important for gestation (Foster et al., 2022). However, a recent study found no overlap in the
1281 amino acid transporting SLCs upregulated in placentas of viviparous placentrophic vertebrates
1282 studied, which included eight representatives from Mammalia, Reptilia, and Chondrichthyes
1283 (Foster et al., 2022). However, *SLC38A3* was upregulated in all viviparous species except *Rattus*
1284 *norvegicus* (Foster et al., 2022).

1285 Cathepsins and phospholipases are important for uterine secretions for embryonic
1286 development in horses, pigs, sheep, and cattle (Bazer, 1975; Satterfield et al., 2007; Song et al.,
1287 2010). Cathepsins are present in yolk sacs of humans and mice. They function to degrade
1288 proteins to free amino acids (Cindrova-Davies et al., 2017). Two genes for cathepsin L (*CTSL1*
1289 and *CTSL2*) are upregulated in the uterus during gestation in *Chalcides ocellatus* (Brandley et al.,
1290 2012). *CTSL* is also upregulated in the uterus during the pre-implantation phase in the Fat-Tailed
1291 Dunnart, *Sminthopsis crassicaudata* (Whittington et al., 2018), and in the uterus of the

1292 chorioallantoic placenta and uterus of the yolk sac placenta during gestation in *Pseudemoia*
1293 *entrecasteauxii* (Griffith et al., 2016).

1294 In viviparous individuals of the reproductively bimodal lizard, *Saiphos equalis*, many genes
1295 for cellular adhesion are upregulated during late gestation (Foster et al., 2020). The authors
1296 postulated that this helps facilitate maternal-fetal signaling and paracellular transport (Foster et
1297 al., 2020). Gao et al. (2019) identified a set of genes in *Phrynocephalus vlangalii* that were
1298 differentially expressed in the uterus during the stage of placentation and these enriched GO
1299 terms functionally related to the process of placentation. This included an estrogen receptor
1300 (*ESRI*) and two growth factor receptors (*GHR* and *IGFIR*) (Gao et al., 2019).

1301 Finally, the proteomes of the ovary and placenta from obligately placentrophic *Mabuya*
1302 lizards can further serve as a useful resource for examining nutrient provisioning in squamates
1303 (Hernández-Díaz et al., 2017). In the placenta they found protein expression involved with
1304 nutrient metabolism, transport, protein synthesis, and embryonic development (Hernández-Díaz
1305 et al., 2017).

1306

1307 (5) Uterine glands: adenogenesis, placenta development and histotrophy

1308 In addition to their role in eggshell deposition in oviparous taxa, uterine glands also secrete
1309 growth factors and cytokines that support placental development in mammals. In humans, these
1310 include transforming growth factor- β (TGF- β), epidermal growth factor (EGF), vascular
1311 endothelial growth factor (VECG), and leukemia inhibitory factor (LIF) (Hempstock et al.,
1312 2004). In eutherians, TGF- β supports placental development by regulating proliferation and
1313 invasion rates of placental cells lines (Caniggia et al., 2000; Hempstock et al., 2004; Lafontaine
1314 et al., 2011).

1315 Histotrophy (also called histiotrophy) occurs when nutrients are secreted into the uterine
1316 lumen from vesicles of the columnar epithelial cells of the uterus and taken up by the embryo.
1317 Histotrophic nutrient provisioning is documented across amniotes including marsupials
1318 (Whittington et al., 2018), several ungulate taxa (Bazer et al., 2011; Han et al., 2016; Gao et al.,
1319 2009), humans (Burton et al., 2002), and appear to occur in some viviparous squamates (van
1320 Dyke et al., 2014). In humans, histotrophic nutrient provisioning occurs during the first trimester.
1321 The intervillous space is filled with fluid containing uterine gland secretions that get
1322 phagocytosed by the syncytiotrophoblasts and are the initial nutrient source for the fetus (Burton
1323 et al., 2002). Two of these glycoproteins are epithelial mucin (*MUC1*) and glycodefin A (*GdA*)
1324 (Burton et al., 2002). Interestingly, the *MUC15* gene is upregulated during gravidity/gestation in
1325 the uterus of oviparous and viviparous *Saiphos equalis* individuals (Foster et al., 2020). This also
1326 occurs in the chorioallantoic placenta of *Pseudemoia entrecasteauxii* during gestation (Griffith et
1327 al., 2016). Several mucins are expressed in the uterus in non-gravid and gravid samples from
1328 oviparous individuals of *Lerista bougainvillii* and *Lampropholis guichenoti* (Griffith et al.,
1329 2016).

1330 A survey of viviparous squamates with modest to extensive placentrophy revealed
1331 prevalence of histotrophic nutrient provisioning rather than hemotrophy, transfer of nutrients
1332 between maternal and fetal blood streams (Blackburn 2015). Embryos of *Chalcides chalcides*
1333 have extensive placentrophy that supports substantial maternal nutrient provisioning and
1334 histotrophy (Blackburn, 2015a). Histotrophy may lessen parent-offspring conflict and give the
1335 mother the control over nutrient provisioning compared to hemotrophy (Blackburn, 2015b).

1336 *Chalcides ocellatus* has less extensive placentrophy than *C. chalcides* but the gestating uterus
1337 still illustrates expression of many genes associated with organic and inorganic nutrient transport

1338 (Blackburn, 2015a). Multiple *TGF-β* genes are differentially expressed in the uterus during
1339 gestation in *C. ocellatus*, however most these are downregulated compared to non-gestational
1340 uterine tissue (Murphy et al., 2012). The influence of *TGF-β* on placental development and
1341 nutrient provisioning in *Chalcides spp.* remains to be explored to my knowledge. A TGF-β
1342 receptor (*TGFBRI*) was associated with placental development in *Phrynocephalus vlangalii*
1343 (Gao et al., 2019).

1344 Essential to histotrophy is adenogenesis, the generation of endometrial glands. Adenogenesis
1345 allows for the secretion of histotrophs. The period of early development during which
1346 adenogenesis occurs is highly variable among vertebrates but it is required for embryonic
1347 survival (Gray et al., 2001, 2002; Spencer & Bazer, 2004). Some genes involved with
1348 adenogenesis in sheep are insulin-like growth factor 1 (*IGF-1*), *IGF-2*, *PAX2*, *LHX1* (also known
1349 as *LIM1*) and *EMX2*, genes in the abdominal-B HOXA cluster, members of both *Wnt* and
1350 Hedgehog (*Hh*) gene families (Fazleabas et al., 2004), prolactin (*PRL*), fibroblast growth factor 7
1351 (*FGF7*), *FGF10*, *FGFR2IIIb*, hepatocyte growth factor (*HGF*), a receptor tyrosine kinase (*c-*
1352 *Met*), and cadherins (Fazleabas, 2007).

1353 In the gestating uterus of *Chalcides ocellatus*, insulin-like growth factor-binding protein 5
1354 (*IGFBP5*) is one of the most significantly downregulated genes compared to non-gestational
1355 uterine tissue (Brandley et al., 2012). *IGFBP5* is evolutionarily conserved and multifunctional,
1356 with an important role in regulating IGF signaling, including that of *IGF-1* and *IGF-2* (Duan &
1357 Allard, 2020). Other than adenogenesis in sheep, IGFs serve an important role in the growth of
1358 fetal and maternal tissues in mammals (Gibson et al., 2001; Kampmann et al., 2019).

1359 Genes involved with histotrophic secretion in the marsupial *Sminthopsis crassicaudata*
1360 include *AP4SI*, *HYOU1*, and *SRPRA* (Whittington et al., 2018). Nutrient transporters

1361 significantly upregulated at this time are *APOL6* (cholesterol transport (Baardman et al., 2013)),
1362 *PLA2G10* (hydrolysis of fatty acids during pregnancy (Miele et al., 1987)) and a wealth of SLCs
1363 (solute carrier proteins for transport of sugar, ions, anions, glucose, fatty acids, calcium and zinc
1364 (Whittington et al., 2018)). Subsequent research has identified downregulated of *HYOUI* at early
1365 and mid-gestation; and downregulation of *SRPRA* at mid-gestation in viviparous *Zootoca*
1366 *vivipara* compared to oviparous (Recknagel et al., 2021a). In a reproductively bimodal skink,
1367 *Saiphos equalis*, *PLA2G10* is upregulated during viviparous late gestation compared to oviparous
1368 late gestation (Foster et al., 2020). Upregulation of SLCs also occurs in the viviparous skink
1369 *Chalcides ocellatus* (Brandley et al., 2012; Van Dyke et al., 2014) and in the uterus during
1370 pregnancy in the grey short-tailed opossum, *Monodelphis domestica* (Hansen, Schilkey & Miller,
1371 2016).

1372 Uterine glands are also important for secretions of eggshell precursors. I speculate that genes
1373 involved with adenogenesis of uterine glands may be similarly used to support histotrophic
1374 nutrient provisioning during transitions to viviparity, but further research is necessary.

1375 Specialized uterine areolar glands are found in some *Mabuya* lizards, a genus with oviparous
1376 species and viviparous species that utilize placentrophy and histotrophy (Corso et al., 1988,
1377 2000; Jerez & Ramírez-Pinilla, 2001; Ramírez-Pinilla, 2006; Vieira et al., 2007; Visser, 1975).

1378 Transcriptomic research focused on histotrophic nutrient provisioning, placental development,
1379 and secretions of eggshell precursors in oviparous and viviparous *Mabuya spp.* would
1380 complement literature on the genus.

1381

1382 (6) *Discussion & future directions—embryonic nutrients, gas, and water supply*

1383 Many genes for placental functions in mammals have deep origins in vertebrates (Rawn &
1384 Cross, 2008). In pairwise comparisons of different viviparous amniotes, there is overlap in
1385 hormones and proteins (SLC superfamily, insulin-like growth factors, aquaporins and solute
1386 carrier proteins, etc.) involved in uterine remodeling, placentation, and placental transport. While
1387 shared genes are recruited to the uterus across viviparous amniotes (Recknagel et al 2021a), there
1388 are no shared genes recruited to the placenta across viviparous reptiles, mammals, and sharks
1389 (Foster et al., 2022). Evolutionarily, this suggests higher conservation of the regulatory networks
1390 associated with uterine responses to viviparity than placental responses to viviparity. The
1391 relationship of these findings to embryonic nutrient provisioning and the evolution of the
1392 amniotic egg requires further investigation. Supplementary Table 2 illustrates how genes
1393 mentioned in text for water, gas, and nutrient transport are expressed in reproductive tissues of
1394 squamates during gestation and gravidity.

1395 If specific genes or physiological processes impact more than one of the Main Five
1396 categories, it could have a disproportionate influence on transitions. Such an overlap has already
1397 been identified in *Zootoca vivipara*, where 11 genes are associated with both eggshell traits and
1398 gestation length (Recknagel et al., 2021a). The solute carrier (*SLC*) gene superfamily is involved
1399 with both nutrient transport (Brandley et al., 2012; Whittington et al., 2018) and eggshell
1400 deposition (Yang et al., 2020). Adenogenesis is essential for histotrophic nutrient provisioning
1401 and secretion of eggshell precursors. Additionally, progesterone production influences both
1402 uterine quiescence, which is an important state to maintain in lengthened embryonic retention,
1403 and it also inhibits hepatic vitellogenesis, an important process for lecithotrophic nutrient
1404 provisioning. Thus, examining the role of *SLC* gene superfamily members, processes of

1405 adenogenesis, and progesterone production during embryonic development in oviparous and
1406 viviparous squamate may reveal how interconnectivity of the Main Five are.

1407

1408 **V. Embryonic Calcium Provisioning**

1409

1410 The embryonic growth stage requires the greatest demand of calcium (Ecay et al., 2017;
1411 Packard & Packard, 1984; Stewart & Ecay, 2010). To support this, peak uterine concentrations
1412 of calcium are highest during either eggshell deposition or during the embryonic growth stage, in
1413 oviparous and viviparous taxa, respectively (Linville et al., 2010; Stewart et al., 2009).
1414 Regardless of parity mode, embryonic metabolism drives calcium uptake (Packard & Packard,
1415 1984). The calcium source(s) utilized have clade-specific implications on the genomic and/or
1416 physiological changes required to transition between parity modes.

1417

1418 *(1) Phylogenetic context of embryonic calcium sources*

1419 Calcium can be acquired by the embryo in three forms: calcium carbonate in the eggshell,
1420 calcium bound to proteins and lipids in the yolk, and/or free ionic calcium from maternal
1421 delivery through the placenta (Stewart & Ecay, 2010). These correspond with five calcium
1422 mobilization patterns: 1) Birds, turtles and crocodiles predominately depend on the eggshell; 2)
1423 Most squamates, regardless of parity mode, predominately depend on the yolk; 3) Some
1424 squamate species are reliant on both the eggshell and yolk; 4) Some viviparous squamate species
1425 are reliant on both the yolk and placenta; and 5) therian mammals and rare viviparous squamates
1426 predominately depend on the placenta (Blackburn, 2015a; Hoenderop, Nilius, & Bindels, 2005;
1427 Jenkins & Simkiss, 1968; Kovacs, 2015; Packard, 1994; Packard & Seymour, 1997; Stewart et

1428 al., 2009, 2009; Stewart & Ecaj, 2010; Thompson, Stewart et al., 1999; Thompson, Stewart, &
1429 Speake, 2000; Ramírez-Pinilla, 2006).

1430 From an evolutionary perspective, squamate eggs might serve as the best models of the
1431 ancestral amniote egg. Unlike birds, oviparous squamates generally rely on yolk calcium rather
1432 than eggshell calcium. The yolk sac of non-avian reptiles is a good model for the transition
1433 between the egg of anamniotes and amniotes (Blackburn, 2020). Taken together and given that
1434 hard calcified eggshells of Archelosaurs are likely derived (as discussed in section III.3)—
1435 squamate eggs may have the closest resemblance to the ancestral amniote egg. Interestingly, to
1436 my knowledge, oviparous squamates do not sequester calcium from the eggshell into the yolk
1437 during incubation (Packard, 1994).

1438

1439 *(2) Hypotheses on calcium mobilization and the evolution of parity modes*

1440 It was hypothesized that predominant reliance on eggshell calcium should constrain lineages
1441 to oviparity because the evolution of viviparity would result in a lost calcium source (hereafter
1442 eggshell calcium constraint hypothesis) (Stewart & Ecaj, 2010; Packard et al., 1977; Packard &
1443 Packard, 1984). This hypothesis suggested that viviparity should only evolve in lineages
1444 predominately reliant on yolk calcium (Packard et al., 1977; Packard & Packard, 1984).
1445 Fittingly, birds, turtles and crocodilians generally rely on eggshell calcium, and they are
1446 constrained to oviparity (Anderson et al., 1987). The eggshell calcium constraint hypothesis
1447 holds true for most viviparous squamates that rely heavily on yolk calcium (Stewart & Castillo,
1448 1984; Stewart & Ecaj, 2010; van Dyke et al., 2014).

1449 Subsequent research revealed that viviparity is not constrained by a prerequisite reliance on
1450 yolk calcium. Oviparous scincid skinks studied thus far are intermediately reliant on eggshell and

1451 yolk calcium (Linville et al., 2010; Shadrix et al., 1994; Stewart et al., 2009; Stewart &
1452 Thompson, 1993; Thompson et al., 2001). Calcium placentrophy contributes substantially to
1453 embryonic development in several viviparous squamates including *Pseudemoia entrecasteauxii*,
1454 *Eulamprus quoyi*, *Zootoca vivipara*, *Saiphos equalis*, and a species of *Mabuya* lizard (Ecay et al.,
1455 2017; Linville et al., 2010; Ramírez-Pinilla, 2006; Ramírez-Pinilla et al., 2011; Stewart &
1456 Thompson, 1993). These taxa, with the exception of *Zootoca vivipara*, are in the family
1457 Scincidae (Burbrink et al., 2020), which is also the family with the most independent origins of
1458 viviparity in squamates (Blackburn, 1982, 1999; Pyron & Burbrink, 2014).

1459 To understand the breadth of physiological conditions from which oviparity and viviparity
1460 evolve in squamates, future research should examine calcium transport in other lineages. Studies
1461 focused on snakes would be particularly informative given the sparse literature on them.
1462 *Helicops angulatus*, a reproductively bimodal water snake from South America, is an ideal
1463 model for this (Braz et al., 2016). Thus far, many oviparous snakes are known to be
1464 intermediately reliant on yolk and eggshell calcium. This has not precluded viviparity from
1465 evolving in these lineages.

1466 The presence of embryos during extended embryonic retention may trigger positive feedback
1467 stimuli for continued uterine calcium secretions which may support placental calcium transport,
1468 and thus incipient calcium matrotrophy (Stewart & Ecay, 2010). This is postulated to resemble
1469 the hormonal and mechanical stress mechanisms implicated in avian eggshell formation and
1470 uterine calcium secretions (Bar, 2009a; Stewart & Ecay, 2010). The influx of calcium late in
1471 viviparous gestation may be triggered in part by embryonic growth that over distends the uterus.
1472 This is seen in studies on myometrial stretch in mammals when uterine overdistention triggers
1473 spikes in calcium (Kao & McCullough, 1975; and see e.g. Wray et al., 2015).

1474 Dramatic changes to activity in chorioallantois should not be required during parity mode
1475 transitions because these homologous tissues (Metcalf & Stock, 1993) transport calcium
1476 regardless of parity mode (Ecay, Stewart & Blackburn, 2004; Tuan & Scott, 1977; Tuan &
1477 Knowles, 1984; Tuan et al., 1978, 1986). Specialized placental structures in some viviparous
1478 squamates enhance calcium provisioning but specialization is not required for placental calcium
1479 transport (Stewart et al., 2009; Stewart & Ecay, 2010; Thompson et al., 2000). Loss of
1480 chorioallantoic calcium transporting capacity would be disadvantageous to either parity mode.
1481 Growing research reveals that, like mammals, placentrophy and viviparity can evolve
1482 concurrently in squamates (Blackburn, 2015a; Ecay et al., 2017; Stewart & Ecay, 2010).

1483 Placing these previously proposed models in a phylogenetic context, the calcium transport
1484 method of oviparous ancestors likely has an influence on the method of calcium transport used
1485 for viviparous taxa—matrotrophic calcium provisioning, lecithotrophic calcium provisioning, or
1486 a combination of the two. Consistent with the basal cap hypothesis—when viviparity arises from
1487 oviparous ancestors with embryos that depended predominately on eggshell calcium, this should
1488 favor a transition to viviparity via incipient calcium matrotrophy because the chorioallantois
1489 already plays the major role in transporting calcium from the eggshell to the embryo. Since the
1490 reproductive mode and calcium provisioning of oviparous ancestors are essentially unknown,
1491 researchers can use the closest oviparous relatives as proxies. Similarly, viviparous taxa that are
1492 in close phylogenetic proximity to oviparous taxa that depend on lecithotrophic calcium
1493 provisioning should remain reliant on yolk calcium. Together, these guidelines provide a
1494 framework from which researchers can form hypotheses about the calcium provisioning method
1495 of a viviparous lineage if the calcium provisioning method of oviparous close relatives are
1496 known, or vice versa. Measurements of the proportional contribution of different calcium sources

1497 during development has only been done in select taxa (e.g. Packard, 1994; Stewart, 2013;
1498 Stewart & Ecy, 2010; Stewart, Ecy & Blackburn 2004). Once validated, the framework (i.e.,
1499 the calcium provisioning method of close relatives) can help increase the speed at which science
1500 measures and infers the evolutionary history of calcium provisioning across amniotes and
1501 squamates. Collection of this data across the squamate phylogeny may enable assignment of
1502 these hypotheses to specific clades.

1503 Embryonic calcium source could have implications on the physiological changes required to
1504 transition between parity modes. Reliance on yolk calcium should render, essentially, no
1505 mechanistic changes for calcium transport. On the other hand, incipient calcium matrotrophy
1506 requires regulatory changes in the uterus, like timing of calcium secretions (Griffith et al., 2015).
1507 However, regardless of parity mode 1) the uterus secretes calcium, 2) the chorioallantois
1508 transports calcium and 3) embryonic metabolism drives uptake of calcium. Assuming maternal
1509 tissue remains responsive to embryonic metabolism, the joint evolution of matrotrophic calcium
1510 provisioning with viviparity may require little to no physiological adjustments.

1511 The diversity of embryonic calcium provisioning patterns in viviparous squamates may not
1512 be fully explained by the eggshell calcium constraint hypothesis (Packard et al., 1977; Packard &
1513 Packard, 1984) or incipient calcium matrotrophy (Stewart & Ecy, 2010). Both hypotheses
1514 implicitly assume that viviparity equates to a lost eggshell. In one viviparous squamate, *Haldea*
1515 *striatula*, and in viviparous populations of two reproductively bimodal lizards, *Zootoca vivipara*
1516 and *Saiphos equalis*, the calcified eggshell is considered as a component of the placenta (Stewart,
1517 2013). Some other viviparous squamates have transient calcified patches on their embryonic
1518 membranes (Blackburn, 1998; Heulin, 1990, 2005; Qualls, 1996) suggesting that uterine calcium
1519 secreting capabilities in early gestation may be retained in some viviparous lineages. In the case

1520 of reversals, it remains unknown how the uterus shifts back to early calcium secretions after
1521 ovulation (Blackburn, 2015b; Griffith et al., 2015).

1522

1523 *(3) Embryonic calcium provisioning mechanisms*

1524 In vertebrates, specialized tissues that recover environmental calcium and transport it into
1525 blood circulation maintain conserved mechanisms for intracellular calcium transport (Bronner
1526 2003; Hoenderop et al., 2005). These include the uterus, chorioallantoic tissues, and yolk
1527 splanchnopleure (Bronner, 2003; Hoenderop et al., 2005; Stewart, 2013). Therefore, uterine and
1528 embryonic tissues may be pre-adapted for maternal and embryonic calcium provisioning.

1529 In birds, a sub-compartment of the mammillary layer of the eggshell is the calcium reserve
1530 body (Chien et al., 2009), which contains microcrystals of calcite that get dissolved and
1531 transported as calcium to the embryo (Chien et al., 2009). Calcium is eroded from the eggshell
1532 by acid released from villus cavity cells (VCCs) in chorioallantoic membrane (Anderson, Gay,
1533 and Schraer, 1981; Narbaitz et al., 1981; Packard & Lohmiller, 2002; Simkiss, 1980). This
1534 increases the carbonic anhydrase activity of the cells enabling calcium to be released into the
1535 cavity between the eggshell and the chorionic epithelium, where it is taken up by capillary
1536 covering cells (CCCs) in chorioallantoic membrane (Coleman & Terepka, 1972). In some
1537 species this erosion leads to a gradual weakening of the eggshell that facilitates hatching (Chien,
1538 Hincke & McKee, 2008). In chickens, transcalcine, a calcium binding protein, is credited for the
1539 calcium transporting capacity of the chorioallantoic membrane (Tuan & Knowles, 1984; Tuan &
1540 Ono, 1986; Tuan & Scott, 1977; Tuan et al., 1978, 1986). The presence of VCCs and CCCs in
1541 the chorioallantois of viviparous squamates would indicate a known route through which calcium
1542 can be absorbed.

1543 Transcellular calcium transport has been modeled as a three-step process involving proteins
1544 calbindin-D9K, calbindin-D28K, and the highly calcium-specific ion channels of the transient
1545 receptor potential vanilloid gene family (*TRPV5* and *TRPV6*) (Stewart & Ecaj, 2010). Across
1546 vertebrates, this machinery is shared in epithelial tissues with significant roles in calcium
1547 transport (Hoenderop et al., 2005). Estrogen and vitamin D3 have regulatory roles in this
1548 process.

1549 Calbindin-D9K, calbindin-D28K, *TRPV5*, and *TRPV6* is involved with calcium exchange in
1550 multiple organs of birds, squamates, and mammals. Broadly, activity of calbindin-D9K and/or
1551 calbindin-D28K is associated with patterns of calcium absorption in the mammalian kidney and
1552 uterus (Bindels, 1993; Luu et al., 2004), murine uterus and placenta (Lafond & Simoneau, 2006;
1553 Koo et al., 2012), and chicken duodenum and uterus (Bar, 2009b; Yang et al., 2013). In humans,
1554 calbindin-D9K and calbindin-D28K are critical to the active transport of Ca²⁺ across placental
1555 cells (Faulk & McIntyre, 1983; Belkacemi, Simoneau & Lafond, 2002; Belkacemi et al., 2004).
1556 A study on rats suggests that calbindin-D9K increases by over 100-fold in the last 7 days of
1557 gestation (Glazier et al., 1992), when the embryo gains the majority of calcium. *TRPV6* is
1558 involved with maternal-fetal calcium transport in mice (Suzuki et al., 2008). Increased *TRPV6*
1559 and calbindin-D28K expression occurs during eggshell formation in chickens (Yang et al.,
1560 2013). Given the involvement of these genes in both eggshell deposition and embryonic calcium
1561 transport, squamates may have exploited this pathway to support transitions. Expression of these
1562 genes during gestation or gravidity in squamates has been detected (e.g. calbindin-d9K in
1563 *Saiphos equalis*, and calbindin-d28k in *Zootoca vivipara*) (Foster et al., 2020; Recknagel et al.,
1564 2021a), and is expanded upon in the following paragraphs.

1565 In several highly matrotrophic lizards, embryonic uptake of calcium is associated with
1566 placental expression of calbindin-D28K (Stewart et al., 2009; Stinnett et al., 2011, 2012). In both
1567 oviparous and viviparous embryos of *Zootoca vivipara*, sharp increase in calcium uptake in late
1568 development coincides with increased calbindin-D28K and PMCA by the chorioallantois
1569 (Stewart et al., 2009, 2011). In oviparous corn snakes, *Pantherophis guttatus*, expression of
1570 calbindin-D28K in the yolk-sac and chorioallantoic membrane coincides with growth of these
1571 tissues and calcium transport activity (Ecay et al., 2004). The chorioallantois of other lizards and
1572 snakes transport calcium to the embryo and express calbindin-D28K and PMCA (Blackburn,
1573 2004; Ecay et al., 2004; Stewart et al., 2010; Stinnett et al., 2012).

1574 Viviparous embryos of *Zootoca vivipara*, a reproductively bimodal lizard, incubated *ex utero*
1575 respond to availability of calcium by increasing expression of calbindin-D28K (Ecay et al.,
1576 2017). In this species, embryonic recognition of environmental calcium stimulates a transcellular
1577 calcium transporting mechanism and may also alter chorioallantoic membrane paracellular
1578 permeability to calcium (Ecay et al., 2017). The authors proposed that there is a calcium sensing
1579 receptor (CaSR) on chorionic epithelial cells to support this in both oviparous and viviparous
1580 *Zootoca vivipara* embryos (Ecay et al., 2017), similar to the CaSRs expressed by vertebrate cells
1581 involved in calcium homeostasis (Brennan et al., 2013).

1582 As mentioned earlier, PMCA activity is associated with eggshell deposition in birds and
1583 oviparous squamates (Bar, Rosenberg, & Hurwitz, 1984; Hincke et al., 2012; Wasserman et al.,
1584 1991). PMCA is also crucial for calcium transport in late embryonic development in rats (Glazier
1585 et al., 1992). In viviparous scincid lizards, *Niveoscincus metallicus*, *N. ocellatus*, and
1586 *Pseudemoia spenceri*, PMCA was expressed in uterine glandular and surface epithelia during
1587 pregnancy but only *P. spenceri* expressed it throughout gestation (Herbert et al., 2006). When

1588 PMCA was not detected by immunoblotting in the yolk splanchnopleure of *Haldea striatula*, a
1589 viviparous snake that relies predominately on yolk calcium (Stewart, 1989; Fregoso, Stewart, &
1590 Ecay, 2010), NCXs were proposed as an alternative transporter of calcium (Fregoso et al., 2012).
1591 NCXs are important for placental calcium transport in humans (Belkacemi et al., 2005).

1592 Calcitropic hormones, those involved with calcium transport, and phosphotropic hormones,
1593 those involved with phosphorous transport, operate via an interconnected pathway (Andrukhova
1594 et al., 2016; Biber, Hernando & Forster, 2013; Blaine, Chonchol & Levi, 2015; Erben &
1595 Andrukhova, 2015). Phospho- and calcitropic hormones are important regulators of fetal serum
1596 mineral concentrations (Kovacs, 2015). Evidence from viviparous amniotes suggests that these
1597 are suitable candidates for embryonic calcium provisioning. In mice, genes encoding parathyroid
1598 hormone (*PTH*) and *PTH*-related peptide (*PTHrP*) are important regulators of placental calcium
1599 transport (Kovacs et al., 1996; Simmonds et al., 2010). A non-exhaustive list of additional
1600 candidates for embryonic calcium provisioning include fibroblast growth factor 23 (Bar, 2009a;
1601 Erben & Andrukhova, 2015; Stewart & Ecay, 2010), the annexin gene family (Matschke et al.,
1602 2006), carbonic anhydrase (Narbaitz et al., 1981; Tuan & Knowles, 1984), and calcium binding
1603 proteins (CaBPs) can be found in the referenced literature.

1604

1605 (4) *Discussion & future directions—calcium provisioning and parity mode evolution*

1606 Phylogenetic frameworks enable researchers to make broader testable hypotheses about the
1607 evolutionary history of calcium provisioning in specific clades. Such a framework is proposed in
1608 section V.2 to infer ancestral parity modes in the context of calcium provisioning in amniotes.
1609 Implications gleaned from taxon-specific studies can be explored in distantly related analogous
1610 groups.

1611 Genes involved with calcium transport in uterine and embryonic tissues have been described
1612 across mammals, birds, and reptiles. Like other amniotes, activity of calbindin-D28K and PMCA
1613 supports embryonic calcium provisioning across diverse oviparous and viviparous squamates.
1614 Their involvement with both eggshell deposition and embryonic calcium provisioning makes
1615 these particularly interesting candidates for parity mode evolution. The regulatory influence of
1616 other molecules in calcium transport, like *PTH*, *PTHrP* and NCXs has not been evaluated
1617 thoroughly in squamates. Additional reviews on mechanisms of embryonic calcium provisioning
1618 in squamates can be found in the literature (Stewart, 2013; Stewart & Eday, 2010).

1619 Additionally, I add a speculation. Perhaps lineages with incipient calcium matrotrophy more
1620 feasibly reverse to oviparity because of the continued role of the uterus in calcium provisioning.
1621 However, this hypothesis only holds up if maternal provisioning of calcium is not synonymous
1622 with maternal provisioning of all nutrients.

1623

1624 **VI. Maternal-Fetal Immune Dynamics**

1625

1626 Medawar (1953) pointed out the paradigm between the peripheral body's normal attack
1627 response to allografts (foreign tissue) and uterine tolerance to embryos (Medawar, 1953). This
1628 was inspired by earlier work by Ray Owen (Owen, 1945). Stricter regulation of the maternal and
1629 fetal immune systems is expected for viviparous reproduction because of contact between uterine
1630 and embryonic tissues. Oviparity may pose less of an immunological challenge. Medawar
1631 suggested barriers, inertness and/or immunosuppression enable pregnancy. This formed the
1632 foundation of decades of medical research on immune dynamics between maternal, embryonic,
1633 and paternal immune factors in utero.

1634 In recent years, there was a call for a reappraisal of Medawar's paradigm (Chaouat, 2010,
1635 2016; Moffett & Loke, 2004, 2006; Mor et al., 2011; Stadtmayer & Wagner, 2020b; Yoshizawa
1636 2016). Moffett & Loke (2006) caution against conceptualizing embryos as analogs of allografts.
1637 To my knowledge, this perspective has yet to reach the evolutionary literature on squamate
1638 parity mode evolution (Foster et al., 2020; Graham et al., 2011; Gao et al., 2019; Murphy &
1639 Thompson, 2011; van Dyke, Brandley, & Thompson, 2014; Murphy, Thompson, & Belov, 2009;
1640 Recknagel et al., 2021a). Importantly, challenges to Medawar's paradigm do not preclude
1641 immunological responses to viviparity. They simply suggest that the immune environment of the
1642 uterus is uniquely evolved to support exposure to foreign tissue.

1643 The uterine immune system has a distinct evolutionary history from the periphery. It enables
1644 cooperative dynamics with foreign tissues. It supports fertilization and early embryonic
1645 development. This should have started evolving, distinct from the periphery, since internal
1646 fertilization first originated. To contextualize this, I discuss the changing landscape of
1647 immunological research at the maternal-fetal interface and what it means in the context of
1648 amniote parity mode evolution. Overall, I hope readers consider how the uterus evolved to
1649 support internal gestation, and which model systems may be appropriate to investigate this.

1650 Most literature on maternal-fetal immune dynamics limits itself to mammals. Squamates may
1651 serve as a better comparative model for understanding the evolution of the uterine immune
1652 system. Active research on the peripheral reptilian immune system (Zimmerman et al., 2010,
1653 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et al., 2017;
1654 Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights on this.

1655

1656 *(1) Comparing amniote immune systems*

1657 Cellular components of the innate immune system are conserved across jawed vertebrates
1658 (Uribe et al., 2011; Zimmerman et al., 2010). The general machinery of the adaptive immune
1659 system is ancient despite divergences and convergences across all domains of life (Ghosh et al.,
1660 2011; Morales et al., 2017; Müller et al., 2018; Rimer et al., 2014). Diversification of antigen
1661 receptor genes likely occurred independently in a lineage-specific fashion (Boehm et al., 2018).
1662 Compared to mammals, the avian immune system requires less antigen (Larsson et al., 1998).
1663 Birds also have faster but shorter antibody responses, potentially due to their higher body
1664 temperatures (Zimmerman, 2010).

1665 Reptiles have the same general components of the mammalian immune system (Zimmerman,
1666 2020). However, the reptilian immune system may not fit neatly into the two arms of mammalian
1667 immune systems—innate and adaptive (Zimmerman, 2010; 2020). Expanding upon this is
1668 beyond the scope of this review, but it is worth considering in future evolutionary research.
1669 Squamates may serve as a better comparative model for understanding the evolution of the
1670 uterine immune system. Active research on the peripheral reptilian immune system (Zimmerman
1671 et al., 2010, 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et
1672 al., 2017; Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights. I
1673 refer readers to articles by Zimmerman et al. (2010, 2020) and Ghorai et al. (2018), and the book
1674 by Williams (2012) for more information on the avian immune system.

1675

1676 (2) *Medawar's paradigm*

1677 Tolerance toward the foreign fetus was postulated to occur through immunological inertness,
1678 immunosuppression or immunotolerance mechanisms (Medawar, 1953). Theoretically,
1679 immunotolerance could be established if there are relatively small quantities of alloantigens

1680 present, resulting in regulatory responses rather than activating responses (Pradeu, 2011).
1681 Contradicting this, the larger the alloantigen difference between the mother and embryo the
1682 bigger and healthier the placenta is in rats (Chaouat et al., 2010). In humans, divergent HLA
1683 profiles between mother and embryo do not lead to detrimental immune responses (Tilburgs,
1684 Scherjon, & Claas, 2010). Instead, cooperative inflammatory responses between maternal and
1685 fetal tissues support reproduction (Stadtmauer et al., 2020a). In humans, microchimeric cell
1686 populations, presence of cells from one individual in another genetically distinct individual, are
1687 now considered a normal expectation of pregnancy (Nelson, 2012).

1688 In his 1991 Nobel Lecture, Medawar acknowledged that maternal and embryonic tissues
1689 have regular exposure to alloantigens (Medawar, 1991). It has become clear that the maternal
1690 immune system actively responds to fetal alloantigen rather than responding solely with
1691 ignorance or anergy (Arck & Hecher, 2013). Neither maternal immunosuppression/privilege nor
1692 embryonic inertness/immaturity fully explain immune dynamics during gestation in mammals,
1693 including those with the simple epitheliochorial placentation (Chaouat et al., 2010; Chavan,
1694 Griffith & Wagner, 2017; Moffett & Loke, 2004, 2006; Stadtmauer & Wagner, 2020a).

1695

1696 *(3) Perspectives on the evolution of the uterine immune system*

1697 Viviparous reproduction existed eons before the origin of mammals and, to my knowledge,
1698 no evidence suggests there was immune conflict within these taxa (Chaouat, 2016). Placentrophy
1699 existed as far back as the invertebrate clade Bryozoa (Ostrovsky, 2013; Schwaha et al., 2019),
1700 suggesting an ancient history for supportive maternal-fetal immune dynamics. Differing from
1701 Medawar's paradigm, Polly Matzinger, who proposed the 'danger model' for the immune system

1702 (Matzinger, 2007), wrote “Reproduction cannot be a danger. It does not make evolutionary
1703 sense” (Chaouat, 2016).

1704 In mammals, immunological cells at the maternal-fetal interface may not function through
1705 self-non-self-discrimination, as they are understood to function in the rest of the body (Chaouat,
1706 2016; Moffett & Loke 2004, 2006). The ‘maternal-fetal interface’ may be better conceptualized
1707 as ‘maternal-fetal intra-action’ given the dynamics between maternal and fetal immune systems
1708 in mammals (Yoshizawa, 2016). It is unclear if these insights apply to other viviparous amniotes.

1709 In mammals, immune factors in the uterus and placenta appear to be specifically evolved to
1710 support maternal-fetal immune dynamics. Several cell types have unique functions and/or
1711 phenotypes in utero—uterine NK (uNK) cells, uterine macrophages, uterine T regulatory cells
1712 (Faas & de Vos, 2017; Mold et al., 2008, 2010; Mold & McCune, 2011). An immunosuppressive
1713 antigen, HLA-G, is almost exclusively expressed by trophoblasts (Faulk & Temple, 1976;
1714 Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al., 1997). Taken from an
1715 evolutionary perspective, this suggests that the uterine immune system in viviparous mammals
1716 evolved unique responses to allogenic tissues that differ from the periphery. Whether the
1717 evolution of this system predates mammals remains to be explored, to my knowledge.

1718 It is suggested that viviparous reproduction is immunologically compatible in species with
1719 less active adaptive immune system, like sharks (Chaouat, 2016). In these clades, innate immune
1720 cells, like uNK cells, may be sufficient to regulate immune responses during pregnancy (Moffett
1721 & Loke, 2004; Chaouat, 2016). Given that there is an unclear distinction between the innate and
1722 adaptive immune system in reptiles (Zimmerman, 2020), determining immunological difficulty
1723 of evolving viviparity in squamates requires further investigation.

1724 In uterine tissue of oviparous and viviparous skinks maternal antigens are expressed prior to
1725 and during gestation and gravidity (Murphy et al., 2009), but the viviparous species in the study
1726 have a unique expression profile of MHC antigens which may ‘hide’ the embryo from the
1727 maternal immune system (Murphy et al., 2009). Similarly, in a reproductively bimodal skink,
1728 *Saiphos equalis*, both oviparous and viviparous gestation is associated with expression of MHC
1729 genes (Foster et al., 2020). Regardless of parity mode, *S. equalis* expresses genes associated with
1730 immunocompetence, including MHC genes including *H2-EA* (Foster et al., 2020). The similar
1731 profile between the oviparous and viviparous state is attributed to the use of very long egg
1732 retention utilized by oviparous *S. equalis* (Foster et al., 2020). This highlights that extended
1733 embryonic retention is accompanied with immunological responses in utero, which is relevant to
1734 the EER model on amniote origins.

1735 Some of these genes expressed by *S. equalis* are also expressed in viviparous *Chalcides*
1736 *ocellatus* during gestation including complement component genes (C3, C9) and MHC genes
1737 (Brandley et al., 2012; Foster et al., 2020). The majority of immune genes expressed during
1738 gestation/gravidity in *S. equalis* have immunoglobulin receptor binding functions (Foster et al.,
1739 2020), an important feature of eutherian pregnancy that prevents rejection of the fetus through
1740 actions of the maternal innate immune system (Alijotas-Reig, Llorba, Gris, 2014)). In another
1741 reproductively bimodal skink, *Zootoca vivipara*, immune system response genes are enriched in
1742 the set of genes under divergent selection in oviparous and viviparous genomes (Recknagel et al.,
1743 2021a).

1744

1745 (4) *Implications of the reptilian immune system and morphology on parity mode evolution*

1746 Ectothermic reptiles may inherently have a more tolerogenic uterine environment compared
1747 to mammals due to their slower antibody response. It can take up to six weeks to reach peak
1748 concentrations (Ingram & Molyneux, 1983; Grey, 1963; Marchalonis et al., 1969; Pye et al.,
1749 2001; Origgi et al., 2001; Work et al., 2000). A slower metabolism also makes several reptiles
1750 more tolerogenic to pathogens (Ghorai & Priyam, 2018).

1751 During pregnancy in the viviparous skink, *Chalcides ocellatus*, there is a reduced response to
1752 in vitro exposure to mitogens concanavalin A (Con A), phytohemagglutinin (PHA), and
1753 *Escherichia coli* lipopolysaccharide (LPS) (Saad & El Deeb, 1990). Oviparous lizards exhibit
1754 immune activation tradeoffs during reproductive cycles (Cox, Peadar, & Cox, 2015; Durso &
1755 French, 2018; French, Johnston, & Moore, 2007; Uller, Isaksson, & Olsson, 2006).

1756 In the majority of viviparous squamates, the eggshell membrane is absorbed during
1757 pregnancy (Blackburn, 1993). In mammals, epitheliochorial placentation (the most superficial
1758 and non-invasive placenta type) is sufficient to cause immunorecognition from the mother.
1759 Specialized placental cells, trophoblasts, may be more common in other viviparous vertebrates
1760 than previously recognized (Blackburn, 2015a). For example, a gene with fusogenic properties
1761 characteristics of trophoblast syncytins was recently identified in the *Mabuya* lizard placenta
1762 (Cornelis et al, 2017). In mammals, trophoblasts are antigen presenting and actively participate
1763 in maternal-fetal immune dynamics.

1764 A few viviparous squamates have placentas with characteristics similar to placentas found in
1765 eutherian mammals—syncytialized cells layers, specialized zones such as areolae and
1766 placentomes, or cellular invasion of maternal tissues by the fetus (Blackburn & Flemming, 2012;
1767 Jerez & Ramírez-Pinilla, 2001; Vieira et al., 2007). The increased contact here may require more

1768 tightly regulated immune dynamics at the maternal-fetal interface compared to other viviparous
1769 squamates.

1770

1771 (5) *The inflammation paradox*

1772 In mammals, implantation evolved from an ancestral inflammatory attachment reaction
1773 (Griffith, Chavan et al., 2017). Inflammation is the most crucial system to support implantation,
1774 but it is also the greatest threat to the continuation of pregnancy (Chavan et al., 2017). This
1775 phenomenon is called the inflammation paradox. In humans, immune cells including uterine
1776 macrophages, T cells of multiple subtypes, uterine natural killer (uNK) cells, dendritic cells, and
1777 natural killer T (NKT) cells increase until implantation and remain abundant in the uterus
1778 throughout first trimester (Bulmer et al., 1991; Bulmer, Williams & Lash, 2010). Early
1779 implantation in humans is characterized by high pro-inflammatory T helper (Th)-1 cells and
1780 cytokines (IL-6, IL-8, and TNF α) (Yoshinaga, 2008). The exploitation of inflammatory
1781 mechanisms for eutherian implantation and the shift toward non-inflammatory activity to
1782 maintain pregnancy may have been key in enabling extended embryonic retention of eutherians
1783 (Griffith, Chavan et al., 2017).

1784 How the inflammation paradox applies to viviparous squamates is unclear, given that
1785 placentation in squamates and mammals is not homologous (Griffith, Van Dyke, & Thompson,
1786 2013). In extrauterine pregnancies of mammals with non-invasive placentas, the embryo will
1787 invade extrauterine tissue because it is not inhibited by uterine secretions (Vogel, 2005; Samuel
1788 & Perry, 1972). However, in *Pseudemoia entrecasteauxii*, a viviparous skink that also has a non-
1789 invasive placenta, extrauterine pregnancy does not result in invasive implantation of extrauterine
1790 tissues (Griffith, Van Dyke, & Thompson, 2013). The inherent invasive nature of mammalian

1791 embryos outside of the uterus, compared to the non-invasive nature of viviparous squamate
1792 embryos studied thus far, suggests that the parent-offspring conflict and the inflammation
1793 paradox may be less pronounced in viviparous squamates compared to viviparous mammals.

1794

1795 *(6) Inertness and barriers at the maternal-fetal interface*

1796 The uterine environment is not inert or sterile (Agostinis et al., 2019; Erlebacher, 2013;
1797 Moffett & Loke, 2006; Munoz-Suano, Hamilton, & Betz, 2011; Murphy, Thompson, & Belov,
1798 2009; Yoshimura, Okamoto, & Tamura, 1997). In humans, the decidual layer of the uterus
1799 during pregnancy is comprised of ~40% leukocytes (Ander, Diamond, & Coyne, 2019; Manaster
1800 & Mandelboim, 2010). This cellular subpopulation has 70% uNK cells, 10-20% antigen
1801 presenting cells (APCs) including macrophages and dendritic cells, and 3-10% T cells of several
1802 subtypes (Abrahams et al., 2004; Hanna et al., 2006; Kämmerer et al., 2006; Le Bouteiller &
1803 Piccinni, 2008; Liu et al., 2017; Manaster & Mandelboim, 2010; Moffett-King, 2002; Moffett &
1804 Loke, 2006; Roussev et al., 2008). There is an abundance of decidual large granular lymphocytes
1805 (LGLs), CD3-NK cells and CD3+ activated cytotoxic T cells, in the human uterus, that have
1806 cytotoxic properties and produce cytokines, and these are affected by fetal MHC molecules
1807 (Rieger, 2002).

1808 Birds also have immunocompetent cells in their oviducts. T and B cells are present in
1809 chicken ovary where they are stimulated by estrogen (Barua & Yoshimura, 1999; Withanage et
1810 al., 2003; Zettergren & Cutlan, 1992). Other immunocompetent cells in the chicken oviduct
1811 include IgG+, IgA+ and CD3+ (Yoshimura, Okamoto, & Tamura, 1997). Immune competent
1812 cells located throughout the mucosal tissue of avian oviductal segments including macrophages,

1813 antigen presenting cells (APCs) expressing MHC class II antigens, helper T cells and cytotoxic T
1814 cells, and premature B cells (Das, Isobe, & Yoshimura, 2008).

1815 Inert barriers between maternal and fetal tissues may 'hide' the embryo. In oviparous taxa,
1816 the eggshell may serve as a barrier. However, the antimicrobial properties of the eggshell matrix
1817 in birds demonstrate that even the eggshell is not inert. The FAS ligand, also called APO-1 or
1818 CD95, in humans and rodent embryonic tissue was proposed to serve as a barrier because it
1819 causes apoptosis of surrounding maternal immune cells (Kayisli et al., 2003; Makrigiannakis et
1820 al., 2008).

1821 Medawar suggested that an impermeable placenta strictly regulates molecular exchanges,
1822 preventing rejection of the embryo (Medawar, 1991). Syncytiotrophoblasts lack cellular junctions
1823 and thus it was postulated to serve as this barrier (Ander et al., 2019). However, the growing data
1824 on bidirectional cellular traffic of APCs, even in mammals with noninvasive placentas, rejected
1825 this hypothesis (Bakkour et al., 2014; Burlingham & Bracamonte-Baran, 2015; Fujiki et al.,
1826 2008; Turin et al., 2007).

1827

1828 *(7) T cell populations and mammalian viviparity*

1829 In mammals, immune-dynamics at the maternal-fetal interface are established through
1830 innate and adaptive immune responses. There is a delicate balance between ratios of Th1, Th2,
1831 Th17, Tregs and memory T cells at the maternal-fetal interface in eutherian mammals during
1832 gestation (Chaouat et al., 1997; Kieffer et al., 2019; Peck & Mellins, 2010; Saito et al., 2010; Wu
1833 et al., 2014). A shift in utero from T helper type 1 (Th1) cells to T helper type 2 (Th2) cells
1834 during gestation in mammals equates to a shift from pro-inflammation to anti-inflammation. The
1835 galectin proteins, GAL-13 and GAL-14, expressed by syncytiotrophoblasts, bind to T cells

1836 where they inhibit activation, induce apoptosis, and enhance interleukin-8 (IL-8) production
1837 (Balogh et al., 2019).

1838 Growing research is revealing the central role of Tregs at the maternal-fetal interface
1839 during pregnancy in mammals (Teles et al., 2013; Wienke et al., 2019). Tregs play a central role
1840 in immunosuppression in mammals (Attias, Al-Aubodah, & Piccirillo, 2019). Differentiation of
1841 Tregs is governed by the transcription factor, *FOXP3* (Ramsdell & Rudensky, 2020).
1842 Alloantigen-dependent, uterine T cell signaling, and immunocompetent embryonic cells and their
1843 products facilitate enhanced regulatory phenotypes of immune cells overall (Ander et al., 2019).

1844 The T-cell dependent adaptive immune system of mammals is unique. This may have
1845 prompted their intricate balance of Treg mediators of immunotolerance at the maternal-fetal
1846 interface (Chaouat, 2016). Birds rely more heavily on B cells. In non-avian reptiles, T helper
1847 cells are functional, but the presence and function of other T cell subsets is unclear (Zimmerman,
1848 2020; Zimmerman, Vogel, & Bowden, 2010). The potential role of T cells and Tregs in
1849 viviparous squamate gestation should not be discounted. Treg-like cells have been identified in a
1850 pufferfish, *Tetraodon nigroviridis* (Wen et al., 2011), suggesting that Tregs may have an ancient
1851 evolutionary history.

1852

1853 (8) *Progesterone, cytokines, and maternal-fetal immune dynamics*

1854 In addition to the role of progesterone in uterine quiescence (embryonic retention) and
1855 hepatic vitellogenesis (nutrient provisioning), it also plays a role in maternal-fetal immune
1856 dynamics. In the uterus of pregnant mammals, progesterone concentrations are associated with
1857 altered B cell immunoglobulin secretion, inhibition of NK-cell mediated cytotoxicity and the shift
1858 from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) dominated immune responses

1859 (Druckmann & Druckmann, 2005). Progesterone is also associated with immunomodulatory
1860 effects (Ortega Brown et al., 1990). During gestation in *Agkistrodon piscivorus*, a viviparous pit
1861 viper, progesterone concentrations are associated with decreased complement performance
1862 (Graham et al., 2011), a portion of the immune system that promotes inflammation, among other
1863 immune functions.

1864 In humans, progesterone induced protein (PIBF) is transported by placental extravillous
1865 trophoblasts to maternal lymphocytes causing the induction of interleukin-10 (IL-10) production,
1866 contributing to the Th2 dominant responses (Szekeres-Bartho, Šučurović, & Mulac-Jeričević,
1867 2018). IL-10 is a potent anti-inflammatory cytokine that is produced by multiple cell types
1868 (Zimmerman, Bowden, & Vogel, 2014). It is associated with Th2 response, and it inhibits Th1
1869 responses. The phenotype of uterine macrophages is affected by trophoblasts when they secrete
1870 IL-10 and macrophage colony-stimulating factor (M-CSF) (Svensson-Arvelund et al., 2021). IL-
1871 10 inhibits IFN- γ and increases in response to infection in chickens (Giansanti, Giardi, & Botti,
1872 2006; Rothwell et al. 2004). In the uterus of the oviparous skink, *Lampropholis guichenoti*,
1873 during gravidity and non-gravidity, IL-10 is expressed (Griffith et al., 2016).

1874 Proinflammatory cytokines may be downregulated during reproductive periods to limit
1875 maladaptive immune responses to the foreign fetus (Zimmerman, Vogel, & Bowden, 2010). In
1876 mammals, IL-1 allows release of hormones in human trophoblasts (Petraglia et al., 1990;
1877 Masuhiro et al., 1990; Yagel et al., 1989), facilitates implantation (Haimovici, Hill, & Anderson,
1878 1991; Hill, 1992; Tartakovsky & Ben-Yair, 1991), and influences the initiation of labor (Romero
1879 et al., 1989, 1992). Regulation of the proinflammatory cytokines tumor necrosis factor (TNF)
1880 and interleukin 1 β (IL-1 β) is of particular importance in eutherian pregnancy (Haider & Knöfler,
1881 2009; Paulesu, Romagnoli, & Bigliardi, 2005; Saito et al., 2010; Tayade et al., 2006).

1882 The uterine tissue of two reproductively bimodal squamates—viviparous individuals of
1883 *Chalcides chalcides*, and oviparous and viviparous individuals of *Zootoca vivipara*—express IL-
1884 1 β (Paulesu et al., 1995, 2005; Romagnoli et al., 2003). In the uterus of the viviparous skink,
1885 *Pseudemoia entrecasteauxii*, during gestation regulation of TNF and IL-1 β at the transcriptional
1886 and post-translation levels, respectively, may reduce inflammation (Hendrawan et al., 2017). The
1887 pro-inflammatory function of IL-1 β in *Pseudemoia entrecasteauxii* may play a role developing a
1888 more complex placenta (Hendrawan et al., 2017). The placenta of *Chalcides chalcides* expresses
1889 pro-inflammatory cytokines, IL-1 α and IL-1 β , at specific times during gestation (Paulesu et al.,
1890 1995). During gestation, *Chalcides ocellatus* also differentially expresses 27 other interleukins
1891 and interleukin related products (Brandley et al., 2012).

1892 The expression of IL-34 in a marsupial, the fat-tailed dunnart, during pre-implantation
1893 (Whittington et al., 2018) may have an immunosuppressive function to help tolerate potential
1894 contact of maternal and fetal tissues when the embryonic shell coat disintegrates (Lindau et al.,
1895 2015). In chickens, IL-34 regulates Th1 and Th17 cytokine production (Truong et al., 2018).
1896 During gestation in *Pseudemoia entrecasteauxii*, IL-16 and IL-1 α are expressed in addition to
1897 three receptors for Th17 family cytokines—IL-17RA, IL-17RC, and IL-17RA (Griffith,
1898 Brandley, et al., 2016, 2017). In the yolk sac of *Pseudemoia entrecasteauxii* during pregnancy
1899 interleukin related molecules, *ILDR1*, *IRAK1*, and *SIGIRR*, are differentially expressed (Griffith
1900 et al., 2016). This profile suggests the presence of tricellular tight junctions and/or tricellulin
1901 (Higashi et al., 2013; Ikenouchi et al., 2005), and regulation of toll-like receptors (TLRs) and/or
1902 IL-1R signaling (Kawagoe et al., 2008; Lin, Lo, & Wu, 2010; Muzio et al., 1997).

1903

1904 (9) *The major histocompatibility complex and maternal-fetal immune dynamics*

1905 A substantial amount of literature on maternal-fetal immune dynamics was focuses on uNK
1906 cells. Uterine NK cells have a distinct phenotype and function from peripheral NK cells. They
1907 have several activating receptors (Manaster & Mandelboim, 2010) but do not exert cytolytic
1908 functions on embryonic trophoblasts that they are in contact with (King, Birkby, & Loke, 1989).
1909 Allorecognition of embryonic placental cells by uNK cells is a key regulator of the maternal-fetal
1910 immune mechanisms that support placentation in mammals (Moffett & Colucci, 2014). When
1911 cells lose their ability to express any HLAs, uNK cells are shown to kill them (Hunt et al., 2005;
1912 Ishitani et al., 2003; King, Allen et al., 2000).

1913 In humans, expression of the classical MHC class I (C-MHCI) molecule HLA-C, and
1914 nonclassical MHC class I (NC-MHCI) molecules HLA-E, HLA-F and HLA-G on trophoblasts
1915 inhibit uNK cell-mediated cytotoxicity (Hunt et al., 2003; King, Burrows et al., 2000). Differing
1916 from this, mismatched HLA-C profiles trigger rejection of the transplanted organs (Petersdorf et
1917 al., 2014). Selection for balanced polymorphisms in HLA-C alleles and their killer
1918 immunoglobulin receptors (KIRs) is proposed to be driven by reproductive success, rather than
1919 immune recognition of pathogens (Trowsdale & Betz, 2006). Dimorphisms of HLA-C emerged
1920 recently within primates (Adams & Parham, 2001).

1921 Similar patterns in MHC profiles have been explored in other viviparous amniotes. C-MHCI
1922 antigen, H2-K, is expressed on giant trophoblast cells of mice and this is attributed to
1923 trophoblast-induced uterine vasculature transformation (Arcellana-Panlilio & Schultz, 1994;
1924 Chatterjee-Hasrouni & Lala, 1982; Hedley et al., 1989; King et al., 1987; Sellens, Jenkinson, &
1925 Billington, 1978). H2-D antigen is co-expressed with H2-K in virtually all their other nucleated
1926 cells (Madeja et al., 2011). However, H2-K expressing trophoblasts lack H2-D expression. This

1927 parallels the expression patterns of C-MHC molecules at the maternal-fetal interface in humans
1928 and may be an evolutionarily conserved pattern (Madeja et al., 2011).

1929 In humans, NC-MHCI molecule, HLA-G, is especially tolerogenic (Carosella et al., 2015;
1930 González et al., 2012; Hviid et al., 2004; Kovats et al., 1990). In adults, HLA-G is almost
1931 exclusively expressed by fetal trophoblasts compared to adult cells (Faulk & Temple, 1976;
1932 King, Burrows et al., 2000; Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al.,
1933 1997). It supports immunotolerance at the maternal-fetal interface (Rebmann et al., 2014). The
1934 role of HLA-G in supporting tolerogenic responses to organ transplants appears to be an
1935 exploitation of its role in immunotolerance in the utero during pregnancy (Rebmann et al., 2014).
1936 HLA-G is upregulated by several molecules that serve essential roles during gestation including
1937 progesterone (Yie, Xiao, & Librach, 2006; Yie et al., 2006), IFN- α , IFN- β , and IFN- γ (Rebmann
1938 et al. 2003; Lefebvre et al., 2001; Ugurel et al., 2001; Yang, Geraghty, & Hunt, 1995), and IL-10
1939 and TGF- β (Cadet et al., 1995; Moreau et al., 1999).

1940 A similar NC-MHCI gene to HLA-G exists in horses (Davies et al., 2006) where it likely
1941 functions to protect the embryo from NK-cell mediated attack (Ott et al., 2014). NC-MHC
1942 molecules with similar structure to HLA-G are also found in Rhesus monkeys (Boyson et al.,
1943 1997) and baboons (Stern et al. 1987). Mice have two NC-MHCI genes that are expressed on the
1944 surface of their placentas and on pre-implanted embryos (Sipes et al., 1996).

1945 In the gestating uterus of the viviparous skink, *Pseudemoia entrecasteauxii*, four putative C-
1946 MHCI and two putative NC-MHCI molecules are expressed (Murphy, Thompson, & Belov,
1947 2009). This pattern resembles the C-MHCI and NC-MHCI expression profiles of mammals,
1948 suggesting that this viviparous skink utilizes a similar physiological mechanism to 'hide' the
1949 embryo (Murphy, Thompson, & Belov, 2009). One of the putative NC-MHCI genes (Psen-

1950 160Ut/Psen-78G) has a substitution at position 150 where a tryptophan is substituted for a
1951 leucine (Murphy, Thompson, & Belov, 2009). When Psen-160Ut/Psen-78G was aligned to NC-
1952 MHC I genes of vertebrates ranging from fish to eutherian mammals, tryptophan was conserved
1953 at position 150 except in Psen-160Ut/Psen-78G and HLA-G (Murphy, Thompson, & Belov,
1954 2009). Whether this reflects an evolutionary history associated with immune tolerance at the
1955 maternal-fetal interface in *Pseudemoia entrecasteauxii* requires further investigation.

1956 MHC I genes are also expressed in reproductive tissues of oviparous skinks (*Ctenotus*
1957 *taeniolatus* and *Lampropholis guichenoti*) during non-reproductive periods and during late
1958 gravidity (Murphy, Thompson, & Belov, 2009). A similar pattern is found in viviparous skinks
1959 *Eulamprus tympanum*, *Niveoscincus metallicus*, *Pseudemoia entrecasteauxii* and the
1960 reproductively bimodal skink *Saiphos equalis* which all express MHC I genes at non-
1961 reproductive periods and during late pregnancy/gravidity (Murphy, Thompson, & Belov, 2009).
1962 MHC gene H2-EA is also expressed during gestation with long egg retention in *Saiphos equalis*.

1963 The butyrophilin subfamily 1 member A (*BTN1A1*) is located in the MHC I region of the
1964 genome in mammals (Trowsdale, 2011). *BTN1A1* is differentially expressed in the uterus during
1965 gestation in a viviparous lizard, *Chalcides ocellatus* (Brandley et al., 2012). *BTN1A1* may have
1966 important antimicrobial properties in chicken eggshells (Mann, Maček, & Olsen, 2006). In
1967 mammals *BTN1A1* is the major protein associated with fat droplets in milk (Jeong et al., 2009).

1968

1969 (10) *Microchimerism and maternal-fetal immune dynamics*

1970 Billingham, Brent and Medawar suggested the concept of actively acquired immunologic
1971 tolerance during pregnancy 70 years ago (Billingham, Brent, & Medawar, 1953; Ribatti, 2015).
1972 Subsequent research over the following decades revealed that substantial transfer of proteins,

1973 parasites and even immunologically active cells occurs between mother and embryo (Adams &
1974 Nelson, 2004; Axiak-Bechtel et al., 2013; Bakkour et al., 2014; Burlingham, 2010; Fujiki et al.,
1975 2008; Gitlin et al., 1965; Khosrotehrani et al., 2005; Owen, 1945; Turin et al., 2007).
1976 Microchimerism, where there is <0.1% donor chimeras in host tissue, is relatively pervasive
1977 among eutherians during pregnancy. It plays a role in establishing tolerance to non-inherited
1978 antigens. For example, cell populations from the mother that are transferred into embryonic
1979 lymph nodes enable the establishment of embryonic Tregs that are tolerogenic toward non-
1980 inherited maternal antigens (Mold et al., 2008).

1981 Microchimeric cellular populations are transferred across all placental types (Axiak-Bechtel
1982 et al., 2013; Bakkour et al., 2014; Fujiki et al., 2008; Khosrotehrani et al., 2005; Turin et al.,
1983 2007). Fetal and maternal cells persist for decades after birth across a range of tissues in mother
1984 and offspring, respectively (Adams & Nelson, 2004; Bakkour et al., 2014; Bayes-Genis et al.,
1985 2005; Bianchi et al., 1996; Evans et al., 1999; Jonsson et al., 2008; Stevens et al., 2004). There is
1986 even a call in the immunology literature to shift from the conventional paradigm of “self vs
1987 other” to instead consider the “self” as inherently chimeric (Nelson, 2012). Given that
1988 epitheliochorial placentation is sufficient to illicit microchimeric cell populations, the occurrence
1989 of similar bidirectional cellular traffic is a reasonable possibility in viviparous squamates.

1990

1991 (11) *Paternal alloantigens*

1992 Under tenants gleaned from transplant medicine, the maternal immune system would illicit
1993 an attack response as early as insemination when maternal tissues are exposed to paternal
1994 alloantigens (Borziak et al., 2016; Schumacher & Zenclussen, 2015; Seavey & Mosmann, 2006).
1995 Instead, maternal cells immunologically recognize them at this time without attack (Schumacher

1996 & Zenclussen, 2015; Seavey & Mosmann, 2006; Zenclussen et al., 2010). Treg expansion, a
1997 process with major influence on maternal-fetal immunotolerance in mammals, is proposed to be
1998 driven by several different factors found in seminal plasma (Baratelli et al., 2005; Teles et al.,
1999 2013). Mothers may maintain fetal-specific Tregs with memory of the paternal alloantigens
2000 (Zenclussen et al., 2010), expediting Treg response in future pregnancies with the same father
2001 (Rowe et al., 2012).

2002 Alloantigen exposure at the time of insemination is not restricted to mammals. Seminal fluid
2003 of chickens contains two MHC I paternal alloantigens and one MHC II alloantigen (Borziak et
2004 al., 2016). It also contains proteins involved in immunity and antimicrobial defenses (Borziak et
2005 al., 2016). In hens, evidence suggests that a protective local immunity to pathogens is established
2006 after exposure to semen but the mechanisms for this remain unclear (Reiber & Conner, 1995;
2007 Reiber, Conner, & Bilgili, 1995).

2008 In mammals, paternal alloantigens and cytokines in seminal fluid drive immune tolerance
2009 (Schjenken & Robertson, 2014). Mammalian seminal plasma contains immune-factors (Kelly,
2010 1995; Schjenken & Robertson, 2014)—TGF- β (Breuss et al., 1993; Chu & Kawinski, 1998;
2011 Slater & Murphy, 1999), IL-8 (Gutsche et al., 2003), and soluble IL-2 receptor (Srivastava,
2012 Lippes, & Srivastava, 1996), prostaglandin E2 (PGE2) and 19-hydroxyprostaglandin E (19-
2013 hydroxy PGE) (Denison et al., 1999), soluble tumor necrosis factor (TNF) receptors (Liabakk et
2014 al., 1993), receptors for the Fc portion of γ -globulin, spermine (Evans, Lee, & Flugelman, 1995),
2015 and complement inhibitors (Kelly, 1995). In horses and pigs, respectively, the proteins CRISP3
2016 (Doty et al., 2011), PSP-I and PSP-II (Rodriguez-Martinez et al., 2010), act as signaling agents
2017 in seminal fluid.

2018 Secretions of growth factors, cytokines and chemokines from cervical and endometrial
2019 tissues immediately following insemination generates a proinflammatory environment that likely
2020 aids in implantation. In the utero-vaginal junction of chickens and the utero-tubal junction of
2021 pigs, expression of several genes were shared following mating compared to non-mating and
2022 these genes were involved with immune-modulation (*IFIT5*, *IFI16*, *MMP27*, *ADAMTS3*, *MMP3*,
2023 *MMP12*) and pH-regulation (*SLC16A2*, *SLC4A9*, *SLC13A1*, *SLC35F1*, *ATP8B3*, *ATP13A3*), a
2024 process essential for implantation (Atikuzzaman et al., 2017, 2015). Instead of mounting an
2025 attack, it appears that the uterine immune system and paternal genes work cooperatively to
2026 support pregnancy in mammals and gravidity in birds. Whether this applies to reptiles, and how
2027 it may influence immune dynamics involved with squamate parity mode evolution, deserves
2028 investigation.

2029

2030 (12) *Discussion and future directions—maternal-fetal immune dynamics & the*
2031 *evolution of parity modes*

2032 Immune processes appear to be important for both oviparity and viviparity—as evidenced
2033 here, in part, by overlapping expression profiles of immune genes in female reproductive tissues
2034 of chickens and pigs, expression of paternal antigens in avian seminal fluid, and uterine
2035 expression of maternal antigens in oviparous and viviparous skinks. This highlights the scientific
2036 advances made since Medawar’s paradigm, when embryos were treated as analogs to allografts.
2037 Nonetheless, viviparity is associated with complex immune dynamics between maternal, fetal,
2038 and paternal tissues.

2039 Overall, evolving appropriate immunological responses is one hurdle of transitions to
2040 viviparity in squamates. This is evidenced by the unique MHC expression profiles identified in

2041 some viviparous skinks compared to oviparous relatives (Murphy et al., 2009); and the detection
2042 of divergent selection in immune response genes in viviparous and oviparous *Zootoca vivipara*
2043 (Recknagel et al., 2021a). Labile parity modes in squamates may be supported if they are more
2044 heavily reliant on the innate immune system for reproduction. However, reptiles may not have
2045 distinguished innate and adaptive immune systems (Zimmerman et al., 2020).

2046 Changes to genes that serve overlapping functions across the Main Five may have a
2047 disproportionate influence on transitions between parity modes. In this section I reviewed two
2048 molecules, *TGF-β* and progesterone, that exert influence on multiple Main Five categories.
2049 Progesterone influences uterine quiescence (embryonic retention), hepatic vitellogenesis
2050 (nutrient provisioning) and regulation of inflammatory responses in utero (maternal-fetal
2051 immune dynamics). Genes in the *TGF-β* family play a role in placental development and
2052 maternal-fetal immune dynamics. *TGF-β* family is implicated in placental development in
2053 eutherians (Hempstock et al., 2004; Caniggia et al., 2000; Lafontaine et al., 2011). A *TGF-β*
2054 receptor protein (*TGFBR1*) was associated with placental development in *Phrynocephalus*
2055 *vlangalii* (Gao et al., 2019). In humans *TGF-β* upregulates tolerogenic HLA-G in utero and is an
2056 immune factor in mammalian seminal fluid. Multiple genes in the *TGF-β* family are also
2057 differentially expressed during gestation in other viviparous lizards, *Pseudemoia entrecasteauxii*
2058 and *Saiphos equalis* (Foster et al., 2020; Griffith et al., 2016). Examining the functions of *TGF-β*
2059 and progesterone across other amniotes may reveal insights into how these molecules influence
2060 the evolution of parity modes.

2061 In mammals, inflammation appears to be involved with two of the Main Five processes—
2062 regulation of maternal-fetal immune dynamics and embryonic retention. It is intriguing to
2063 consider the implications this has for the interconnectedness of the Main Five. Greater

2064 interconnectedness would suggest that changes to few genes involved with the Main Five could
2065 cause a cascading effect to support more labile transitions between parity modes.

2066 Implantation and parturition in therian mammals evolved from a shared inflammatory
2067 attachment reaction (Hansen et al., 2017). The process of implantation has important
2068 implications for maternal-fetal exchanges of inorganic and organic material and maternal-fetal
2069 immune dynamics. Given that inflammation is associated with implantation and parturition
2070 implicates it in gas, water, and nutrient provisioning (including calcium here), maternal-fetal
2071 immune dynamics and length of embryonic retention. However, implantation in mammals and
2072 viviparous squamates is not homologous (Griffith, Van Dyke, & Thompson, 2013). Therefore, it
2073 is difficult to make inferences about how substantial the influence of inflammation is on the
2074 evolution of parity modes in squamates. Nonetheless, the abundant literature on uterine
2075 inflammatory processes during human pregnancy and the evolution of inflammatory processes
2076 that supported the evolution of viviparity in mammals (Challis et al., 2009; Chavan, Griffith, &
2077 Wagner, 2017; Mor et al., 2011; Griffith, Chavan et al., 2017; Stadtmauer & Wagner, 2020a)
2078 serve as indispensable resources for exploring the role of inflammation in squamate viviparity. I
2079 resist expanding on this further. I suspect that the immune system plays a central role in dictating
2080 the plasticity of parity modes. However, further work is necessary to validate this.

2081

2082

2083 **VII. Conclusions**

2084

2085 (1) Through holistic consideration of the unique complexity of parity mode evolution, within
2086 the context of genomic and transcriptomic studies across interdisciplinary fields, this

2087 review provided a new perspective on the history of parity mode transitions in amniotes
2088 and squamates. The overlapping activity of immune genes in utero, genes for calcium
2089 transport, placentation, and hormonal regulation across mammals, birds, and reptiles hint
2090 at discoveries to be made. There is a fascinating history to the evolutionary physiology
2091 and genomics of reproduction in amniotes that is ripe for downstream research.

2092 (2) Changes to gene(s) or physiological processes associated with more than one of the Main
2093 Five should disproportionately influence parity mode evolution—*SLC* gene superfamily,
2094 TGF- β , *BMPRI*B, progesterone, *PMCA*, calbindin-D28K, *SPP1*, sustained functioning of
2095 the corpora lutea and inflammation, and the genes associated with both gestation length
2096 and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).

2097 (3) Growing evidence in the medical literature suggests that immune system interactions at
2098 the maternal-fetal interface in mammals did not evolve simply through tolerance,
2099 evasion, or suppression (Chaouat, 2016; Chavan, Griffith, & Wagner, 2017; Moffett &
2100 Loke, 2004, 2006). Instead, maternal-fetal immune dynamics have a deep evolutionary
2101 history that enables both embryo and mother interact cooperatively (Yoshizawa, 2016).
2102 Future research on amniote parity mode evolution should consider maternal-fetal immune
2103 dynamics in this context. Nonetheless, viviparity and extended embryonic retention are
2104 assuredly associated with immunological responses in squamates (e.g. Foster et al.,
2105 2020).

2106 (4) Compared to viviparous endothermic amniotes, ectothermy likely influences parity mode
2107 evolution differently because it entails slower antibody responses and a greater reliance
2108 on climatic conditions for embryonic development. This and the Cold Climate
2109 Hypothesis are likely relevant to the origin of the amniotic egg and squamate parity mode

2110 evolution. Climatic shifts during the origin of amniotes should be explored for their
2111 consistency with the EER model.

2112 (5) Two new mechanisms for transitions between oviparity and viviparity, without
2113 necessitating intermediate stages, stand out from the cumulative research on the Main
2114 Five. These are presented here (Conclusions 6 and 7) as tools to be broadened and
2115 challenged with the goal of advancing scientific insight on the subject.

2116 (6) The genomics and physiology of amniote parity mode evolution does not preclude an
2117 origin of viviparity in the MRCA of Lepidosauria. I propose the following mechanism—a
2118 change to the phenotype or function of mammillary knobs occurred in the MRCA of
2119 Lepidosauria, instantaneously preventing calcium carbonate deposition (basal cap
2120 hypothesis); the eggshell loss enabled uterine exposure to chorioallantoic progesterone
2121 production (extending embryonic retention) and incipient calcium matrotrophy
2122 (supporting embryonic development); parturition occurred via 1) placental progesterone
2123 withdrawal or 2) overdistension of the uterus triggers contractions. This is one way to
2124 imagine viviparity evolving in the MRCA of Lepidosauria.

2125 a. Hypothesis testing: If the genes that code for the KS-proteoglycan, “mammillan”,
2126 that makes up mammillary knobs are absent or non-functional across squamates
2127 and tuatara, then this would support the basal cap hypothesis. To test this, the
2128 genes must be identified in Archelosaur genomes and proteomes. Additionally,
2129 ancestral state reconstructions on the eggshell and eggshell membrane should be
2130 generated across oviparous and viviparous Archelosaurs, utilizing current
2131 recommendations for characterizing eggshell microstructure (Legendre et al.,

2132 2022). This will require also developing a system to accurately characterize
2133 eggshell membranes.

2134 (7) As discussed, the calcium secreting capacity of the uterus is maintained in oviparous and
2135 viviparous squamates. Nonetheless, a reversal back to oviparity may evolve most easily
2136 within viviparous clades with matrotrophic calcium provisioning through the following
2137 sequence of events—calcium secretions in utero stick to the eggshell membrane instead
2138 of being absorbed by the chorioallantois; oviposition can then occur early in embryonic
2139 development in one of two ways 1) the death of corpora lutea or 2) the calcified eggshell
2140 blocks a threshold of chorioallantoic progesterone production from reaching uterine
2141 tissue; the calcified eggshell provides embryonic calcium that is transported upon
2142 embryonic metabolic demand.

2143 a. Hypothesis testing: Recent reversals should have physiological or genomic
2144 remnants of a viviparous past. Given that viviparous squamates generally have
2145 more active uterine immune systems to support gestation, oviparous reversals
2146 should 1) have more immune genes expressed in utero than ancestrally oviparous
2147 squamates, and 2) these immune genes should have stronger signatures of relaxed
2148 selection than immune genes expressed in a close relative during viviparous
2149 gestation.

2150 (8) If the scientific community agrees to utilize squamates as a model for studying the
2151 evolutionary parity mode of amniotes, then consider the following—1) oviparous *Z.*
2152 *vivipara* and *P. przewalskii*, differentially express genes during gravidity and these were
2153 associated with eggshell traits and stage of eggshell gland development, respectively
2154 (Gao et al., 2019; Foster et al., 2022); 2) Only two or zero genes are differentially

2155 expressed during gravity in *Lerista bougainvillii*, and *Lampropholis guichenoti*,
2156 respectively (Griffith et al., 2016). 3) This suggests that embryonic retention until the
2157 limb bud phase, common to squamates, does not necessarily require regulatory changes
2158 in the uterus. If we extrapolate this to stem amniotes, the egg could have been retained
2159 without a problem. The EER model is the most realistic explanation for the origin of the
2160 amniote egg. If we accept this, then all oviparous squamates that differentially express a
2161 substantial number of genes during gravity can be understood as reversals.

2162 (9) If we accept point eight as true, then *Saiphos equalis* and *Zootoca vivipara* represent
2163 reproductively bimodal species (RBS) that have transitioned from viviparity back to
2164 oviparity; and RBS *Lerista bougainvillii* represents a species that has transitioned from
2165 oviparity to viviparity. Future work should examine the ultimate causes for these recent
2166 transitions, which will have the benefit of informing how science understands edge cases
2167 of viviparous squamates that don't fit the Cold Climate Hypothesis.

2168 (10) My opinion, based on the cumulative evidence and the lack of uterine differential
2169 gene expression in a non-RBS truly oviparous skink during gravity, *Lampropholis*
2170 *guichenoti*, is that the earliest amniote egg was oviparous with extended embryonic
2171 retention. *L. guichenoti* therefore serves as an adequate model for the first amniote egg. If
2172 found broadly, ancestral oviparity without gene expression fits neatly into Medawar's
2173 Paradigm. It explains the easiest way amniotes likely originated.

2174 (11) It is my opinion that the original amniote egg did not have a mammillary layer.
2175 Instead, it makes logical sense that the egg became ensheathed in an eggshell membrane,
2176 followed by calcium deposition that looks comparable to what we see in squamates. It
2177 later evolved to form the unique microstructure we see in Archosaurs.

2178

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