

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

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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 with no intermediate stages; and make predictions on
22 the directionality of transitions in two reproductively bimodal species. Furthermore, I
23 contextualize the maternal-fetal immune dynamics in light of modern medical understanding that
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 my conclusion
27 that the first amniote was oviparous with extended embryonic retention. I encourage the
28 scientific community to utilize this manuscript as a resource in comparative genomics studies,
29 embrace the complexity of the system, and thoughtfully consider new hypotheses proposed.

30 *Key Words:* reproductive mode, parity modes, oviparity, squamates, eggshell deposition,
31 embryonic retention, embryonic calcium transport, maternal-fetal interface, comparative
32 evolutionary physiology.

33

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91 **I. Introduction**

92

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

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

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

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

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

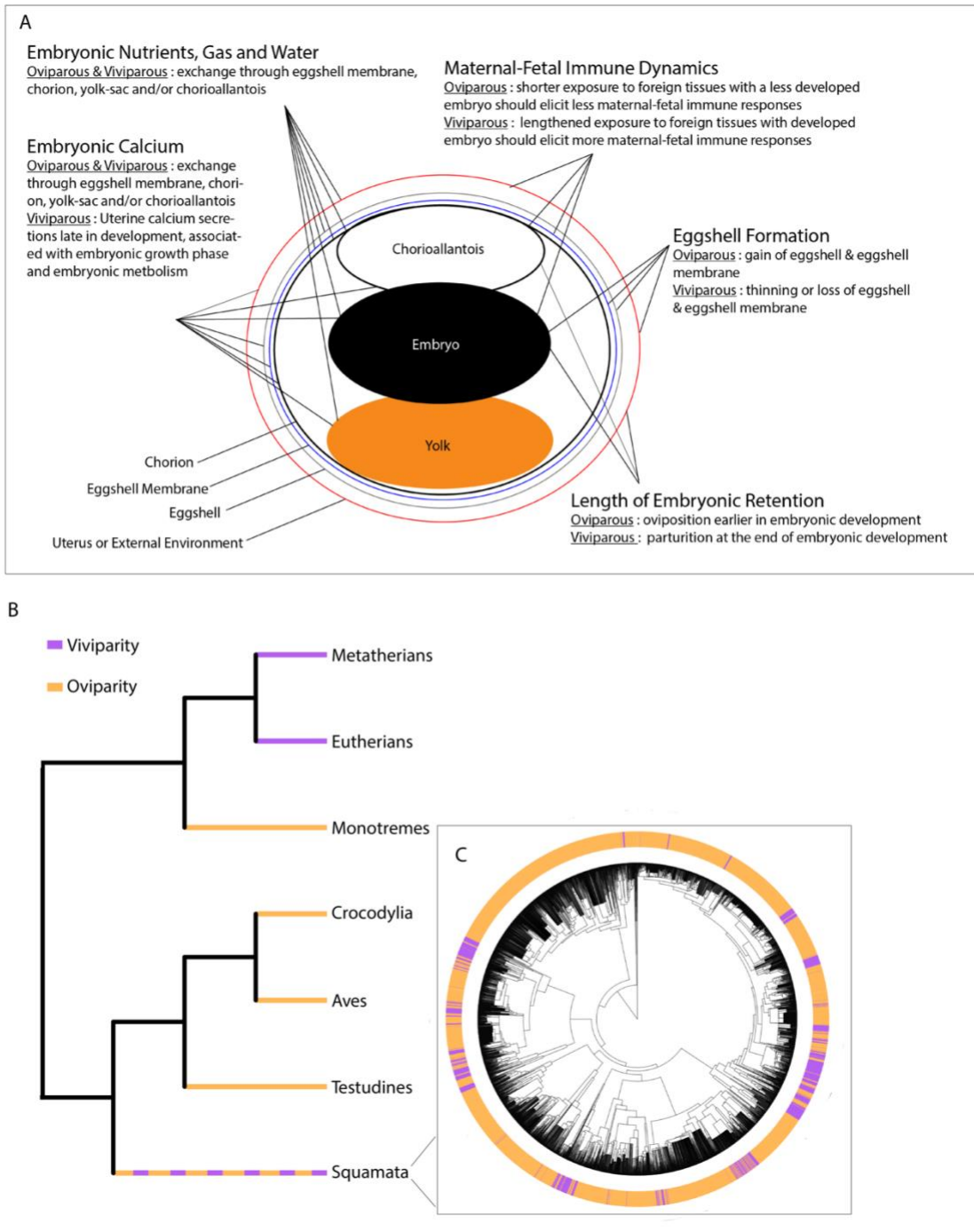
146 Discoveries of viviparity in ancient amniotes are numerous, dating back to the Early
147 Permian (Chuliver, Scanferla & Smith, 2022; Motani et al., 2014; Piñeiro et al., 2012; Jian et al.,
148 2023). A viviparous most recent common ancestor of amniotes is not unreasonable. Most
149 compelling is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

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

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

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

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



190

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

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

198

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

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

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

222

223 *(1) Terminology*

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

235

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

237 Several physiological features are expected to change during transitions between
238 oviparity and viviparity (Figure 1). I break this down into five physiological features (hereafter
239 Main Five)—1) length of embryonic retention (Murphy & Thompson, 2011; Packard et al.,
240 1977)—only viviparous mothers retain the embryo for the entirety of development; 2) eggshell

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

250

251 **II. Length of Embryonic Retention**

252

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

259

260(1) *Parturition & oviposition*

261 The genes and hormones involved with initiating and ending gestation may provide insights
262 into the tools squamates can co-opt to change the length of embryonic retention during parity
263 mode transitions. Parturition terminates embryonic retention. Parturition can be divided into four

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

271

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

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

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

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

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

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

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

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

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

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

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

369

370 (ii) *Activation & progesterone withdrawal*

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

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

382 Some similar patterns are associated with oviposition in birds. In chickens, *Gallus gallus*,
383 prostaglandin F (PGF) concentrations increase in the hours leading up to oviposition (Takahashi
384 et al., 2004). Experimental injection of oxytocin and arginine vasotocin (AVT), similar
385 neurohypophyseal peptides, revealed that uterine tissues of chickens, *Gallus gallus*, maintain
386 responsiveness to oxytocin but are more sensitive toward arginine vasotocin (Ewy, 1970).
387 Murphy & Thompson (2011) provide a rather exhaustive list of resources on progesterone and
388 estrogen assays across oviparous and viviparous squamates. Future research should consider
389 exploring parallels between mechanisms of activation in mammals and squamates. Any process
390 that can trigger or stall activation should lead to extended embryonic retention.

391

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

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

399 growing embryo plays a role in parturition (Lefebvre et al., 1995; Tamizian & Arulkumaran,
400 2004; Wray et al., 2015).

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

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

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

429 Placental CRH production has only been identified in primates thus far (Challis et al., 2005;
430 Emanuel et al., 1994; Florio et al., 2002; Hillhouse & Grammatopoulos, 2001; Karteris et al.,
431 1998; Mendelson, 2009; Robinson et al., 1989). Placental CRH production may, therefore, be
432 unique to primates. However, the amino acid sequence of CRH is highly conserved in vertebrates
433 (Noy et al., 2017), indicating there is a possibility for shared function across diverse taxa. Like
434 CRH cycling in mammals, timely fluctuations of AVT stimulates uterine contractions, enables
435 oviposition in birds, turtles, and lizards (Ewy, 1970; Fergusson & Bradshaw, 1991; Guillette Jr &
436 Jones, 1980; Jones et al., 1987; Rzasa, 1978; Wu et al., 2019).

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

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

452 $\text{PGF}_{2\alpha}$ decreases progesterone concentrations during stimulation (De Rensis et al., 2012). In
453 humans, biosynthesis of PGs is driven largely by the enzyme cyclooxygenase (*COX*)-2 rather
454 than *COX-1* (i.e., prostaglandin synthase-2 and -1) (Slater et al., 1995, 1999). This helps
455 maintain the decreased progesterone/estrogen ratio of stimulation. In ovariectomized viviparous
456 Garter snakes, *Thamnophis*, increased estrogen stimulated thickness of uterine epithelial cells
457 and glandular activity, whereas administration of progesterone had little influence on uterine
458 histology (Mead et al., 1981). Uterine pig models revealed that estrogen stimulates involuntary
459 contraction and relaxation (peristalsis) of the uterus (Mueller et al., 2006).

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

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

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

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

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

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

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

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

528

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

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

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

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

550

551(3) *Pre-term birth & embryonic retention mechanisms*

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

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

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

570

571(4) *Discussion & future directions—embryonic retention and parity mode evolution*

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

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

589

590 **III. Eggshell Formation**

591

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

600 Birds have hard calcareous eggshells. Other than two lineages of geckos with hard shells,
601 oviparous squamates have parchment-shelled eggs with a thin layer of calcium deposits on the
602 outer surface of the shell membrane (Blackburn & Stewart, 2021; Choi et al., 2018).

603 Monotremata (egg-laying mammals) have an eggshell but far less has been documented about its
604 structure compared to other amniotes (Legendre et al., 2022). The structure and physiological

605 mechanisms involved with eggshell calcification are most well resolved in birds (Choi et al.,
606 2018; Francesch et al., 1997; Jonchère et al., 2010, 2012; Rose-Martel, Du, & Hincke, 2012).
607 Eggshell deposition in tuatara and squamates differs dramatically (Choi et al., 2018). Viviparous
608 squamates lack an eggshell, absorb the eggshell during gestation, or have a thin layer of calcium
609 deposits.

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

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

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

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

642

643 (1) *Mineral composition of eggshells*

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

651 In birds, the organic components of uterine fluid promote the formation of calcite
 652 (Hernández-Hernández, Gomez-Morales et al., 2008; Hernández-Hernández, Rodriguez, et al.,
 653 2008; Hernández-Hernández, Vidal et al., 2008). Most amniotes use this polymorph (Hernández-
 654 Hernández, Gomez-Morales et al., 2008; Hernández-Hernández, Rodriguez, et al., 2008;
 655 Legendre et al., 2022). However, turtle eggshells are predominately developed with aragonite
 656 (Choi et al., 2022; Mikhailov, 1997). The eggshell of most squamates consists of an inner fibrous
 657 protein layer overlain by calcium carbonate that can be a single layer or scattered crystals (Choi
 658 et al., 2018; Packard & DeMarco, 1991; Stewart et al., 2010).

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

668 **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

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

671

672

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

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

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

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

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

715 In the oviparous Przewalski's toadhead agama lizard, *Phrynocephalus przewalskii*, 148 genes
716 are highly expressed in the uterus during the stage of eggshell gland development (Gao et al.,
717 2019). Only three of these are highly expressed in *P. vlangalii*, a viviparous close relative at this

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

721

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

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

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

740 copper deficiency, causes distorted formations of the eggshell membrane in birds (Arias et al.,
741 1997; Chowdhury & Davis, 1995; Hincke et al., 2012).

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

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

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

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

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

788 Extending to the ancestral state of amniotes (e.g. Jiang et al., 2023; Laurin, 2005; Romero,
789 1957), absence of functional “mammillan” with P-FCD in squamates and mammals would be
790 consistent with a derived state of calcified eggshells in Archelosaurs. Absence of functional
791 “mammillan” with P-FCD exclusively in Lepidosaurians would be consistent with the basal cap
792 hypothesis. Presence of functional “mammillan” with P-FCD across Amniota would be
793 consistent with the conventional understanding that the amniote egg evolved to prevent
794 desiccation and enable gas exchange following oviposition of eggs on land (Romero, 1957).
795 Overall, identifying the evolutionary trajectories of the biosynthetic pathway of “mammillan”
796 across amniotes is likely to create a better picture of the evolution of the amniote egg.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

899

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

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

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

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

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

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

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

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

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

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

966

967 (5) Eggshell formation termination

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

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

980

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

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

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

997

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

999 The process of eggshell formation is more resolved in birds compared to non-avian reptiles
1000 and monotremes (Choi et al., 2018; Frankenberg & Renfree 2018). I described some overlaps
1001 gleaned from the literature which prove as curious candidates for further research
1002 (Supplementary Table 1). Of particular interest are avian eggshell matrix proteins (Alföldi et al.,
1003 2011; Le Roy et al., 2021; Tian et al., 2010; Xie et al., 2022), genes with biomineralizations
1004 functions, candidate genes associated with eggshell traits in *Zootoca vivipara* (Recknagel et al.,
1005 2021a), and the homologs for avian eggshell matrix proteins identified in the *Anolis carolinensis*
1006 genome (Alföldi et al., 2011; Tian et al., 2010). Additionally, genes purported to be important for
1007 eggshell calcification in chickens associated with eggshell gland formation in an oviparous
1008 lizard, *Phrynocephalus przewalskii*, are relevant—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*,
1009 *RRBPI* and *TRAMI* (Brionne et al., 2014; Gao et al., 2019). Overlaps between the genes
1010 associated with gestation length and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a)
1011 hint at genes that could potentially evolve to innately effect multiple traits relevant to parity
1012 mode transitions. The basal cap hypothesis also offers a simple evolutionary mechanism to
1013 investigate the evolutionary history of amniote parity mode evolution (see section III.3).
1014 Alternatives to the basal cap hypothesis are that dissimilar eggshells and eggshell deposition

1015 processes evolved through selective pressure, genetic drift, or both. Fortunately, the basal cap
1016 hypothesis can be utilized to ascertain the likelihood of this.

1017

1018 **IV. Placentation & Transport of Embryonic Water, Gas, and Nutrients**

1019

1020 The evolutionary pressures on fluid allocation, gas exchange and nutrient transport should
1021 differ between oviparous and viviparous taxa because their sources of all or some of these
1022 resources differ (Blackburn, 1992; Bonnet et al., 2001; Bonnet, Naulleau & Shine, 2017; van
1023 Dyke et al., 2014). In viviparity, maternal gas and water are accessed through the chorioallantois,
1024 which is especially important in the latter half of development (van Dyke et al., 2014; Carter,
1025 2012). Nutrients can be available from the yolk, maternal transfer, or both yolk and maternal
1026 transfer.

1027 While viviparity is associated with shared patterns of uterine gene expression during amniote
1028 gestation (Recknagel et al., 2021a), the same does not occur in viviparous amniote placentas
1029 (Foster et al., 2022). Instead, different genes that serve similar functions are recruited to the
1030 placenta across independent origins of viviparity (Foster et al., 2022). Additionally, where other
1031 amniotes can rely on the albumen for fluid allocation, squamates lack an albumen (Blackburn &
1032 Stewart, 2021). The eggshells of various squamates supports uptake of water from the
1033 environment (Blackburn & Stewart, 2021). The evolutionary implications of this have not been
1034 documented to my knowledge.

1035

1036 *(1) Anatomy & methods of water, gas & nutrient provisioning*

1037 The embryonic membranes regulate embryonic fluid transport, nutrient supply, respiration,
1038 immunity, and waste (Brace, 1997; Burton & Tullett, 1985; Ferner & Mess, 2011; Packard &
1039 Packard, 1980). Fluids are important for the developing embryo because they prevent desiccation
1040 and compression (Ferner & Mess, 2011; Packard & Packard, 1980). Over-abundance or under
1041 abundance of embryonic sac fluids leads to reproductive failure (Chamberlain et al., 1984;
1042 Fedakâr et al., 2016; Hadi, Hodson & Strickland, 1994; Mercer et al., 1984). Water is the
1043 predominant resource provisioned from the mother in most viviparous squamates (Lourdais et
1044 al., 2015).

1045 Oxygen flux in embryonic mammals is largely determined by oxygen-diffusing capacity of
1046 the placenta, the rates of blood flow in the umbilical and uterine arteries, and the oxygen
1047 capacities and affinities of fetal and maternal blood (Carter, 2009). Reptilian and mammalian
1048 blood vessels differ in basic characteristics such as capillary density, capillary surface, and
1049 oxygen diffusion gradients (Pough, 1980). Oviparous taxa regulate gas exchange through pores
1050 in their eggshells.

1051 Patterns of embryonic nutrient exchange can be broadly categorized into lecithotrophy,
1052 obtaining nutrients from the yolk, and placentrophy or matrotrophy, obtaining nutrients from the
1053 mother. Taxa belonging to Archelosauridae are lecithotrophic. The ancestral state of mammals
1054 was most likely oviparous matrotrophy that later evolved into viviparous matrotrophy in therians
1055 (Blackburn, 2005). The ancestral state of reptiles was likely lecithotrophy (Blackburn, 2005).
1056 Most viviparous squamates are lecithotrophic, some are lecithotrophic and matrotrophic, and a
1057 few have specializations for substantial matrotrophy (e.g. Blackburn, 2015a, Blackburn, 1985b;
1058 Stewart & Thompson, 1993; Thompson, Stewart et al., 1999; van Dyke et al., 2014). Even in
1059 lecithotrophic viviparous squamates some degree of organic or inorganic nutrients pass through

1060 the chorioallantoic placenta (Blackburn, 2005; Swain & Jones, 1997, 2000; Stewart & Eday,
1061 2010; Thompson, Stewart et al., 1999; Thompson & Speake, 2002). Reversals may be most
1062 unlikely in lineages that have specialized placentas for substantial nutrient exchange because
1063 they would need to re-evolve lecithotrophy. Highly matrotrophic squamates are extremely rare
1064 (Blackburn, 2015a).

1065

1066 *(2) Evolutionary history of yolk-sac formation and yolk processing*

1067 Vitellogenesis is the process of yolk formation in the oocyte, providing the embryo with a
1068 valuable source of nutrients, primarily through the accumulation of precursor proteins to yolk,
1069 vitellogenins. Vitellogenin is produced in the liver, called hepatic vitellogenesis, and transported
1070 to the maturing ovum (Ho, 1987). Vitellogenins were lost in all mammals except monotremes
1071 (Brawand, Wahli & Kaessmann, 2008). They are a primary source of nutrition for other
1072 amniotes. Functionally similar to vitellogenin, caseins have persisted in all mammalian milks
1073 (Brawand et al., 2008). Active functioning of the yolk sac is restricted to the first trimester in
1074 placental mammals, and it is postulated to provide nutrients to the embryo (Kuzima et al., 2023).
1075 The detection of glycodelin in the yolk sac epithelium also supports this (Burton et al., 2002). In
1076 the yolk-sac of bats, dogs, and non-human primates the mesoderm derived layer is absorptive
1077 and may transfer substances from the exocoelomic cavity where the yolk sac is located (Enders
1078 et al., 1976; Freyer & Renfree, 2009; King & Wilson, 1983; Lee et al., 1983).

1079 The morphology of the yolk-sac and process of vitellogenesis differs between birds and non-
1080 avian reptiles. In birds, during the process of meroblastic cleavage, the zygote's cells divide
1081 while the yolk component does not. The yolk forms a large, fluid, non-cellularized mass
1082 surrounded by the extraembryonic yolk sac. The formation of the yolk-sac placenta in birds has

1083 the following pattern—first the bilaminar omphalopleure forms and then trilaminar
1084 omphalopleure; blood vessels move into folds of the extraembryonic endoderm, becoming
1085 stratified epithelium; the folds carrying the blood vessels reach the peripheral regions of the yolk
1086 only and the center of the yolk mass remains uncellularized (Starck, 2021). Intensive
1087 development of hemopoietic tissue surrounding the blood vessels during most of embryonic
1088 development, thus far, appears to be unique to birds (Starck, 2021). Compared to non-avian
1089 sauropsids, the unique pattern of yolk processing in birds facilitates faster embryonic
1090 development (Blackburn, 2021).

1091 The yolk sac characteristic of non-avian reptilian eggs serves as a model for the transition
1092 between the egg of anamniotes and amniotes (Blackburn, 2020). A series of recent papers,
1093 covering species of snakes, lizards, crocodiles, and turtles, indicate that these taxa utilize similar
1094 developmental pathways of yolk-sac formation and yolk processing that differs from birds
1095 (Blackburn, 2020, 2021; Blackburn et al., 2019; Elinson et al., 2014; Elinson & Stewart 2014;
1096 Stinnett et al., 2011). Across these taxa, a bilaminar/trilaminar omphalopleure overgrows the
1097 yolk mass, and the yolk mass gets invaded by proliferating endodermal cells that phagocytose
1098 the yolk material. These cells form clumps, progressively filling the yolk mass. Small blood
1099 vessels derived from yolk sac vasculature invade the yolk sac cavity and the endodermal cells
1100 arrange in monolayers around these vessels, forming “spaghetti bands” (Blackburn, 2021). The
1101 yolk sac of *Pantherophis guttatus* is one suitable model for studying the transition of the yolk-
1102 sac from anamniotes to amniotes (Elinson & Stewart, 2014; Elinson et al., 2014).

1103 A major difference between non-avian reptilian yolk-sac formation is the morphology and
1104 extent of vascularization and cellularization in the yolk sac cavity (Starck, 2021). Birds have a
1105 yolk-sac with absorptive endodermal lining that digests nutrients and send them into blood

1106 circulation (Starck, 2021) whereas snakes, lizards, turtles, and crocodylians have a yolk sac that
1107 becomes invaded by endodermal cells that proliferate and phagocytose yolk material (Blackburn,
1108 2021). In these taxa, yolk material becomes cellularized, digested, and transported by vitelline
1109 vessels to the developing embryo (Blackburn, 2021). Factors involved with cellularization of the
1110 yolk-sac are proposed to include cell cycle regulators and structural proteins (Elinson et al.,
1111 2014). Generation of these cells are suspected to be reliant on processes of angiogenesis and are
1112 likely transcriptionally active (Elinson et al., 2014). Few transcriptomic profiles of yolk-sac
1113 placentas in reptiles have been documented to my knowledge (Griffith et al., 2016). Significant
1114 overlaps in the yolk-sac transcriptomes of human, mice, and chicken—including apolipoproteins
1115 and SLC transporters—however, suggest functional conservation (Cindrova-Davies et al., 2017).

1116 As discussed in a previous section, progesterone inhibits myometrial contractility, but it also
1117 inhibits estrogen-induced hepatic vitellogenin synthesis (Custodia-Lora, Novillo, & Callard,
1118 2004; Callard et al., 1992). Variable progesterone concentrations in circulation throughout
1119 gestation in viviparous squamates may reflect a trade-off to allow estrogen expression to support
1120 hepatic vitellogenin synthesis during embryonic development, thus supporting nutrient
1121 provisioning during the lengthened embryonic retention. Although hepatic vitellogenesis usually
1122 ceases during gestation, vitellogenin synthesis and mother-to-embryo transfer was detected in
1123 one viviparous fish, *Xenotoca eiseni*, during gestation (Iida et al., 2019). Future research should
1124 consider the timing of vitellogenin synthesis throughout the reproductive cycle in gestating and
1125 non-gestating viviparous squamates to investigate this further.

1126

1127 (3) *Evolutionary history of placentrophy in mammals & squamates*

1128 Traditionally, it was thought that placentrophy evolved after viviparity in squamates
1129 (Packard, Tracy, & Roth, 1977; Shine & Bull, 1979). Further research demonstrated that
1130 placentrophy and viviparity evolved simultaneously (incipient matrotrophy) in mammals and
1131 may have in squamates (Blackburn, 1985, 1992, 2005, 2006; Stewart & Eday, 2010). The
1132 incipient matrotrophy model relies on evidence that 1) uterine provisioning of nutrients predates
1133 the origin of viviparity (Blackburn 1985, 1992, 2006), 2) uterine and embryonic tissues have a
1134 close anatomical and physiological association in viviparous taxa and 3) some degree of
1135 placental transfer of organic or inorganic molecules occurs in viviparous taxa (Stewart & Eday,
1136 2010). In squamates, the potential for both incipient matrotrophy and evolution of placentrophy
1137 after viviparity is supported (Stewart & Eday, 2010). Facultative placental nutrient provisioning
1138 and incipient matrotrophy may have driven the evolution of squamates with substantial
1139 matrotrophic nutrient provisioning (Stewart, 2020; Swain & Jones, 2000).

1140 Placentation and implantation are not homologous in mammals compared to squamates
1141 (Griffith, van Dyke & Thompson, 2013). Several placental specializations for gas and nutrient
1142 exchange are unique to mammals including erosion of the uterine mucosa, extensively invasive
1143 implantation, hemochorial contact, retention of a vascularized choriovitelline membrane, and
1144 countercurrent patterns of blood flow (Blackburn, 2005). This enables extensive exchange of
1145 nutrients in addition to water and gas. The vast majority of viviparous squamates have the most
1146 superficial type of chorioallantoic placenta called epitheliochorial placenta (Blackburn, 1993).

1147 Nutrient provisioning through placentrophy is obligate for embryonic development in only
1148 five lineages of squamates, all of which are scincid lizards (Blackburn, 2000; Flemming &
1149 Blackburn, 2003; Ramírez-Pinilla et al., 2011; van Dyke et al., 2014). *Pseudemoia*
1150 *pagenstecheri*, a lizard with a highly specialized placenta, out-performs lecithotrophic oviparous

1151 close relatives in the relative amount of nutrients it transfers to the embryo (Stewart et al., 2009).
1152 *Pseudemoia entrecasteauxii* is a moderately matrotrophic viviparous skink, with roughly half of
1153 embryonic nutrient uptake from the yolk and half through a specialized cyto-epitheliochorial
1154 placenta (Adams et al., 2005; Speake et al., 2004; Stewart & Thompson, 1993, 2009).

1155 Specializations of the chorioallantoic placenta for nutrient provisioning in some squamates
1156 include elaborate specializations for uterine secretion and absorption, including placentomes,
1157 chorionic areolae, hypertrophied uterine mucosa, and chorionic epithelia modified for absorption
1158 (Blackburn, 2005). In squamates, specializations for gas exchange across the chorioallantoic
1159 placenta include decreased diffusion distance between maternal and fetal capillaries, uterine
1160 vascularity, shell membrane deterioration, and modifications of both fetal and maternal blood
1161 properties (Blackburn, 1998, 2005; Blackburn & Lorenz, 2003; Blackburn & Vitt, 2002).

1162 Mammalian placenta-specific genes have deep origins in vertebrates (Rawn & Cross, 2008).
1163 Placentation to support viviparity likely employs genes that are ancestral to the chorioallantois.
1164 However, one study that looked at placentation and gene expression across a small sample of
1165 divergent amniotes found only one gene with a placentrophy-specific pattern of gene expression,
1166 *DIO3* (Griffith, Brandley et al., 2017). In mammals, *DIO3* is an imprinted gene and
1167 preferentially paternally expressed. The authors suggest that the gene may increase offspring
1168 resource uptake during pregnancy in the horse and a viviparous lizard, *Pseudemoia*
1169 *entrecasteauxii*, where it is recruited to the placenta (Griffith, Brandley et al., 2017).

1170

1171 (4) Genes involved with embryonic water, gas, and nutrient transport

1172 Water transport in animals is regulated by a family of molecular water channels called
1173 aquaporins (AQs or AQPs) (Borgnia et al., 1999). In humans, *AQP1*, *AQP3*, *AQP4*, *AQP8* and

1174 *AQP9* are found in the placenta but further research is needed to understand how these influence
1175 water fluxes between maternal and fetal tissues (Damiano, 2011). Transcriptomic analysis on
1176 uterine tissue of the gestating, viviparous skink, *Chalcides ocellatus*, reveal differential
1177 expression of *AQP1*, *AQP3*, *AQP5*, *AQP6*, *AQP8*, *AQP9* and *AQP11* when compared to non-
1178 gestating uteruses (Brandley et al., 2012). In birds, *AQP1* is expressed in the chorioallantoic
1179 membrane, and it is suggested to influence angiogenesis throughout embryonic development
1180 (Ribatti et al., 2002). In a viviparous lizard, *Pseudemoia entrecasteauxii*, *AQP8* and *AQP9* were
1181 more highly expressed in the chorioallantoic placenta compared to the yolk-sac placenta (Griffith
1182 et al., 2016). During gestation in both oviparous and viviparous populations of the reproductively
1183 bimodal skink, *Saiphos equalis*, several genes involved with water homeostasis are upregulated
1184 in the uterus including *AQP1*, *AQP3* and *AQP12B* (Foster et al., 2020). In uteruses of *Saiphos*
1185 *equalis*, *AQP5* and *AQP8* are upregulated during oviparous late gestation compared to viviparous
1186 late gestation. In sheep, *AQP3* is differentially expressed during gestation, where it serves a dual
1187 role of water transport to the embryo and fetal urea export (Johnston et al., 2000). This is similar
1188 to the function of *AQP9* in humans (Damiano, 2011). Immunocytochemistry reveals that *AQP1*
1189 and *AQP3* are expressed in the uterus of the highly placentrophic South American scincid lizard,
1190 *Mabuya sp.* (Wooding et al., 2010). In *Zootoca vivipara*, *AQP9* is upregulated at midgestation
1191 (Recknagel et al., 2021a).

1192 Some molecules are implicated in the regulation of aquaporins including insulin (INS),
1193 human chorionic gonadotropin (HcG), cyclic adenosine monophosphate (cAMP) and cystic
1194 fibrosis transmembrane conductance regulator (CFTR) (Damiano, 2011). Genes predicted to be
1195 involved with reproduction in *Anolis carolinensis* are enriched for the GO term for cAMP-
1196 mediated signaling (Alföldi, Di Palma, et al., 2011). Further comparative research should be

1197 done to elucidate the functional differences of aquaporins in oviparous and viviparous amniotes
1198 and how they relate to the differing conditions under which these embryos develop.

1199 Genes involved embryonic oxygen transport precede the origin of amniotes. Hemoproteins
1200 arose in evolutionary history well before they were used for placental oxygen transfer (Hardison
1201 1998). In mammals, adult (Alpha: HBA; Beta: HBB, HBD) and embryonic hemoglobins (Alpha:
1202 HBZ, HBA; Beta: HBE, HBG, and HBH) are involved with oxygen transport (Carter, 2012).
1203 Some of these are unique to eutherian mammals following a series of duplication events (Opazo
1204 et al., 2008). However, fetal hemoglobins are found in turtles, lizards, and snakes (Pough, 1980).
1205 HBA, HBB and HBM are all significantly downregulated in the uterine tissue of the viviparous
1206 African Ocellated Skink, *Chalcides ocellatus*, during gestation compared to non-gestation
1207 (Brandley et al., 2012). The oxygen demands of reptile embryos are relatively low until stage 30,
1208 when most oviparous taxa oviposit (Shine & Thompson, 2006). In viviparous and oviparous
1209 species with long egg retention, embryonic demand for maternal provision of oxygen and
1210 removal of CO₂ increases at this stage.

1211 Improper water, gas and nutrient exchange can occur due to poor chorioallantoic blood flow
1212 (Wootton et al., 1977). Thus, viviparous taxa require greater degrees of vascularization and
1213 vasodilation to facilitate enhanced requirements for maternal resources compared to oviparous
1214 taxa. Rather than increasing the size of the placenta, increasingly dense blood vessels can support
1215 fetal growth without compromising space for embryonic growth as occurs in some pigs (Ford,
1216 1997; Vonnahme et al., 2002). Embryonic vascularization and vasodilation are dependent on
1217 signals from the endoderm (Jin et al., 2005; Vokes & Krieg, 2002; Wilt, 1965). In oviparous
1218 individuals of *Saiphos equalis*, populations with extended egg retention, there is expansion of the
1219 uterine vascular bed and thickening of the chorioallantoic tissue that supports increased

1220 embryonic growth in the later portion of oviparous gravidity (Parker et al., 2010). In the
1221 viviparous scincid lizard, *Eulamprus quoyii*, angiogenesis, the formation of new blood vessels,
1222 and expansion of the vessel-dense elliptical area of the uterus is associated with supporting
1223 increased embryonic oxygen demand (Murphy et al., 2010).

1224 Several protein-coding genes are known to be involved with angiogenesis, vascularization,
1225 and vasodilation in utero. One study that examined expression patterns across chickens
1226 (oviparous), horses (viviparous), two viviparous squamates, and one oviparous squamate found
1227 that no examined genes for angiogenesis showed a viviparity-specific expression pattern
1228 (Griffith, Brandley et al., 2017). However, other than the chicken, the only oviparous taxa
1229 included in this study was a reproductively bimodal skink, *Lerista bougainvillii* (Griffith,
1230 Brandley et al., 2017). Alternatively, differential gene expression analyses on oviparous and
1231 viviparous individuals of *Zootoca vivipara*, revealed pathways for angiogenesis enriched in
1232 viviparous female reproductive tissues; and pathways for angiogenesis were enriched across
1233 genes under divergent selection in oviparous and viviparous *Z. vivipara* individuals.

1234 In the uterine tissue of gestating viviparous skinks and rats, several genes for angiogenesis
1235 are upregulated—*EPASI*, *HIF1A* and *VEGFA* (Brandley et al., 2012; Whittington et al., 2015,
1236 2017). Other proteins involved in vascularization and vasodilation in utero include members of
1237 the vascular endothelial growth factor (*VEGF*) gene family, VEGF receptors (*VEGFRs*),
1238 placental growth factor (*PGF*) and nitric oxide synthase (*NOS*) (Blomberg et al., 2010; Chen,
1239 Wang et al., 2015; Gilbert, 2010; Reynolds et al., 2006; Risau, 1997; Torry et al., 2003;
1240 Vonnahme et al., 2001). In *Saiphos equalis*, different homologs of *NOS* experience different
1241 patterns of gene expression across the oviparous and viviparous stages of gestation/gravidity
1242 (Foster et al., 2020). One homolog of *NOS* is upregulated during oviparous late gestation, and

1243 another is upregulated during viviparous late gestation (Foster et al., 2020). Several genes
1244 involved with angiogenesis and vascular morphogenesis are downregulated in the pre-
1245 implantation uterus of a marsupial, the Fat Tailed Dunnart, *Sminthopsis crassicaudata*—
1246 *ADGRA2, ADGRB2, ANGPTL1, EPHB4, ISM1, PDZRN3, RHOJ, TNMD,* and *VEGFD*
1247 (Whittington et al., 2018).

1248 In humans, immune factors are also responsible for increasing embryonic blood supply.
1249 Embryonic non-classical MHC class I molecule, HLA-G, and uterine natural killer (uNK) cells
1250 support increased embryonic blood supply (Moffett & Loke, 2006; Rajagopalan et al., 2006). A
1251 similar pattern of utilizing immune properties to support embryonic blood supply has not been
1252 yet identified in squamates.

1253 Lipids are a main energy source for embryos. Lipoprotein lipase (LPL) is an important
1254 enzyme in lipid transport. LPL is significantly expressed on the syncytiotrophoblasts, specialized
1255 placental cells, of humans (Lindegaard et al., 2005) and the endometrium of cows (Forde et al.,
1256 2011), and pigs (Ramsay et al., 1991), where it plays a role in lipid mobilization. A viviparous
1257 lizard, *Pseudemoia entrecasteauxii*, increases capacity for lipid transport toward the end of
1258 pregnancy (Griffith, van Dyke & Thompson, 2013). The uterine tissue of the yolk-sac placenta in
1259 this species had significantly higher expression of LPL than the uterine tissues of the
1260 chorioallantoic placenta (Griffith, van Dyke & Thompson, 2013), leading the authors to suggest
1261 that the yolk-sac placenta is the major site of lipid transport. LPL expression was not detected
1262 during pregnancy in the viviparous skink, *Chalcides ocellatus* (Blackburn, 1992; Brandley et al.,
1263 2012). Instead, lipid transport may be facilitated by fatty acid binding proteins in this species
1264 (Chmurzyńska, 2006; Brandley et al., 2012). These are also active on mammalian placenta
1265 (Haggarty, 2002).

1266 Apolipoproteins are also suitable candidates for transport of fatty acids, cholesterol, and
1267 phospholipids. Five of these (*APOA1*, *APOA2*, *APOA4*, *APOE*, and *APOM*) and *APOA1BP* are
1268 significantly upregulated in the pregnant uterus of the viviparous skink, *Chalcides ocellatus*
1269 (Brandley et al., 2012). *APOA1BP* is also upregulated in the uterus of the chorioallantoic
1270 placenta and yolk-sac placenta compared to non-gestational uterine tissues in *Pseudemoia*
1271 *entrecaeauxii* (Griffith et al., 2016). Additionally, upregulation of 136 genes that encode solute
1272 carrier proteins (SLCs) in the pregnant uterus of *Chalcides ocellatus* are associated with
1273 transport of inorganic ions, metals, glucose, amino acids, peptides, fatty acids, and carboxylic
1274 acids (Brandley et al., 2012).

1275 Supply of amino acids is required for embryonic development. SLCs have important
1276 transport functions, including the transport of amino acids, and thus they are considered to be
1277 important for gestation (Foster et al., 2022). However, a recent study found no overlap in the
1278 amino acid transporting SLCs upregulated in placentas of viviparous placentrophic vertebrates
1279 studied, which included eight representatives from Mammalia, Reptilia, and Chondrichthyes
1280 (Foster et al., 2022). However, *SLC38A3* was upregulated in all viviparous species except *Rattus*
1281 *norvegicus* (Foster et al., 2022).

1282 Cathepsins and phospholipases are important for uterine secretions for embryonic
1283 development in horses, pigs, sheep, and cattle (Bazer, 1975; Satterfield et al., 2007; Song et al.,
1284 2010). Cathepsins are present in yolk sacs of humans and mice. They function to degrade
1285 proteins to free amino acids (Cindrova-Davies et al., 2017). Two genes for cathepsin L (*CTSL1*
1286 and *CTSL2*) are upregulated in the uterus during gestation in *Chalcides ocellatus* (Brandley et al.,
1287 2012). *CTSL* is also upregulated in the uterus during the pre-implantation phase in the Fat-Tailed
1288 Dunnart, *Sminthopsis crassicaudata* (Whittington et al., 2018), and in the uterus of the

1289 chorioallantoic placenta and uterus of the yolk sac placenta during gestation in *Pseudemoia*
1290 *entrecasteauxii* (Griffith et al., 2016).

1291 In viviparous individuals of the reproductively bimodal lizard, *Saiphos equalis*, many genes
1292 for cellular adhesion are upregulated during late gestation (Foster et al., 2020). The authors
1293 postulated that this helps facilitate maternal-fetal signaling and paracellular transport (Foster et
1294 al., 2020). Gao et al. (2019) identified a set of genes in *Phrynocephalus vlangalii* that were
1295 differentially expressed in the uterus during the stage of placentation and these enriched GO
1296 terms functionally related to the process of placentation. This included an estrogen receptor
1297 (*ESRI*) and two growth factor receptors (*GHR* and *IGFIR*) (Gao et al., 2019).

1298 Finally, the proteomes of the ovary and placenta from obligately placentrophic *Mabuya*
1299 lizards can further serve as a useful resource for examining nutrient provisioning in squamates
1300 (Hernández-Díaz et al., 2017). In the placenta they found protein expression involved with
1301 nutrient metabolism, transport, protein synthesis, and embryonic development (Hernández-Díaz
1302 et al., 2017).

1303

1304 (5) Uterine glands: adenogenesis, placenta development and histotrophy

1305 In addition to their role in eggshell deposition in oviparous taxa, uterine glands also secrete
1306 growth factors and cytokines that support placental development in mammals. In humans, these
1307 include transforming growth factor- β (TGF- β), epidermal growth factor (EGF), vascular
1308 endothelial growth factor (VECG), and leukemia inhibitory factor (LIF) (Hempstock et al.,
1309 2004). In eutherians, TGF- β supports placental development by regulating proliferation and
1310 invasion rates of placental cells lines (Caniggia et al., 2000; Hempstock et al., 2004; Lafontaine
1311 et al., 2011).

1312 Histotrophy (also called histiotrophy) occurs when nutrients are secreted into the uterine
1313 lumen from vesicles of the columnar epithelial cells of the uterus and taken up by the embryo.
1314 Histotrophic nutrient provisioning is documented across amniotes including marsupials
1315 (Whittington et al., 2018), several ungulate taxa (Bazer et al., 2011; Han et al., 2016; Gao et al.,
1316 2009), humans (Burton et al., 2002), and appear to occur in some viviparous squamates (van
1317 Dyke et al., 2014). In humans, histotrophic nutrient provisioning occurs during the first trimester.
1318 The intervillous space is filled with fluid containing uterine gland secretions that get
1319 phagocytosed by the syncytiotrophoblasts and are the initial nutrient source for the fetus (Burton
1320 et al., 2002). Two of these glycoproteins are epithelial mucin (*MUC1*) and glycodefin A (*GdA*)
1321 (Burton et al., 2002). Interestingly, the *MUC15* gene is upregulated during gravidity/gestation in
1322 the uterus of oviparous and viviparous *Saiphos equalis* individuals (Foster et al., 2020). This also
1323 occurs in the chorioallantoic placenta of *Pseudemoia entrecasteauxii* during gestation (Griffith et
1324 al., 2016). Several mucins are expressed in the uterus in non-gravid and gravid samples from
1325 oviparous individuals of *Lerista bougainvillii* and *Lampropholis guichenoti* (Griffith et al.,
1326 2016).

1327 A survey of viviparous squamates with modest to extensive placentrophy revealed
1328 prevalence of histotrophic nutrient provisioning rather than hemotrophy, transfer of nutrients
1329 between maternal and fetal blood streams (Blackburn 2015). Embryos of *Chalcides chalcides*
1330 have extensive placentrophy that supports substantial maternal nutrient provisioning and
1331 histotrophy (Blackburn, 2015a). Histotrophy may lessen parent-offspring conflict and give the
1332 mother the control over nutrient provisioning compared to hemotrophy (Blackburn, 2015b).

1333 *Chalcides ocellatus* has less extensive placentrophy than *C. chalcides* but the gestating uterus
1334 still illustrates expression of many genes associated with organic and inorganic nutrient transport

1335 (Blackburn, 2015a). Multiple *TGF-β* genes are differentially expressed in the uterus during
1336 gestation in *C. ocellatus*, however most these are downregulated compared to non-gestational
1337 uterine tissue (Murphy et al., 2012). The influence of *TGF-β* on placental development and
1338 nutrient provisioning in *Chalcides spp.* remains to be explored to my knowledge. A TGF-β
1339 receptor (*TGFBRI*) was associated with placental development in *Phrynocephalus vlangalii*
1340 (Gao et al., 2019).

1341 Essential to histotrophy is adenogenesis, the generation of endometrial glands. Adenogenesis
1342 allows for the secretion of histotrophs. The period of early development during which
1343 adenogenesis occurs is highly variable among vertebrates but it is required for embryonic
1344 survival (Gray et al., 2001, 2002; Spencer & Bazer, 2004). Some genes involved with
1345 adenogenesis in sheep are insulin-like growth factor 1 (*IGF-1*), *IGF-2*, *PAX2*, *LHX1* (also known
1346 as *LIM1*) and *EMX2*, genes in the abdominal-B HOXA cluster, members of both *Wnt* and
1347 Hedgehog (*Hh*) gene families (Fazleabas et al., 2004), prolactin (*PRL*), fibroblast growth factor 7
1348 (*FGF7*), *FGF10*, *FGFR2IIIb*, hepatocyte growth factor (*HGF*), a receptor tyrosine kinase (*c-*
1349 *Met*), and cadherins (Fazleabas, 2007).

1350 In the gestating uterus of *Chalcides ocellatus*, insulin-like growth factor-binding protein 5
1351 (*IGFBP5*) is one of the most significantly downregulated genes compared to non-gestational
1352 uterine tissue (Brandley et al., 2012). *IGFBP5* is evolutionarily conserved and multifunctional,
1353 with an important role in regulating IGF signaling, including that of *IGF-1* and *IGF-2* (Duan &
1354 Allard, 2020). Other than adenogenesis in sheep, IGFs serve an important role in the growth of
1355 fetal and maternal tissues in mammals (Gibson et al., 2001; Kampmann et al., 2019).

1356 Genes involved with histotrophic secretion in the marsupial *Sminthopsis crassicaudata*
1357 include *AP4SI*, *HYOU1*, and *SRPRA* (Whittington et al., 2018). Nutrient transporters

1358 significantly upregulated at this time are *APOL6* (cholesterol transport (Baardman et al., 2013)),
1359 *PLA2G10* (hydrolysis of fatty acids during pregnancy (Miele et al., 1987)) and a wealth of SLCs
1360 (solute carrier proteins for transport of sugar, ions, anions, glucose, fatty acids, calcium and zinc
1361 (Whittington et al., 2018)). Subsequent research has identified downregulated of *HYOUI* at early
1362 and mid-gestation; and downregulation of *SRPRA* at mid-gestation in viviparous *Zootoca*
1363 *vivipara* compared to oviparous (Recknagel et al., 2021a). In a reproductively bimodal skink,
1364 *Saiphos equalis*, *PLA2G10* is upregulated during viviparous late gestation compared to oviparous
1365 late gestation (Foster et al., 2020). Upregulation of SLCs also occurs in the viviparous skink
1366 *Chalcides ocellatus* (Brandley et al., 2012; Van Dyke et al., 2014) and in the uterus during
1367 pregnancy in the grey short-tailed opossum, *Monodelphis domestica* (Hansen, Schilkey & Miller,
1368 2016).

1369 Uterine glands are also important for secretions of eggshell precursors. I speculate that genes
1370 involved with adenogenesis of uterine glands may be similarly used to support histotrophic
1371 nutrient provisioning during transitions to viviparity, but further research is necessary.

1372 Specialized uterine areolar glands are found in some *Mabuya* lizards, a genus with oviparous
1373 species and viviparous species that utilize placentrophy and histotrophy (Corso et al., 1988,
1374 2000; Jerez & Ramírez-Pinilla, 2001; Ramírez-Pinilla, 2006; Vieira et al., 2007; Visser, 1975).

1375 Transcriptomic research focused on histotrophic nutrient provisioning, placental development,
1376 and secretions of eggshell precursors in oviparous and viviparous *Mabuya spp.* would
1377 complement literature on the genus.

1378

1379 (6) *Discussion & future directions—embryonic nutrients, gas, and water supply*

1380 Many genes for placental functions in mammals have deep origins in vertebrates (Rawn &
1381 Cross, 2008). In pairwise comparisons of different viviparous amniotes, there is overlap in
1382 hormones and proteins (SLC superfamily, insulin-like growth factors, aquaporins and solute
1383 carrier proteins, etc.) involved in uterine remodeling, placentation, and placental transport. While
1384 shared genes are recruited to the uterus across viviparous amniotes (Recknagel et al 2021a), there
1385 are no shared genes recruited to the placenta across viviparous reptiles, mammals, and sharks
1386 (Foster et al., 2022). Evolutionarily, this suggests higher conservation of the regulatory networks
1387 associated with uterine responses to viviparity than placental responses to viviparity. The
1388 relationship of these findings to embryonic nutrient provisioning and the evolution of the
1389 amniotic egg requires further investigation. Supplementary Table 2 illustrates how genes
1390 mentioned in text for water, gas, and nutrient transport are expressed in reproductive tissues of
1391 squamates during gestation and gravidity.

1392 If specific genes or physiological processes impact more than one of the Main Five
1393 categories, it could have a disproportionate influence on transitions. Such an overlap has already
1394 been identified in *Zootoca vivipara*, where 11 genes are associated with both eggshell traits and
1395 gestation length (Recknagel et al., 2021a). The solute carrier (*SLC*) gene superfamily is involved
1396 with both nutrient transport (Brandley et al., 2012; Whittington et al., 2018) and eggshell
1397 deposition (Yang et al., 2020). Adenogenesis is essential for histotrophic nutrient provisioning
1398 and secretion of eggshell precursors. Additionally, progesterone production influences both
1399 uterine quiescence, which is an important state to maintain in lengthened embryonic retention,
1400 and it also inhibits hepatic vitellogenesis, an important process for lecithotrophic nutrient
1401 provisioning. Thus, examining the role of *SLC* gene superfamily members, processes of

1402 adenogenesis, and progesterone production during embryonic development in oviparous and
1403 viviparous squamate may reveal how interconnectivity of the Main Five are.

1404

1405 **V. Embryonic Calcium Provisioning**

1406

1407 The embryonic growth stage requires the greatest demand of calcium (Ecay et al., 2017;
1408 Packard & Packard, 1984; Stewart & Ecay, 2010). To support this, peak uterine concentrations
1409 of calcium are highest during either eggshell deposition or during the embryonic growth stage, in
1410 oviparous and viviparous taxa, respectively (Linville et al., 2010; Stewart et al., 2009).
1411 Regardless of parity mode, embryonic metabolism drives calcium uptake (Packard & Packard,
1412 1984). The calcium source(s) utilized have clade-specific implications on the genomic and/or
1413 physiological changes required to transition between parity modes.

1414

1415 *(1) Phylogenetic context of embryonic calcium sources*

1416 Calcium can be acquired by the embryo in three forms: calcium carbonate in the eggshell,
1417 calcium bound to proteins and lipids in the yolk, and/or free ionic calcium from maternal
1418 delivery through the placenta (Stewart & Ecay, 2010). These correspond with five calcium
1419 mobilization patterns: 1) Birds, turtles and crocodiles predominately depend on the eggshell; 2)
1420 Most squamates, regardless of parity mode, predominately depend on the yolk; 3) Some
1421 squamate species are reliant on both the eggshell and yolk; 4) Some viviparous squamate species
1422 are reliant on both the yolk and placenta; and 5) therian mammals and rare viviparous squamates
1423 predominately depend on the placenta (Blackburn, 2015a; Hoenderop, Nilius, & Bindels, 2005;
1424 Jenkins & Simkiss, 1968; Kovacs, 2015; Packard, 1994; Packard & Seymour, 1997; Stewart et

1425 al., 2009, 2009; Stewart & Ecy, 2010; Thompson, Stewart et al., 1999; Thompson, Stewart, &
1426 Speake, 2000; Ramírez-Pinilla, 2006).

1427 From an evolutionary perspective, squamate eggs might serve as the best models of the
1428 ancestral amniote egg. Unlike birds, oviparous squamates generally rely on yolk calcium rather
1429 than eggshell calcium. The yolk sac of non-avian reptiles is a good model for the transition
1430 between the egg of anamniotes and amniotes (Blackburn, 2020). Taken together and given that
1431 hard calcified eggshells of Archelosaurs are likely derived (as discussed in section III.3)—
1432 squamate eggs may have the closest resemblance to the ancestral amniote egg. Interestingly, to
1433 my knowledge, oviparous squamates do not sequester calcium from the eggshell into the yolk
1434 during incubation (Packard, 1994).

1435

1436 *(2) Hypotheses on calcium mobilization and the evolution of parity modes*

1437 It was hypothesized that predominant reliance on eggshell calcium should constrain lineages
1438 to oviparity because the evolution of viviparity would result in a lost calcium source (hereafter
1439 eggshell calcium constraint hypothesis) (Stewart & Ecy, 2010; Packard et al., 1977; Packard &
1440 Packard, 1984). This hypothesis suggested that viviparity should only evolve in lineages
1441 predominately reliant on yolk calcium (Packard et al., 1977; Packard & Packard, 1984).

1442 Fittingly, birds, turtles and crocodilians generally rely on eggshell calcium, and they are
1443 constrained to oviparity (Anderson et al., 1987). The eggshell calcium constraint hypothesis
1444 holds true for most viviparous squamates that rely heavily on yolk calcium (Stewart & Castillo,
1445 1984; Stewart & Ecy, 2010; van Dyke et al., 2014).

1446 Subsequent research revealed that viviparity is not constrained by a prerequisite reliance on
1447 yolk calcium. Oviparous scincid skinks studied thus far are intermediately reliant on eggshell and

1448 yolk calcium (Linville et al., 2010; Shadrix et al., 1994; Stewart et al., 2009; Stewart &
1449 Thompson, 1993; Thompson et al., 2001). Calcium placentrophy contributes substantially to
1450 embryonic development in several viviparous squamates including *Pseudemoia entrecasteauxii*,
1451 *Eulamprus quoyi*, *Zootoca vivipara*, *Saiphos equalis*, and a species of *Mabuya* lizard (Ecay et al.,
1452 2017; Linville et al., 2010; Ramírez-Pinilla, 2006; Ramírez-Pinilla et al., 2011; Stewart &
1453 Thompson, 1993). These taxa, with the exception of *Zootoca vivipara*, are in the family
1454 Scincidae (Burbrink et al., 2020), which is also the family with the most independent origins of
1455 viviparity in squamates (Blackburn, 1982, 1999; Pyron & Burbrink, 2014).

1456 To understand the breadth of physiological conditions from which oviparity and viviparity
1457 evolve in squamates, future research should examine calcium transport in other lineages. Studies
1458 focused on snakes would be particularly informative given the sparse literature on them.

1459 *Helicops angulatus*, a reproductively bimodal water snake from South America, is an ideal
1460 model for this (Braz et al., 2016). Thus far, many oviparous snakes are known to be
1461 intermediately reliant on yolk and eggshell calcium. This has not precluded viviparity from
1462 evolving in these lineages.

1463 The presence of embryos during extended embryonic retention may trigger positive feedback
1464 stimuli for continued uterine calcium secretions which may support placental calcium transport,
1465 and thus incipient calcium matrotrophy (Stewart & Ecay, 2010). This is postulated to resemble
1466 the hormonal and mechanical stress mechanisms implicated in avian eggshell formation and
1467 uterine calcium secretions (Bar, 2009a; Stewart & Ecay, 2010). The influx of calcium late in
1468 viviparous gestation may be triggered in part by embryonic growth that over distends the uterus.
1469 This is seen in studies on myometrial stretch in mammals when uterine overdistention triggers
1470 spikes in calcium (Kao & McCullough, 1975; and see e.g. Wray et al., 2015).

1471 Dramatic changes to activity in chorioallantois should not be required during parity mode
1472 transitions because these homologous tissues (Metcalf & Stock, 1993) transport calcium
1473 regardless of parity mode (Ecay, Stewart & Blackburn, 2004; Tuan & Scott, 1977; Tuan &
1474 Knowles, 1984; Tuan et al., 1978, 1986). Specialized placental structures in some viviparous
1475 squamates enhance calcium provisioning but specialization is not required for placental calcium
1476 transport (Stewart et al., 2009; Stewart & Ecay, 2010; Thompson et al., 2000). Loss of
1477 chorioallantoic calcium transporting capacity would be disadvantageous to either parity mode.
1478 Growing research reveals that, like mammals, placentrophy and viviparity can evolve
1479 concurrently in squamates (Blackburn, 2015a; Ecay et al., 2017; Stewart & Ecay, 2010).

1480 Placing these previously proposed models in a phylogenetic context, the calcium transport
1481 method of oviparous ancestors likely has an influence on the method of calcium transport used
1482 for viviparous taxa—matrotrophic calcium provisioning, lecithotrophic calcium provisioning, or
1483 a combination of the two. Consistent with the basal cap hypothesis—when viviparity arises from
1484 oviparous ancestors with embryos that depended predominately on eggshell calcium, this should
1485 favor a transition to viviparity via incipient calcium matrotrophy because the chorioallantois
1486 already plays the major role in transporting calcium from the eggshell to the embryo. Since the
1487 reproductive mode and calcium provisioning of oviparous ancestors are essentially unknown,
1488 researchers can use the closest oviparous relatives as proxies. Similarly, viviparous taxa that are
1489 in close phylogenetic proximity to oviparous taxa that depend on lecithotrophic calcium
1490 provisioning should remain reliant on yolk calcium. Together, these guidelines provide a
1491 framework from which researchers can form hypotheses about the calcium provisioning method
1492 of a viviparous lineage if the calcium provisioning method of oviparous close relatives are
1493 known, or vice versa. Measurements of the proportional contribution of different calcium sources

1494 during development has only been done in select taxa (e.g. Packard, 1994; Stewart, 2013;
1495 Stewart & Ecy, 2010; Stewart, Ecy & Blackburn 2004). Once validated, the framework (i.e.,
1496 the calcium provisioning method of close relatives) can help increase the speed at which science
1497 measures and infers the evolutionary history of calcium provisioning across amniotes and
1498 squamates. Collection of this data across the squamate phylogeny may enable assignment of
1499 these hypotheses to specific clades.

1500 Embryonic calcium source could have implications on the physiological changes required to
1501 transition between parity modes. Reliance on yolk calcium should render, essentially, no
1502 mechanistic changes for calcium transport. On the other hand, incipient calcium matrotrophy
1503 requires regulatory changes in the uterus, like timing of calcium secretions (Griffith et al., 2015).
1504 However, regardless of parity mode 1) the uterus secretes calcium, 2) the chorioallantois
1505 transports calcium and 3) embryonic metabolism drives uptake of calcium. Assuming maternal
1506 tissue remains responsive to embryonic metabolism, the joint evolution of matrotrophic calcium
1507 provisioning with viviparity may require little to no physiological adjustments.

1508 The diversity of embryonic calcium provisioning patterns in viviparous squamates may not
1509 be fully explained by the eggshell calcium constraint hypothesis (Packard et al., 1977; Packard &
1510 Packard, 1984) or incipient calcium matrotrophy (Stewart & Ecy, 2010). Both hypotheses
1511 implicitly assume that viviparity equates to a lost eggshell. In one viviparous squamate, *Haldea*
1512 *striatula*, and in viviparous populations of two reproductively bimodal lizards, *Zootoca vivipara*
1513 and *Saiphos equalis*, the calcified eggshell is considered as a component of the placenta (Stewart,
1514 2013). Some other viviparous squamates have transient calcified patches on their embryonic
1515 membranes (Blackburn, 1998; Heulin, 1990, 2005; Qualls, 1996) suggesting that uterine calcium
1516 secreting capabilities in early gestation may be retained in some viviparous lineages. In the case

1517 of reversals, it remains unknown how the uterus shifts back to early calcium secretions after
1518 ovulation (Blackburn, 2015b; Griffith et al., 2015).

1519

1520 *(3) Embryonic calcium provisioning mechanisms*

1521 In vertebrates, specialized tissues that recover environmental calcium and transport it into
1522 blood circulation maintain conserved mechanisms for intracellular calcium transport (Bronner
1523 2003; Hoenderop et al., 2005). These include the uterus, chorioallantoic tissues, and yolk
1524 splanchnopleure (Bronner, 2003; Hoenderop et al., 2005; Stewart, 2013). Therefore, uterine and
1525 embryonic tissues may be pre-adapted for maternal and embryonic calcium provisioning.

1526 In birds, a sub-compartment of the mammillary layer of the eggshell is the calcium reserve
1527 body (Chien et al., 2009), which contains microcrystals of calcite that get dissolved and
1528 transported as calcium to the embryo (Chien et al., 2009). Calcium is eroded from the eggshell
1529 by acid released from villus cavity cells (VCCs) in chorioallantoic membrane (Anderson, Gay,
1530 and Schraer, 1981; Narbaitz et al., 1981; Packard & Lohmiller, 2002; Simkiss, 1980). This
1531 increases the carbonic anhydrase activity of the cells enabling calcium to be released into the
1532 cavity between the eggshell and the chorionic epithelium, where it is taken up by capillary
1533 covering cells (CCCs) in chorioallantoic membrane (Coleman & Terepka, 1972). In some
1534 species this erosion leads to a gradual weakening of the eggshell that facilitates hatching (Chien,
1535 Hincke & McKee, 2008). In chickens, transcalcin, a calcium binding protein, is credited for the
1536 calcium transporting capacity of the chorioallantoic membrane (Tuan & Knowles, 1984; Tuan &
1537 Ono, 1986; Tuan & Scott, 1977; Tuan et al., 1978, 1986). The presence of VCCs and CCCs in
1538 the chorioallantois of viviparous squamates would indicate a known route through which calcium
1539 can be absorbed.

1540 Transcellular calcium transport has been modeled as a three-step process involving proteins
1541 calbindin-D9K, calbindin-D28K, and the highly calcium-specific ion channels of the transient
1542 receptor potential vanilloid gene family (*TRPV5* and *TRPV6*) (Stewart & Ecaj, 2010). Across
1543 vertebrates, this machinery is shared in epithelial tissues with significant roles in calcium
1544 transport (Hoenderop et al., 2005). Estrogen and vitamin D3 have regulatory roles in this
1545 process.

1546 Calbindin-D9K, calbindin-D28K, *TRPV5*, and *TRPV6* is involved with calcium exchange in
1547 multiple organs of birds, squamates, and mammals. Broadly, activity of calbindin-D9K and/or
1548 calbindin-D28K is associated with patterns of calcium absorption in the mammalian kidney and
1549 uterus (Bindels, 1993; Luu et al., 2004), murine uterus and placenta (Lafond & Simoneau, 2006;
1550 Koo et al., 2012), and chicken duodenum and uterus (Bar, 2009b; Yang et al., 2013). In humans,
1551 calbindin-D9K and calbindin-D28K are critical to the active transport of Ca²⁺ across placental
1552 cells (Faulk & McIntyre, 1983; Belkacemi, Simoneau & Lafond, 2002; Belkacemi et al., 2004).
1553 A study on rats suggests that calbindin-D9K increases by over 100-fold in the last 7 days of
1554 gestation (Glazier et al., 1992), when the embryo gains the majority of calcium. *TRPV6* is
1555 involved with maternal-fetal calcium transport in mice (Suzuki et al., 2008). Increased *TRPV6*
1556 and calbindin-D28K expression occurs during eggshell formation in chickens (Yang et al.,
1557 2013). Given the involvement of these genes in both eggshell deposition and embryonic calcium
1558 transport, squamates may have exploited this pathway to support transitions. Expression of these
1559 genes during gestation or gravidity in squamates has been detected (e.g. calbindin-d9K in
1560 *Saiphos equalis*, and calbindin-d28k in *Zootoca vivipara*) (Foster et al., 2020; Recknagel et al.,
1561 2021a), and is expanded upon in the following paragraphs.

1562 In several highly matrotrophic lizards, embryonic uptake of calcium is associated with
1563 placental expression of calbindin-D28K (Stewart et al., 2009; Stinnett et al., 2011, 2012). In both
1564 oviparous and viviparous embryos of *Zootoca vivipara*, sharp increase in calcium uptake in late
1565 development coincides with increased calbindin-D28K and PMCA by the chorioallantois
1566 (Stewart et al., 2009, 2011). In oviparous corn snakes, *Pantherophis guttatus*, expression of
1567 calbindin-D28K in the yolk-sac and chorioallantoic membrane coincides with growth of these
1568 tissues and calcium transport activity (Ecay et al., 2004). The chorioallantois of other lizards and
1569 snakes transport calcium to the embryo and express calbindin-D28K and PMCA (Blackburn,
1570 2004; Ecay et al., 2004; Stewart et al., 2010; Stinnett et al., 2012).

1571 Viviparous embryos of *Zootoca vivipara*, a reproductively bimodal lizard, incubated *ex utero*
1572 respond to availability of calcium by increasing expression of calbindin-D28K (Ecay et al.,
1573 2017). In this species, embryonic recognition of environmental calcium stimulates a transcellular
1574 calcium transporting mechanism and may also alter chorioallantoic membrane paracellular
1575 permeability to calcium (Ecay et al., 2017). The authors proposed that there is a calcium sensing
1576 receptor (CaSR) on chorionic epithelial cells to support this in both oviparous and viviparous
1577 *Zootoca vivipara* embryos (Ecay et al., 2017), similar to the CaSRs expressed by vertebrate cells
1578 involved in calcium homeostasis (Brennan et al., 2013).

1579 As mentioned earlier, PMCA activity is associated with eggshell deposition in birds and
1580 oviparous squamates (Bar, Rosenberg, & Hurwitz, 1984; Hincke et al., 2012; Wasserman et al.,
1581 1991). PMCA is also crucial for calcium transport in late embryonic development in rats (Glazier
1582 et al., 1992). In viviparous scincid lizards, *Niveoscincus metallicus*, *N. ocellatus*, and
1583 *Pseudemoia spenceri*, PMCA was expressed in uterine glandular and surface epithelia during
1584 pregnancy but only *P. spenceri* expressed it throughout gestation (Herbert et al., 2006). When

1585 PMCA was not detected by immunoblotting in the yolk splanchnopleure of *Haldea striatula*, a
1586 viviparous snake that relies predominately on yolk calcium (Stewart, 1989; Fregoso, Stewart, &
1587 Ecay, 2010), NCXs were proposed as an alternative transporter of calcium (Fregoso et al., 2012).
1588 NCXs are important for placental calcium transport in humans (Belkacemi et al., 2005).

1589 Calcitropic hormones, those involved with calcium transport, and phosphotropic hormones,
1590 those involved with phosphorous transport, operate via an interconnected pathway (Andrukhova
1591 et al., 2016; Biber, Hernando & Forster, 2013; Blaine, Chonchol & Levi, 2015; Erben &
1592 Andrukhova, 2015). Phospho- and calcitropic hormones are important regulators of fetal serum
1593 mineral concentrations (Kovacs, 2015). Evidence from viviparous amniotes suggests that these
1594 are suitable candidates for embryonic calcium provisioning. In mice, genes encoding parathyroid
1595 hormone (*PTH*) and *PTH*-related peptide (*PTHrP*) are important regulators of placental calcium
1596 transport (Kovacs et al., 1996; Simmonds et al., 2010). A non-exhaustive list of additional
1597 candidates for embryonic calcium provisioning include fibroblast growth factor 23 (Bar, 2009a;
1598 Erben & Andrukhova, 2015; Stewart & Ecay, 2010), the annexin gene family (Matschke et al.,
1599 2006), carbonic anhydrase (Narbaitz et al., 1981; Tuan & Knowles, 1984), and calcium binding
1600 proteins (CaBPs) can be found in the referenced literature.

1601

1602 (4) *Discussion & future directions—calcium provisioning and parity mode evolution*

1603 Phylogenetic frameworks enable researchers to make broader testable hypotheses about the
1604 evolutionary history of calcium provisioning in specific clades. Such a framework is proposed in
1605 section V.2 to infer ancestral parity modes in the context of calcium provisioning in amniotes.
1606 Implications gleaned from taxon-specific studies can be explored in distantly related analogous
1607 groups.

1608 Genes involved with calcium transport in uterine and embryonic tissues have been described
1609 across mammals, birds, and reptiles. Like other amniotes, activity of calbindin-D28K and PMCA
1610 supports embryonic calcium provisioning across diverse oviparous and viviparous squamates.
1611 Their involvement with both eggshell deposition and embryonic calcium provisioning makes
1612 these particularly interesting candidates for parity mode evolution. The regulatory influence of
1613 other molecules in calcium transport, like *PTH*, *PTHrP* and NCXs has not been evaluated
1614 thoroughly in squamates. Additional reviews on mechanisms of embryonic calcium provisioning
1615 in squamates can be found in the literature (Stewart, 2013; Stewart & Eday, 2010).

1616 Additionally, I add a speculation. Perhaps lineages with incipient calcium matrotrophy more
1617 feasibly reverse to oviparity because of the continued role of the uterus in calcium provisioning.
1618 However, this hypothesis only holds up if maternal provisioning of calcium is not synonymous
1619 with maternal provisioning of all nutrients.

1620

1621 **VI. Maternal-Fetal Immune Dynamics**

1622

1623 Medawar (1953) pointed out the paradigm between the peripheral body's normal attack
1624 response to allografts (foreign tissue) and uterine tolerance to embryos (Medawar, 1953). This
1625 was inspired by earlier work by Ray Owen (Owen, 1945). Stricter regulation of the maternal and
1626 fetal immune systems is expected for viviparous reproduction because of contact between uterine
1627 and embryonic tissues. Oviparity may pose less of an immunological challenge. Medawar
1628 suggested barriers, inertness and/or immunosuppression enable pregnancy. This formed the
1629 foundation of decades of medical research on immune dynamics between maternal, embryonic,
1630 and paternal immune factors in utero.

1631 In recent years, there was a call for a reappraisal of Medawar’s paradigm (Chaouat, 2010,
1632 2016; Moffett & Loke, 2004, 2006; Mor et al., 2011; Stadtmayer & Wagner, 2020b; Yoshizawa
1633 2016). Moffett & Loke (2006) caution against conceptualizing embryos as analogs of allografts.
1634 To my knowledge, this perspective has yet to reach the evolutionary literature on squamate
1635 parity mode evolution (Foster et al., 2020; Graham et al., 2011; Gao et al., 2019; Murphy &
1636 Thompson, 2011; van Dyke, Brandley, & Thompson, 2014; Murphy, Thompson, & Belov, 2009;
1637 Recknagel et al., 2021a). Importantly, challenges to Medawar’s paradigm do not preclude
1638 immunological responses to viviparity. They simply suggest that the immune environment of the
1639 uterus is uniquely evolved to support exposure to foreign tissue.

1640 The uterine immune system has a distinct evolutionary history from the periphery. It enables
1641 cooperative dynamics with foreign tissues. It supports fertilization and early embryonic
1642 development. This should have started evolving, distinct from the periphery, since internal
1643 fertilization first originated. To contextualize this, I discuss the changing landscape of
1644 immunological research at the maternal-fetal interface and what it means in the context of
1645 amniote parity mode evolution. Overall, I hope readers consider how the uterus evolved to
1646 support internal gestation, and which model systems may be appropriate to investigate this.

1647 Most literature on maternal-fetal immune dynamics limits itself to mammals. Squamates may
1648 serve as a better comparative model for understanding the evolution of the uterine immune
1649 system. Active research on the peripheral reptilian immune system (Zimmerman et al., 2010,
1650 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et al., 2017;
1651 Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights on this.

1652

1653 *(1) Comparing amniote immune systems*

1654 Cellular components of the innate immune system are conserved across jawed vertebrates
1655 (Uribe et al., 2011; Zimmerman et al., 2010). The general machinery of the adaptive immune
1656 system is ancient despite divergences and convergences across all domains of life (Ghosh et al.,
1657 2011; Morales et al., 2017; Müller et al., 2018; Rimer et al., 2014). Diversification of antigen
1658 receptor genes likely occurred independently in a lineage-specific fashion (Boehm et al., 2018).
1659 Compared to mammals, the avian immune system requires less antigen (Larsson et al., 1998).
1660 Birds also have faster but shorter antibody responses, potentially due to their higher body
1661 temperatures (Zimmerman, 2010).

1662 Reptiles have the same general components of the mammalian immune system (Zimmerman,
1663 2020). However, the reptilian immune system may not fit neatly into the two arms of mammalian
1664 immune systems—innate and adaptive (Zimmerman, 2010; 2020). Expanding upon this is
1665 beyond the scope of this review, but it is worth considering in future evolutionary research.
1666 Squamates may serve as a better comparative model for understanding the evolution of the
1667 uterine immune system. Active research on the peripheral reptilian immune system (Zimmerman
1668 et al., 2010, 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et
1669 al., 2017; Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights. I
1670 refer readers to articles by Zimmerman et al. (2010, 2020) and Ghorai et al. (2018), and the book
1671 by Williams (2012) for more information on the avian immune system.

1672

1673 (2) *Medawar's paradigm*

1674 Tolerance toward the foreign fetus was postulated to occur through immunological inertness,
1675 immunosuppression or immunotolerance mechanisms (Medawar, 1953). Theoretically,
1676 immunotolerance could be established if there are relatively small quantities of alloantigens

1677 present, resulting in regulatory responses rather than activating responses (Pradeu, 2011).
1678 Contradicting this, the larger the alloantigen difference between the mother and embryo the
1679 bigger and healthier the placenta is in rats (Chaouat et al., 2010). In humans, divergent HLA
1680 profiles between mother and embryo do not lead to detrimental immune responses (Tilburgs,
1681 Scherjon, & Claas, 2010). Instead, cooperative inflammatory responses between maternal and
1682 fetal tissues support reproduction (Stadtmauer et al., 2020a). In humans, microchimeric cell
1683 populations, presence of cells from one individual in another genetically distinct individual, are
1684 now considered a normal expectation of pregnancy (Nelson, 2012).

1685 In his 1991 Nobel Lecture, Medawar acknowledged that maternal and embryonic tissues
1686 have regular exposure to alloantigens (Medawar, 1991). It has become clear that the maternal
1687 immune system actively responds to fetal alloantigen rather than responding solely with
1688 ignorance or anergy (Arck & Hecher, 2013). Neither maternal immunosuppression/privilege nor
1689 embryonic inertness/immaturity fully explain immune dynamics during gestation in mammals,
1690 including those with the simple epitheliochorial placentation (Chaouat et al., 2010; Chavan,
1691 Griffith & Wagner, 2017; Moffett & Loke, 2004, 2006; Stadtmauer & Wagner, 2020a).

1692

1693 *(3) Perspectives on the evolution of the uterine immune system*

1694 Viviparous reproduction existed eons before the origin of mammals and, to my knowledge,
1695 no evidence suggests there was immune conflict within these taxa (Chaouat, 2016). Placentrophy
1696 existed as far back as the invertebrate clade Bryozoa (Ostrovsky, 2013; Schwaha et al., 2019),
1697 suggesting an ancient history for supportive maternal-fetal immune dynamics. Differing from
1698 Medawar's paradigm, Polly Matzinger, who proposed the 'danger model' for the immune system

1699 (Matzinger, 2007), wrote “Reproduction cannot be a danger. It does not make evolutionary
1700 sense” (Chaouat, 2016).

1701 In mammals, immunological cells at the maternal-fetal interface may not function through
1702 self-non-self-discrimination, as they are understood to function in the rest of the body (Chaouat,
1703 2016; Moffett & Loke 2004, 2006). The ‘maternal-fetal interface’ may be better conceptualized
1704 as ‘maternal-fetal intra-action’ given the dynamics between maternal and fetal immune systems
1705 in mammals (Yoshizawa, 2016). It is unclear if these insights apply to other viviparous amniotes.

1706 In mammals, immune factors in the uterus and placenta appear to be specifically evolved to
1707 support maternal-fetal immune dynamics. Several cell types have unique functions and/or
1708 phenotypes in utero—uterine NK (uNK) cells, uterine macrophages, uterine T regulatory cells
1709 (Faas & de Vos, 2017; Mold et al., 2008, 2010; Mold & McCune, 2011). An immunosuppressive
1710 antigen, HLA-G, is almost exclusively expressed by trophoblasts (Faulk & Temple, 1976;
1711 Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al., 1997). Taken from an
1712 evolutionary perspective, this suggests that the uterine immune system in viviparous mammals
1713 evolved unique responses to allogenic tissues that differ from the periphery. Whether the
1714 evolution of this system predates mammals remains to be explored, to my knowledge.

1715 It is suggested that viviparous reproduction is immunologically compatible in species with
1716 less active adaptive immune system, like sharks (Chaouat, 2016). In these clades, innate immune
1717 cells, like uNK cells, may be sufficient to regulate immune responses during pregnancy (Moffett
1718 & Loke, 2004; Chaouat, 2016). Given that there is an unclear distinction between the innate and
1719 adaptive immune system in reptiles (Zimmerman, 2020), determining immunological difficulty
1720 of evolving viviparity in squamates requires further investigation.

1721 In uterine tissue of oviparous and viviparous skinks maternal antigens are expressed prior to
1722 and during gestation and gravidity (Murphy et al., 2009), but the viviparous species in the study
1723 have a unique expression profile of MHC antigens which may ‘hide’ the embryo from the
1724 maternal immune system (Murphy et al., 2009). Similarly, in a reproductively bimodal skink,
1725 *Saiphos equalis*, both oviparous and viviparous gestation is associated with expression of MHC
1726 genes (Foster et al., 2020). Regardless of parity mode, *S. equalis* expresses genes associated with
1727 immunocompetence, including MHC genes including *H2-EA* (Foster et al., 2020). The similar
1728 profile between the oviparous and viviparous state is attributed to the use of very long egg
1729 retention utilized by oviparous *S. equalis* (Foster et al., 2020). This highlights that extended
1730 embryonic retention is accompanied with immunological responses in utero, which is relevant to
1731 the EER model on amniote origins.

1732 Some of these genes expressed by *S. equalis* are also expressed in viviparous *Chalcides*
1733 *ocellatus* during gestation including complement component genes (C3, C9) and MHC genes
1734 (Brandley et al., 2012; Foster et al., 2020). The majority of immune genes expressed during
1735 gestation/gravidity in *S. equalis* have immunoglobulin receptor binding functions (Foster et al.,
1736 2020), an important feature of eutherian pregnancy that prevents rejection of the fetus through
1737 actions of the maternal innate immune system (Alijotas-Reig, Llurba, Gris, 2014)). In another
1738 reproductively bimodal skink, *Zootoca vivipara*, immune system response genes are enriched in
1739 the set of genes under divergent selection in oviparous and viviparous genomes (Recknagel et al.,
1740 2021a).

1741

1742 (4) *Implications of the reptilian immune system and morphology on parity mode evolution*

1743 Ectothermic reptiles may inherently have a more tolerogenic uterine environment compared
1744 to mammals due to their slower antibody response. It can take up to six weeks to reach peak
1745 concentrations (Ingram & Molyneux, 1983; Grey, 1963; Marchalonis et al., 1969; Pye et al.,
1746 2001; Origgi et al., 2001; Work et al., 2000). A slower metabolism also makes several reptiles
1747 more tolerogenic to pathogens (Ghorai & Priyam, 2018).

1748 During pregnancy in the viviparous skink, *Chalcides ocellatus*, there is a reduced response to
1749 in vitro exposure to mitogens concanavalin A (Con A), phytohemagglutinin (PHA), and
1750 *Escherichia coli* lipopolysaccharide (LPS) (Saad & El Deeb, 1990). Oviparous lizards exhibit
1751 immune activation tradeoffs during reproductive cycles (Cox, Peadar, & Cox, 2015; Durso &
1752 French, 2018; French, Johnston, & Moore, 2007; Uller, Isaksson, & Olsson, 2006).

1753 In the majority of viviparous squamates, the eggshell membrane is absorbed during
1754 pregnancy (Blackburn, 1993). In mammals, epitheliochorial placentation (the most superficial
1755 and non-invasive placenta type) is sufficient to cause immunorecognition from the mother.
1756 Specialized placental cells, trophoblasts, may be more common in other viviparous vertebrates
1757 than previously recognized (Blackburn, 2015a). For example, a gene with fusogenic properties
1758 characteristics of trophoblast syncytins was recently identified in the *Mabuya* lizard placenta
1759 (Cornelis et al, 2017). In mammals, trophoblasts are antigen presenting and actively participate
1760 in maternal-fetal immune dynamics.

1761 A few viviparous squamates have placentas with characteristics similar to placentas found in
1762 eutherian mammals—syncytialized cells layers, specialized zones such as areolae and
1763 placentomes, or cellular invasion of maternal tissues by the fetus (Blackburn & Flemming, 2012;
1764 Jerez & Ramírez-Pinilla, 2001; Vieira et al., 2007). The increased contact here may require more

1765 tightly regulated immune dynamics at the maternal-fetal interface compared to other viviparous
1766 squamates.

1767

1768 (5) *The inflammation paradox*

1769 In mammals, implantation evolved from an ancestral inflammatory attachment reaction
1770 (Griffith, Chavan et al., 2017). Inflammation is the most crucial system to support implantation,
1771 but it is also the greatest threat to the continuation of pregnancy (Chavan et al., 2017). This
1772 phenomenon is called the inflammation paradox. In humans, immune cells including uterine
1773 macrophages, T cells of multiple subtypes, uterine natural killer (uNK) cells, dendritic cells, and
1774 natural killer T (NKT) cells increase until implantation and remain abundant in the uterus
1775 throughout first trimester (Bulmer et al., 1991; Bulmer, Williams & Lash, 2010). Early
1776 implantation in humans is characterized by high pro-inflammatory T helper (Th)-1 cells and
1777 cytokines (IL-6, IL-8, and TNF α) (Yoshinaga, 2008). The exploitation of inflammatory
1778 mechanisms for eutherian implantation and the shift toward non-inflammatory activity to
1779 maintain pregnancy may have been key in enabling extended embryonic retention of eutherians
1780 (Griffith, Chavan et al., 2017).

1781 How the inflammation paradox applies to viviparous squamates is unclear, given that
1782 placentation in squamates and mammals is not homologous (Griffith, Van Dyke, & Thompson,
1783 2013). In extrauterine pregnancies of mammals with non-invasive placentas, the embryo will
1784 invade extrauterine tissue because it is not inhibited by uterine secretions (Vogel, 2005; Samuel
1785 & Perry, 1972). However, in *Pseudemoia entrecasteauxii*, a viviparous skink that also has a non-
1786 invasive placenta, extrauterine pregnancy does not result in invasive implantation of extrauterine
1787 tissues (Griffith, Van Dyke, & Thompson, 2013). The inherent invasive nature of mammalian

1788 embryos outside of the uterus, compared to the non-invasive nature of viviparous squamate
1789 embryos studied thus far, suggests that the parent-offspring conflict and the inflammation
1790 paradox may be less pronounced in viviparous squamates compared to viviparous mammals.

1791

1792 *(6) Inertness and barriers at the maternal-fetal interface*

1793 The uterine environment is not inert or sterile (Agostinis et al., 2019; Erlebacher, 2013;
1794 Moffett & Loke, 2006; Munoz-Suano, Hamilton, & Betz, 2011; Murphy, Thompson, & Belov,
1795 2009; Yoshimura, Okamoto, & Tamura, 1997). In humans, the decidual layer of the uterus
1796 during pregnancy is comprised of ~40% leukocytes (Ander, Diamond, & Coyne, 2019; Manaster
1797 & Mandelboim, 2010). This cellular subpopulation has 70% uNK cells, 10-20% antigen
1798 presenting cells (APCs) including macrophages and dendritic cells, and 3-10% T cells of several
1799 subtypes (Abrahams et al., 2004; Hanna et al., 2006; Kämmerer et al., 2006; Le Bouteiller &
1800 Piccinni, 2008; Liu et al., 2017; Manaster & Mandelboim, 2010; Moffett-King, 2002; Moffett &
1801 Loke, 2006; Roussev et al., 2008). There is an abundance of decidual large granular lymphocytes
1802 (LGLs), CD3-NK cells and CD3+ activated cytotoxic T cells, in the human uterus, that have
1803 cytotoxic properties and produce cytokines, and these are affected by fetal MHC molecules
1804 (Rieger, 2002).

1805 Birds also have immunocompetent cells in their oviducts. T and B cells are present in
1806 chicken ovary where they are stimulated by estrogen (Barua & Yoshimura, 1999; Withanage et
1807 al., 2003; Zettergren & Cutlan, 1992). Other immunocompetent cells in the chicken oviduct
1808 include IgG+, IgA+ and CD3+ (Yoshimura, Okamoto, & Tamura, 1997). Immune competent
1809 cells located throughout the mucosal tissue of avian oviductal segments including macrophages,

1810 antigen presenting cells (APCs) expressing MHC class II antigens, helper T cells and cytotoxic T
1811 cells, and premature B cells (Das, Isobe, & Yoshimura, 2008).

1812 Inert barriers between maternal and fetal tissues may 'hide' the embryo. In oviparous taxa,
1813 the eggshell may serve as a barrier. However, the antimicrobial properties of the eggshell matrix
1814 in birds demonstrate that even the eggshell is not inert. The FAS ligand, also called APO-1 or
1815 CD95, in humans and rodent embryonic tissue was proposed to serve as a barrier because it
1816 causes apoptosis of surrounding maternal immune cells (Kayisli et al., 2003; Makrigiannakis et
1817 al., 2008).

1818 Medawar suggested that an impermeable placenta strictly regulates molecular exchanges,
1819 preventing rejection of the embryo (Medawar, 1991). Syncytiotrophoblasts lack cellular junctions
1820 and thus it was postulated to serve as this barrier (Ander et al., 2019). However, the growing data
1821 on bidirectional cellular traffic of APCs, even in mammals with noninvasive placentas, rejected
1822 this hypothesis (Bakkour et al., 2014; Burlingham & Bracamonte-Baran, 2015; Fujiki et al.,
1823 2008; Turin et al., 2007).

1824

1825 *(7) T cell populations and mammalian viviparity*

1826 In mammals, immune-dynamics at the maternal-fetal interface are established through
1827 innate and adaptive immune responses. There is a delicate balance between ratios of Th1, Th2,
1828 Th17, Tregs and memory T cells at the maternal-fetal interface in eutherian mammals during
1829 gestation (Chaouat et al., 1997; Kieffer et al., 2019; Peck & Mellins, 2010; Saito et al., 2010; Wu
1830 et al., 2014). A shift in utero from T helper type 1 (Th1) cells to T helper type 2 (Th2) cells
1831 during gestation in mammals equates to a shift from pro-inflammation to anti-inflammation. The
1832 galectin proteins, GAL-13 and GAL-14, expressed by syncytiotrophoblasts, bind to T cells

1833 where they inhibit activation, induce apoptosis, and enhance interleukin-8 (IL-8) production
1834 (Balogh et al., 2019).

1835 Growing research is revealing the central role of Tregs at the maternal-fetal interface
1836 during pregnancy in mammals (Teles et al., 2013; Wienke et al., 2019). Tregs play a central role
1837 in immunosuppression in mammals (Attias, Al-Aubodah, & Piccirillo, 2019). Differentiation of
1838 Tregs is governed by the transcription factor, *FOXP3* (Ramsdell & Rudensky, 2020).

1839 Alloantigen-dependent, uterine T cell signaling, and immunocompetent embryonic cells and their
1840 products facilitate enhanced regulatory phenotypes of immune cells overall (Ander et al., 2019).

1841 The T-cell dependent adaptive immune system of mammals is unique. This may have
1842 prompted their intricate balance of Treg mediators of immunotolerance at the maternal-fetal
1843 interface (Chaouat, 2016). Birds rely more heavily on B cells. In non-avian reptiles, T helper
1844 cells are functional, but the presence and function of other T cell subsets is unclear (Zimmerman,
1845 2020; Zimmerman, Vogel, & Bowden, 2010). The potential role of T cells and Tregs in
1846 viviparous squamate gestation should not be discounted. Treg-like cells have been identified in a
1847 pufferfish, *Tetraodon nigroviridis* (Wen et al., 2011), suggesting that Tregs may have an ancient
1848 evolutionary history.

1849

1850 (8) Progesterone, cytokines, and maternal-fetal immune dynamics

1851 In addition to the role of progesterone in uterine quiescence (embryonic retention) and
1852 hepatic vitellogenesis (nutrient provisioning), it also plays a role in maternal-fetal immune
1853 dynamics. In the uterus of pregnant mammals, progesterone concentrations are associated with
1854 altered B cell immunoglobulin secretion, inhibition of NK-cell mediated cytotoxicity and the shift
1855 from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) dominated immune responses

1856 (Druckmann & Druckmann, 2005). Progesterone is also associated with immunomodulatory
1857 effects (Ortega Brown et al., 1990). During gestation in *Agkistrodon piscivorus*, a viviparous pit
1858 viper, progesterone concentrations are associated with decreased complement performance
1859 (Graham et al., 2011), a portion of the immune system that promotes inflammation, among other
1860 immune functions.

1861 In humans, progesterone induced protein (PIBF) is transported by placental extravillous
1862 trophoblasts to maternal lymphocytes causing the induction of interleukin-10 (IL-10) production,
1863 contributing to the Th2 dominant responses (Szekeres-Bartho, Šučurović, & Mulac-Jeričević,
1864 2018). IL-10 is a potent anti-inflammatory cytokine that is produced by multiple cell types
1865 (Zimmerman, Bowden, & Vogel, 2014). It is associated with Th2 response, and it inhibits Th1
1866 responses. The phenotype of uterine macrophages is affected by trophoblasts when they secrete
1867 IL-10 and macrophage colony-stimulating factor (M-CSF) (Svensson-Arvelund et al., 2021). IL-
1868 10 inhibits IFN- γ and increases in response to infection in chickens (Giansanti, Giardi, & Botti,
1869 2006; Rothwell et al. 2004). In the uterus of the oviparous skink, *Lampropholis guichenoti*,
1870 during gravidity and non-gravidity, IL-10 is expressed (Griffith et al., 2016).

1871 Proinflammatory cytokines may be downregulated during reproductive periods to limit
1872 maladaptive immune responses to the foreign fetus (Zimmerman, Vogel, & Bowden, 2010). In
1873 mammals, IL-1 allows release of hormones in human trophoblasts (Petraglia et al., 1990;
1874 Masuhiro et al., 1990; Yagel et al., 1989), facilitates implantation (Haimovici, Hill, & Anderson,
1875 1991; Hill, 1992; Tartakovsky & Ben-Yair, 1991), and influences the initiation of labor (Romero
1876 et al., 1989, 1992). Regulation of the proinflammatory cytokines tumor necrosis factor (TNF)
1877 and interleukin 1B (IL-1 β) is of particular importance in eutherian pregnancy (Haider & Knöfler,
1878 2009; Paulesu, Romagnoli, & Bigliardi, 2005; Saito et al., 2010; Tayade et al., 2006).

1879 The uterine tissue of two reproductively bimodal squamates—viviparous individuals of
1880 *Chalcides chalcides*, and oviparous and viviparous individuals of *Zootoca vivipara*—express IL-
1881 1β (Paulesu et al., 1995, 2005; Romagnoli et al., 2003). In the uterus of the viviparous skink,
1882 *Pseudemoia entrecasteauxii*, during gestation regulation of TNF and IL- 1β at the transcriptional
1883 and post-translation levels, respectively, may reduce inflammation (Hendrawan et al., 2017). The
1884 pro-inflammatory function of IL- 1β in *Pseudemoia entrecasteauxii* may play a role developing a
1885 more complex placenta (Hendrawan et al., 2017). The placenta of *Chalcides chalcides* expresses
1886 pro-inflammatory cytokines, IL- 1α and IL- 1β , at specific times during gestation (Paulesu et al.,
1887 1995). During gestation, *Chalcides ocellatus* also differentially expresses 27 other interleukins
1888 and interleukin related products (Brandley et al., 2012).

1889 The expression of IL-34 in a marsupial, the fat-tailed dunnart, during pre-implantation
1890 (Whittington et al., 2018) may have an immunosuppressive function to help tolerate potential
1891 contact of maternal and fetal tissues when the embryonic shell coat disintegrates (Lindau et al.,
1892 2015). In chickens, IL-34 regulates Th1 and Th17 cytokine production (Truong et al., 2018).
1893 During gestation in *Pseudemoia entrecasteauxii*, IL-16 and IL- 1α are expressed in addition to
1894 three receptors for Th17 family cytokines—IL-17RA, IL-17RC, and IL-17RA (Griffith,
1895 Brandley, et al., 2016, 2017). In the yolk sac of *Pseudemoia entrecasteauxii* during pregnancy
1896 interleukin related molecules, *ILDR1*, *IRAK1*, and *SIGIRR*, are differentially expressed (Griffith
1897 et al., 2016). This profile suggests the presence of tricellular tight junctions and/or tricellulin
1898 (Higashi et al., 2013; Ikenouchi et al., 2005), and regulation of toll-like receptors (TLRs) and/or
1899 IL-1R signaling (Kawagoe et al., 2008; Lin, Lo, & Wu, 2010; Muzio et al., 1997).

1900

1901 (9) *The major histocompatibility complex and maternal-fetal immune dynamics*

1902 A substantial amount of literature on maternal-fetal immune dynamics was focuses on uNK
1903 cells. Uterine NK cells have a distinct phenotype and function from peripheral NK cells. They
1904 have several activating receptors (Manaster & Mandelboim, 2010) but do not exert cytolytic
1905 functions on embryonic trophoblasts that they are in contact with (King, Birkby, & Loke, 1989).
1906 Allorecognition of embryonic placental cells by uNK cells is a key regulator of the maternal-fetal
1907 immune mechanisms that support placentation in mammals (Moffett & Colucci, 2014). When
1908 cells lose their ability to express any HLAs, uNK cells are shown to kill them (Hunt et al., 2005;
1909 Ishitani et al., 2003; King, Allen et al., 2000).

1910 In humans, expression of the classical MHC class I (C-MHCI) molecule HLA-C, and
1911 nonclassical MHC class I (NC-MHCI) molecules HLA-E, HLA-F and HLA-G on trophoblasts
1912 inhibit uNK cell-mediated cytotoxicity (Hunt et al., 2003; King, Burrows et al., 2000). Differing
1913 from this, mismatched HLA-C profiles trigger rejection of the transplanted organs (Petersdorf et
1914 al., 2014). Selection for balanced polymorphisms in HLA-C alleles and their killer
1915 immunoglobulin receptors (KIRs) is proposed to be driven by reproductive success, rather than
1916 immune recognition of pathogens (Trowsdale & Betz, 2006). Dimorphisms of HLA-C emerged
1917 recently within primates (Adams & Parham, 2001).

1918 Similar patterns in MHC profiles have been explored in other viviparous amniotes. C-MHCI
1919 antigen, H2-K, is expressed on giant trophoblast cells of mice and this is attributed to
1920 trophoblast-induced uterine vasculature transformation (Arcellana-Panlilio & Schultz, 1994;
1921 Chatterjee-Hasrouni & Lala, 1982; Hedley et al., 1989; King et al., 1987; Sellens, Jenkinson, &
1922 Billington, 1978). H2-D antigen is co-expressed with H2-K in virtually all their other nucleated
1923 cells (Madeja et al., 2011). However, H2-K expressing trophoblasts lack H2-D expression. This

1924 parallels the expression patterns of C-MHC molecules at the maternal-fetal interface in humans
1925 and may be an evolutionarily conserved pattern (Madeja et al., 2011).

1926 In humans, NC-MHCI molecule, HLA-G, is especially tolerogenic (Carosella et al., 2015;
1927 González et al., 2012; Hviid et al., 2004; Kovats et al., 1990). In adults, HLA-G is almost
1928 exclusively expressed by fetal trophoblasts compared to adult cells (Faulk & Temple, 1976;
1929 King, Burrows et al., 2000; Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al.,
1930 1997). It supports immunotolerance at the maternal-fetal interface (Rebmann et al., 2014). The
1931 role of HLA-G in supporting tolerogenic responses to organ transplants appears to be an
1932 exploitation of its role in immunotolerance in the utero during pregnancy (Rebmann et al., 2014).
1933 HLA-G is upregulated by several molecules that serve essential roles during gestation including
1934 progesterone (Yie, Xiao, & Librach, 2006; Yie et al., 2006), IFN- α , IFN- β , and IFN- γ (Rebmann
1935 et al. 2003; Lefebvre et al., 2001; Ugurel et al., 2001; Yang, Geraghty, & Hunt, 1995), and IL-10
1936 and TGF- β (Cadet et al., 1995; Moreau et al., 1999).

1937 A similar NC-MHCI gene to HLA-G exists in horses (Davies et al., 2006) where it likely
1938 functions to protect the embryo from NK-cell mediated attack (Ott et al., 2014). NC-MHC
1939 molecules with similar structure to HLA-G are also found in Rhesus monkeys (Boyson et al.,
1940 1997) and baboons (Stern et al. 1987). Mice have two NC-MHCI genes that are expressed on the
1941 surface of their placentas and on pre-implanted embryos (Sipes et al., 1996).

1942 In the gestating uterus of the viviparous skink, *Pseudemoia entrecasteauxii*, four putative C-
1943 MHCI and two putative NC-MHCI molecules are expressed (Murphy, Thompson, & Belov,
1944 2009). This pattern resembles the C-MHCI and NC-MHCI expression profiles of mammals,
1945 suggesting that this viviparous skink utilizes a similar physiological mechanism to 'hide' the
1946 embryo (Murphy, Thompson, & Belov, 2009). One of the putative NC-MHCI genes (Psen-

1947 160Ut/Psen-78G) has a substitution at position 150 where a tryptophan is substituted for a
1948 leucine (Murphy, Thompson, & Belov, 2009). When Psen-160Ut/Psen-78G was aligned to NC-
1949 MHC I genes of vertebrates ranging from fish to eutherian mammals, tryptophan was conserved
1950 at position 150 except in Psen-160Ut/Psen-78G and HLA-G (Murphy, Thompson, & Belov,
1951 2009). Whether this reflects an evolutionary history associated with immune tolerance at the
1952 maternal-fetal interface in *Pseudemoia entrecasteauxii* requires further investigation.

1953 MHC I genes are also expressed in reproductive tissues of oviparous skinks (*Ctenotus*
1954 *taeniolatus* and *Lampropholis guichenoti*) during non-reproductive periods and during late
1955 gravidity (Murphy, Thompson, & Belov, 2009). A similar pattern is found in viviparous skinks
1956 *Eulamprus tympanum*, *Niveoscincus metallicus*, *Pseudemoia entrecasteauxii* and the
1957 reproductively bimodal skink *Saiphos equalis* which all express MHC I genes at non-
1958 reproductive periods and during late pregnancy/gravidity (Murphy, Thompson, & Belov, 2009).
1959 MHC gene H2-EA is also expressed during gestation with long egg retention in *Saiphos equalis*.

1960 The butyrophilin subfamily 1 member A (*BTN1A1*) is located in the MHC I region of the
1961 genome in mammals (Trowsdale, 2011). *BTN1A1* is differentially expressed in the uterus during
1962 gestation in a viviparous lizard, *Chalcides ocellatus* (Brandley et al., 2012). *BTN1A1* may have
1963 important antimicrobial properties in chicken eggshells (Mann, Maček, & Olsen, 2006). In
1964 mammals *BTN1A1* is the major protein associated with fat droplets in milk (Jeong et al., 2009).

1965

1966 (10) *Microchimerism and maternal-fetal immune dynamics*

1967 Billingham, Brent and Medawar suggested the concept of actively acquired immunologic
1968 tolerance during pregnancy 70 years ago (Billingham, Brent, & Medawar, 1953; Ribatti, 2015).
1969 Subsequent research over the following decades revealed that substantial transfer of proteins,

1970 parasites and even immunologically active cells occurs between mother and embryo (Adams &
1971 Nelson, 2004; Axiak-Bechtel et al., 2013; Bakkour et al., 2014; Burlingham, 2010; Fujiki et al.,
1972 2008; Gitlin et al., 1965; Khosrotehrani et al., 2005; Owen, 1945; Turin et al., 2007).
1973 Microchimerism, where there is <0.1% donor chimeras in host tissue, is relatively pervasive
1974 among eutherians during pregnancy. It plays a role in establishing tolerance to non-inherited
1975 antigens. For example, cell populations from the mother that are transferred into embryonic
1976 lymph nodes enable the establishment of embryonic Tregs that are tolerogenic toward non-
1977 inherited maternal antigens (Mold et al., 2008).

1978 Microchimeric cellular populations are transferred across all placental types (Axiak-Bechtel
1979 et al., 2013; Bakkour et al., 2014; Fujiki et al., 2008; Khosrotehrani et al., 2005; Turin et al.,
1980 2007). Fetal and maternal cells persist for decades after birth across a range of tissues in mother
1981 and offspring, respectively (Adams & Nelson, 2004; Bakkour et al., 2014; Bayes-Genis et al.,
1982 2005; Bianchi et al., 1996; Evans et al., 1999; Jonsson et al., 2008; Stevens et al., 2004). There is
1983 even a call in the immunology literature to shift from the conventional paradigm of “self vs
1984 other” to instead consider the “self” as inherently chimeric (Nelson, 2012). Given that
1985 epitheliochorial placentation is sufficient to illicit microchimeric cell populations, the occurrence
1986 of similar bidirectional cellular traffic is a reasonable possibility in viviparous squamates.

1987

1988 (11) *Paternal alloantigens*

1989 Under tenants gleaned from transplant medicine, the maternal immune system would illicit
1990 an attack response as early as insemination when maternal tissues are exposed to paternal
1991 alloantigens (Borziak et al., 2016; Schumacher & Zenclussen, 2015; Seavey & Mosmann, 2006).
1992 Instead, maternal cells immunologically recognize them at this time without attack (Schumacher

1993 & Zenclussen, 2015; Seavey & Mosmann, 2006; Zenclussen et al., 2010). Treg expansion, a
1994 process with major influence on maternal-fetal immunotolerance in mammals, is proposed to be
1995 driven by several different factors found in seminal plasma (Baratelli et al., 2005; Teles et al.,
1996 2013). Mothers may maintain fetal-specific Tregs with memory of the paternal alloantigens
1997 (Zenclussen et al., 2010), expediting Treg response in future pregnancies with the same father
1998 (Rowe et al., 2012).

1999 Alloantigen exposure at the time of insemination is not restricted to mammals. Seminal fluid
2000 of chickens contains two MHC I paternal alloantigens and one MHC II alloantigen (Borziak et
2001 al., 2016). It also contains proteins involved in immunity and antimicrobial defenses (Borziak et
2002 al., 2016). In hens, evidence suggests that a protective local immunity to pathogens is established
2003 after exposure to semen but the mechanisms for this remain unclear (Reiber & Conner, 1995;
2004 Reiber, Conner, & Bilgili, 1995).

2005 In mammals, paternal alloantigens and cytokines in seminal fluid drive immune tolerance
2006 (Schjenken & Robertson, 2014). Mammalian seminal plasma contains immune-factors (Kelly,
2007 1995; Schjenken & Robertson, 2014)—TGF- β (Breuss et al., 1993; Chu & Kawinski, 1998;
2008 Slater & Murphy, 1999), IL-8 (Gutsche et al., 2003), and soluble IL-2 receptor (Srivastava,
2009 Lippes, & Srivastava, 1996), prostaglandin E2 (PGE2) and 19-hydroxyprostaglandin E (19-
2010 hydroxy PGE) (Denison et al., 1999), soluble tumor necrosis factor (TNF) receptors (Liabakk et
2011 al., 1993), receptors for the Fc portion of γ -globulin, spermine (Evans, Lee, & Flugelman, 1995),
2012 and complement inhibitors (Kelly, 1995). In horses and pigs, respectively, the proteins CRISP3
2013 (Doty et al., 2011), PSP-I and PSP-II (Rodriguez-Martinez et al., 2010), act as signaling agents
2014 in seminal fluid.

2015 Secretions of growth factors, cytokines and chemokines from cervical and endometrial
2016 tissues immediately following insemination generates a proinflammatory environment that likely
2017 aids in implantation. In the utero-vaginal junction of chickens and the utero-tubal junction of
2018 pigs, expression of several genes were shared following mating compared to non-mating and
2019 these genes were involved with immune-modulation (*IFIT5*, *IFI16*, *MMP27*, *ADAMTS3*, *MMP3*,
2020 *MMP12*) and pH-regulation (*SLC16A2*, *SLC4A9*, *SLC13A1*, *SLC35F1*, *ATP8B3*, *ATP13A3*), a
2021 process essential for implantation (Atikuzzaman et al., 2017, 2015). Instead of mounting an
2022 attack, it appears that the uterine immune system and paternal genes work cooperatively to
2023 support pregnancy in mammals and gravidity in birds. Whether this applies to reptiles, and how
2024 it may influence immune dynamics involved with squamate parity mode evolution, deserves
2025 investigation.

2026

2027 (12) *Discussion and future directions—maternal-fetal immune dynamics & the*
2028 *evolution of parity modes*

2029 Immune processes appear to be important for both oviparity and viviparity—as evidenced
2030 here, in part, by overlapping expression profiles of immune genes in female reproductive tissues
2031 of chickens and pigs, expression of paternal antigens in avian seminal fluid, and uterine
2032 expression of maternal antigens in oviparous and viviparous skinks. This highlights the scientific
2033 advances made since Medawar’s paradigm, when embryos were treated as analogs to allografts.
2034 Nonetheless, viviparity is associated with complex immune dynamics between maternal, fetal,
2035 and paternal tissues.

2036 Overall, evolving appropriate immunological responses is one hurdle of transitions to
2037 viviparity in squamates. This is evidenced by the unique MHC expression profiles identified in

2038 some viviparous skinks compared to oviparous relatives (Murphy et al., 2009); and the detection
2039 of divergent selection in immune response genes in viviparous and oviparous *Zootoca vivipara*
2040 (Recknagel et al., 2021a). Labile parity modes in squamates may be supported if they are more
2041 heavily reliant on the innate immune system for reproduction. However, reptiles may not have
2042 distinguished innate and adaptive immune systems (Zimmerman et al., 2020).

2043 Changes to genes that serve overlapping functions across the Main Five may have a
2044 disproportionate influence on transitions between parity modes. In this section I reviewed two
2045 molecules, *TGF-β* and progesterone, that exert influence on multiple Main Five categories.
2046 Progesterone influences uterine quiescence (embryonic retention), hepatic vitellogenesis
2047 (nutrient provisioning) and regulation of inflammatory responses in utero (maternal-fetal
2048 immune dynamics). Genes in the *TGF-β* family play a role in placental development and
2049 maternal-fetal immune dynamics. *TGF-β* family is implicated in placental development in
2050 eutherians (Hempstock et al., 2004; Caniggia et al., 2000; Lafontaine et al., 2011). A *TGF-β*
2051 receptor protein (*TGFBR1*) was associated with placental development in *Phrynocephalus*
2052 *vlangalii* (Gao et al., 2019). In humans *TGF-β* upregulates tolerogenic HLA-G in utero and is an
2053 immune factor in mammalian seminal fluid. Multiple genes in the *TGF-β* family are also
2054 differentially expressed during gestation in other viviparous lizards, *Pseudemoia entrecasteauxii*
2055 and *Saiphos equalis* (Foster et al., 2020; Griffith et al., 2016). Examining the functions of *TGF-β*
2056 and progesterone across other amniotes may reveal insights into how these molecules influence
2057 the evolution of parity modes.

2058 In mammals, inflammation appears to be involved with two of the Main Five processes—
2059 regulation of maternal-fetal immune dynamics and embryonic retention. It is intriguing to
2060 consider the implications this has for the interconnectedness of the Main Five. Greater

2061 interconnectedness would suggest that changes to few genes involved with the Main Five could
2062 cause a cascading effect to support more labile transitions between parity modes.

2063 Implantation and parturition in therian mammals evolved from a shared inflammatory
2064 attachment reaction (Hansen et al., 2017). The process of implantation has important
2065 implications for maternal-fetal exchanges of inorganic and organic material and maternal-fetal
2066 immune dynamics. Given that inflammation is associated with implantation and parturition
2067 implicates it in gas, water, and nutrient provisioning (including calcium here), maternal-fetal
2068 immune dynamics and length of embryonic retention. However, implantation in mammals and
2069 viviparous squamates is not homologous (Griffith, Van Dyke, & Thompson, 2013). Therefore, it
2070 is difficult to make inferences about how substantial the influence of inflammation is on the
2071 evolution of parity modes in squamates. Nonetheless, the abundant literature on uterine
2072 inflammatory processes during human pregnancy and the evolution of inflammatory processes
2073 that supported the evolution of viviparity in mammals (Challis et al., 2009; Chavan, Griffith, &
2074 Wagner, 2017; Mor et al., 2011; Griffith, Chavan et al., 2017; Stadtmauer & Wagner, 2020a)
2075 serve as indispensable resources for exploring the role of inflammation in squamate viviparity. I
2076 resist expanding on this further. I suspect that the immune system plays a central role in dictating
2077 the plasticity of parity modes. However, further work is necessary to validate this.

2078

2079

2080 **VII. Conclusions**

2081

2082 (1) Through holistic consideration of the unique complexity of parity mode evolution, within
2083 the context of genomic and transcriptomic studies across interdisciplinary fields, this

2084 review provided a new perspective on the history of parity mode transitions in amniotes
2085 and squamates. The overlapping activity of immune genes in utero, genes for calcium
2086 transport, placentation, and hormonal regulation across mammals, birds, and reptiles hint
2087 at discoveries to be made. There is a fascinating history to the evolutionary physiology
2088 and genomics of reproduction in amniotes that is ripe for downstream research.

2089 (2) Changes to gene(s) or physiological processes associated with more than one of the Main
2090 Five should disproportionately influence parity mode evolution—*SLC* gene superfamily,
2091 *TGF-β*, *BMPRI1B*, progesterone, *PMCA*, calbindin-D28K, *SPP1*, sustained functioning of
2092 the corpora lutea and inflammation, and the genes associated with both gestation length
2093 and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).

2094 (3) Growing evidence in the medical literature suggests that immune system interactions at
2095 the maternal-fetal interface in mammals did not evolve simply through tolerance,
2096 evasion, or suppression (Chaouat, 2016; Chavan, Griffith, & Wagner, 2017; Moffett &
2097 Loke, 2004, 2006). Instead, maternal-fetal immune dynamics have a deep evolutionary
2098 history that enables both embryo and mother interact cooperatively (Yoshizawa, 2016).
2099 Future research on amniote parity mode evolution should consider maternal-fetal immune
2100 dynamics in this context. Nonetheless, viviparity and extended embryonic retention are
2101 assuredly associated with immunological responses in squamates (e.g. Foster et al.,
2102 2020).

2103 (4) Compared to viviparous endothermic amniotes, ectothermy likely influences parity mode
2104 evolution differently because it entails slower antibody responses and a greater reliance
2105 on climatic conditions for embryonic development. This and the Cold Climate
2106 Hypothesis are likely relevant to the origin of the amniotic egg and squamate parity mode

2107 evolution. Climatic shifts during the origin of amniotes should be explored for their
2108 consistency with the EER model.

2109 (5) Two new mechanisms for transitions between oviparity and viviparity, without
2110 necessitating intermediate stages, stand out from the cumulative research on the Main
2111 Five. These are presented here (Conclusions 6 and 7) as tools to be broadened and
2112 challenged with the goal of advancing scientific insight on the subject.

2113 (6) The genomics and physiology of amniote parity mode evolution does not preclude an
2114 origin of viviparity in the MRCA of Lepidosauria. I propose the following mechanism—a
2115 change to the phenotype or function of mammillary knobs occurred in the MRCA of
2116 Lepidosauria, instantaneously preventing calcium carbonate deposition (basal cap
2117 hypothesis); the eggshell loss enabled uterine exposure to chorioallantoic progesterone
2118 production (extending embryonic retention) and incipient calcium matrotrophy
2119 (supporting embryonic development); parturition occurred via 1) placental progesterone
2120 withdrawal or 2) overdistension of the uterus triggers contractions. This is one way to
2121 imagine viviparity evolving in the MRCA of Lepidosauria.

2122 a. Hypothesis testing: If the genes that code for the KS-proteoglycan, “mammillan”,
2123 that makes up mammillary knobs are absent or non-functional across squamates
2124 and tuatara, then this would support the basal cap hypothesis. To test this
2125 hypothesis, the genes must be identified in Archelosaur genomes and proteomes.
2126 Additionally, ancestral state reconstructions on the eggshell and eggshell
2127 membrane should be generated across oviparous and viviparous Archelosaurs,
2128 utilizing current recommendations for characterizing eggshell microstructure

2129 (Legendre et al., 2022). This will require also developing a system to accurately
2130 characterize eggshell membranes.

2131 (7) As discussed, the calcium secreting capacity of the uterus is maintained in oviparous
2132 viviparous squamates. Nonetheless, a reversal back to oviparity may evolve most easily
2133 within viviparous clades with matrotrophic calcium provisioning through the following
2134 sequence of events—calcium secretions in utero stick to the eggshell membrane instead
2135 of being absorbed by the chorioallantois; oviposition can then occur early in embryonic
2136 development in one of two ways 1) the death of corpora lutea or 2) the calcified eggshell
2137 blocks a threshold of chorioallantoic progesterone production from reaching uterine
2138 tissue; the calcified eggshell provides embryonic calcium that is transported upon
2139 embryonic metabolic demand.

2140 a. Hypothesis testing: Recent reversals should have physiological or genomic
2141 remnants of a viviparous past. Given that viviparous squamates generally have
2142 more active uterine immune systems to support gestation, oviparous reversals
2143 should 1) have more immune genes expressed in utero than ancestrally oviparous
2144 squamates, and 2) these immune genes should have stronger signatures of relaxed
2145 selection than immune genes expressed in a close relative during viviparous
2146 gestation.

2147 (8) If the scientific community agrees to utilize squamates as a model for studying the
2148 evolutionary parity mode of amniotes, then consider the following—1) oviparous *Z.*
2149 *vivipara* and *P. przewalskii*, differentially express genes during gravidity and these were
2150 associated with eggshell traits and stage of eggshell gland development, respectively
2151 (Gao et al., 2019; Foster et al., 2022); 2) Only two or zero genes are differentially

2152 expressed during gravity in *Lerista bougainvillii*, and *Lampropholis guichenoti*,
2153 respectively (Griffith et al., 2016). 3) This suggests that embryonic retention until the
2154 limb bud phase, common to squamates, does not necessarily require regulatory changes
2155 in the uterus. If we extrapolate this to stem amniotes, the egg could have been retained
2156 without a problem. The EER model is the most realistic explanation for the origin of the
2157 amniote egg. If we accept this, then all oviparous squamates that differentially express a
2158 substantial number of genes during gravity can be understood as reversals.

2159 (9) If we accept point eight as true, then *Saiphos equalis* represents a reproductively bimodal
2160 species that has transitioned from viviparity back to oviparity; and *Lerista bougainvillii*
2161 represents a species that has transitioned from oviparity to viviparity. Future work should
2162 examine the ultimate causes for these recent transitions, which will have the benefit of
2163 informing how science understands edge cases of viviparous squamates that don't fit the
2164 Cold Climate Hypothesis.

2165 (10) My opinion, based on the cumulative evidence and the lack of differential gene
2166 expression in some oviparous squamates—including *Lampropholis guichenoti* which is
2167 not reproductively bimodal—is that the earliest amniotes were oviparous with extended
2168 embryonic retention.

2169
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2176 **IX. References**

2177

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