

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 (Main Five) expected to
15 change during transitions between parity modes: eggshell formation, embryonic retention,
16 placentation, calcium transport, and maternal-fetal immune dynamics. Throughout, I offer
17 alternative perspectives and testable hypotheses regarding proximate causes of parity mode
18 evolution in amniotes and squamates. Should viviparity have evolved early in the history of
19 Lepidosauria, I offer the basal cap hypothesis as a proximate explanation. The framework of this
20 hypothesis can be extended to amniotes to infer their ancestral state. Medawar’s paradigm
21 contextualizes embryos as analogous to allografts. However, an abundance of research across
22 mammals, birds, and reptiles demonstrates that the maternal immune response to
23 gestation/gravidity cannot be explained by immunosuppression, inertness, evasion, or
24 immunological barriers. However, a rare example of a species with an apparently inert response
25 to oviparous gravidity is *Lampropholis guichenoti*, an oviparous skink that differentially
26 expresses zero genes during gravidity—making it a reasonable model for the original amniote
27 egg. Overall, this review grounds itself in the historical literature while offering a modern
28 perspective on a subject that has fascinated scientists for centuries—the origin of amniotes.
29 Based on the cumulative evidence across the Main Five, I provide a mechanism through which

30 squamates may reverse back to oviparity; and make predictions on the directionality of
31 transitions in three reproductively bimodal species. I encourage the scientific community to
32 utilize this manuscript as a resource in comparative genomics studies, embrace the complexity of
33 the system, and thoughtfully consider the framework proposed.

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

37

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95 **I. Introduction**

96

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

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

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

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

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

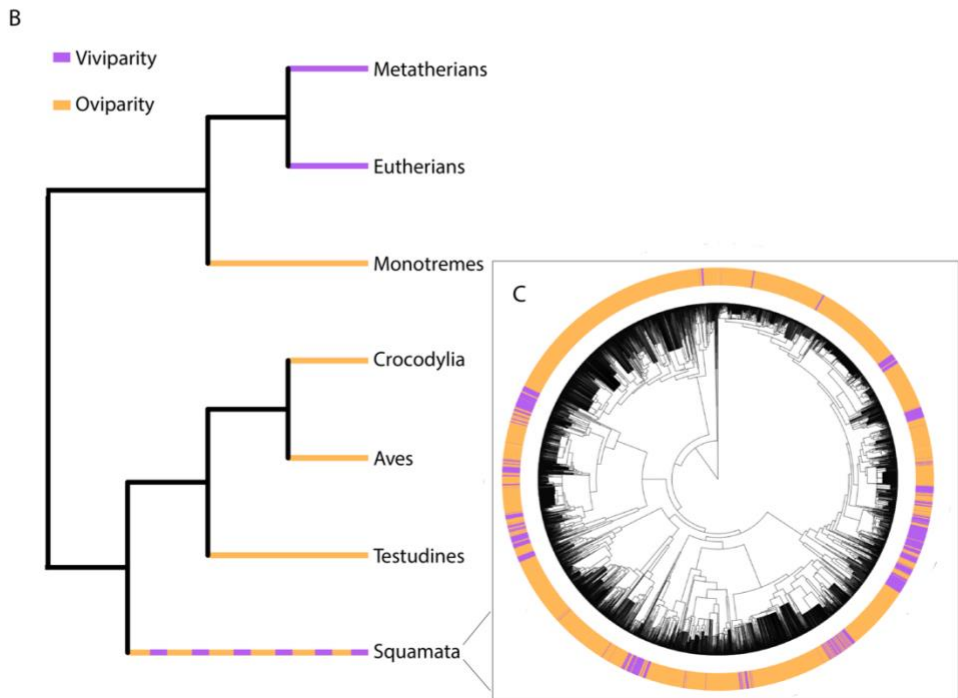
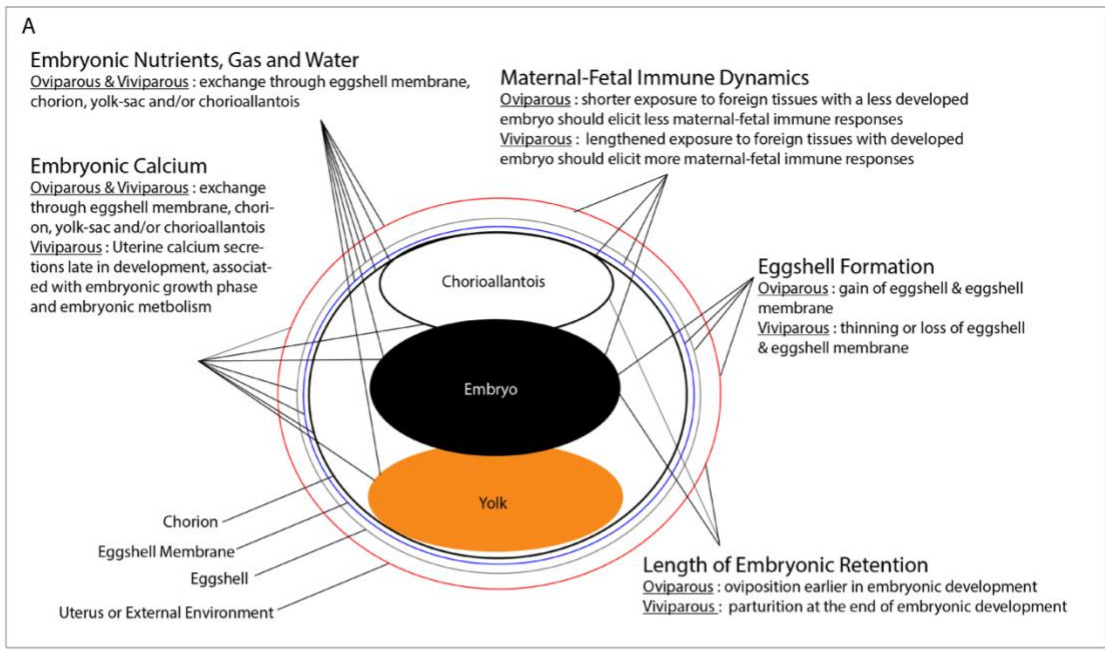
150 Discoveries of viviparity in ancient amniotes are numerous, dating back to the Early
151 Permian (Chuliver, Scanferla & Smith, 2022; Motani et al., 2014; Piñeiro et al., 2012; Jian et al.,
152 2023). A viviparous last common ancestor of amniotes may not be unreasonable. A compelling
153 example is the report that *Ikechosaurus sp.*, a basal archosauromorph, that reached an articulated
154 stage of embryonic development inside of a parchment shelled egg (Jiang et al., 2023). This and
155 the ancestral state reconstruction generated in the study bring support to the extended embryonic
156 retention model (EER) of amniotes origins (Jiang et al., 2023; Hubrecht, 1910). The EER model
157 postulates that amniote fetal membranes arose through pressure to support exposure to maternal-
158 fetal tissues during extended embryonic retention (see Laurin et al., 2005 for a summary of
159 earlier ancestral reconstructions of EER). As Romer (1957) phrased it “It was the egg which
160 came ashore first; the adult followed”. This is consistent with EER, which is compatible with
161 both oviparity and viviparity (Laurin, 2005; Mossman 1987). Throughout this review,
162 considering viviparity as the most extreme form of extended embryonic retention, I hope to
163 persuade readers to consider the EER model in a new light. I lay this out through a testable

164 hypothesis on the ancestral eggshell of amniotes and Lepidosaurs that can be extended to
165 amniotes (section III.3), a phylogenetic framework to infer ancestral states based on mechanisms
166 of maternal-embryonic calcium provisioning (section V.2), and evolutionary pathways that may
167 support transitions between parity modes (section VII.6 and VII.7).

168 It is sensible to equate the EER with pre-adaptations of the egg to land. Without
169 substantial amounts of water, converting yolk nutrients to somatic tissue is impossible
170 (Thompson & Speake, 2003). Water is the primary resource provisioned by the mother of
171 viviparous squamates and it is stored in extraembryonic membranes (Lourdais et al., 2015). For
172 example, improper 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). If the amniote egg evolved via the EER model, it may have prompted the origin of
176 extraembryonic membranes of amniotes to support embryonic water uptake despite the deficit of
177 water in utero compared to an aqueous environment. This translates to an egg washed ashore that
178 already evolved to withstand dryer environments.

179 Although models that restrict parity mode evolution to be unidirectional (from oviparity
180 to viviparity) are shown to be poor fits for squamates (Pyron & Burbrink; Recknagel et al.,
181 2021b), there is resistance to the proposition that viviparity originated early in Squamata (e.g.
182 Griffith et al., 2015). The most recent ancestral state reconstruction, built from biomineralization
183 and parity mode data across 80 extinct and extant amniotes using a single structured Markov
184 model, inferred viviparity with extended embryonic retention in the first amniotes and in the
185 most recent common ancestor of Lepidosaurs (squamates and sphenodontians) (Jiang et al.,
186 2023). However, maximum parsimony, and alternative maximum likelihood and Bayesian

187 reconstructions did not estimate viviparity in the most recent common ancestor of Lepidosaurus
 188 (Jiang et al., 2023). A testable hypothesis regarding a molecular mechanism that may have
 189 supported a transition to viviparity at the base of squamates and extended embryonic retention at
 190 the base of amniotes will help conclude these decades long debates.



191

192 **Figure 1:** Schematic demonstrating (A) the anticipated processes that change during transitions
193 between oviparity and viviparity, and the organs associated with those changes. Lines from the
194 process to different organs indicate the organs expected to be involved with the evolutionary
195 shift between oviparous and viviparous phenotypes. (B) relationships between major amniote
196 clades and their associated reproductive mode, and (C) the variation of reproductive modes
197 across squamates. The squamate phylogeny is adapted from Pyron et al., (2016) and reproductive
198 modes of squamate species from Pyron & Burbrink (2014).

199

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

212 With a deep review of interdisciplinary literature across amniotes and associated
213 supplementary materials, I explore genomic and physiological features of gestation and
214 gravidity, including those that could be exploited to support labile shifts, ancestral viviparous

215 states in amniotes and squamates, and those that may facilitate or impede reversals. I propose the
216 framework of the basal cap hypothesis to help elucidate the ancestral parity modes of squamates
217 and amniotes. It details how squamates may have transitioned to viviparity (an extreme form of
218 extended embryonic retention) early in their evolutionary history. I advocate for using squamates
219 as a model to understand the ancestral state of the amniote egg. Future work should consider this
220 thoughtfully and embrace the complexity of the system. I hope this manuscript serves as a
221 foundation for further research on the evolutionary history of the amniote egg and reproductive
222 mode evolution.

223

224 *(1) Terminology*

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

237

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

239 Several physiological features are expected to change during transitions between
240 oviparity and viviparity (Figure 1). I break this down into five physiological features (hereafter
241 Main Five)—1) length of embryonic retention (Murphy & Thompson, 2011; Packard et al.,
242 1977)—only viviparous mothers retain the embryo for the entirety of development; 2) eggshell
243 formation (Heulin et al., 2005; Packard et al., 1977; van Dyke et al., 2014)—viviparous embryos
244 generally do not have an eggshell; 3) placental development for maternal-fetal exchange of
245 required water, gas and/or nutrients (Blackburn, 1992, 2015; Thompson et al., 2000; Thompson
246 & Speake, 2006); 4) embryonic calcium provisioning (Packard et al., 1985; Shadrix et al., 1994;
247 Thompson & Speake, 2006)—sources of embryonic calcium and timing of uterine calcium
248 secretions generally differs between oviparous and viviparous reproduction; 5) maternal-fetal
249 immune dynamics (e.g., Graham et al., 2011; Hendrawan et al., 2017; Foster et al., 2020)—
250 viviparous reproduction is associated with maternal and embryonic exposure to foreign tissues,
251 which is likely to require enhanced regulation of maternal-fetal immune systems.

252

253 **II. Length of Embryonic Retention**

254

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

261

262(1) *Parturition & oviposition*

263 The genes and hormones involved with initiating and ending gestation may provide insights
264 into the tools squamates can co-opt to change the length of embryonic retention during parity
265 mode transitions. Parturition terminates embryonic retention. Parturition can be divided into four
266 parts (Terzidou, 2007; Vannuccini et al., 2016)—quiescence (Phase 0), activation (Phase 1),
267 stimulation (Phase 2) and involution (Phase 3). In eutherian mammals, several processes
268 contribute to the initiation and termination of gestation including inflammation (Challis et al.,
269 2009; Hansen et al., 2017), maternal recognition of pregnancy (MRP), mechanical stretch of
270 uterine tissues (Sooranna et al., 2004; Shynlova et al., 2008), and fluctuating concentrations of
271 corticotropin-releasing hormone, progesterone, and estrogen (Challis et al., 2000; Condon et al.,
272 2004; Shaw & Renfree, 2001).

273

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

275 Extended embryonic retention could be achieved by triggering mechanisms that extend
276 uterine quiescence, inactivity of the uterus. Inhibition of myometrial contractions through
277 sustained progesterone production supports quiescence across different viviparous amniotes
278 (Bazer, 1992; Casey & MacDonald, 1997; Fergusson & Bradshaw, 1991; Ilicic et al., 2017;
279 Murphy & Thompson, 2011; Putnam et al., 1991; Soloff et al., 2011). The corpus luteum (or
280 plurally called corpora lutea), a transient progesterone-producing organ, produces progesterone
281 during gestation. Extended lifespan of the corpus luteum likely aided the evolution of viviparity
282 in mammals (Amoroso, 1968; Callard et al., 1992; Stouffer & Hennebold, 2015). Thus, early
283 research on squamate viviparity also explored the influence of corpus luteum lifespan. The

284 lifespan of corpora lutea associates with oviparous egg retention and oviposition (Diaz, Alonso-
285 Gomez & Delgado, 1994; Fox & Guillette 1987; Jones & Guillette 1982). Eggshell formation in
286 oviparous Whiptail lizards, *Cnemidophorus uniparens*, is even disrupted by experimental
287 removal of corpora lutea (Cuellar, 1979). The lifespan of corpora lutea do not consistently
288 correlate with length of embryonic retention in viviparous squamates like it does in mammals
289 (Albergotti & Guillette, 2011; Callard et al., 1992).

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

300 Different genes are signaled by embryos for MRP across mammals. Human chorionic
301 gonadotropin hormone (hCG) establishes MRP (Ross, 1979; Behrman et al., 1993; Duncan,
302 McNeilly, & Illingworth, 1998; Duncan, 2000; Ticconi et al., 2007). In pigs, MRP is
303 hypothesized to be triggered by collaborative signaling of estradiol (E2) and prostaglandins
304 (PGs) (Geisert et al., 2023). Similarly, glycoproteins, estradiol and prostaglandin E2 (PGE2)
305 have been implicated in signaling MRP in horses (Klein & Troedsson, 2011; Klein, 2016). In
306 ruminants, embryonic signaling of IFN- τ establishes MRP (Bazer, 2013; Bazer, Spencer & Ott,

307 1997; Thatcher et al., 1995). During gestation in the uterus of viviparous African Ocellated
308 skinks, *Chalcides ocellatus*, four receptors for interferon alpha, beta, omega, and gamma are
309 differentially expressed but no expression of IFN- τ was detected compared to non-gestational
310 uterine tissue (Brandley et al., 2012). I was unable to find expression patterns of MRP signaling
311 homologs in other squamate reproductive tissues. Should MRP occur in squamates, it may be
312 signaled by genes that are clade-specific, like in mammals. This makes comparatively evaluating
313 the influence of MRP on the evolution of viviparity an interesting avenue for future research.

314 The evolution of viviparous extended embryonic retention may be sufficiently supported by
315 maintenance of chorioallantoic progesterone production coupled with eggshell loss (Griffith,
316 Brandley et al., 2017). This theory may be broadly applicable across amniotes given that the
317 most recent common ancestor of amniotes likely had a chorioallantois with an endocrine
318 function (Griffith, Brandley et al., 2017). Following death of the corpus luteum during gestation,
319 placental progesterone production supports extended embryonic retention in eutherian mammals
320 (Castracane & Goldzieher, 1986; Ellinwood et al., 1989; Nakajima et al., 1991; Rothchild, 2003;
321 Spencer & Bazer, 2004). Viviparous Italian Three-toed Skinks, *Chalcides chalcides*, shift to
322 chorioallantoic progesterone production following degradation of corpora lutea during gestation
323 (Guarino et al., 1998). The placenta of viviparous Southern Snow Skinks, *Carinascincus*
324 *microlepidotus*, produces minimal progesterone but has a strong capacity to convert
325 pregnenolone to progesterone (Girling & Jones, 2003). Whereas all genes involved with a known
326 biosynthesis pathway for progesterone production are expressed in the placenta of horses, *Equus*
327 *caballus*, only some of these genes were detected in the chorioallantois of chickens, *Gallus*
328 *gallus*, viviparous Southern Grass Skinks, *Pseudemoia entrecasteauxii*, and oviparous and
329 viviparous Southeastern Sliders, *Lerista bougainvillii* (Griffith, Brandley et al., 2017). Thus, if

330 chorioallantoic progesterone production has supported multiple origins of viviparity in amniotes,
331 it is not evidenced by a conserved ancestral gene expression pattern for the biosynthesis of
332 progesterone (Griffith, Brandley et al., 2017). Nonetheless, parity trait genes in a reproductively
333 bimodal lizard, *Zootoca vivipara*, are associated with progesterone-binding functions (Recknagel
334 et al., 2021a)—highlighting the role of progesterone in squamate reproduction.

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

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

371

372 (ii) *Activation & progesterone withdrawal*

373 The activation stage of parturition is marked by the withdrawal, or functional withdrawal, of
374 progesterone leading to an estrogen dominated response during the next state, stimulation
375 (Bakker, Pierce, & Myers, 2017; Fergusson & Bradshaw, 1991). Progesterone may withdraw in

376 response to environmental stimuli in reptiles during parturition (Shine & Guillette, 1988). In
377 mammals, activation is marked by increasing concentrations of corticotropin-releasing hormone
378 and contraction associated proteins (CAPs) including connexin-43, prostaglandins, oxytocin
379 receptors, prostanoid receptors and cell signaling proteins (Bakker et al., 2017; Ilicic et al., 2017;
380 Leadon et al., 1982; Pashen & Allen, 1979; Whittle et al., 2000). Pro-inflammatory cytokines
381 and chemokines, prostaglandin synthase-2 (*COX-2*, also referred to as *PTGS2*), and NF- κ B also
382 influence activation in mammals (Christiaens et al., 2008; Lappas et al., 2002; Lappas & Rice,
383 2007; Lindström & Bennett, 2005; Olson, 2003; Terzidou, 2007).

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

393

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

395 Mechanical stretch, electrical gradients, inflammatory processes, and hormonal regulation
396 contribute to stimulation, the phase when contractions, cervical ripening and dilation occur.
397 Stimulation involves contributions from maternal and fetal tissues. As early as 460 BC there was
398 uncertainty over the proportional influence of mother or fetus on the initiation of parturition.

399 Hippocrates proposed that the fetus initiates parturition by pushing its feet on the fundus of the
400 uterus. Although the reality is not so cartoonish, mechanical stretch of the uterus from the
401 growing embryo plays a role in parturition (Lefebvre et al., 1995; Tamizian & Arulkumaran,
402 2004; Wray et al., 2015).

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

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

421 Rensis et al., 2012; Olson & Hertelendy, 1983; Park et al., 2005; Sykes et al., 2014; Terzidou,
422 2007).

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

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

439 Prostaglandin E₂ (PGE₂) and prostaglandin F_{2α} (PGF_{2α}) influence, respectively, uterine
440 contractions and cervical relaxation for partition across many amniotes including humans, *Homo*
441 *sapiens* (Terzidou, 2007), domestic pigs (De Rensis et al. 2012), domestic chickens (Hertelendy
442 et al., 1974; Olson et al., 1986), and Loggerhead Sea turtles (Guillette et al., 1991). Injections of
443 PGF_{2α} and PGE₂ induce parturition in viviparous Yarrow's Spiny lizards, *Sceloporus jarrovi*, and

444 Raukawa geckos, *Woodworthia maculatus* (Cree & Guillette, 1991; Guillette et al., 1992).
445 However, no injected dosages of PGF_{2α} or PGE₂ induced oviposition in oviparous Collard
446 lizards, *Crotaphytus collaris*, Eastern Fence lizards, *Sceloporus undulatus*, Six-lined
447 racerunners, *Aspidoscelis sexlineatus*, or Striped Plateau lizards, *Sceloporus virgatus* (Guillette et
448 al., 1991). It is interesting that injections of PGF_{2α} and PGE₂ induced parturition in viviparous
449 lizards but did not induce oviposition in oviparous lizards studied. Given this, it is plausible that
450 regulatory or functional changes to PGF_{2α} and/or PGE₂ in squamates could facilitate changes to
451 the length of embryonic retention to support transitions between reproductive modes. However,
452 induction of parturition with PGF_{2α} in viviparous *Woodworthia maculatus* only worked with
453 pre-treatment of β-adrenoceptor (Cree & Guillette, 1991).

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

462 The softening of the cervix is important during the stimulation stage of parturition. A
463 hormone related to insulin, *relaxin*, promotes myometrial softening in humans, *Homo sapiens*,
464 domestic pigs, and turtles (Mercado-Simmen et al., 1982; Sorbera et al., 1988; Weiss &
465 Goldsmith, 2001). The cervix also gets softer by actions of PGE₂. PGE₂ activates pro-
466 inflammatory cytokines, interleukin (IL)-8 and tumor necrosis factor (TNF)-α, which activates

467 the collagenases and matrix metalloproteinases for cervical softening (Bakker et al., 2017). This
468 causes a positive feedback loop between IL-8 and PGE₂ synthesis (Denison et al., 1998;
469 Denison, Calder & Kelly, 1999; Terzidou, 2007; Li et al., 2010). Upregulated of IL-8 is also
470 promoted by the protein complex NF-κB during parturition in humans (Elliott, 2001). Similar
471 patterns were observed during parturition in mice and baboons (Mendelson & Condon, 2005;
472 Mendelson, 2009).

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

485 Altered expression or phenotype of contractility agonists, oxytocin receptors and estrogen
486 receptors, and contractility antagonists, progesterone receptors and β-adrenergic receptors
487 (Ravanos et al., 2015) may also change the length of embryonic retention to support transitions
488 between parity modes. Differences in length of embryonic retention in oviparous and viviparous
489 agamas, *Phrynocephalus przewalskii* and *Phrynocephalus vlangalii*, appears to be driven by

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

509 Recently, in humans, the only Classical Major Histocompatibility Antigen (C-MHC)
510 expressed by trophoblasts (specialized placental cells) was associated with parturition when it
511 was discovered that HLA-C is significantly increased during laboring term and preterm placentas
512 compared to non-laboring placentas (Hackmon et al., 2017). The authors suggested a mechanism

513 where fetal HLA-C open conformers on the placenta provoke inflammation of maternal tissues,
514 leading to parturition (Hackmon et al., 2017). Expression of MHC alloantigens, foreign antigens
515 to the host, by fetal cells is also associated with parturition in cows and horses (Benedictusa,
516 Koets & Ruttena, 2015; Davies et al., 2004; Joosten et al., 1991; Rapacz-Leonard et al., 2018).
517 Around one month prior to parturition in cows, endometrial epithelium thins and eventually
518 disappears completely, putting the antigen-presenting trophoblasts (Adams et al., 2007) in
519 contact with maternal connective tissue of the endometrium (Podhalicz-Dzięgielewska et al.,
520 2000). Fetal MHC alloantigens are proposed to promote the loosening of maternal and fetal
521 tissues (Benedictusa et al., 2015). MHC molecules are expressed during gestation in some
522 squamates (Murphy, Thompson & Belov, 2009) but their role in oviposition or parturition has
523 not yet been considered to my knowledge. Identifying the presence or absence of MHC
524 alloantigens on embryonic tissues before and during partition across more diverse taxa may
525 reveal how ubiquitous the influence of embryonic MHC molecules is on this.

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

530

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

532 The physiology of avian oviposition is dependent on a circadian schedule (Williams, 2012).
533 A general model of an “open period”, when eggs are laid are separated by “laying gaps”
534 (Williams, 2012). Chicken ovulation and oviposition cycles leave an 8-hour open period where
535 luteinizing hormone (LH) and progesterone surge, initiating ovulation and continuing the cycle.

536 At the extreme, the ancient murrelet, *Synthliboramphus antiquus*, oviposits a two-egg clutch on
537 seven-day intervals (Williams, 2012). Longer laying intervals have been associated with longer
538 intervals between initiation of yolk development (Astheimer & Grau, 1990). Differing from
539 birds, oviparous squamates retain eggs longer than the ovarian cycle (Tinkle & Gibbons, 1977).
540 This suggests that oviparous squamates may rely on different molecular mechanisms to support
541 oviposition than birds.

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

552

553(3) *Pre-term birth & embryonic retention mechanisms*

554 The literature on pre-term birth may be a fruitful avenue of research to inform understanding
555 on the evolutionary genomics of embryonic retention length. Slower increases of CRH (Ellis et
556 al., 2002) and higher expression of Neurokinin B, for example, are associated with pre-term birth
557 in humans (Torricelli et al., 2007). Injections of RU486, a progesterone receptor (PGR)
558 antagonist, promoted pre-term labor in rhesus macaques but the progression of physiological

559 activity differed from normal parturition (Haluska et al., 1987). Examining homologs of genes
560 involved with human pre-term birth in squamates may provide further candidates for genes that
561 could impact the length of embryonic retention in squamates. Some evolutionary studies are
562 taking implications of pre-term birth into account. For example, a comparative evolutionary
563 transcriptomics study across therians, monotremes, squamates, and an amphibian recently
564 associated *HAND2* with preterm birth in Eutherian mammals (Marinić et al., 2021).

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

572

573(4) *Discussion & future directions—embryonic retention and parity mode evolution*

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

582 luteum across a broader range of taxa, production and circulation of homologs for AVT and
583 CRH or other similarly structured genes, expression of fetal alloantigens and inflammatory
584 cytokines in utero, and the influence of uterine overdistention on contractions. Regarding
585 squamate parity mode transitions, the role of uterine overdistention in mammalian parturition
586 suggests a lack of uterine overdistention may be one hurdle for reversals back to oviparity.
587 Understanding the evolutionary physiology and genomics of embryonic retention in oviparous
588 and viviparous squamates will benefit from focused attention on reproductively bimodal species
589 (Whittington et al., 2022) and from genomics/physiological research across more taxa that vary
590 in reproductive modes.

591

592 **III. Eggshell Formation**

593

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

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

605 Monotremata (egg-laying mammals) have an eggshell but far less has been documented about its
606 structure compared to other amniotes (Legendre et al., 2022). The structure and physiological
607 mechanisms involved with eggshell calcification are most well resolved in birds (Choi et al.,
608 2018; Francesch et al., 1997; Jonchère et al., 2010, 2012; Rose-Martel, Du, & Hincke, 2012).
609 Eggshell deposition in tuatara and squamates differs dramatically (Choi et al., 2018). Viviparous
610 squamates lack an eggshell, absorb the eggshell during gestation, or have a thin layer of calcium
611 deposits.

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

623 The genetic drivers of eggshell formation are not resolved in squamates. Two oviparous
624 lizards, *Lerista bougainvillii* and *Lampropholis guichenoti*, differentially express either zero or
625 two genes, respectively, in utero in non-gravid vs gravid comparisons (Griffith et al., 2016).
626 However, this study only measured gene expression at one developmental stage, making it
627 difficult to infer if regulatory changes influence eggshell formation. Nonetheless, oviparous

628 *Saiphos equalis* and *Phrynocephalus przewalskii* have extensive differential expression during
629 gravidity (Foster et al., 2020; Gao et al 2019). It is interesting to see drastically different uterine
630 gene expression profiles associated with oviparity, given that shared genes are recruited to the
631 uterus to support viviparity across diverse amniotes (Recknagel et al., 2021a). Under the
632 assumption that conserved traits should be accompanied with more similar gene expression
633 profiles than convergent traits, uterine gene expression profiles in themselves currently reveal
634 more conserved regulatory networks in utero for squamate viviparity than oviparity.

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

644

645 (1) *Mineral composition of eggshells*

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

651 processes in invertebrates (Hincke et al., 2012). It was recently shown to control avian eggshell
 652 mineralization (Rodríguez-Navarro et al., 2015).

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

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

670 **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

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

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

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

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

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

717 In the oviparous Przewalski's toadhead agama lizard, *Phrynocephalus przewalskii*, 148 genes
718 are highly expressed in the uterus during the stage of eggshell gland development (Gao et al.,
719 2019). Only three of these are highly expressed in *P. vlangalii*, a viviparous close relative at this
720 time, suggesting differences in oviparous and viviparous eggshell gland development requires
721 regulatory changes to dozens of genes (Gao et al., 2019). In the opossum, a marsupial,
722 proliferation of uterine glands is not induced by the conceptus (Griffith et al., 2019).

723

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

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

736 Eggshell formation begins with the eggshell membrane. Two unciliated cell types in the
737 uterus contribute to eggshell membrane formation in a viviparous skink, *Chalcides ocellatus*
738 *tiligugu* (Corso et al., 2000). One secretes sulfated glycosaminoglycans to form the inner shell
739 membrane, and the other which secretes acidic glycoproteins to form the outer layers (Corso et

740 al., 2000). Simple alveolar glands in the lamina propria secrete collagen fibers (Corso et al.,
741 2000). Inhibition of fiber formation or cross-linking, typically caused by aminopropionitrile or a
742 copper deficiency, causes distorted formations of the eggshell membrane in birds (Arias et al.,
743 1997; Chowdhury & Davis, 1995; Hincke et al., 2012).

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

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

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

786 applying it to the evolution of oviparity and viviparity in amniotes. If a version of the avian
787 eggshell was the ancestral microstructure of oviparous amniotes, the loss of basal caps could
788 result in a rapid loss of the eggshell and thus a relatively fast transition to viviparity or extended
789 embryonic retention.

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

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

804 Several pieces of biological evidence lend themselves to an early origin of viviparity in
805 Lepidosauria and the basal cap hypothesis including—the lack of homology between the semi-
806 rigid shells of testudines and Lepidosauria (Legendre et al., 2022), the later stage of embryonic
807 development when eggs are commonly oviposited in squamates (Blackburn, 1995), and the more
808 predominant reliance on yolk calcium rather than eggshell calcium in squamates compared to

809 Archelosaurs (Packard, 1994; Stewart & Ecaý 2010). Viviparity in the most recent common
810 ancestor of Lepidosaurians may provide clear evolutionary insights on these phenomena.

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

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

832 Originally considered avian-specific, several homologs of avian eggshell matrix proteins
833 have now been identified in non-avian reptiles and mammals (Le Roy et al., 2021). A recent
834 study found a significantly reduced number of intact avian eggshell matrix proteins in viviparous
835 squamates compared to oviparous squamates, a pattern that was especially apparent in snakes
836 (Xie et al., 2022). This study also found that *OC-17* was only absent in viviparous squamates but
837 was always present in the oviparous species in the dataset (Xie et al., 2022). Due to this, and the
838 central role of *OC-17* in avian eggshell formation in birds, they ascribe losing intact *OC17* with
839 the prevention of reversals back to oviparity (Xie et al., 2022). However, given that *OC-17* is
840 implicated in initiation of mineralization in the mammillary cone layer, which is absent in
841 squamates, the necessity of *OC-17* for squamates eggshell formation requires further
842 investigation. Other genes, like osteopontin (*OPN* or *SPPI*), also play a central role in
843 biomineralization of the avian eggshell and should be investigated in squamates.

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

850 *OC-116* is homologous to mammalian *MEPE*, which plays a role in bone and teeth
851 mineralization (Bardet et al., 2010a, 2010b). In birds, *OC-116* influences shell thickness, elastic
852 modulus, and egg shape (Le Roy et al., 2021). *OC-116* was identified in a crocodile, *Crocodylus*
853 *siamensis*, proteome (Le Roy et al., 2021; Mikšík et al., 2018). Synteny analysis across seven
854 turtle species and platypus (*Ornithorhynchus anatinus*) revealed absence of *MEPE/OC116* (Le

855 Roy et al., 2021). Other genes and lncRNAs are purported to be important for the quality of
856 eggshell formation in hens—*FGF14*, *COL25A1*, *GPX8*, and several members of the solute
857 carrier protein (*SLC*) gene family (Yang et al., 2020). Research into lncRNAs activity in
858 squamate reproductive tissues during embryonic development represents another valuable track
859 for research.

860 Various evolutionary genomics studies have revealed squamate-specific candidates for shell
861 formation (e.g. Recknagel et al., 2021a; Gao et al., 2020). Some of these candidates span the
862 major clades of amniotes. Seven of the genes expressed during eggshell gland development in
863 *Phrynocephalus przewalskii*—*HYPOU1*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*, *RRBP1* and
864 *TRAMI*—are purported to be important for eggshell calcification in chickens (Brionne et al.,
865 2014). Given this overlap across species that diverged over 300 million years ago (Shen et al.,
866 2011), these are excellent candidates for further exploration.

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

878 *LGMN*, appears to support both oviparous and viviparous gestation in different ways. There are a
879 number of ways to approach exploring how *LGMN* may support both maternal-fetal
880 interconnectivity (viviparous individuals) and eggshell formation (oviparous individuals). Cell-
881 to-cell communication analysis using single cell data on uteruses of a reproductively bimodal
882 species would enable researchers to identify different interaction networks of *LGMN* and
883 associated cells in oviparous vs viviparous individuals.

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

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

901

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

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

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

923 *BMPER* and seven *BMPs* are expressed during gestation in *Chalcides ocellatus*, a viviparous
924 skink (Brandley et al., 2012). Most of these are upregulated (Brandley et al. 2012). *BMP* genes
925 are expressed during both gravidity and non-gravidity in oviparous *Lerista bougainvillii* and
926 *Lampropholis guichenoti* (Griffith et al., 2016). *BMP2* is upregulated in oviparous late gestation
927 compared to viviparous late gestation in the reproductively bimodal lizard, *Saiphos equalis*
928 (Foster et al., 2020).

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

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

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

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

968

969 (5) *Eggshell formation termination*

970 When eggshell formation is terminated, the egg is still bathed in the supersaturated
971 calcium and bicarbonate ion fluid (Hincke et al., 2012). Some component(s) of the terminal
972 uterine fluid may prevent precipitation of calcium carbonate (Gautron, Hincke & Nys, 1997),
973 such as phosphate anions (Lin & Singer, 2005). The presence of phosphorous in the superficial
974 layers of the chicken shell suggest it may be a factor preventing the deposition of calcite crystals
975 in the terminal stage. Additionally, the high concentration of *OCX-32* in the outer eggshell and
976 cuticle, suggest that the gene may inhibit proteinaceous crystal growth in the terminal stage of
977 eggshell calcification (Gautron, Hincke, Mann et al., 2001). It is informative to viviparous
978 reproduction and consistent with the basal cap hypothesis that exposure to precursors of the
979 eggshell does not necessitate eggshell deposition. The influence of phosphate anions and *OCX-*
980 *32* on inhibition of calcium carbonate precipitation on the eggshell membrane of viviparous
981 squamate embryos has not been examined to my knowledge.

982

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

984 Oviparous amniotes rotate the egg for calcium formation and viviparous mammals rotate the
985 embryos for parturition. One hurdle to reversing back to oviparity may be re-evolving rotation of
986 the egg for shell formation early in gravidity (Griffith et al., 2015). Given the complex
987 musculature of the uterus across taxa, that allows for multidirectional force for parturition and
988 eggshell formation, it is difficult to determine the degree of difficulty for re-evolving appropriate
989 timing of egg-rotation. Cadherins and hormonal signaling support embryonic attachment (Wu et
990 al., 2011; Biazik et al., 2012), which can prevent rotation of the egg. Oviparous taxa lack
991 embryonic attachment, enabling the uterus to rotate the egg for eggshell formation. This rotation

992 does not happen until later in gestation for eutherian mammals when, for example, the embryo
993 detaches and cadherins become less concentrated (Wu et al., 2011). Perhaps a candidate gene for
994 studying this is, a cadherin *CDH5*, the only gene that is differentially expressed in all viviparous
995 squamates studied thus far studied (Recknagel et al., 2021a). Genes that enrich the GO term for
996 “voltage-gated calcium channel activity” are also useful candidates for investigating uterine
997 rotation associated with eggshell formation because voltage-gated calcium channels effect the
998 action potential of cells and can cause muscle contractions.

999

1000 (7) *Discussion & future directions—eggshell formation and parity mode evolution*

1001 The process of eggshell formation is more resolved in birds compared to non-avian reptiles
1002 and monotremes (Choi et al., 2018; Frankenberg & Renfree 2018). I described some overlaps
1003 gleaned from the literature which prove as curious candidates for further research
1004 (Supplementary Table 1). Of particular interest are avian eggshell matrix proteins (Alföldi et al.,
1005 2011; Le Roy et al., 2021; Tian et al., 2010; Xie et al., 2022), genes with biomineralizations
1006 functions, candidate genes associated with eggshell traits in *Zootoca vivipara* (Recknagel et al.,
1007 2021a), and the homologs for avian eggshell matrix proteins identified in the *Anolis carolinensis*
1008 genome (Alföldi et al., 2011; Tian et al., 2010). Additionally, genes purported to be important for
1009 eggshell calcification in chickens associated with eggshell gland formation in an oviparous
1010 lizard, *Phrynocephalus przewalskii*, are relevant—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*,
1011 *RRBP1* and *TRAMI* (Brionne et al., 2014; Gao et al., 2019). Overlaps between the genes
1012 associated with gestation length and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a)
1013 hint at genes that could potentially evolve to innately effect multiple traits relevant to parity
1014 mode transitions. The basal cap hypothesis also offers a simple evolutionary mechanism to

1015 investigate the evolutionary history of amniote parity mode evolution (see section III.3).
1016 Alternatives to the basal cap hypothesis are that dissimilar eggshells and eggshell deposition
1017 processes evolved through selective pressure, genetic drift, or both. Fortunately, the basal cap
1018 hypothesis can be utilized to ascertain the likelihood of this.

1019

1020 **IV. Placentation & Transport of Embryonic Water, Gas, and Nutrients**

1021

1022 The evolutionary pressures on fluid allocation, gas exchange and nutrient transport should
1023 differ between oviparous and viviparous taxa because their sources of all or some of these
1024 resources differ (Blackburn, 1992; Bonnet et al., 2001; Bonnet, Naulleau & Shine, 2017; van
1025 Dyke et al., 2014). In viviparity, maternal gas and water are accessed through the chorioallantois,
1026 which is especially important in the latter half of development (van Dyke et al., 2014; Carter,
1027 2012). Nutrients can be available from the yolk, maternal transfer, or both yolk and maternal
1028 transfer.

1029 While viviparity is associated with shared patterns of uterine gene expression during amniote
1030 gestation (Recknagel et al., 2021a), the same does not occur in viviparous amniote placentas
1031 (Foster et al., 2022). Instead, different genes that serve similar functions are recruited to the
1032 placenta across independent origins of viviparity (Foster et al., 2022). Additionally, where other
1033 amniotes can rely on the albumen for fluid allocation, squamates lack an albumen (Blackburn &
1034 Stewart, 2021). The eggshells of various squamates supports uptake of water from the
1035 environment (Blackburn & Stewart, 2021). The evolutionary implications of this have not been
1036 documented to my knowledge.

1037

1038 *(1) Anatomy & methods of water, gas & nutrient provisioning*

1039 The embryonic membranes regulate embryonic fluid transport, nutrient supply, respiration,
1040 immunity, and waste (Brace, 1997; Burton & Tullett, 1985; Ferner & Mess, 2011; Packard &
1041 Packard, 1980). Fluids are important for the developing embryo because they prevent desiccation
1042 and compression (Ferner & Mess, 2011; Packard & Packard, 1980). Over-abundance or under
1043 abundance of embryonic sac fluids leads to reproductive failure (Chamberlain et al., 1984;
1044 Fedakâr et al., 2016; Hadi, Hodson & Strickland, 1994; Mercer et al., 1984). Water is the
1045 predominant resource provisioned from the mother in most viviparous squamates (Lourdais et
1046 al., 2015).

1047 Oxygen flux in embryonic mammals is largely determined by oxygen-diffusing capacity of
1048 the placenta, the rates of blood flow in the umbilical and uterine arteries, and the oxygen
1049 capacities and affinities of fetal and maternal blood (Carter, 2009). Reptilian and mammalian
1050 blood vessels differ in basic characteristics such as capillary density, capillary surface, and
1051 oxygen diffusion gradients (Pough, 1980). Oviparous taxa regulate gas exchange through pores
1052 in their eggshells.

1053 Patterns of embryonic nutrient exchange can be broadly categorized into lecithotrophy,
1054 obtaining nutrients from the yolk, and placentrophy or matrotrophy, obtaining nutrients from the
1055 mother. Taxa belonging to Archelosauridae are lecithotrophic. The ancestral state of mammals
1056 was most likely oviparous matrotrophy that later evolved into viviparous matrotrophy in therians
1057 (Blackburn, 2005). The ancestral state of reptiles was likely lecithotrophy (Blackburn, 2005).
1058 Most viviparous squamates are lecithotrophic, some are lecithotrophic and matrotrophic, and a
1059 few have specializations for substantial matrotrophy (e.g. Blackburn, 2015a, Blackburn, 1985b;
1060 Stewart & Thompson, 1993; Thompson, Stewart et al., 1999; van Dyke et al., 2014). Even in

1061 lecithotrophic viviparous squamates some degree of organic or inorganic nutrients pass through
1062 the chorioallantoic placenta (Blackburn, 2005; Swain & Jones, 1997, 2000; Stewart & Eca, 2010; Thompson, Stewart et al., 1999; Thompson & Speake, 2002). Reversals may be most
1063 unlikely in lineages that have specialized placentas for substantial nutrient exchange because
1064 they would need to re-evolve lecithotrophy. Highly matrotrophic squamates are extremely rare
1065 (Blackburn, 2015a).

1067

1068 *(2) Evolutionary history of yolk-sac formation and yolk processing*

1069 Vitellogenesis is the process of yolk formation in the oocyte, providing the embryo with a
1070 valuable source of nutrients, primarily through the accumulation of precursor proteins to yolk,
1071 vitellogenins. Vitellogenin is produced in the liver, called hepatic vitellogenesis, and transported
1072 to the maturing ovum (Ho, 1987). Vitellogenins were lost in all mammals except monotremes
1073 (Brawand, Wahli & Kaessmann, 2008). They are a primary source of nutrition for other
1074 amniotes. Functionally similar to vitellogenin, caseins have persisted in all mammalian milks
1075 (Brawand et al., 2008). Active functioning of the yolk sac is restricted to the first trimester in
1076 placental mammals, and it is postulated to provide nutrients to the embryo (Kuzima et al., 2023).
1077 The detection of glycodelin in the yolk sac epithelium also supports this (Burton et al., 2002). In
1078 the yolk-sac of bats, dogs, and non-human primates the mesoderm derived layer is absorptive
1079 and may transfer substances from the exocoelomic cavity where the yolk sac is located (Enders
1080 et al., 1976; Freyer & Renfree, 2009; King & Wilson, 1983; Lee et al., 1983).

1081 The morphology of the yolk-sac and process of vitellogenesis differs between birds and non-
1082 avian reptiles. In birds, during the process of meroblastic cleavage, the zygote's cells divide
1083 while the yolk component does not. The yolk forms a large, fluid, non-cellularized mass

1084 surrounded by the extraembryonic yolk sac. The formation of the yolk-sac placenta in birds has
1085 the following pattern—first the bilaminar omphalopleure forms and then trilaminar
1086 omphalopleure; blood vessels move into folds of the extraembryonic endoderm, becoming
1087 stratified epithelium; the folds carrying the blood vessels reach the peripheral regions of the yolk
1088 only and the center of the yolk mass remains uncellularized (Starck, 2021). Intensive
1089 development of hemopoietic tissue surrounding the blood vessels during most of embryonic
1090 development, thus far, appears to be unique to birds (Starck, 2021). Compared to non-avian
1091 sauropsids, the unique pattern of yolk processing in birds facilitates faster embryonic
1092 development (Blackburn, 2021).

1093 The yolk sac characteristic of non-avian reptilian eggs serves as a model for the transition
1094 between the egg of anamniotes and amniotes (Blackburn, 2020). A series of recent papers,
1095 covering species of snakes, lizards, crocodiles, and turtles, indicate that these taxa utilize similar
1096 developmental pathways of yolk-sac formation and yolk processing that differs from birds
1097 (Blackburn, 2020, 2021; Blackburn et al., 2019; Elinson et al., 2014; Elinson & Stewart 2014;
1098 Stinnett et al., 2011). Across these taxa, a bilaminar/trilaminar omphalopleure overgrows the
1099 yolk mass, and the yolk mass gets invaded by proliferating endodermal cells that phagocytose
1100 the yolk material. These cells form clumps, progressively filling the yolk mass. Small blood
1101 vessels derived from yolk sac vasculature invade the yolk sac cavity and the endodermal cells
1102 arrange in monolayers around these vessels, forming “spaghetti bands” (Blackburn, 2021). The
1103 yolk sac of *Pantherophis guttatus* is one suitable model for studying the transition of the yolk-
1104 sac from anamniotes to amniotes (Elinson & Stewart, 2014; Elinson et al., 2014).

1105 A major difference between non-avian reptilian yolk-sac formation is the morphology and
1106 extent of vascularization and cellularization in the yolk sac cavity (Starck, 2021). Birds have a

1107 yolk-sac with absorptive endodermal lining that digests nutrients and send them into blood
1108 circulation (Starck, 2021) whereas snakes, lizards, turtles, and crocodilians have a yolk sac that
1109 becomes invaded by endodermal cells that proliferate and phagocytose yolk material (Blackburn,
1110 2021). In these taxa, yolk material becomes cellularized, digested, and transported by vitelline
1111 vessels to the developing embryo (Blackburn, 2021). Factors involved with cellularization of the
1112 yolk-sac are proposed to include cell cycle regulators and structural proteins (Elinson et al.,
1113 2014). Generation of these cells are suspected to be reliant on processes of angiogenesis and are
1114 likely transcriptionally active (Elinson et al., 2014). Few transcriptomic profiles of yolk-sac
1115 placentas in reptiles have been documented to my knowledge (Griffith et al., 2016). Significant
1116 overlaps in the yolk-sac transcriptomes of human, mice, and chicken—including apolipoproteins
1117 and SLC transporters—however, suggest functional conservation (Cindrova-Davies et al., 2017).

1118 As discussed in a previous section, progesterone inhibits myometrial contractility, but it also
1119 inhibits estrogen-induced hepatic vitellogenin synthesis (Custodia-Lora, Novillo, & Callard,
1120 2004; Callard et al., 1992). Variable progesterone concentrations in circulation throughout
1121 gestation in viviparous squamates may reflect a trade-off to allow estrogen expression to support
1122 hepatic vitellogenin synthesis during embryonic development, thus supporting nutrient
1123 provisioning during the lengthened embryonic retention. Although hepatic vitellogenesis usually
1124 ceases during gestation, vitellogenin synthesis and mother-to-embryo transfer was detected in
1125 one viviparous fish, *Xenotoca eiseni*, during gestation (Iida et al., 2019). Future research should
1126 consider the timing of vitellogenin synthesis throughout the reproductive cycle in gestating and
1127 non-gestating viviparous squamates to investigate this further.

1128

1129 (3) *Evolutionary history of placentrophy in mammals & squamates*

1130 Traditionally, it was thought that placentrophy evolved after viviparity in squamates
1131 (Packard, Tracy, & Roth, 1977; Shine & Bull, 1979). Further research demonstrated that
1132 placentrophy and viviparity evolved simultaneously (incipient matrotrophy) in mammals and
1133 may have in squamates (Blackburn, 1985, 1992, 2005, 2006; Stewart & Eday, 2010). The
1134 incipient matrotrophy model relies on evidence that 1) uterine provisioning of nutrients predates
1135 the origin of viviparity (Blackburn 1985, 1992, 2006), 2) uterine and embryonic tissues have a
1136 close anatomical and physiological association in viviparous taxa and 3) some degree of
1137 placental transfer of organic or inorganic molecules occurs in viviparous taxa (Stewart & Eday,
1138 2010). In squamates, the potential for both incipient matrotrophy and evolution of placentrophy
1139 after viviparity is supported (Stewart & Eday, 2010). Facultative placental nutrient provisioning
1140 and incipient matrotrophy may have driven the evolution of squamates with substantial
1141 matrotrophic nutrient provisioning (Stewart, 2020; Swain & Jones, 2000).

1142 Placentation and implantation are not homologous in mammals compared to squamates
1143 (Griffith, van Dyke & Thompson, 2013). Several placental specializations for gas and nutrient
1144 exchange are unique to mammals including erosion of the uterine mucosa, extensively invasive
1145 implantation, hemochorial contact, retention of a vascularized choriovitelline membrane, and
1146 countercurrent patterns of blood flow (Blackburn, 2005). This enables extensive exchange of
1147 nutrients in addition to water and gas. The vast majority of viviparous squamates have the most
1148 superficial type of chorioallantoic placenta called epitheliochorial placenta (Blackburn, 1993).

1149 Nutrient provisioning through placentrophy is obligate for embryonic development in only
1150 five lineages of squamates, all of which are scincid lizards (Blackburn, 2000; Flemming &
1151 Blackburn, 2003; Ramírez-Pinilla et al., 2011; van Dyke et al., 2014). *Pseudemoia*
1152 *pagenstecheri*, a lizard with a highly specialized placenta, out-performs lecithotrophic oviparous

1153 close relatives in the relative amount of nutrients it transfers to the embryo (Stewart et al., 2009).
1154 *Pseudemoia entrecasteauxii* is a moderately matrotrophic viviparous skink, with roughly half of
1155 embryonic nutrient uptake from the yolk and half through a specialized cyto-epitheliochorial
1156 placenta (Adams et al., 2005; Speake et al., 2004; Stewart & Thompson, 1993, 2009).

1157 Specializations of the chorioallantoic placenta for nutrient provisioning in some squamates
1158 include elaborate specializations for uterine secretion and absorption, including placentomes,
1159 chorionic areolae, hypertrophied uterine mucosa, and chorionic epithelia modified for absorption
1160 (Blackburn, 2005). In squamates, specializations for gas exchange across the chorioallantoic
1161 placenta include decreased diffusion distance between maternal and fetal capillaries, uterine
1162 vascularity, shell membrane deterioration, and modifications of both fetal and maternal blood
1163 properties (Blackburn, 1998, 2005; Blackburn & Lorenz, 2003; Blackburn & Vitt, 2002).

1164 Mammalian placenta-specific genes have deep origins in vertebrates (Rawn & Cross, 2008).
1165 Placentation to support viviparity likely employs genes that are ancestral to the chorioallantois.
1166 However, one study that looked at placentation and gene expression across a small sample of
1167 divergent amniotes found only one gene with a placentrophy-specific pattern of gene expression,
1168 *DIO3* (Griffith, Brandley et al., 2017). In mammals, *DIO3* is an imprinted gene and
1169 preferentially paternally expressed. The authors suggest that the gene may increase offspring
1170 resource uptake during pregnancy in the horse and a viviparous lizard, *Pseudemoia*
1171 *entrecasteauxii*, where it is recruited to the placenta (Griffith, Brandley et al., 2017).

1172

1173 (4) Genes involved with embryonic water, gas, and nutrient transport

1174 Water transport in animals is regulated by a family of molecular water channels called
1175 aquaporins (AQs or AQPs) (Borgnia et al., 1999). In humans, *AQP1*, *AQP3*, *AQP4*, *AQP8* and

1176 *AQP9* are found in the placenta but further research is needed to understand how these influence
1177 water fluxes between maternal and fetal tissues (Damiano, 2011). Transcriptomic analysis on
1178 uterine tissue of the gestating, viviparous skink, *Chalcides ocellatus*, reveal differential
1179 expression of *AQP1*, *AQP3*, *AQP5*, *AQP6*, *AQP8*, *AQP9* and *AQP11* when compared to non-
1180 gestating uteruses (Brandley et al., 2012). In birds, *AQP1* is expressed in the chorioallantoic
1181 membrane, and it is suggested to influence angiogenesis throughout embryonic development
1182 (Ribatti et al., 2002). In a viviparous lizard, *Pseudemoia entrecasteauxii*, *AQP8* and *AQP9* were
1183 more highly expressed in the chorioallantoic placenta compared to the yolk-sac placenta (Griffith
1184 et al., 2016). During gestation in both oviparous and viviparous populations of the reproductively
1185 bimodal skink, *Saiphos equalis*, several genes involved with water homeostasis are upregulated
1186 in the uterus including *AQP1*, *AQP3* and *AQP12B* (Foster et al., 2020). In uteruses of *Saiphos*
1187 *equalis*, *AQP5* and *AQP8* are upregulated during oviparous late gestation compared to viviparous
1188 late gestation. In sheep, *AQP3* is differentially expressed during gestation, where it serves a dual
1189 role of water transport to the embryo and fetal urea export (Johnston et al., 2000). This is similar
1190 to the function of *AQP9* in humans (Damiano, 2011). Immunocytochemistry reveals that *AQP1*
1191 and *AQP3* are expressed in the uterus of the highly placentrophic South American scincid lizard,
1192 *Mabuya sp.* (Wooding et al., 2010). In *Zootoca vivipara*, *AQP9* is upregulated at midgestation
1193 (Recknagel et al., 2021a).

1194 Some molecules are implicated in the regulation of aquaporins including insulin (INS),
1195 human chorionic gonadotropin (HcG), cyclic adenosine monophosphate (cAMP) and cystic
1196 fibrosis transmembrane conductance regulator (CFTR) (Damiano, 2011). Genes predicted to be
1197 involved with reproduction in *Anolis carolinensis* are enriched for the GO term for cAMP-
1198 mediated signaling (Alföldi, Di Palma, et al., 2011). Further comparative research should be

1199 done to elucidate the functional differences of aquaporins in oviparous and viviparous amniotes
1200 and how they relate to the differing conditions under which these embryos develop.

1201 Genes involved embryonic oxygen transport precede the origin of amniotes. Hemoproteins
1202 arose in evolutionary history well before they were used for placental oxygen transfer (Hardison
1203 1998). In mammals, adult (Alpha: HBA; Beta: HBB, HBD) and embryonic hemoglobins (Alpha:
1204 HBZ, HBA; Beta: HBE, HBG, and HBH) are involved with oxygen transport (Carter, 2012).
1205 Some of these are unique to eutherian mammals following a series of duplication events (Opazo
1206 et al., 2008). However, fetal hemoglobins are found in turtles, lizards, and snakes (Pough, 1980).
1207 HBA, HBB and HBM are all significantly downregulated in the uterine tissue of the viviparous
1208 African Ocellated Skink, *Chalcides ocellatus*, during gestation compared to non-gestation
1209 (Brandley et al., 2012). The oxygen demands of reptile embryos are relatively low until stage 30,
1210 when most oviparous taxa oviposit (Shine & Thompson, 2006). In viviparous and oviparous
1211 species with long egg retention, embryonic demand for maternal provision of oxygen and
1212 removal of CO₂ increases at this stage.

1213 Improper water, gas and nutrient exchange can occur due to poor chorioallantoic blood flow
1214 (Wootton et al., 1977). Thus, viviparous taxa require greater degrees of vascularization and
1215 vasodilation to facilitate enhanced requirements for maternal resources compared to oviparous
1216 taxa. Rather than increasing the size of the placenta, increasingly dense blood vessels can support
1217 fetal growth without compromising space for embryonic growth as occurs in some pigs (Ford,
1218 1997; Vonnahme et al., 2002). Embryonic vascularization and vasodilation are dependent on
1219 signals from the endoderm (Jin et al., 2005; Vokes & Krieg, 2002; Wilt, 1965). In oviparous
1220 individuals of *Saiphos equalis*, populations with extended egg retention, there is expansion of the
1221 uterine vascular bed and thickening of the chorioallantoic tissue that supports increased

1222 embryonic growth in the later portion of oviparous gravidity (Parker et al., 2010). In the
1223 viviparous scincid lizard, *Eulamprus quoyii*, angiogenesis, the formation of new blood vessels,
1224 and expansion of the vessel-dense elliptical area of the uterus is associated with supporting
1225 increased embryonic oxygen demand (Murphy et al., 2010).

1226 Several protein-coding genes are known to be involved with angiogenesis, vascularization,
1227 and vasodilation in utero. One study that examined expression patterns across chickens
1228 (oviparous), horses (viviparous), two viviparous squamates, and one oviparous squamate found
1229 that no examined genes for angiogenesis showed a viviparity-specific expression pattern
1230 (Griffith, Brandley et al., 2017). However, other than the chicken, the only oviparous taxa
1231 included in this study was a reproductively bimodal skink, *Lerista bougainvillii* (Griffith,
1232 Brandley et al., 2017). Alternatively, differential gene expression analyses on oviparous and
1233 viviparous individuals of *Zootoca vivipara*, revealed pathways for angiogenesis enriched in
1234 viviparous female reproductive tissues; and pathways for angiogenesis were enriched across
1235 genes under divergent selection in oviparous and viviparous *Z. vivipara* individuals.

1236 In the uterine tissue of gestating viviparous skinks and rats, several genes for angiogenesis
1237 are upregulated—*EPASI*, *HIF1A* and *VEGFA* (Brandley et al., 2012; Whittington et al., 2015,
1238 2017). Other proteins involved in vascularization and vasodilation in utero include members of
1239 the vascular endothelial growth factor (*VEGF*) gene family, VEGF receptors (*VEGFRs*),
1240 placental growth factor (*PGF*) and nitric oxide synthase (*NOS*) (Blomberg et al., 2010; Chen,
1241 Wang et al., 2015; Gilbert, 2010; Reynolds et al., 2006; Risau, 1997; Torry et al., 2003;
1242 Vonnahme et al., 2001). In *Saiphos equalis*, different homologs of *NOS* experience different
1243 patterns of gene expression across the oviparous and viviparous stages of gestation/gravidity
1244 (Foster et al., 2020). One homolog of *NOS* is upregulated during oviparous late gestation, and

1245 another is upregulated during viviparous late gestation (Foster et al., 2020). Several genes
1246 involved with angiogenesis and vascular morphogenesis are downregulated in the pre-
1247 implantation uterus of a marsupial, the Fat Tailed Dunnart, *Sminthopsis crassicaudata*—
1248 *ADGRA2, ADGRB2, ANGPTL1, EPHB4, ISM1, PDZRN3, RHOJ, TNMD,* and *VEGFD*
1249 (Whittington et al., 2018).

1250 In humans, immune factors are also responsible for increasing embryonic blood supply.
1251 Embryonic non-classical MHC class I molecule, HLA-G, and uterine natural killer (uNK) cells
1252 support increased embryonic blood supply (Moffett & Loke, 2006; Rajagopalan et al., 2006). A
1253 similar pattern of utilizing immune properties to support embryonic blood supply has not been
1254 yet identified in squamates.

1255 Lipids are a main energy source for embryos. Lipoprotein lipase (LPL) is an important
1256 enzyme in lipid transport. LPL is significantly expressed on the syncytiotrophoblasts, specialized
1257 placental cells, of humans (Lindegaard et al., 2005) and the endometrium of cows (Forde et al.,
1258 2011), and pigs (Ramsay et al., 1991), where it plays a role in lipid mobilization. A viviparous
1259 lizard, *Pseudemoia entrecasteauxii*, increases capacity for lipid transport toward the end of
1260 pregnancy (Griffith, van Dyke & Thompson, 2013). The uterine tissue of the yolk-sac placenta in
1261 this species had significantly higher expression of LPL than the uterine tissues of the
1262 chorioallantoic placenta (Griffith, van Dyke & Thompson, 2013), leading the authors to suggest
1263 that the yolk-sac placenta is the major site of lipid transport. LPL expression was not detected
1264 during pregnancy in the viviparous skink, *Chalcides ocellatus* (Blackburn, 1992; Brandley et al.,
1265 2012). Instead, lipid transport may be facilitated by fatty acid binding proteins in this species
1266 (Chmurzyńska, 2006; Brandley et al., 2012). These are also active on mammalian placenta
1267 (Haggarty, 2002).

1268 Apolipoproteins are also suitable candidates for transport of fatty acids, cholesterol, and
1269 phospholipids. Five of these (*APOA1*, *APOA2*, *APOA4*, *APOE*, and *APOM*) and *APOA1BP* are
1270 significantly upregulated in the pregnant uterus of the viviparous skink, *Chalcides ocellatus*
1271 (Brandley et al., 2012). *APOA1BP* is also upregulated in the uterus of the chorioallantoic
1272 placenta and yolk-sac placenta compared to non-gestational uterine tissues in *Pseudemoia*
1273 *entrecaeauxii* (Griffith et al., 2016). Additionally, upregulation of 136 genes that encode solute
1274 carrier proteins (SLCs) in the pregnant uterus of *Chalcides ocellatus* are associated with
1275 transport of inorganic ions, metals, glucose, amino acids, peptides, fatty acids, and carboxylic
1276 acids (Brandley et al., 2012).

1277 Supply of amino acids is required for embryonic development. SLCs have important
1278 transport functions, including the transport of amino acids, and thus they are considered to be
1279 important for gestation (Foster et al., 2022). However, a recent study found no overlap in the
1280 amino acid transporting SLCs upregulated in placentas of viviparous placentrophic vertebrates
1281 studied, which included eight representatives from Mammalia, Reptilia, and Chondrichthyes
1282 (Foster et al., 2022). However, *SLC38A3* was upregulated in all viviparous species except *Rattus*
1283 *norvegicus* (Foster et al., 2022).

1284 Cathepsins and phospholipases are important for uterine secretions for embryonic
1285 development in horses, pigs, sheep, and cattle (Bazer, 1975; Satterfield et al., 2007; Song et al.,
1286 2010). Cathepsins are present in yolk sacs of humans and mice. They function to degrade
1287 proteins to free amino acids (Cindrova-Davies et al., 2017). Two genes for cathepsin L (*CTSL1*
1288 and *CTSL2*) are upregulated in the uterus during gestation in *Chalcides ocellatus* (Brandley et al.,
1289 2012). *CTSL* is also upregulated in the uterus during the pre-implantation phase in the Fat-Tailed
1290 Dunnart, *Sminthopsis crassicaudata* (Whittington et al., 2018), and in the uterus of the

1291 chorioallantoic placenta and uterus of the yolk sac placenta during gestation in *Pseudemoia*
1292 *entrecasteauxii* (Griffith et al., 2016).

1293 In viviparous individuals of the reproductively bimodal lizard, *Saiphos equalis*, many genes
1294 for cellular adhesion are upregulated during late gestation (Foster et al., 2020). The authors
1295 postulated that this helps facilitate maternal-fetal signaling and paracellular transport (Foster et
1296 al., 2020). Gao et al. (2019) identified a set of genes in *Phrynocephalus vlangalii* that were
1297 differentially expressed in the uterus during the stage of placentation and these enriched GO
1298 terms functionally related to the process of placentation. This included an estrogen receptor
1299 (*ESRI*) and two growth factor receptors (*GHR* and *IGFIR*) (Gao et al., 2019).

1300 Finally, the proteomes of the ovary and placenta from obligately placentrophic *Mabuya*
1301 lizards can further serve as a useful resource for examining nutrient provisioning in squamates
1302 (Hernández-Díaz et al., 2017). In the placenta they found protein expression involved with
1303 nutrient metabolism, transport, protein synthesis, and embryonic development (Hernández-Díaz
1304 et al., 2017).

1305

1306 (5) Uterine glands: adenogenesis, placenta development and histotrophy

1307 In addition to their role in eggshell deposition in oviparous taxa, uterine glands also secrete
1308 growth factors and cytokines that support placental development in mammals. In humans, these
1309 include transforming growth factor- β (TGF- β), epidermal growth factor (EGF), vascular
1310 endothelial growth factor (VECG), and leukemia inhibitory factor (LIF) (Hempstock et al.,
1311 2004). In eutherians, TGF- β supports placental development by regulating proliferation and
1312 invasion rates of placental cells lines (Caniggia et al., 2000; Hempstock et al., 2004; Lafontaine
1313 et al., 2011).

1314 Histotrophy (also called histiotrophy) occurs when nutrients are secreted into the uterine
1315 lumen from vesicles of the columnar epithelial cells of the uterus and taken up by the embryo.
1316 Histotrophic nutrient provisioning is documented across amniotes including marsupials
1317 (Whittington et al., 2018), several ungulate taxa (Bazer et al., 2011; Han et al., 2016; Gao et al.,
1318 2009), humans (Burton et al., 2002), and appear to occur in some viviparous squamates (van
1319 Dyke et al., 2014). In humans, histotrophic nutrient provisioning occurs during the first trimester.
1320 The intervillous space is filled with fluid containing uterine gland secretions that get
1321 phagocytosed by the syncytiotrophoblasts and are the initial nutrient source for the fetus (Burton
1322 et al., 2002). Two of these glycoproteins are epithelial mucin (*MUC1*) and glycodefin A (*GdA*)
1323 (Burton et al., 2002). Interestingly, the *MUC15* gene is upregulated during gravidity/gestation in
1324 the uterus of oviparous and viviparous *Saiphos equalis* individuals (Foster et al., 2020). This also
1325 occurs in the chorioallantoic placenta of *Pseudemoia entrecasteauxii* during gestation (Griffith et
1326 al., 2016). Several mucins are expressed in the uterus in non-gravid and gravid samples from
1327 oviparous individuals of *Lerista bougainvillii* and *Lampropholis guichenoti* (Griffith et al.,
1328 2016).

1329 A survey of viviparous squamates with modest to extensive placentrophy revealed
1330 prevalence of histotrophic nutrient provisioning rather than hemotrophy, transfer of nutrients
1331 between maternal and fetal blood streams (Blackburn 2015). Embryos of *Chalcides chalcides*
1332 have extensive placentrophy that supports substantial maternal nutrient provisioning and
1333 histotrophy (Blackburn, 2015a). Histotrophy may lessen parent-offspring conflict and give the
1334 mother the control over nutrient provisioning compared to hemotrophy (Blackburn, 2015b).

1335 *Chalcides ocellatus* has less extensive placentrophy than *C. chalcides* but the gestating uterus
1336 still illustrates expression of many genes associated with organic and inorganic nutrient transport

1337 (Blackburn, 2015a). Multiple *TGF-β* genes are differentially expressed in the uterus during
1338 gestation in *C. ocellatus*, however most these are downregulated compared to non-gestational
1339 uterine tissue (Murphy et al., 2012). The influence of *TGF-β* on placental development and
1340 nutrient provisioning in *Chalcides spp.* remains to be explored to my knowledge. A TGF-β
1341 receptor (*TGFBRI*) was associated with placental development in *Phrynocephalus vlangalii*
1342 (Gao et al., 2019).

1343 Essential to histotrophy is adenogenesis, the generation of endometrial glands. Adenogenesis
1344 allows for the secretion of histotrophs. The period of early development during which
1345 adenogenesis occurs is highly variable among vertebrates but it is required for embryonic
1346 survival (Gray et al., 2001, 2002; Spencer & Bazer, 2004). Some genes involved with
1347 adenogenesis in sheep are insulin-like growth factor 1 (*IGF-1*), *IGF-2*, *PAX2*, *LHX1* (also known
1348 as *LIM1*) and *EMX2*, genes in the abdominal-B HOXA cluster, members of both *Wnt* and
1349 Hedgehog (*Hh*) gene families (Fazleabas et al., 2004), prolactin (*PRL*), fibroblast growth factor 7
1350 (*FGF7*), *FGF10*, *FGFR2IIIb*, hepatocyte growth factor (*HGF*), a receptor tyrosine kinase (*c-*
1351 *Met*), and cadherins (Fazleabas, 2007).

1352 In the gestating uterus of *Chalcides ocellatus*, insulin-like growth factor-binding protein 5
1353 (*IGFBP5*) is one of the most significantly downregulated genes compared to non-gestational
1354 uterine tissue (Brandley et al., 2012). *IGFBP5* is evolutionarily conserved and multifunctional,
1355 with an important role in regulating IGF signaling, including that of *IGF-1* and *IGF-2* (Duan &
1356 Allard, 2020). Other than adenogenesis in sheep, IGFs serve an important role in the growth of
1357 fetal and maternal tissues in mammals (Gibson et al., 2001; Kampmann et al., 2019).

1358 Genes involved with histotrophic secretion in the marsupial *Sminthopsis crassicaudata*
1359 include *AP4SI*, *HYOU1*, and *SRPRA* (Whittington et al., 2018). Nutrient transporters

1360 significantly upregulated at this time are *APOL6* (cholesterol transport (Baardman et al., 2013)),
1361 *PLA2G10* (hydrolysis of fatty acids during pregnancy (Miele et al., 1987)) and a wealth of SLCs
1362 (solute carrier proteins for transport of sugar, ions, anions, glucose, fatty acids, calcium and zinc
1363 (Whittington et al., 2018)). Subsequent research has identified downregulated of *HYOUI* at early
1364 and mid-gestation; and downregulation of *SRPRA* at mid-gestation in viviparous *Zootoca*
1365 *vivipara* compared to oviparous (Recknagel et al., 2021a). In a reproductively bimodal skink,
1366 *Saiphos equalis*, *PLA2G10* is upregulated during viviparous late gestation compared to oviparous
1367 late gestation (Foster et al., 2020). Upregulation of SLCs also occurs in the viviparous skink
1368 *Chalcides ocellatus* (Brandley et al., 2012; Van Dyke et al., 2014) and in the uterus during
1369 pregnancy in the grey short-tailed opossum, *Monodelphis domestica* (Hansen, Schilkey & Miller,
1370 2016).

1371 Uterine glands are also important for secretions of eggshell precursors. I speculate that genes
1372 involved with adenogenesis of uterine glands may be similarly used to support histotrophic
1373 nutrient provisioning during transitions to viviparity, but further research is necessary.

1374 Specialized uterine areolar glands are found in some *Mabuya* lizards, a genus with oviparous
1375 species and viviparous species that utilize placentrophy and histotrophy (Corso et al., 1988,
1376 2000; Jerez & Ramírez-Pinilla, 2001; Ramírez-Pinilla, 2006; Vieira et al., 2007; Visser, 1975).

1377 Transcriptomic research focused on histotrophic nutrient provisioning, placental development,
1378 and secretions of eggshell precursors in oviparous and viviparous *Mabuya spp.* would
1379 complement literature on the genus.

1380

1381 (6) *Discussion & future directions—embryonic nutrients, gas, and water supply*

1382 Many genes for placental functions in mammals have deep origins in vertebrates (Rawn &
1383 Cross, 2008). In pairwise comparisons of different viviparous amniotes, there is overlap in
1384 hormones and proteins (SLC superfamily, insulin-like growth factors, aquaporins and solute
1385 carrier proteins, etc.) involved in uterine remodeling, placentation, and placental transport. While
1386 shared genes are recruited to the uterus across viviparous amniotes (Recknagel et al 2021a), there
1387 are no shared genes recruited to the placenta across viviparous reptiles, mammals, and sharks
1388 (Foster et al., 2022). Evolutionarily, this suggests higher conservation of the regulatory networks
1389 associated with uterine responses to viviparity than placental responses to viviparity. The
1390 relationship of these findings to embryonic nutrient provisioning and the evolution of the
1391 amniotic egg requires further investigation. Supplementary Table 2 illustrates how genes
1392 mentioned in text for water, gas, and nutrient transport are expressed in reproductive tissues of
1393 squamates during gestation and gravidity.

1394 If specific genes or physiological processes impact more than one of the Main Five
1395 categories, it could have a disproportionate influence on transitions. Such an overlap has already
1396 been identified in *Zootoca vivipara*, where 11 genes are associated with both eggshell traits and
1397 gestation length (Recknagel et al., 2021a). The solute carrier (*SLC*) gene superfamily is involved
1398 with both nutrient transport (Brandley et al., 2012; Whittington et al., 2018) and eggshell
1399 deposition (Yang et al., 2020). Adenogenesis is essential for histotrophic nutrient provisioning
1400 and secretion of eggshell precursors. Additionally, progesterone production influences both
1401 uterine quiescence, which is an important state to maintain in lengthened embryonic retention,
1402 and it also inhibits hepatic vitellogenesis, an important process for lecithotrophic nutrient
1403 provisioning. Thus, examining the role of *SLC* gene superfamily members, processes of

1404 adenogenesis, and progesterone production during embryonic development in oviparous and
1405 viviparous squamate may reveal how interconnectivity of the Main Five are.

1406

1407 **V. Embryonic Calcium Provisioning**

1408

1409 The embryonic growth stage requires the greatest demand of calcium (Ecay et al., 2017;
1410 Packard & Packard, 1984; Stewart & Ecay, 2010). To support this, peak uterine concentrations
1411 of calcium are highest during either eggshell deposition or during the embryonic growth stage, in
1412 oviparous and viviparous taxa, respectively (Linville et al., 2010; Stewart et al., 2009).
1413 Regardless of parity mode, embryonic metabolism drives calcium uptake (Packard & Packard,
1414 1984). The calcium source(s) utilized have clade-specific implications on the genomic and/or
1415 physiological changes required to transition between parity modes.

1416

1417 *(1) Phylogenetic context of embryonic calcium sources*

1418 Calcium can be acquired by the embryo in three forms: calcium carbonate in the eggshell,
1419 calcium bound to proteins and lipids in the yolk, and/or free ionic calcium from maternal
1420 delivery through the placenta (Stewart & Ecay, 2010). These correspond with five calcium
1421 mobilization patterns: 1) Birds, turtles and crocodiles predominately depend on the eggshell; 2)
1422 Most squamates, regardless of parity mode, predominately depend on the yolk; 3) Some
1423 squamate species are reliant on both the eggshell and yolk; 4) Some viviparous squamate species
1424 are reliant on both the yolk and placenta; and 5) therian mammals and rare viviparous squamates
1425 predominately depend on the placenta (Blackburn, 2015a; Hoenderop, Nilius, & Bindels, 2005;
1426 Jenkins & Simkiss, 1968; Kovacs, 2015; Packard, 1994; Packard & Seymour, 1997; Stewart et

1427 al., 2009, 2009; Stewart & Eca, 2010; Thompson, Stewart et al., 1999; Thompson, Stewart, &
1428 Speake, 2000; Ramírez-Pinilla, 2006).

1429 From an evolutionary perspective, squamate eggs might serve as the best models of the
1430 ancestral amniote egg. Unlike birds, oviparous squamates generally rely on yolk calcium rather
1431 than eggshell calcium. The yolk sac of non-avian reptiles is a good model for the transition
1432 between the egg of anamniotes and amniotes (Blackburn, 2020). Taken together and given that
1433 hard calcified eggshells of Archelosaurs are likely derived (as discussed in section III.3)—
1434 squamate eggs may have the closest resemblance to the ancestral amniote egg. Interestingly, to
1435 my knowledge, oviparous squamates do not sequester calcium from the eggshell into the yolk
1436 during incubation (Packard, 1994).

1437

1438 *(2) Hypotheses on calcium mobilization and the evolution of parity modes*

1439 It was hypothesized that predominant reliance on eggshell calcium should constrain lineages
1440 to oviparity because the evolution of viviparity would result in a lost calcium source (hereafter
1441 eggshell calcium constraint hypothesis) (Stewart & Eca, 2010; Packard et al., 1977; Packard &
1442 Packard, 1984). This hypothesis suggested that viviparity should only evolve in lineages
1443 predominately reliant on yolk calcium (Packard et al., 1977; Packard & Packard, 1984).
1444 Fittingly, birds, turtles and crocodilians generally rely on eggshell calcium, and they are
1445 constrained to oviparity (Anderson et al., 1987). The eggshell calcium constraint hypothesis
1446 holds true for most viviparous squamates that rely heavily on yolk calcium (Stewart & Castillo,
1447 1984; Stewart & Eca, 2010; van Dyke et al., 2014).

1448 Subsequent research revealed that viviparity is not constrained by a prerequisite reliance on
1449 yolk calcium. Oviparous scincid skinks studied thus far are intermediately reliant on eggshell and

1450 yolk calcium (Linville et al., 2010; Shadrix et al., 1994; Stewart et al., 2009; Stewart &
1451 Thompson, 1993; Thompson et al., 2001). Calcium placentrophy contributes substantially to
1452 embryonic development in several viviparous squamates including *Pseudemoia entrecasteauxii*,
1453 *Eulamprus quoyi*, *Zootoca vivipara*, *Saiphos equalis*, and a species of *Mabuya* lizard (Ecay et al.,
1454 2017; Linville et al., 2010; Ramírez-Pinilla, 2006; Ramírez-Pinilla et al., 2011; Stewart &
1455 Thompson, 1993). These taxa, with the exception of *Zootoca vivipara*, are in the family
1456 Scincidae (Burbrink et al., 2020), which is also the family with the most independent origins of
1457 viviparity in squamates (Blackburn, 1982, 1999; Pyron & Burbrink, 2014).

1458 To understand the breadth of physiological conditions from which oviparity and viviparity
1459 evolve in squamates, future research should examine calcium transport in other lineages. Studies
1460 focused on snakes would be particularly informative given the sparse literature on them.

1461 *Helicops angulatus*, a reproductively bimodal water snake from South America, is an ideal
1462 model for this (Braz et al., 2016). Thus far, many oviparous snakes are known to be
1463 intermediately reliant on yolk and eggshell calcium. This has not precluded viviparity from
1464 evolving in these lineages.

1465 The presence of embryos during extended embryonic retention may trigger positive feedback
1466 stimuli for continued uterine calcium secretions which may support placental calcium transport,
1467 and thus incipient calcium matrotrophy (Stewart & Ecay, 2010). This is postulated to resemble
1468 the hormonal and mechanical stress mechanisms implicated in avian eggshell formation and
1469 uterine calcium secretions (Bar, 2009a; Stewart & Ecay, 2010). The influx of calcium late in
1470 viviparous gestation may be triggered in part by embryonic growth that over distends the uterus.
1471 This is seen in studies on myometrial stretch in mammals when uterine overdistention triggers
1472 spikes in calcium (Kao & McCullough, 1975; and see e.g. Wray et al., 2015).

1473 Dramatic changes to activity in chorioallantois should not be required during parity mode
1474 transitions because these homologous tissues (Metcalf & Stock, 1993) transport calcium
1475 regardless of parity mode (Ecay, Stewart & Blackburn, 2004; Tuan & Scott, 1977; Tuan &
1476 Knowles, 1984; Tuan et al., 1978, 1986). Specialized placental structures in some viviparous
1477 squamates enhance calcium provisioning but specialization is not required for placental calcium
1478 transport (Stewart et al., 2009; Stewart & Ecay, 2010; Thompson et al., 2000). Loss of
1479 chorioallantoic calcium transporting capacity would be disadvantageous to either parity mode.
1480 Growing research reveals that, like mammals, placentrophy and viviparity can evolve
1481 concurrently in squamates (Blackburn, 2015a; Ecay et al., 2017; Stewart & Ecay, 2010).

1482 Placing these previously proposed models in a phylogenetic context, the calcium transport
1483 method of oviparous ancestors likely has an influence on the method of calcium transport used
1484 for viviparous taxa—matrotrophic calcium provisioning, lecithotrophic calcium provisioning, or
1485 a combination of the two. Consistent with the basal cap hypothesis—when viviparity arises from
1486 oviparous ancestors with embryos that depended predominately on eggshell calcium, this should
1487 favor a transition to viviparity via incipient calcium matrotrophy because the chorioallantois
1488 already plays the major role in transporting calcium from the eggshell to the embryo. Since the
1489 reproductive mode and calcium provisioning of oviparous ancestors are essentially unknown,
1490 researchers can use the closest oviparous relatives as proxies. Similarly, viviparous taxa that are
1491 in close phylogenetic proximity to oviparous taxa that depend on lecithotrophic calcium
1492 provisioning should remain reliant on yolk calcium. Together, these guidelines provide a
1493 framework from which researchers can form hypotheses about the calcium provisioning method
1494 of a viviparous lineage if the calcium provisioning method of oviparous close relatives are
1495 known, or vice versa. Measurements of the proportional contribution of different calcium sources

1496 during development has only been done in select taxa (e.g. Packard, 1994; Stewart, 2013;
1497 Stewart & Ecy, 2010; Stewart, Ecy & Blackburn 2004). Once validated, the framework (i.e.,
1498 the calcium provisioning method of close relatives) can help increase the speed at which science
1499 measures and infers the evolutionary history of calcium provisioning across amniotes and
1500 squamates. Collection of this data across the squamate phylogeny may enable assignment of
1501 these hypotheses to specific clades.

1502 Embryonic calcium source could have implications on the physiological changes required to
1503 transition between parity modes. Reliance on yolk calcium should render, essentially, no
1504 mechanistic changes for calcium transport. On the other hand, incipient calcium matrotrophy
1505 requires regulatory changes in the uterus, like timing of calcium secretions (Griffith et al., 2015).
1506 However, regardless of parity mode 1) the uterus secretes calcium, 2) the chorioallantois
1507 transports calcium and 3) embryonic metabolism drives uptake of calcium. Assuming maternal
1508 tissue remains responsive to embryonic metabolism, the joint evolution of matrotrophic calcium
1509 provisioning with viviparity may require little to no physiological adjustments.

1510 The diversity of embryonic calcium provisioning patterns in viviparous squamates may not
1511 be fully explained by the eggshell calcium constraint hypothesis (Packard et al., 1977; Packard &
1512 Packard, 1984) or incipient calcium matrotrophy (Stewart & Ecy, 2010). Both hypotheses
1513 implicitly assume that viviparity equates to a lost eggshell. In one viviparous squamate, *Haldea*
1514 *striatula*, and in viviparous populations of two reproductively bimodal lizards, *Zootoca vivipara*
1515 and *Saiphos equalis*, the calcified eggshell is considered as a component of the placenta (Stewart,
1516 2013). Some other viviparous squamates have transient calcified patches on their embryonic
1517 membranes (Blackburn, 1998; Heulin, 1990, 2005; Qualls, 1996) suggesting that uterine calcium
1518 secreting capabilities in early gestation may be retained in some viviparous lineages. In the case

1519 of reversals, it remains unknown how the uterus shifts back to early calcium secretions after
1520 ovulation (Blackburn, 2015b; Griffith et al., 2015).

1521

1522 *(3) Embryonic calcium provisioning mechanisms*

1523 In vertebrates, specialized tissues that recover environmental calcium and transport it into
1524 blood circulation maintain conserved mechanisms for intracellular calcium transport (Bronner
1525 2003; Hoenderop et al., 2005). These include the uterus, chorioallantoic tissues, and yolk
1526 splanchnopleure (Bronner, 2003; Hoenderop et al., 2005; Stewart, 2013). Therefore, uterine and
1527 embryonic tissues may be pre-adapted for maternal and embryonic calcium provisioning.

1528 In birds, a sub-compartment of the mammillary layer of the eggshell is the calcium reserve
1529 body (Chien et al., 2009), which contains microcrystals of calcite that get dissolved and
1530 transported as calcium to the embryo (Chien et al., 2009). Calcium is eroded from the eggshell
1531 by acid released from villus cavity cells (VCCs) in chorioallantoic membrane (Anderson, Gay,
1532 and Schraer, 1981; Narbaitz et al., 1981; Packard & Lohmiller, 2002; Simkiss, 1980). This
1533 increases the carbonic anhydrase activity of the cells enabling calcium to be released into the
1534 cavity between the eggshell and the chorionic epithelium, where it is taken up by capillary
1535 covering cells (CCCs) in chorioallantoic membrane (Coleman & Terepka, 1972). In some
1536 species this erosion leads to a gradual weakening of the eggshell that facilitates hatching (Chien,
1537 Hincke & McKee, 2008). In chickens, transcalcin, a calcium binding protein, is credited for the
1538 calcium transporting capacity of the chorioallantoic membrane (Tuan & Knowles, 1984; Tuan &
1539 Ono, 1986; Tuan & Scott, 1977; Tuan et al., 1978, 1986). The presence of VCCs and CCCs in
1540 the chorioallantois of viviparous squamates would indicate a known route through which calcium
1541 can be absorbed.

1542 Transcellular calcium transport has been modeled as a three-step process involving proteins
1543 calbindin-D9K, calbindin-D28K, and the highly calcium-specific ion channels of the transient
1544 receptor potential vanilloid gene family (*TRPV5* and *TRPV6*) (Stewart & Ecaj, 2010). Across
1545 vertebrates, this machinery is shared in epithelial tissues with significant roles in calcium
1546 transport (Hoenderop et al., 2005). Estrogen and vitamin D3 have regulatory roles in this
1547 process.

1548 Calbindin-D9K, calbindin-D28K, *TRPV5*, and *TRPV6* is involved with calcium exchange in
1549 multiple organs of birds, squamates, and mammals. Broadly, activity of calbindin-D9K and/or
1550 calbindin-D28K is associated with patterns of calcium absorption in the mammalian kidney and
1551 uterus (Bindels, 1993; Luu et al., 2004), murine uterus and placenta (Lafond & Simoneau, 2006;
1552 Koo et al., 2012), and chicken duodenum and uterus (Bar, 2009b; Yang et al., 2013). In humans,
1553 calbindin-D9K and calbindin-D28K are critical to the active transport of Ca²⁺ across placental
1554 cells (Faulk & McIntyre, 1983; Belkacemi, Simoneau & Lafond, 2002; Belkacemi et al., 2004).
1555 A study on rats suggests that calbindin-D9K increases by over 100-fold in the last 7 days of
1556 gestation (Glazier et al., 1992), when the embryo gains the majority of calcium. *TRPV6* is
1557 involved with maternal-fetal calcium transport in mice (Suzuki et al., 2008). Increased *TRPV6*
1558 and calbindin-D28K expression occurs during eggshell formation in chickens (Yang et al.,
1559 2013). Given the involvement of these genes in both eggshell deposition and embryonic calcium
1560 transport, squamates may have exploited this pathway to support transitions. Expression of these
1561 genes during gestation or gravidity in squamates has been detected (e.g. calbindin-d9K in
1562 *Saiphos equalis*, and calbindin-d28k in *Zootoca vivipara*) (Foster et al., 2020; Recknagel et al.,
1563 2021a), and is expanded upon in the following paragraphs.

1564 In several highly matrotrophic lizards, embryonic uptake of calcium is associated with
1565 placental expression of calbindin-D28K (Stewart et al., 2009; Stinnett et al., 2011, 2012). In both
1566 oviparous and viviparous embryos of *Zootoca vivipara*, sharp increase in calcium uptake in late
1567 development coincides with increased calbindin-D28K and PMCA by the chorioallantois
1568 (Stewart et al., 2009, 2011). In oviparous corn snakes, *Pantherophis guttatus*, expression of
1569 calbindin-D28K in the yolk-sac and chorioallantoic membrane coincides with growth of these
1570 tissues and calcium transport activity (Ecay et al., 2004). The chorioallantois of other lizards and
1571 snakes transport calcium to the embryo and express calbindin-D28K and PMCA (Blackburn,
1572 2004; Ecay et al., 2004; Stewart et al., 2010; Stinnett et al., 2012).

1573 Viviparous embryos of *Zootoca vivipara*, a reproductively bimodal lizard, incubated *ex utero*
1574 respond to availability of calcium by increasing expression of calbindin-D28K (Ecay et al.,
1575 2017). In this species, embryonic recognition of environmental calcium stimulates a transcellular
1576 calcium transporting mechanism and may also alter chorioallantoic membrane paracellular
1577 permeability to calcium (Ecay et al., 2017). The authors proposed that there is a calcium sensing
1578 receptor (CaSR) on chorionic epithelial cells to support this in both oviparous and viviparous
1579 *Zootoca vivipara* embryos (Ecay et al., 2017), similar to the CaSRs expressed by vertebrate cells
1580 involved in calcium homeostasis (Brennan et al., 2013).

1581 As mentioned earlier, PMCA activity is associated with eggshell deposition in birds and
1582 oviparous squamates (Bar, Rosenberg, & Hurwitz, 1984; Hincke et al., 2012; Wasserman et al.,
1583 1991). PMCA is also crucial for calcium transport in late embryonic development in rats (Glazier
1584 et al., 1992). In viviparous scincid lizards, *Niveoscincus metallicus*, *N. ocellatus*, and
1585 *Pseudemoia spenceri*, PMCA was expressed in uterine glandular and surface epithelia during
1586 pregnancy but only *P. spenceri* expressed it throughout gestation (Herbert et al., 2006). When

1587 PMCA was not detected by immunoblotting in the yolk splanchnopleure of *Haldea striatula*, a
1588 viviparous snake that relies predominately on yolk calcium (Stewart, 1989; Fregoso, Stewart, &
1589 Ecay, 2010), NCXs were proposed as an alternative transporter of calcium (Fregoso et al., 2012).
1590 NCXs are important for placental calcium transport in humans (Belkacemi et al., 2005).

1591 Calcitropic hormones, those involved with calcium transport, and phosphotropic hormones,
1592 those involved with phosphorous transport, operate via an interconnected pathway (Andrukhova
1593 et al., 2016; Biber, Hernando & Forster, 2013; Blaine, Chonchol & Levi, 2015; Erben &
1594 Andrukhova, 2015). Phospho- and calcitropic hormones are important regulators of fetal serum
1595 mineral concentrations (Kovacs, 2015). Evidence from viviparous amniotes suggests that these
1596 are suitable candidates for embryonic calcium provisioning. In mice, genes encoding parathyroid
1597 hormone (*PTH*) and *PTH*-related peptide (*PTHrP*) are important regulators of placental calcium
1598 transport (Kovacs et al., 1996; Simmonds et al., 2010). A non-exhaustive list of additional
1599 candidates for embryonic calcium provisioning include fibroblast growth factor 23 (Bar, 2009a;
1600 Erben & Andrukhova, 2015; Stewart & Ecay, 2010), the annexin gene family (Matschke et al.,
1601 2006), carbonic anhydrase (Narbaitz et al., 1981; Tuan & Knowles, 1984), and calcium binding
1602 proteins (CaBPs) can be found in the referenced literature.

1603

1604 (4) *Discussion & future directions—calcium provisioning and parity mode evolution*

1605 Phylogenetic frameworks enable researchers to make broader testable hypotheses about the
1606 evolutionary history of calcium provisioning in specific clades. Such a framework is proposed in
1607 section V.2 to infer ancestral parity modes in the context of calcium provisioning in amniotes.
1608 Implications gleaned from taxon-specific studies can be explored in distantly related analogous
1609 groups.

1610 Genes involved with calcium transport in uterine and embryonic tissues have been described
1611 across mammals, birds, and reptiles. Like other amniotes, activity of calbindin-D28K and PMCA
1612 supports embryonic calcium provisioning across diverse oviparous and viviparous squamates.
1613 Their involvement with both eggshell deposition and embryonic calcium provisioning makes
1614 these particularly interesting candidates for parity mode evolution. The regulatory influence of
1615 other molecules in calcium transport, like *PTH*, *PTHrP* and NCXs has not been evaluated
1616 thoroughly in squamates. Additional reviews on mechanisms of embryonic calcium provisioning
1617 in squamates can be found in the literature (Stewart, 2013; Stewart & Eday, 2010).

1618 Additionally, I add a speculation. Perhaps lineages with incipient calcium matrotrophy more
1619 feasibly reverse to oviparity because of the continued role of the uterus in calcium provisioning.
1620 However, this hypothesis only holds up if maternal provisioning of calcium is not synonymous
1621 with maternal provisioning of all nutrients.

1622

1623 **VI. Maternal-Fetal Immune Dynamics**

1624

1625 Medawar (1953) pointed out the paradigm between the peripheral body's normal attack
1626 response to allografts (foreign tissue) and uterine tolerance to embryos (Medawar, 1953). This
1627 was inspired by earlier work by Ray Owen (Owen, 1945). Stricter regulation of the maternal and
1628 fetal immune systems is expected for viviparous reproduction because of contact between uterine
1629 and embryonic tissues. Oviparity may pose less of an immunological challenge. Medawar
1630 suggested barriers, inertness and/or immunosuppression enable pregnancy. This formed the
1631 foundation of decades of medical research on immune dynamics between maternal, embryonic,
1632 and paternal immune factors in utero.

1633 In recent years, there was a call for a reappraisal of Medawar's paradigm (Chaouat, 2010,
1634 2016; Moffett & Loke, 2004, 2006; Mor et al., 2011; Stadtmayer & Wagner, 2020b; Yoshizawa
1635 2016). Moffett & Loke (2006) caution against conceptualizing embryos as analogs of allografts.
1636 To my knowledge, this perspective has yet to reach the evolutionary literature on squamate
1637 parity mode evolution (Foster et al., 2020; Graham et al., 2011; Gao et al., 2019; Murphy &
1638 Thompson, 2011; van Dyke, Brandley, & Thompson, 2014; Murphy, Thompson, & Belov, 2009;
1639 Recknagel et al., 2021a). Importantly, challenges to Medawar's paradigm do not preclude
1640 immunological responses to viviparity. They simply suggest that the immune environment of the
1641 uterus is uniquely evolved to support exposure to foreign tissue.

1642 The uterine immune system has a distinct evolutionary history from the periphery. It enables
1643 cooperative dynamics with foreign tissues. It supports fertilization and early embryonic
1644 development. This should have started evolving, distinct from the periphery, since internal
1645 fertilization first originated. To contextualize this, I discuss the changing landscape of
1646 immunological research at the maternal-fetal interface and what it means in the context of
1647 amniote parity mode evolution. Overall, I hope readers consider how the uterus evolved to
1648 support internal gestation, and which model systems may be appropriate to investigate this.

1649 Most literature on maternal-fetal immune dynamics limits itself to mammals. Squamates may
1650 serve as a better comparative model for understanding the evolution of the uterine immune
1651 system. Active research on the peripheral reptilian immune system (Zimmerman et al., 2010,
1652 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et al., 2017;
1653 Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights on this.

1654

1655 *(1) Comparing amniote immune systems*

1656 Cellular components of the innate immune system are conserved across jawed vertebrates
1657 (Uribe et al., 2011; Zimmerman et al., 2010). The general machinery of the adaptive immune
1658 system is ancient despite divergences and convergences across all domains of life (Ghosh et al.,
1659 2011; Morales et al., 2017; Müller et al., 2018; Rimer et al., 2014). Diversification of antigen
1660 receptor genes likely occurred independently in a lineage-specific fashion (Boehm et al., 2018).
1661 Compared to mammals, the avian immune system requires less antigen (Larsson et al., 1998).
1662 Birds also have faster but shorter antibody responses, potentially due to their higher body
1663 temperatures (Zimmerman, 2010).

1664 Reptiles have the same general components of the mammalian immune system (Zimmerman,
1665 2020). However, the reptilian immune system may not fit neatly into the two arms of mammalian
1666 immune systems—innate and adaptive (Zimmerman, 2010; 2020). Expanding upon this is
1667 beyond the scope of this review, but it is worth considering in future evolutionary research.
1668 Squamates may serve as a better comparative model for understanding the evolution of the
1669 uterine immune system. Active research on the peripheral reptilian immune system (Zimmerman
1670 et al., 2010, 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et
1671 al., 2017; Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights. I
1672 refer readers to articles by Zimmerman et al. (2010, 2020) and Ghorai et al. (2018), and the book
1673 by Williams (2012) for more information on the avian immune system.

1674

1675 (2) *Medawar's paradigm*

1676 Tolerance toward the foreign fetus was postulated to occur through immunological inertness,
1677 immunosuppression or immunotolerance mechanisms (Medawar, 1953). Theoretically,
1678 immunotolerance could be established if there are relatively small quantities of alloantigens

1679 present, resulting in regulatory responses rather than activating responses (Pradeu, 2011).
1680 Contradicting this, the larger the alloantigen difference between the mother and embryo the
1681 bigger and healthier the placenta is in rats (Chaouat et al., 2010). In humans, divergent HLA
1682 profiles between mother and embryo do not lead to detrimental immune responses (Tilburgs,
1683 Scherjon, & Claas, 2010). Instead, cooperative inflammatory responses between maternal and
1684 fetal tissues support reproduction (Stadtmauer et al., 2020a). In humans, microchimeric cell
1685 populations, presence of cells from one individual in another genetically distinct individual, are
1686 now considered a normal expectation of pregnancy (Nelson, 2012).

1687 In his 1991 Nobel Lecture, Medawar acknowledged that maternal and embryonic tissues
1688 have regular exposure to alloantigens (Medawar, 1991). It has become clear that the maternal
1689 immune system actively responds to fetal alloantigen rather than responding solely with
1690 ignorance or anergy (Arck & Hecher, 2013). Neither maternal immunosuppression/privilege nor
1691 embryonic inertness/immaturity fully explain immune dynamics during gestation in mammals,
1692 including those with the simple epitheliochorial placentation (Chaouat et al., 2010; Chavan,
1693 Griffith & Wagner, 2017; Moffett & Loke, 2004, 2006; Stadtmauer & Wagner, 2020a).

1694

1695 *(3) Perspectives on the evolution of the uterine immune system*

1696 Viviparous reproduction existed eons before the origin of mammals and, to my knowledge,
1697 no evidence suggests there was immune conflict within these taxa (Chaouat, 2016). Placentrophly
1698 existed as far back as the invertebrate clade Bryozoa (Ostrovsky, 2013; Schwaha et al., 2019),
1699 suggesting an ancient history for supportive maternal-fetal immune dynamics. Differing from
1700 Medawar's paradigm, Polly Matzinger, who proposed the 'danger model' for the immune system

1701 (Matzinger, 2007), wrote “Reproduction cannot be a danger. It does not make evolutionary
1702 sense” (Chaouat, 2016).

1703 In mammals, immunological cells at the maternal-fetal interface may not function through
1704 self-non-self-discrimination, as they are understood to function in the rest of the body (Chaouat,
1705 2016; Moffett & Loke 2004, 2006). The ‘maternal-fetal interface’ may be better conceptualized
1706 as ‘maternal-fetal intra-action’ given the dynamics between maternal and fetal immune systems
1707 in mammals (Yoshizawa, 2016). It is unclear if these insights apply to other viviparous amniotes.

1708 In mammals, immune factors in the uterus and placenta appear to be specifically evolved to
1709 support maternal-fetal immune dynamics. Several cell types have unique functions and/or
1710 phenotypes in utero—uterine NK (uNK) cells, uterine macrophages, uterine T regulatory cells
1711 (Faas & de Vos, 2017; Mold et al., 2008, 2010; Mold & McCune, 2011). An immunosuppressive
1712 antigen, HLA-G, is almost exclusively expressed by trophoblasts (Faulk & Temple, 1976;
1713 Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al., 1997). Taken from an
1714 evolutionary perspective, this suggests that the uterine immune system in viviparous mammals
1715 evolved unique responses to allogenic tissues that differ from the periphery. Whether the
1716 evolution of this system predates mammals remains to be explored, to my knowledge.

1717 It is suggested that viviparous reproduction is immunologically compatible in species with
1718 less active adaptive immune system, like sharks (Chaouat, 2016). In these clades, innate immune
1719 cells, like uNK cells, may be sufficient to regulate immune responses during pregnancy (Moffett
1720 & Loke, 2004; Chaouat, 2016). Given that there is an unclear distinction between the innate and
1721 adaptive immune system in reptiles (Zimmerman, 2020), determining immunological difficulty
1722 of evolving viviparity in squamates requires further investigation.

1723 In uterine tissue of oviparous and viviparous skinks maternal antigens are expressed prior to
1724 and during gestation and gravidity (Murphy et al., 2009), but the viviparous species in the study
1725 have a unique expression profile of MHC antigens which may ‘hide’ the embryo from the
1726 maternal immune system (Murphy et al., 2009). Similarly, in a reproductively bimodal skink,
1727 *Saiphos equalis*, both oviparous and viviparous gestation is associated with expression of MHC
1728 genes (Foster et al., 2020). Regardless of parity mode, *S. equalis* expresses genes associated with
1729 immunocompetence, including MHC genes including *H2-EA* (Foster et al., 2020). The similar
1730 profile between the oviparous and viviparous state is attributed to the use of very long egg
1731 retention utilized by oviparous *S. equalis* (Foster et al., 2020). This highlights that extended
1732 embryonic retention is accompanied with immunological responses in utero, which is relevant to
1733 the EER model on amniote origins.

1734 Some of these genes expressed by *S. equalis* are also expressed in viviparous *Chalcides*
1735 *ocellatus* during gestation including complement component genes (C3, C9) and MHC genes
1736 (Brandley et al., 2012; Foster et al., 2020). The majority of immune genes expressed during
1737 gestation/gravidity in *S. equalis* have immunoglobulin receptor binding functions (Foster et al.,
1738 2020), an important feature of eutherian pregnancy that prevents rejection of the fetus through
1739 actions of the maternal innate immune system (Alijotas-Reig, Llorba, Gris, 2014)). In another
1740 reproductively bimodal skink, *Zootoca vivipara*, immune system response genes are enriched in
1741 the set of genes under divergent selection in oviparous and viviparous genomes (Recknagel et al.,
1742 2021a).

1743

1744 (4) *Implications of the reptilian immune system and morphology on parity mode evolution*

1745 Ectothermic reptiles may inherently have a more tolerogenic uterine environment compared
1746 to mammals due to their slower antibody response. It can take up to six weeks to reach peak
1747 concentrations (Ingram & Molyneux, 1983; Grey, 1963; Marchalonis et al., 1969; Pye et al.,
1748 2001; Origgi et al., 2001; Work et al., 2000). A slower metabolism also makes several reptiles
1749 more tolerogenic to pathogens (Ghorai & Priyam, 2018).

1750 During pregnancy in the viviparous skink, *Chalcides ocellatus*, there is a reduced response to
1751 in vitro exposure to mitogens concanavalin A (Con A), phytohemagglutinin (PHA), and
1752 *Escherichia coli* lipopolysaccharide (LPS) (Saad & El Deeb, 1990). Oviparous lizards exhibit
1753 immune activation tradeoffs during reproductive cycles (Cox, Peadar, & Cox, 2015; Durso &
1754 French, 2018; French, Johnston, & Moore, 2007; Uller, Isaksson, & Olsson, 2006).

1755 In the majority of viviparous squamates, the eggshell membrane is absorbed during
1756 pregnancy (Blackburn, 1993). In mammals, epitheliochorial placentation (the most superficial
1757 and non-invasive placenta type) is sufficient to cause immunorecognition from the mother.
1758 Specialized placental cells, trophoblasts, may be more common in other viviparous vertebrates
1759 than previously recognized (Blackburn, 2015a). For example, a gene with fusogenic properties
1760 characteristics of trophoblast syncytins was recently identified in the *Mabuya* lizard placenta
1761 (Cornelis et al, 2017). In mammals, trophoblasts are antigen presenting and actively participate
1762 in maternal-fetal immune dynamics.

1763 A few viviparous squamates have placentas with characteristics similar to placentas found in
1764 eutherian mammals—syncytialized cells layers, specialized zones such as areolae and
1765 placentomes, or cellular invasion of maternal tissues by the fetus (Blackburn & Flemming, 2012;
1766 Jerez & Ramírez-Pinilla, 2001; Vieira et al., 2007). The increased contact here may require more

1767 tightly regulated immune dynamics at the maternal-fetal interface compared to other viviparous
1768 squamates.

1769

1770 (5) *The inflammation paradox*

1771 In mammals, implantation evolved from an ancestral inflammatory attachment reaction
1772 (Griffith, Chavan et al., 2017). Inflammation is the most crucial system to support implantation,
1773 but it is also the greatest threat to the continuation of pregnancy (Chavan et al., 2017). This
1774 phenomenon is called the inflammation paradox. In humans, immune cells including uterine
1775 macrophages, T cells of multiple subtypes, uterine natural killer (uNK) cells, dendritic cells, and
1776 natural killer T (NKT) cells increase until implantation and remain abundant in the uterus
1777 throughout first trimester (Bulmer et al., 1991; Bulmer, Williams & Lash, 2010). Early
1778 implantation in humans is characterized by high pro-inflammatory T helper (Th)-1 cells and
1779 cytokines (IL-6, IL-8, and TNF α) (Yoshinaga, 2008). The exploitation of inflammatory
1780 mechanisms for eutherian implantation and the shift toward non-inflammatory activity to
1781 maintain pregnancy may have been key in enabling extended embryonic retention of eutherians
1782 (Griffith, Chavan et al., 2017).

1783 How the inflammation paradox applies to viviparous squamates is unclear, given that
1784 placentation in squamates and mammals is not homologous (Griffith, Van Dyke, & Thompson,
1785 2013). In extrauterine pregnancies of mammals with non-invasive placentas, the embryo will
1786 invade extrauterine tissue because it is not inhibited by uterine secretions (Vogel, 2005; Samuel
1787 & Perry, 1972). However, in *Pseudemoia entrecasteauxii*, a viviparous skink that also has a non-
1788 invasive placenta, extrauterine pregnancy does not result in invasive implantation of extrauterine
1789 tissues (Griffith, Van Dyke, & Thompson, 2013). The inherent invasive nature of mammalian

1790 embryos outside of the uterus, compared to the non-invasive nature of viviparous squamate
1791 embryos studied thus far, suggests that the parent-offspring conflict and the inflammation
1792 paradox may be less pronounced in viviparous squamates compared to viviparous mammals.

1793

1794 *(6) Inertness and barriers at the maternal-fetal interface*

1795 The uterine environment is not inert or sterile (Agostinis et al., 2019; Erlebacher, 2013;
1796 Moffett & Loke, 2006; Munoz-Suano, Hamilton, & Betz, 2011; Murphy, Thompson, & Belov,
1797 2009; Yoshimura, Okamoto, & Tamura, 1997). In humans, the decidual layer of the uterus
1798 during pregnancy is comprised of ~40% leukocytes (Ander, Diamond, & Coyne, 2019; Manaster
1799 & Mandelboim, 2010). This cellular subpopulation has 70% uNK cells, 10-20% antigen
1800 presenting cells (APCs) including macrophages and dendritic cells, and 3-10% T cells of several
1801 subtypes (Abrahams et al., 2004; Hanna et al., 2006; Kämmerer et al., 2006; Le Bouteiller &
1802 Piccinni, 2008; Liu et al., 2017; Manaster & Mandelboim, 2010; Moffett-King, 2002; Moffett &
1803 Loke, 2006; Roussev et al., 2008). There is an abundance of decidual large granular lymphocytes
1804 (LGLs), CD3-NK cells and CD3+ activated cytotoxic T cells, in the human uterus, that have
1805 cytotoxic properties and produce cytokines, and these are affected by fetal MHC molecules
1806 (Rieger, 2002).

1807 Birds also have immunocompetent cells in their oviducts. T and B cells are present in
1808 chicken ovary where they are stimulated by estrogen (Barua & Yoshimura, 1999; Withanage et
1809 al., 2003; Zettergren & Cutlan, 1992). Other immunocompetent cells in the chicken oviduct
1810 include IgG+, IgA+ and CD3+ (Yoshimura, Okamoto, & Tamura, 1997). Immune competent
1811 cells located throughout the mucosal tissue of avian oviductal segments including macrophages,

1812 antigen presenting cells (APCs) expressing MHC class II antigens, helper T cells and cytotoxic T
1813 cells, and premature B cells (Das, Isobe, & Yoshimura, 2008).

1814 Inert barriers between maternal and fetal tissues may 'hide' the embryo. In oviparous taxa,
1815 the eggshell may serve as a barrier. However, the antimicrobial properties of the eggshell matrix
1816 in birds demonstrate that even the eggshell is not inert. The FAS ligand, also called APO-1 or
1817 CD95, in humans and rodent embryonic tissue was proposed to serve as a barrier because it
1818 causes apoptosis of surrounding maternal immune cells (Kayisli et al., 2003; Makrigiannakis et
1819 al., 2008).

1820 Medawar suggested that an impermeable placenta strictly regulates molecular exchanges,
1821 preventing rejection of the embryo (Medawar, 1991). Syncytiotrophoblasts lack cellular junctions
1822 and thus it was postulated to serve as this barrier (Ander et al., 2019). However, the growing data
1823 on bidirectional cellular traffic of APCs, even in mammals with noninvasive placentas, rejected
1824 this hypothesis (Bakkour et al., 2014; Burlingham & Bracamonte-Baran, 2015; Fujiki et al.,
1825 2008; Turin et al., 2007).

1826

1827 *(7) T cell populations and mammalian viviparity*

1828 In mammals, immune-dynamics at the maternal-fetal interface are established through
1829 innate and adaptive immune responses. There is a delicate balance between ratios of Th1, Th2,
1830 Th17, Tregs and memory T cells at the maternal-fetal interface in eutherian mammals during
1831 gestation (Chaouat et al., 1997; Kieffer et al., 2019; Peck & Mellins, 2010; Saito et al., 2010; Wu
1832 et al., 2014). A shift in utero from T helper type 1 (Th1) cells to T helper type 2 (Th2) cells
1833 during gestation in mammals equates to a shift from pro-inflammation to anti-inflammation. The
1834 galectin proteins, GAL-13 and GAL-14, expressed by syncytiotrophoblasts, bind to T cells

1835 where they inhibit activation, induce apoptosis, and enhance interleukin-8 (IL-8) production
1836 (Balogh et al., 2019).

1837 Growing research is revealing the central role of Tregs at the maternal-fetal interface
1838 during pregnancy in mammals (Teles et al., 2013; Wienke et al., 2019). Tregs play a central role
1839 in immunosuppression in mammals (Attias, Al-Aubodah, & Piccirillo, 2019). Differentiation of
1840 Tregs is governed by the transcription factor, *FOXP3* (Ramsdell & Rudensky, 2020).

1841 Alloantigen-dependent, uterine T cell signaling, and immunocompetent embryonic cells and their
1842 products facilitate enhanced regulatory phenotypes of immune cells overall (Ander et al., 2019).

1843 The T-cell dependent adaptive immune system of mammals is unique. This may have
1844 prompted their intricate balance of Treg mediators of immunotolerance at the maternal-fetal
1845 interface (Chaouat, 2016). Birds rely more heavily on B cells. In non-avian reptiles, T helper
1846 cells are functional, but the presence and function of other T cell subsets is unclear (Zimmerman,
1847 2020; Zimmerman, Vogel, & Bowden, 2010). The potential role of T cells and Tregs in
1848 viviparous squamate gestation should not be discounted. Treg-like cells have been identified in a
1849 pufferfish, *Tetraodon nigroviridis* (Wen et al., 2011), suggesting that Tregs may have an ancient
1850 evolutionary history.

1851

1852 (8) *Progesterone, cytokines, and maternal-fetal immune dynamics*

1853 In addition to the role of progesterone in uterine quiescence (embryonic retention) and
1854 hepatic vitellogenesis (nutrient provisioning), it also plays a role in maternal-fetal immune
1855 dynamics. In the uterus of pregnant mammals, progesterone concentrations are associated with
1856 altered B cell immunoglobulin secretion, inhibition of NK-cell mediated cytotoxicity and the shift
1857 from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) dominated immune responses

1858 (Druckmann & Druckmann, 2005). Progesterone is also associated with immunomodulatory
1859 effects (Ortega Brown et al., 1990). During gestation in *Agkistrodon piscivorus*, a viviparous pit
1860 viper, progesterone concentrations are associated with decreased complement performance
1861 (Graham et al., 2011), a portion of the immune system that promotes inflammation, among other
1862 immune functions.

1863 In humans, progesterone induced protein (PIBF) is transported by placental extravillous
1864 trophoblasts to maternal lymphocytes causing the induction of interleukin-10 (IL-10) production,
1865 contributing to the Th2 dominant responses (Szekeres-Bartho, Šučurović, & Mulac-Jeričević,
1866 2018). IL-10 is a potent anti-inflammatory cytokine that is produced by multiple cell types
1867 (Zimmerman, Bowden, & Vogel, 2014). It is associated with Th2 response, and it inhibits Th1
1868 responses. The phenotype of uterine macrophages is affected by trophoblasts when they secrete
1869 IL-10 and macrophage colony-stimulating factor (M-CSF) (Svensson-Arvelund et al., 2021). IL-
1870 10 inhibits IFN- γ and increases in response to infection in chickens (Giansanti, Giardi, & Botti,
1871 2006; Rothwell et al. 2004). In the uterus of the oviparous skink, *Lampropholis guichenoti*,
1872 during gravidity and non-gravidity, IL-10 is expressed (Griffith et al., 2016).

1873 Proinflammatory cytokines may be downregulated during reproductive periods to limit
1874 maladaptive immune responses to the foreign fetus (Zimmerman, Vogel, & Bowden, 2010). In
1875 mammals, IL-1 allows release of hormones in human trophoblasts (Petraglia et al., 1990;
1876 Masuhiro et al., 1990; Yagel et al., 1989), facilitates implantation (Haimovici, Hill, & Anderson,
1877 1991; Hill, 1992; Tartakovsky & Ben-Yair, 1991), and influences the initiation of labor (Romero
1878 et al., 1989, 1992). Regulation of the proinflammatory cytokines tumor necrosis factor (TNF)
1879 and interleukin 1B (IL-1 β) is of particular importance in eutherian pregnancy (Haider & Knöfler,
1880 2009; Paulesu, Romagnoli, & Bigliardi, 2005; Saito et al., 2010; Tayade et al., 2006).

1881 The uterine tissue of two reproductively bimodal squamates—viviparous individuals of
1882 *Chalcides chalcides*, and oviparous and viviparous individuals of *Zootoca vivipara*—express IL-
1883 1β (Paulesu et al., 1995, 2005; Romagnoli et al., 2003). In the uterus of the viviparous skink,
1884 *Pseudemoia entrecasteauxii*, during gestation regulation of TNF and IL- 1β at the transcriptional
1885 and post-translation levels, respectively, may reduce inflammation (Hendrawan et al., 2017). The
1886 pro-inflammatory function of IL- 1β in *Pseudemoia entrecasteauxii* may play a role developing a
1887 more complex placenta (Hendrawan et al., 2017). The placenta of *Chalcides chalcides* expresses
1888 pro-inflammatory cytokines, IL- 1α and IL- 1β , at specific times during gestation (Paulesu et al.,
1889 1995). During gestation, *Chalcides ocellatus* also differentially expresses 27 other interleukins
1890 and interleukin related products (Brandley et al., 2012).

1891 The expression of IL-34 in a marsupial, the fat-tailed dunnart, during pre-implantation
1892 (Whittington et al., 2018) may have an immunosuppressive function to help tolerate potential
1893 contact of maternal and fetal tissues when the embryonic shell coat disintegrates (Lindau et al.,
1894 2015). In chickens, IL-34 regulates Th1 and Th17 cytokine production (Truong et al., 2018).
1895 During gestation in *Pseudemoia entrecasteauxii*, IL-16 and IL- 1α are expressed in addition to
1896 three receptors for Th17 family cytokines—IL-17RA, IL-17RC, and IL-17RA (Griffith,
1897 Brandley, et al., 2016, 2017). In the yolk sac of *Pseudemoia entrecasteauxii* during pregnancy
1898 interleukin related molecules, *ILDR1*, *IRAK1*, and *SIGIRR*, are differentially expressed (Griffith
1899 et al., 2016). This profile suggests the presence of tricellular tight junctions and/or tricellulin
1900 (Higashi et al., 2013; Ikenouchi et al., 2005), and regulation of toll-like receptors (TLRs) and/or
1901 IL-1R signaling (Kawagoe et al., 2008; Lin, Lo, & Wu, 2010; Muzio et al., 1997).

1902

1903 (9) *The major histocompatibility complex and maternal-fetal immune dynamics*

1904 A substantial amount of literature on maternal-fetal immune dynamics was focuses on uNK
1905 cells. Uterine NK cells have a distinct phenotype and function from peripheral NK cells. They
1906 have several activating receptors (Manaster & Mandelboim, 2010) but do not exert cytolytic
1907 functions on embryonic trophoblasts that they are in contact with (King, Birkby, & Loke, 1989).
1908 Allorecognition of embryonic placental cells by uNK cells is a key regulator of the maternal-fetal
1909 immune mechanisms that support placentation in mammals (Moffett & Colucci, 2014). When
1910 cells lose their ability to express any HLAs, uNK cells are shown to kill them (Hunt et al., 2005;
1911 Ishitani et al., 2003; King, Allen et al., 2000).

1912 In humans, expression of the classical MHC class I (C-MHCI) molecule HLA-C, and
1913 nonclassical MHC class I (NC-MHCI) molecules HLA-E, HLA-F and HLA-G on trophoblasts
1914 inhibit uNK cell-mediated cytotoxicity (Hunt et al., 2003; King, Burrows et al., 2000). Differing
1915 from this, mismatched HLA-C profiles trigger rejection of the transplanted organs (Petersdorf et
1916 al., 2014). Selection for balanced polymorphisms in HLA-C alleles and their killer
1917 immunoglobulin receptors (KIRs) is proposed to be driven by reproductive success, rather than
1918 immune recognition of pathogens (Trowsdale & Betz, 2006). Dimorphisms of HLA-C emerged
1919 recently within primates (Adams & Parham, 2001).

1920 Similar patterns in MHC profiles have been explored in other viviparous amniotes. C-MHCI
1921 antigen, H2-K, is expressed on giant trophoblast cells of mice and this is attributed to
1922 trophoblast-induced uterine vasculature transformation (Arcellana-Panlilio & Schultz, 1994;
1923 Chatterjee-Hasrouni & Lala, 1982; Hedley et al., 1989; King et al., 1987; Sellens, Jenkinson, &
1924 Billington, 1978). H2-D antigen is co-expressed with H2-K in virtually all their other nucleated
1925 cells (Madeja et al., 2011). However, H2-K expressing trophoblasts lack H2-D expression. This

1926 parallels the expression patterns of C-MHC molecules at the maternal-fetal interface in humans
1927 and may be an evolutionarily conserved pattern (Madeja et al., 2011).

1928 In humans, NC-MHCI molecule, HLA-G, is especially tolerogenic (Carosella et al., 2015;
1929 González et al., 2012; Hviid et al., 2004; Kovats et al., 1990). In adults, HLA-G is almost
1930 exclusively expressed by fetal trophoblasts compared to adult cells (Faulk & Temple, 1976;
1931 King, Burrows et al., 2000; Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al.,
1932 1997). It supports immunotolerance at the maternal-fetal interface (Rebmann et al., 2014). The
1933 role of HLA-G in supporting tolerogenic responses to organ transplants appears to be an
1934 exploitation of its role in immunotolerance in the utero during pregnancy (Rebmann et al., 2014).
1935 HLA-G is upregulated by several molecules that serve essential roles during gestation including
1936 progesterone (Yie, Xiao, & Librach, 2006; Yie et al., 2006), IFN- α , IFN- β , and IFN- γ (Rebmann
1937 et al. 2003; Lefebvre et al., 2001; Ugurel et al., 2001; Yang, Geraghty, & Hunt, 1995), and IL-10
1938 and TGF- β (Cadet et al., 1995; Moreau et al., 1999).

1939 A similar NC-MHCI gene to HLA-G exists in horses (Davies et al., 2006) where it likely
1940 functions to protect the embryo from NK-cell mediated attack (Ott et al., 2014). NC-MHC
1941 molecules with similar structure to HLA-G are also found in Rhesus monkeys (Boyson et al.,
1942 1997) and baboons (Stern et al. 1987). Mice have two NC-MHCI genes that are expressed on the
1943 surface of their placentas and on pre-implanted embryos (Sipes et al., 1996).

1944 In the gestating uterus of the viviparous skink, *Pseudemoia entrecasteauxii*, four putative C-
1945 MHCI and two putative NC-MHCI molecules are expressed (Murphy, Thompson, & Belov,
1946 2009). This pattern resembles the C-MHCI and NC-MHCI expression profiles of mammals,
1947 suggesting that this viviparous skink utilizes a similar physiological mechanism to 'hide' the
1948 embryo (Murphy, Thompson, & Belov, 2009). One of the putative NC-MHCI genes (Psen-

1949 160Ut/Psen-78G) has a substitution at position 150 where a tryptophan is substituted for a
1950 leucine (Murphy, Thompson, & Belov, 2009). When Psen-160Ut/Psen-78G was aligned to NC-
1951 MHC I genes of vertebrates ranging from fish to eutherian mammals, tryptophan was conserved
1952 at position 150 except in Psen-160Ut/Psen-78G and HLA-G (Murphy, Thompson, & Belov,
1953 2009). Whether this reflects an evolutionary history associated with immune tolerance at the
1954 maternal-fetal interface in *Pseudemoia entrecasteauxii* requires further investigation.

1955 MHC I genes are also expressed in reproductive tissues of oviparous skinks (*Ctenotus*
1956 *taeniolatus* and *Lampropholis guichenoti*) during non-reproductive periods and during late
1957 gravidity (Murphy, Thompson, & Belov, 2009). A similar pattern is found in viviparous skinks
1958 *Eulamprus tympanum*, *Niveoscincus metallicus*, *Pseudemoia entrecasteauxii* and the
1959 reproductively bimodal skink *Saiphos equalis* which all express MHC I genes at non-
1960 reproductive periods and during late pregnancy/gravidity (Murphy, Thompson, & Belov, 2009).
1961 MHC gene H2-EA is also expressed during gestation with long egg retention in *Saiphos equalis*.

1962 The butyrophilin subfamily 1 member A (*BTN1A1*) is located in the MHC I region of the
1963 genome in mammals (Trowsdale, 2011). *BTN1A1* is differentially expressed in the uterus during
1964 gestation in a viviparous lizard, *Chalcides ocellatus* (Brandley et al., 2012). *BTN1A1* may have
1965 important antimicrobial properties in chicken eggshells (Mann, Maček, & Olsen, 2006). In
1966 mammals *BTN1A1* is the major protein associated with fat droplets in milk (Jeong et al., 2009).

1967

1968 (10) *Microchimerism and maternal-fetal immune dynamics*

1969 Billingham, Brent and Medawar suggested the concept of actively acquired immunologic
1970 tolerance during pregnancy 70 years ago (Billingham, Brent, & Medawar, 1953; Ribatti, 2015).
1971 Subsequent research over the following decades revealed that substantial transfer of proteins,

1972 parasites and even immunologically active cells occurs between mother and embryo (Adams &
1973 Nelson, 2004; Axiak-Bechtel et al., 2013; Bakkour et al., 2014; Burlingham, 2010; Fujiki et al.,
1974 2008; Gitlin et al., 1965; Khosrotehrani et al., 2005; Owen, 1945; Turin et al., 2007).
1975 Microchimerism, where there is <0.1% donor chimeras in host tissue, is relatively pervasive
1976 among eutherians during pregnancy. It plays a role in establishing tolerance to non-inherited
1977 antigens. For example, cell populations from the mother that are transferred into embryonic
1978 lymph nodes enable the establishment of embryonic Tregs that are tolerogenic toward non-
1979 inherited maternal antigens (Mold et al., 2008).

1980 Microchimeric cellular populations are transferred across all placental types (Axiak-Bechtel
1981 et al., 2013; Bakkour et al., 2014; Fujiki et al., 2008; Khosrotehrani et al., 2005; Turin et al.,
1982 2007). Fetal and maternal cells persist for decades after birth across a range of tissues in mother
1983 and offspring, respectively (Adams & Nelson, 2004; Bakkour et al., 2014; Bayes-Genis et al.,
1984 2005; Bianchi et al., 1996; Evans et al., 1999; Jonsson et al., 2008; Stevens et al., 2004). There is
1985 even a call in the immunology literature to shift from the conventional paradigm of “self vs
1986 other” to instead consider the “self” as inherently chimeric (Nelson, 2012). Given that
1987 epitheliochorial placentation is sufficient to illicit microchimeric cell populations, the occurrence
1988 of similar bidirectional cellular traffic is a reasonable possibility in viviparous squamates.

1989

1990 (11) *Paternal alloantigens*

1991 Under tenants gleaned from transplant medicine, the maternal immune system would illicit
1992 an attack response as early as insemination when maternal tissues are exposed to paternal
1993 alloantigens (Borziak et al., 2016; Schumacher & Zenclussen, 2015; Seavey & Mosmann, 2006).
1994 Instead, maternal cells immunologically recognize them at this time without attack (Schumacher

1995 & Zenclussen, 2015; Seavey & Mosmann, 2006; Zenclussen et al., 2010). Treg expansion, a
1996 process with major influence on maternal-fetal immunotolerance in mammals, is proposed to be
1997 driven by several different factors found in seminal plasma (Baratelli et al., 2005; Teles et al.,
1998 2013). Mothers may maintain fetal-specific Tregs with memory of the paternal alloantigens
1999 (Zenclussen et al., 2010), expediting Treg response in future pregnancies with the same father
2000 (Rowe et al., 2012).

2001 Alloantigen exposure at the time of insemination is not restricted to mammals. Seminal fluid
2002 of chickens contains two MHC I paternal alloantigens and one MHC II alloantigen (Borziak et
2003 al., 2016). It also contains proteins involved in immunity and antimicrobial defenses (Borziak et
2004 al., 2016). In hens, evidence suggests that a protective local immunity to pathogens is established
2005 after exposure to semen but the mechanisms for this remain unclear (Reiber & Conner, 1995;
2006 Reiber, Conner, & Bilgili, 1995).

2007 In mammals, paternal alloantigens and cytokines in seminal fluid drive immune tolerance
2008 (Schjenken & Robertson, 2014). Mammalian seminal plasma contains immune-factors (Kelly,
2009 1995; Schjenken & Robertson, 2014)—TGF- β (Breuss et al., 1993; Chu & Kawinski, 1998;
2010 Slater & Murphy, 1999), IL-8 (Gutsche et al., 2003), and soluble IL-2 receptor (Srivastava,
2011 Lippes, & Srivastava, 1996), prostaglandin E2 (PGE2) and 19-hydroxyprostaglandin E (19-
2012 hydroxy PGE) (Denison et al., 1999), soluble tumor necrosis factor (TNF) receptors (Liabakk et
2013 al., 1993), receptors for the Fc portion of γ -globulin, spermine (Evans, Lee, & Flugelman, 1995),
2014 and complement inhibitors (Kelly, 1995). In horses and pigs, respectively, the proteins CRISP3
2015 (Doty et al., 2011), PSP-I and PSP-II (Rodriguez-Martinez et al., 2010), act as signaling agents
2016 in seminal fluid.

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

2028

2029 (12) *Discussion and future directions—maternal-fetal immune dynamics & the*
2030 *evolution of parity modes*

2031 Immune processes appear to be important for both oviparity and viviparity—as evidenced
2032 here, in part, by overlapping expression profiles of immune genes in female reproductive tissues
2033 of chickens and pigs, expression of paternal antigens in avian seminal fluid, and uterine
2034 expression of maternal antigens in oviparous and viviparous skinks. This highlights the scientific
2035 advances made since Medawar’s paradigm, when embryos were treated as analogs to allografts.
2036 Nonetheless, viviparity is associated with complex immune dynamics between maternal, fetal,
2037 and paternal tissues.

2038 Overall, evolving appropriate immunological responses is one hurdle of transitions to
2039 viviparity in squamates. This is evidenced by the unique MHC expression profiles identified in

2040 some viviparous skinks compared to oviparous relatives (Murphy et al., 2009); and the detection
2041 of divergent selection in immune response genes in viviparous and oviparous *Zootoca vivipara*
2042 (Recknagel et al., 2021a). Labile parity modes in squamates may be supported if they are more
2043 heavily reliant on the innate immune system for reproduction. However, reptiles may not have
2044 distinguished innate and adaptive immune systems (Zimmerman et al., 2020).

2045 Changes to genes that serve overlapping functions across the Main Five may have a
2046 disproportionate influence on transitions between parity modes. In this section I reviewed two
2047 molecules, *TGF-β* and progesterone, that exert influence on multiple Main Five categories.
2048 Progesterone influences uterine quiescence (embryonic retention), hepatic vitellogenesis
2049 (nutrient provisioning) and regulation of inflammatory responses in utero (maternal-fetal
2050 immune dynamics). Genes in the *TGF-β* family play a role in placental development and
2051 maternal-fetal immune dynamics. *TGF-β* family is implicated in placental development in
2052 eutherians (Hempstock et al., 2004; Caniggia et al., 2000; Lafontaine et al., 2011). A *TGF-β*
2053 receptor protein (*TGFBR1*) was associated with placental development in *Phrynocephalus*
2054 *vlangalii* (Gao et al., 2019). In humans *TGF-β* upregulates tolerogenic HLA-G in utero and is an
2055 immune factor in mammalian seminal fluid. Multiple genes in the *TGF-β* family are also
2056 differentially expressed during gestation in other viviparous lizards, *Pseudemoia entrecasteauxii*
2057 and *Saiphos equalis* (Foster et al., 2020; Griffith et al., 2016). Examining the functions of *TGF-β*
2058 and progesterone across other amniotes may reveal insights into how these molecules influence
2059 the evolution of parity modes.

2060 In mammals, inflammation appears to be involved with two of the Main Five processes—
2061 regulation of maternal-fetal immune dynamics and embryonic retention. It is intriguing to
2062 consider the implications this has for the interconnectedness of the Main Five. Greater

2063 interconnectedness would suggest that changes to few genes involved with the Main Five could
2064 cause a cascading effect to support more labile transitions between parity modes.

2065 Implantation and parturition in therian mammals evolved from a shared inflammatory
2066 attachment reaction (Hansen et al., 2017). The process of implantation has important
2067 implications for maternal-fetal exchanges of inorganic and organic material and maternal-fetal
2068 immune dynamics. Given that inflammation is associated with implantation and parturition
2069 implicates it in gas, water, and nutrient provisioning (including calcium here), maternal-fetal
2070 immune dynamics and length of embryonic retention. However, implantation in mammals and
2071 viviparous squamates is not homologous (Griffith, Van Dyke, & Thompson, 2013). Therefore, it
2072 is difficult to make inferences about how substantial the influence of inflammation is on the
2073 evolution of parity modes in squamates. Nonetheless, the abundant literature on uterine
2074 inflammatory processes during human pregnancy and the evolution of inflammatory processes
2075 that supported the evolution of viviparity in mammals (Challis et al., 2009; Chavan, Griffith, &
2076 Wagner, 2017; Mor et al., 2011; Griffith, Chavan et al., 2017; Stadtmauer & Wagner, 2020a)
2077 serve as indispensable resources for exploring the role of inflammation in squamate viviparity. I
2078 resist expanding on this further. I suspect that the immune system plays a central role in dictating
2079 the plasticity of parity modes. However, further work is necessary to validate this.

2080

2081

2082 **VII. Conclusions**

2083

2084 (1) Through holistic consideration of the unique complexity of parity mode evolution, within
2085 the context of genomic and transcriptomic studies across interdisciplinary fields, this

2086 review provided a new perspective on the history of parity mode transitions in amniotes
2087 and squamates. The overlapping activity of immune genes in utero, genes for calcium
2088 transport, placentation, and hormonal regulation across mammals, birds, and reptiles hint
2089 at discoveries to be made. There is a fascinating history to the evolutionary physiology
2090 and genomics of reproduction in amniotes that is ripe for downstream research.

2091 (2) Changes to gene(s) or physiological processes associated with more than one of the Main
2092 Five should disproportionately influence parity mode evolution—*SLC* gene superfamily,
2093 TGF- β , *BMPRI*B, progesterone, *PMCA*, calbindin-D28K, *SPP1*, sustained functioning of
2094 the corpora lutea and inflammation, and the genes associated with both gestation length
2095 and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).

2096 (3) Growing evidence in the medical literature suggests that immune system interactions at
2097 the maternal-fetal interface in mammals did not evolve simply through immunotolerance,
2098 evasion, immunosuppression, or immunological barriers (Chaouat, 2016; Chavan,
2099 Griffith, & Wagner, 2017; Moffett & Loke, 2004, 2006). Instead, maternal-fetal immune
2100 dynamics have a deep evolutionary history that enables both embryo and mother to
2101 interact cooperatively (Yoshizawa, 2016). Viviparity and extended embryonic retention
2102 are assuredly associated with immunological responses across amniotes, including
2103 squamates (e.g. Foster et al., 2020). Oviparous birds and squamates are also known to
2104 differentially express genes during gravidity, with one exception to my knowledge,
2105 *Lampropholis guichenoti* (Griffith et al., 2016).

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

2109 Hypothesis are likely relevant to the origin of the amniotic egg and squamate parity mode
2110 evolution. Climatic shifts during the origin of amniotes should be explored for their
2111 consistency with the EER model.

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

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

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

2132 (Legendre et al., 2022). This will require also developing a system to accurately
2133 characterize eggshell membranes.

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

2142 a. Hypothesis testing: Recent reversals should have physiological or genomic
2143 remnants of a viviparous past. Given that viviparous squamates generally have
2144 more active uterine immune systems to support gestation, oviparous reversals
2145 should 1) have more immune genes expressed in utero than ancestrally oviparous
2146 squamates, and 2) these immune genes should have stronger signatures of relaxed
2147 selection than immune genes expressed in a close relative during viviparous
2148 gestation.

2149 (8) Throughout this review, I highlighted the immunological problem of pregnancy by
2150 examining evidence for Medawar's Paradigm across birds, reptiles, and mammals. In
2151 doing so, I identified only one species that does not differentially express any genes while
2152 the egg is in utero, *Lampropholis guichenoti* (Griffith et al., 2016). Given that an
2153 immunological response to gravidity is evidenced in birds and multiple oviparous

2154 squamates, we can understand that *L. guichenoti* either achieves gestation through tenants
2155 of Medawar's Paradigm or that gravidity is not an immunological problem in this species.
2156 (9) I also demonstrated how Medawar's Paradigm is not a good explanation for viviparous or
2157 oviparous gestation/gravidity in amniotes. Some work also suggests that viviparity in
2158 anamniotes causes no immunological problems (Chaouat, 2016). Therefore, I
2159 conceptualize amniotes as originating in an immunological environment that tolerated
2160 exposure to the egg without an immunological issue. I suggest researchers utilize
2161 *Lampropholis guichenoti* as a model for the origin of the amniote egg. If supported by
2162 future research, then oviparous populations of *Saiphos equalis* and *Zootoca vivipara* may
2163 represent reversals because they have substantial differential gene expression during
2164 gravidity (Foster et al., 2020; Recknagel et al., 2021) and the oviparous population of
2165 *Lerista bougainvillii*, which has only two differentially expressed genes during gravidity,
2166 may represent an ancestrally oviparous state (Griffith et al., 2016). Future work can test
2167 this by applying point 7.A in this conclusion and should measure differentially expressed
2168 genes across stages of gravidity in *L. bougainvillii*.

2169 (10) Given that the mammillary layer is described as unique to Archelosaurs, the original
2170 oviparous amniote eggshell may have lacked a mammillary layer. Instead, it makes
2171 logical sense that the original oviparous amniote egg became ensheathed in an eggshell
2172 membrane, followed by calcium deposition that looks comparable to what we see in
2173 squamates. We can test this by using the framework of the basal cap hypothesis,
2174 described briefly in point 6 of this conclusion and at length in section III.3.

2175
2176

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