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

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Abstract

There is a current lack of consensus on the ancestral parity mode, oviparity (egg-laying) and viviparity (live-birth), of amniotes and squamates (snakes and lizards). How transitions between parity modes occur at the genomic level has primary importance on how science conceptualizes the origin of amniotes, and highly variable parity modes in Squamata. Within the context of interdisciplinary literature—medical, poultry science, reproductive biology, and evolutionary biology—I review the genomics and physiology of five broad processes (Main Five) expected to change during transitions between parity modes: eggshell formation, embryonic retention, placentation, calcium transport, and maternal-fetal immune dynamics. Throughout, I offer alternative perspectives and testable hypotheses regarding proximate causes of parity mode evolution in amniotes and squamates. Should viviparity have evolved early in the history of Lepidosaurs, I offer the basal cap hypothesis as a proximate explanation. The framework of this hypothesis can be extended to amniotes to infer their ancestral state. Medawar's paradigm contextualizes embryos as analogous to allografts. However, an abundance of research across mammals, birds, and reptiles demonstrates that the maternal immune response to gestation/gravidity cannot be explained by immunosuppression, inertness, evasion, or immunological barriers. However, a rare example of a species with an apparently inert response to oviparous gravidity is *Lampropholis guichenoti*, an oviparous skink that differentially expresses zero genes during gravidity—making it a reasonable model for the original amniote egg. Overall, this review grounds itself in the historical literature while offering a modern perspective on a subject that has fascinated scientists for centuries—the origin of amniotes. Based on the cumulative evidence across the Main Five, I provide a mechanism through which

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

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

Contents

I. Introduction

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

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

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

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

144 *Saiphos equalis* proved the possibility of reversals when a viviparous individual oviposited an
145 egg prior to birthing fully developed young within the same litter (Laird et al., 2019). The
146 unusual absence of an egg-tooth in oviparous Arabian Sand Boas, *Eryx jayakari* (Lynch &
147 Wagner, 2010; Staub & Emberton, 2002) serves as additional biological evidence of a reversal,
148 though this has been challenged (Griffith et al., 2015). Importantly, extended embryonic
149 retention, characteristic of oviparous squamates compared to birds, is viewed as compatible with
150 labile transitions (Jiang et al., 2023). Current expectations are that oviparity may re-evolve more
151 easily in squamate lineages that recently evolved viviparity and which have not lost specific
152 avian eggshell-matrix proteins (Laird et al., 2019; Xie et al., 2022).
153 Discoveries of viviparity in ancient amniotes are numerous, dating back to the Early
154 Permian (Chuliver, Scanferla & Smith, 2022; Motani et al., 2014; Piñeiro et al., 2012; Jian et al.,
155 2023). A viviparous last common ancestor of amniotes may not be unreasonable. A compelling
156 example is the report that *Ikechosaurus sp.*, a basal archosauromorph, that reached an articulated
157 stage of embryonic development inside of a parchment shelled egg (Jiang et al., 2023). This and
158 the ancestral state reconstruction generated in the study bring support to the extended embryonic
159 retention model (EER) of amniotes origins (Jiang et al., 2023; Hubrecht, 1910). The EER model
160 postulates that amniote fetal membranes arose through pressure to support exposure to maternal-
161 fetal tissues during extended embryonic retention (see Laurin et al., 2005 for a summary of
162 earlier ancestral reconstructions of EER). As Romer (1957) phrased it “It was the egg which
163 came ashore first; the adult followed”. This is consistent with EER, which is compatible with
164 both oviparity and viviparity (Laurin, 2005; Mossman 1987). Throughout this review,
165 considering viviparity as the most extreme form of extended embryonic retention, I hope to
166 persuade readers to consider the EER model in a new light. I lay this out through a testable

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

It is sensible to equate the EER with pre-adaptations of the egg to land. Without substantial amounts of water, converting yolk nutrients to somatic tissue is impossible (Thompson & Speake, 2003). Water is the primary resource provisioned by the mother of viviparous squamates and it is stored in extraembryonic membranes (Lourdais et al., 2015). For example, improper water and gas exchange are associated with poor chorioallantoic blood flow (Wootton et al., 1977). In oviparous *Saiphos equalis*, a species with extended embryonic retention, the chorioallantois thickens to support embryonic growth in late development (Parker et al., 2010). If the amniote egg evolved via the EER model, it may have prompted the origin of extraembryonic membranes of amniotes to support embryonic water uptake despite the deficit of water in utero compared to an aqueous environment. This translates to an egg washed ashore that already evolved to withstand dryer environments.

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

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

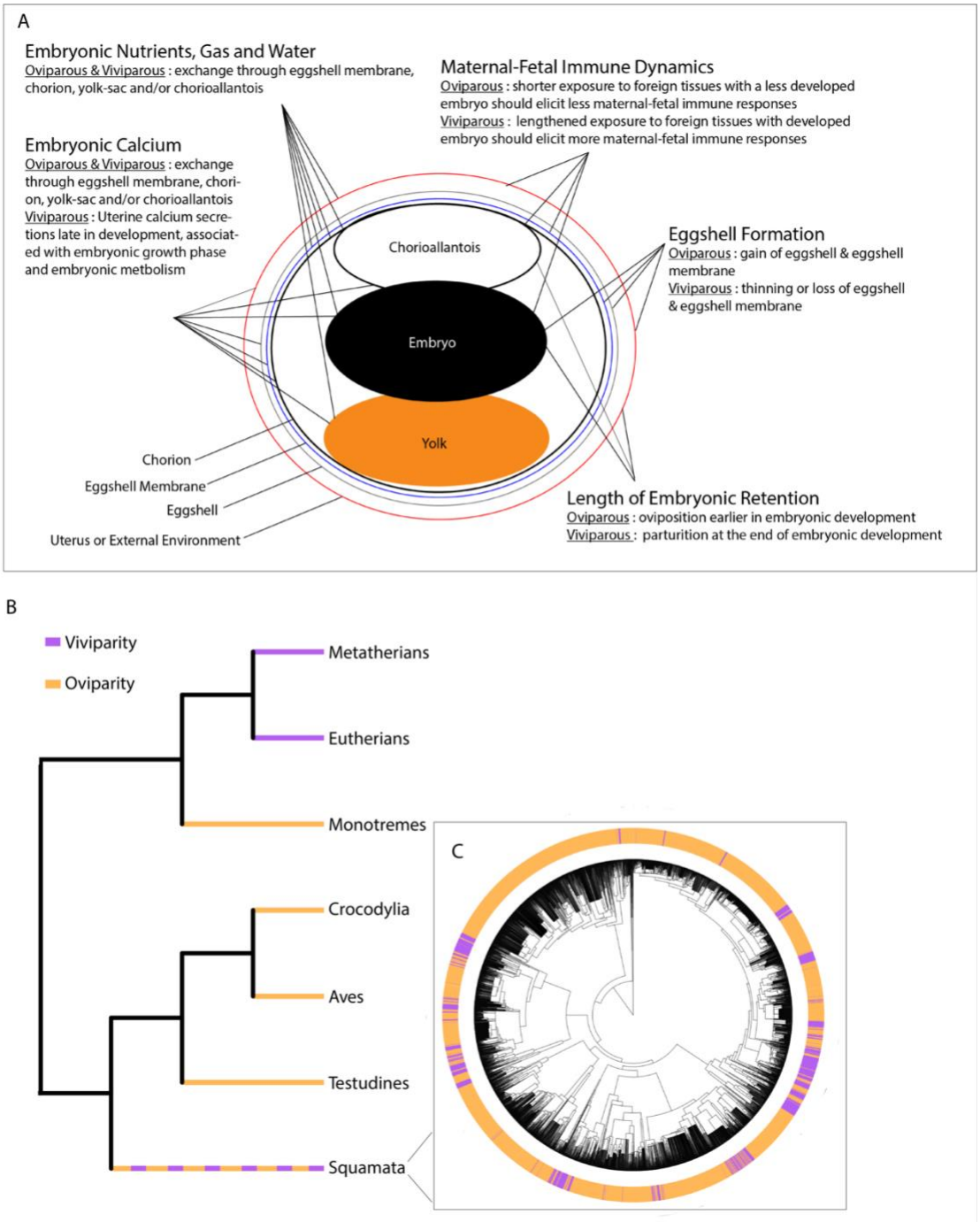

Figure 1: Schematic demonstrating (A) the anticipated processes that change during transitions between oviparity and viviparity, and the organs associated with those changes. Lines from the process to different organs indicate the organs expected to be involved with the evolutionary shift between oviparous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

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

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

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

(1) Terminology

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

(1) Main five physiological changes of parity mode transitions

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

II. Length of Embryonic Retention

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

(1) Parturition & oviposition

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

(i) Quiescence & sustained progesterone production in reproductive tissues

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

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

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

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

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

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

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

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

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

(ii) Activation & progesterone withdrawal

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

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

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

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

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

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

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

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

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

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

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

Prostaglandin E_2 (PGE_2) and prostaglandin F2α ($PGF_{2\alpha}$) influence, respectively, uterine contractions and cervical relaxation for parition across many amniotes including humans, *Homo sapiens* (Terzidou, 2007), domestic pigs (De Rensis et al. 2012), domestic chickens (Hertelendy et al., 1974; Olson et al., 1986), and Loggerhead Sea turtles (Guillette et al., 1991). Injections of $PGF_{2\alpha}$ and PGE_2 induce parturition in viviparous Yarrow's Spiny lizards, *Sceloporus jarrovi,* and

447 Raukawa geckos, *Woodworthia maculatus* (Cree & Guillette, 1991; Guillette et al., 1992).
448 However, no injected dosages of $PGF_{2\alpha}$ or PGE_2 induced oviposition in oviparous Collard
449 lizards, *Crotaphytus collarus*, Eastern Fence lizards, *Sceloporus undulatus*, Six-lined
450 racerunners, *Aspidoscelis sexlineatus*, or Striped Plateau lizards, *Sceloporus virgatus* (Guillette et
451 al., 1991). It is interesting that injections of $PGF_{2\alpha}$ and PGE_2 induced parturition in viviparous
452 lizards but did not induce oviposition in oviparous lizards studied. Given this, it is plausible that
453 regulatory or functional changes to $PGF_{2\alpha}$ and/or PGE_2 in squamates could facilitate changes to
454 the length of embryonic retention to support transitions between reproductive modes. However,
455 induction of parturition with $PGF_{2\alpha}$ in viviparous *Woodworthia maculatus* only worked with
456 pre-treatment of β-adrenoeceptor (Cree & Guillette, 1991).
457 $PGF_{2\alpha}$ decreases progesterone concentrations during stimulation (De Rensis et al., 2012). In
458 humans, biosynthesis of PGs is driven largely by the enzyme cyclooxygenase (*COX*)-*2* rather
459 than *COX-1* (i.e., prostaglandin synthase-2 and -1) (Slater et al., 1995, 1999). This helps
460 maintain the decreased progesterone/estrogen ratio of stimulation. In ovariectomize viviparous
461 Garter snakes, *Thamnophis*, increased estrogen stimulated thickness of uterine epithelial cells
462 and glandular activity, whereas administration of progesterone had little influence on uterine
463 histology (Mead et al., 1981). Uterine pig models revealed that estrogen stimulates involuntary
464 contraction and relaxation (peristalsis) of the uterus (Mueller et al., 2006).
465 The softening of the cervix is important during the stimulation stage of parturition. A
466 hormone related to insulin, *relaxin*, promotes myometrial softening in humans, *Homo sapiens*,
467 domestic pigs, and turtles (Mercado-Simmen et al., 1982; Sorbera et al., 1988; Weiss &
468 Goldsmith, 2001). The cervix also gets softer by actions of PGE_2. PGE_2 activates pro-
469 inflammatory cytokines, interleukin (IL)-8 and tumor necrosis factor (TNF)-α, which activates

the collagenases and matrix metalloproteinases for cervical softening (Bakker et al., 2017). This causes a positive feedback loop between IL-8 and PGE_2 synthesis (Denison et al., 1998; Denison, Calder & Kelly, 1999; Terzidou, 2007; Li et al., 2010). Upregulated of IL-8 is also promoted by the protein complex NF-kB during parturition in humans (Elliott, 2001). Similar patterns were observed during parturition in mice and baboons (Mendelson & Condon, 2005; Mendelson, 2009).

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

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

493 regulatory differences of prostaglandins, *COX-2*, an *AVT* receptor (*MTR*), β-adrenergic receptors,
494 and estrogen receptors. During oviposition, *P. przewalskii*, exhibited the following: promotion of
495 contractions through downregulation of β-adrenergic receptor (*ADRB2*), and upregulation of
496 *COX-2* and prostaglandin, and absent (potentially lost) expression of two estrogen receptors
497 (*ESR1* and *ESR2*) and the AVT receptor, *MTR* (Gao et al., 2019). During the stage of gestation
498 corresponding to oviposition, viviparous sister-species, *P. vlangalii*, exhibited the following
499 alternate pattern: inhibition of contractions caused by upregulation of *ADRB2* and
500 downregulation of two estrogen receptors (*ESR1, ESR2*), *MTR*, *COX-2*, and prostaglandin (Gao
501 et al., 2019). Some viviparous squamates, *Saiphos equalis*, *Chalcides ocellatus*, and *Pseudemoia*
502 *entrecasteauxii*, share some of these expression patterns (*COX-2*, *MTR*, and *ADRB*, respectively)
503 thought to be involved with extended embryonic retention in viviparous *P. vlangalii* (Brandley et
504 al., 2012; Foster et al., 2020; Gao et al., 2019; Griffith et al., 2016); and *ADRB2* is upregulated at
505 mid-gestation in viviparous *Zootoca vivipara* compared to oviparous counterpart (Recknagel et
506 al., 2021a). Overexpressed genes in viviparous uterine tissues of *Zootoca vivipara* also
507 functionally enriched pathways for beta 1 and beta 2 adrenergic receptor signaling pathways
508 (Recknagel et al., 2021a). This study, which compared uterine expression profiles during
509 gestation across viviparous species of squamates, rodents, canines, ungulates, and humans,
510 concluded that shared regulatory networks are recruited to support viviparity (Reckangel et al.,
511 2021a).

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

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

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

(2) Unique qualities of oviposition & parturition in Sauropsids

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

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

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

(3) Pre-term birth & embryonic retention mechanisms

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

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

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

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

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

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

III. Eggshell Formation

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

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

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

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

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

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

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

(1) Mineral composition of eggshells

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

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

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

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

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: • 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

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

(2) Uterine glands & the evolution of parity modes

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 & Ecay, 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).

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

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

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

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

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

743 al., 2000). Simple alveolar glands in the lamina propria secrete collagen fibers (Corso et al.,
744 2000). Inhibition of fiber formation or cross-linking, typically caused by aminopropionitrile or a
745 copper deficiency, causes distorted formations of the eggshell membrane in birds (Arias et al.,
746 1997; Chowdhury & Davis, 1995; Hincke et al., 2012).

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

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

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

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

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

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

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

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

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

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

Originally considered avian-specific, several homologs of avian eggshell matrix proteins have now been identified in non-avian reptiles and mammals (Le Roy et al., 2021). A recent study found a significantly reduced number of intact avian eggshell matrix proteins in viviparous squamates compared to oviparous squamates, a pattern that was especially apparent in snakes (Xie et al., 2022). This study also found that *OC-17* was only absent in viviparous squamates but was always present in the oviparous species in the dataset (Xie et al., 2022). Due to this, and the central role of *OC-17* in avian eggshell formation in birds, they ascribe losing intact *OC17* with the prevention of reversals back to oviparity (Xie et al., 2022). However, given that *OC-17* is implicated in initiation of mineralization in the mammillary cone layer, which is absent in squamates, the necessity of *OC-17* for squamates eggshell formation requires further investigation. Other genes, like osteopontin (*OPN* or *SPP1*), also play a central role in biomineralization of the avian eggshell and should be investigated in squamates.

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

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

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

863 Various evolutionary genomics studies have revealed squamate-specific candidates for shell
864 formation (e.g. Recknagel et al., 2021a; Gao et al., 2020). Some of these candidates span the
865 major clades of amniotes. Seven of the genes expressed during eggshell gland development in
866 *Phrynocephalus przewalskii —HYPOU1, KCNMA1, P4HB, PRDX4, PTN, RRBP1* and
867 *TRAM1*—are purported to be important for eggshell calcification in chickens (Brionne et al.,
868 2014). Given this overlap across species that diverged over 300 million years ago (Shen et al.,
869 2011), these are excellent candidates for further exploration.

870 A functional genomics study harnessed hybridizations of oviparous and viviparous
871 individuals of *Zootoca vivipara* to reveal 17 SNPs and 38 genes associated with eggshell traits
872 (Recknagel et al., 2021a). These genes enriched terms related to cell communication and the
873 immune system, while differentially expressed gene during gravidity enriched pathways for
874 transforming growth factor (Recknagel et al., 2021a). The three loci with the strongest
875 association with eggshell traits mapped closely to *LGMN*, *LYPLA1*, and *CRTC1* (Recknagel et
876 al., 2021a). The association of these genes with eggshell traits is particularly interesting. *LGMN*,
877 for example, is involved with the cadherin pathway. Cadherins have an established role in
878 squamate reproduction. In squamates, previous literature discusses how cadherins influence
879 embryonic attachment in viviparous taxa (Wu et al., 2011). *LGMN* is also differentially
880 expressed across many viviparous squamates and mammals (Recknagel et al., 2021a). Thus,

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

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

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

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

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

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

926 *BMPER* and seven *BMP*s are expressed during gestation in *Chalcides ocellatus*, a viviparous
927 skink (Brandley et al., 2012). Most of these are upregulated (Brandley et al. 2012). *BMP* genes
928 are expressed during both gravidity and non-gravidity in oviparous *Lerista bougainvillii* and
929 *Lampropholis guichenoti* (Griffith et al., 2016). *BMP2* is upregulated in oviparous late gestation
930 compared to viviparous late gestation in the reproductively bimodal lizard, *Saiphos equalis*
931 (Foster et al., 2020).
932 Differential expression of *BMPR1B* is associated with differences in eggshell quality in
933 chickens (Yang et al., 2020). Another study associated stage-specific high-expression of
934 *BMPR1B* with the stage corresponding to extended embryonic retention and placentation in
935 *Phrynocephalus vlangalii* (Gao et al., 2019). They identified a co-expression network of highly
936 expressed genes, including *BMPR1B*, that they associated with placentation (Gao et al., 2019).
937 *BMPR1B* also reaches significant levels of differential expression in uterine tissues of other
938 gestating viviparous lizards, *Chalcides ocellatus* and *Pseudemoia entrecasteauxii*, compared to
939 non-gestational uterine tissue (Brandley et al., 2012; Griffith et al., 2016). Receptors for *BMP*s
940 are also expressed in the uterus during gestation in other viviparous lizards, *Phrynocephalus*
941 *vlangalii* and *Pseudemoia entrecasteauxii* (Gao et al., 2019; Griffith et al., 2016). Perhaps
942 unsurprisingly, *BMPR1B* is also differentially expressed in the uterus of viviparous *Zootoca*
943 *vivipara* compared to oviparous individuals during gestation.
944 The potential role of these genes in squamate eggshell formation remains unclear. *BMP*s
945 influence on dorsal-ventral axis patterning during early embryogenesis and growth of skeletal
946 structures in post-natal tissues (Medeiros & Crump, 2012). It may be difficult to disentangle their
947 roles in embryonic development, placental development, and eggshell deposition. Future
948 research on them may inform scientific understanding of parity mode evolution.

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

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

(5) Eggshell formation termination

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

(6) Rotating the egg for eggshell formation

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

995 does not happen until later in gestation for eutherian mammals when, for example, the embryo
996 detaches and cadherins become less concentrated (Wu et al., 2011). Perhaps a candidate gene for
997 studying this is, a cadherin *CDH5*, the only gene that is differentially expressed in all viviparous
998 squamates studied thus far studied (Recknagel et al., 2021a). Genes that enrich the GO term for
999 "voltage-gated calcium channel activity" are also useful candidates for investigating uterine
1000 rotation associated with eggshell formation because voltage-gated calcium channels effect the
1001 action potential of cells and can cause muscle contractions.
1002
1003 *(7) Discussion & future directions—eggshell formation and parity mode evolution*
1004 The process of eggshell formation is more resolved in birds compared to non-avian reptiles
1005 and monotremes (Choi et al., 2018; Frankenberg & Renfree 2018). I described some overlaps
1006 gleaned from the literature which prove as curious candidates for further research
1007 (Supplementary Table 1). Of particular interest are avian eggshell matrix proteins (Alföldi et al.,
1008 2011; Le Roy et al., 2021; Tian et al., 2010; Xie et al., 2022), genes with biomineralizations
1009 functions, candidate genes associated with eggshell traits in *Zootoca vivipara* (Recknagel et al.,
1010 2021a), and the homologs for avian eggshell matrix proteins identified in the *Anolis carolinensis*
1011 genome (Alföldi et al., 2011; Tian et al., 2010).Additionally, genes purported to be important for
1012 eggshell calcification in chickens associated with eggshell gland formation in an oviparous
1013 lizard, *Phrynocephalus przewalskii*, are relevant—*HYPOU1, KCNMA1, P4HB, PRDX4, PTN*,
1014 *RRBP1* and *TRAM1* (Brionne et al., 2014; Gao et al., 2019). Overlaps between the genes
1015 associated with gestation length and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a)
1016 hint at genes that could potentially evolve to innately effect multiple traits relevant to parity
1017 mode transitions. The basal cap hypothesis also offers a simple evolutionary mechanism to

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(3) Evolutionary history of placentrophy in mammals & squamates

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

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

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

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

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

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

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

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

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

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

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

Genes involved embryonic oxygen transport precede the origin of amniotes. Hemoproteins arose in evolutionary history well before they were used for placental oxygen transfer (Hardison 1998). In mammals, adult (Alpha: HBA; Beta: HBB, HBD) and embryonic hemoglobins (Alpha: HBZ, HBA; Beta: HBE, HBG, and HBH) are involved with oxygen transport (Carter, 2012). Some of these are unique to eutherian mammals following a series of duplication events (Opazo et al., 2008). However, fetal hemoglobins are found in turtles, lizards, and snakes (Pough, 1980). HBA, HBB and HBM are all significantly downregulated in the uterine tissue of the viviparous African Ocellated Skink, *Chalcides ocellatus*, during gestation compared to non-gestation (Brandley et al., 2012). The oxygen demands of reptile embryos are relatively low until stage 30, when most oviparous taxa oviposit (Shine & Thompson, 2006). In viviparous and oviparous species with long egg retention, embryonic demand for maternal provision of oxygen and removal of CO_2 increases at this stage.

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

1225 embryonic growth in the later portion of oviparous gravidity (Parker et al., 2010). In the
1226 viviparous scincid lizard, *Eulamprus quoyii*, angiogenesis, the formation of new blood vessels,
1227 and expansion of the vessel-dense elliptical area of the uterus is associated with supporting
1228 increased embryonic oxygen demand (Murphy et al., 2010).
1229 Several protein-coding genes are known to be involved with angiogenesis, vascularization,
1230 and vasodilation in utero. One study that examined expression patterns across chickens
1231 (oviparous), horses (viviparous), two viviparous squamates, and one oviparous squamate found
1232 that no examined genes for angiogenesis showed a viviparity-specific expression pattern
1233 (Griffith, Brandley et al., 2017). However, other than the chicken, the only oviparous taxa
1234 included in this study was a reproductively bimodal skink, *Lerista bougainvillii* (Griffith,
1235 Brandley et al., 2017). Alternatively, differential gene expression analyses on oviparous and
1236 viviparous individuals of *Zootoca vivipara*, revealed pathways for angiogenesis enriched in
1237 viviparous female reproductive tissues; and pathways for angiogenesis were enriched across
1238 genes under divergent selection in oviparous and viviparous *Z. vivipara* individuals.
1239 In the uterine tissue of gestating viviparous skinks and rats, several genes for angiogenesis
1240 are upregulated—*EPAS1, HIF1A* and *VEGFA* (Brandley et al., 2012; Whittington et al., 2015,
1241 2017). Other proteins involved in vascularization and vasodilation in utero include members of
1242 the vascular endothelial growth factor (*VEGF*) gene family, VEGF receptors (*VEGFR*s),
1243 placental growth factor (*PGF*) and nitric oxide synthase (*NOS*) (Blomberg et al., 2010; Chen,
1244 Wang et al., 2015; Gilbert, 2010; Reynolds et al., 2006; Risau, 1997; Torry et al., 2003;
1245 Vonnahme et al., 2001). In *Saiphos equalis*, different homologs of *NOS* experience different
1246 patterns of gene expression across the oviparous and viviparous stages of gestation/gravidity
1247 (Foster et al., 2020). One homolog of *NOS* is upregulated during oviparous late gestation, and

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

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

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

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

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

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

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

In viviparous individuals of the reproductively bimodal lizard, *Saiphos equalis*, many genes for cellular adhesion are upregulated during late gestation (Foster et al., 2020). The authors postulated that this helps facilitate maternal-fetal signaling and paracellular transport (Foster et al., 2020). Gao et al. (2019) identified a set of genes in *Phrynocephalus vlangalii* that were differentially expressed in the uterus during the stage of placentation and these enriched GO terms functionally related to the process of placentation. This included an estrogen receptor (*ESR1*) and two growth factor receptors (*GHR* and *IGF1R*) (Gao et al., 2019).

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

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

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

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

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

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

(Blackburn, 2015a). Multiple *TGF-β* genes are differentially expressed in the uterus during gestation in *C. ocellatus*, however most these are downregulated compared to non-gestational uterine tissue (Murphy et al., 2012). The influence of *TGF-β* on placental development and nutrient provisioning in *Chalcides spp.* remains to be explored to my knowledge. A TGF-β receptor (*TGFBR1*) was associated with placental development in *Phrynocephalus vlangalii* (Gao et al., 2019).

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

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

Genes involved with histotrophic secretion in the marsupial *Sminthopsis crassicaudata* include *AP4S1*, *HYOU1*, and *SRPRA* (Whittington et al., 2018). Nutrient transporters

significantly upregulated at this time are *APOL6* (cholesterol transport (Baardman et al., 2013)), *PLA2G10* (hydrolysis of fatty acids during pregnancy (Miele et al., 1987)) and a wealth of SLCs (solute carrier proteins for transport of sugar, ions, anions, glucose, fatty acids, calcium and zinc (Whittington et al., 2018)). Subsequent research has identified downregulated of *HYOU1* at early and mid-gestation; and downregulation of *SRPRA* at mid-gestation in viviparous *Zootoca vivipara* compared to oviparous (Recknagel et al., 2021a). In a reproductively bimodal skink, *Saiphos equalis*, *PLA2G10* is upregulated during viviparous late gestation compared to oviparous late gestation (Foster et al., 2020). Upregulation of SLCs also occurs in the viviparous skink *Chalcides ocellatus* (Brandley et al., 2012; Van Dyke et al., 2014) and in the uterus during pregnancy in the grey short-tailed opossum, *Monodelphis domestica* (Hansen, Schilkey & Miller, 2016).

Uterine glands are also important for secretions of eggshell precursors. I speculate that genes involved with adenogenesis of uterine glands may be similarly used to support histotrophic nutrient provisioning during transitions to viviparity, but further research is necessary. Specialized uterine areolar glands are found in some *Mabuya* lizards, a genus with oviparous species and viviparous species that utilize placentrophy and histotrophy (Corso et al., 1988, 2000; Jerez & Ramírez-Pinilla, 2001; Ramírez-Pinilla, 2006; Vieira et al., 2007; Visser, 1975). Transcriptomic research focused on histotrophic nutrient provisioning, placental development, and secretions of eggshell precursors in oviparous and viviparous *Mabuya spp*. would complement literature on the genus.

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

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

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

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

V. Embryonic Calcium Provisioning

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

(1) Phylogenetic context of embryonic calcium sources

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

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

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

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

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

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

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

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

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

1476 Dramatic changes to activity in chorioallantois should not be required during parity mode
1477 transitions because these homologous tissues (Metcalfe & Stock, 1993) transport calcium
1478 regardless of parity mode (Ecay, Stewart & Blackburn, 2004; Tuan & Scott, 1977; Tuan &
1479 Knowles, 1984; Tuan et al., 1978, 1986). Specialized placental structures in some viviparous
1480 squamates enhance calcium provisioning but specialization is not required for placental calcium
1481 transport (Stewart et al., 2009; Stewart & Ecay, 2010; Thompson et al., 2000). Loss of
1482 chorioallantoic calcium transporting capacity would be disadvantageous to either parity mode.
1483 Growing research reveals that, like mammals, placentrophy and viviparity can evolve
1484 concurrently in squamates (Blackburn, 2015a; Ecay et al., 2017; Stewart & Ecay, 2010).
1485 Placing these previously proposed models in a phylogenetic context, the calcium transport
1486 method of oviparous ancestors likely has an influence on the method of calcium transport used
1487 for viviparous taxa—matrotrophic calcium provisioning, lecithotrophic calcium provisioning, or
1488 a combination of the two. Consistent with the basal cap hypothesis—when viviparity arises from
1489 oviparous ancestors with embryos that depended predominately on eggshell calcium, this should
1490 favor a transition to viviparity via incipient calcium matrotrophy because the chorioallantois
1491 already plays the major role in transporting calcium from the eggshell to the embryo. Since the
1492 reproductive mode and calcium provisioning of oviparous ancestors are essentially unknown,
1493 researchers can use the closest oviparous relatives as proxies. Similarly, viviparous taxa that are
1494 in close phylogenetic proximity to oviparous taxa that depend on lecithotrophic calcium
1495 provisioning should remain reliant on yolk calcium. Together, these guidelines provide a
1496 framework from which researchers can form hypotheses about the calcium provisioning method
1497 of a viviparous lineage if the calcium provisioning method of oviparous close relatives are
1498 known, or vice versa. Measurements of the proportional contribution of different calcium sources

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

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

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

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

(3) Embryonic calcium provisioning mechanisms

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

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

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

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

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

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

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

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

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

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

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

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

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

VI. Maternal-Fetal Immune Dynamics

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

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

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

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

(1) Comparing amniote immune systems

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

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

(2) Medawar's paradigm

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(5) The inflammation paradox

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

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

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

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

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

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

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

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

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

(7) T cell populations and mammalian viviparity

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(11) Paternal alloantigens

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

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

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

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

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

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

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

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

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

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

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

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

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

VII. Conclusions

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

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

(2) Changes to gene(s) or physiological processes associated with more than one of the Main Five should disproportionately influence parity mode evolution—*SLC* gene superfamily, TGF-β, *BMPR1B*, progesterone, *PMCA*, calbindin-D28K, *SPP1*, sustained functioning of the corpora lutea and inflammation, and the genes associated with both gestation length and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).

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

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

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

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

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

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

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

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

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

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

squamates, we can understand that *L. guichenoti* either achieves gestation through tenants of Medawar's Paradigm or that gravidity is not an immunological problem in this species.

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

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

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