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The ovarian structure and oogenesis in the *Podarcis siculus* lizard: a comprehensive overview spanning over sixty years

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ABSTRACT

Oogenesis in oviparous vertebrates begins with a clustered gonad, a structure that may appear simple at first glance, but which conceals a certain complexity in the differentiation of follicles and the maturation of germ cells. The primordial follicle, originating from the germinal bed, undergoes a series of morphological changes involving both follicular cells and oocytes. This differentiation process requires a coordinated interplay between intrinsic factors and extrinsic signaling molecules. In this review, the process is described thanks to the research conducted over the years on the wall lizard *Podarcis siculus*. Overall, these studies have enabled the identification of the precise phases and molecules underlying follicular differentiation, the formulation of a hypothesis regarding the biseasonal origin of a currently annual reproductive cycle, and the recognition of the factors contributing to damage to the reproductive cycle of terrestrial oviparous vertebrates, caused by physical events such as temperature variations and chemical events such as environmental pollutants and endocrine disruptors.

1. Introduction

The 1960s are considered the decade in which several previously neglected scientific disciplines began to gain interest and establish themselves. In those years, many biologists promoted the study of comparative endocrinology and animal reproduction.

Over the years, numerous studies have explored the role of neuro-endocrine relationships, the hypothalamic-pituitary-gonadal axes, gametogenesis, and the reproductive cycles in amphibians and reptiles. Regarding the latter, Italian researchers have invested considerable effort in the study of the Italian wall lizard, *Podarcis siculus*, formerly known as *Lacerta sicula* Rafinesque (from the name of the biologist Constantine Samuel Rafinesque-Schmaltz who first described the species). Wild populations of this reptile were and still are abundant in Italy, particularly in the peninsular regions and in the two largest islands, Sicily and Sardinia. These animals, once captured in the wild, can be kept in a terrarium without difficulties. Adults mate, and females continue to lay eggs even in captivity. Like birds and many other lacertids, *P. siculus* has a ZZ/ZW chromosomal sex determination system in which females are the heterogametic sex (ZW) (Olmo, 2005).

The first morphological observations of the endocrine glands (pituitary, adrenal, thyroid) and of both male and female gonads had been accompanied by immunocytochemical, biochemical and molecular biology investigations, which have allowed us to understand the role of various hormones in triggering and regulating the processes underlying the reproductive cycle and development. In particular, many studies have focused on gametogenesis, leading to the characterization of the annual reproductive cycle of males and females (Filosa, 1973; Botte et al., 1976; Angelini et al., 1986; Della Ragione et al., 2005; Rosati et al., 2014).

Since the reproductive system of these lizards shares many structural and functional similarities with other reptiles and birds, the data collected have represented a starting point or understanding the reproductive processes of many other vertebrates, which are much more difficult to study, due to the complexity of the capture, maintenance, and manipulation procedures. Furthermore, the structure of *Podarcis* testes, consisting of seminiferous tubules, is very similar to that of mammalian testes, which has made them an alternative experimental model for studying spermatogenesis also in mammals.

Last but not least, in more recent years, the knowledge acquired thanks to this model has facilitated eco-cyto-toxicological studies aimed at identifying, monitoring over time and mitigating the harmful effects of environmental contaminants (metals, pesticides, endocrine disruptors) on reproductive processes.

This review brings together data from over 60 years of research on the female gonad of *Podarcis*, spanning from oogenesis to endocrine

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control of reproduction. The findings have highlighted the close relationship between the growing oocyte and the follicular cells, which play a crucial role in nourishing and protecting the oocyte, as well as controlling the entire reproductive process. The summarized results also highlight the latest findings on the effects of human activity on ovarian health, hormonal interference from pollutants, and harm to offspring.

2. The annual reproductive cycle of *P. siculus*

P. siculus lizard is characterized by an annual reproductive cycle, well documented based on both morphological (Botte et al., 1976) and endocrinological (Carnevali et al., 1991; Gobbetti et al., 1995) parameters. Female lizards experience one to three ovulatory waves during spring and early summer, preceded by morphophysiological modifications of the ovary, described below in paragraph 4. In late July, when the temperature is still favorable for reproduction, a resting period of refractoriness to ambient and hormonal cues occurs. This is followed by a fall recrudescence, in which ovarian functions are partially resumed but soon halted by the beginning of the winter stasis, which lasts until the following spring (Filosa, 1973; Botte et al., 1976). This particular bias is also observed in males, where spermatogenesis resumes but spermiation does not occur (Angelini et al., 1986). This suggests that the fall recrudescence may be a remnant of a biphasic reproductive cycle present in the past for this species (Motta et al., 2011). Indeed, according to these authors, the *Podarcis siculus* originates from a species that inhabited North Africa, reproducing during spring and the mild winter season typical of those latitudes. Migrating to Europe, where the winters are colder, would have resulted in the suppression of autumn ovulation. Currently, other species of the genus Podarcis are present in North Africa such as *P. vaucheri*. Interestingly, these species, like *P. siculus*, present an autumnal recrudescence without reproducing (Mamou et al., 2017).

3. The hormonal regulation of reproductive cycle in *P. siculus*

3.1. Gonadotropic hormones

In reptiles, as well as other vertebrates, the ovarian secretion of sexual steroids is regulated by the hypothalamus-pituitary-gonad (HPG) axis (Plant, 2015). At the start of the breeding season, long days and warm temperatures trigger the hypothalamic release of the Gonadotropin-Releasing Hormone (GnRH), which in turn stimulates the pituitary release of gonadotropins (GTHs). The pituitary gonadotropins stimulate gonadal activity and the secretion of sex hormones.

In mammals, the distinct roles of two pituitary GTHs, follicle stimulating hormone (FSH) and luteinizing hormone (LH), in regulating ovarian function are well established (Kaprara and Huhtaniemi, 2018). FSH regulates oogonial proliferation, oocyte growth, and differentiation, while LH stimulates ovulation and steroidogenesis (Oduwole et al., 2021). However, in many other vertebrates, the situation remains unclear. For many taxa, it is still uncertain whether both GTHs are present. Two distinct forms of GTHs, similar to mammalian FSH and LH, have been identified in cartilaginous fish, in bony fish (teleosts), amphibians and birds (Licht et al., 1976; Papkoff et al., 1982; Quérat et al., 2001; Oba et al., 2001; Li and Cheng, 2018). In fish, the FSH and LH redundant signaling suggests that these two GTHs function in an overlapping manner (Xie et al., 2017). Among reptiles, the information is fragmented and often inconsistent between taxa. In turtles and alligators, two distinct GTHs, seemingly homologous to mammalian LH and FSH, were identified (Licht et al., 1976). In contrast, reptiles belonging to the order Squamata, i.e., lizards and snakes, seemed to deviate from this pattern, possessing a single pituitary GTH that combines FSH- and LH-like activity (Licht, 1979). More recent studies on *P. siculus* have revealed that the lizard genome contains nucleotide sequences similar to those encoding the β subunits of both mammalian FSH and LH (Borrelli et al., 1997). Additionally, morphologically distinct FSH-containing and LH-containing cells are present in the pituitary gland of *P. siculus*. In total, these gonadotropic cells occupied approximately 10.5 % of the pars distalis area, with 10 % secreting FSH and only 0.5 % LH (Desantis et al., 1998, 2000).

The extremely low population of LH cells aligns with the lack of evidence for an LH receptor in squamates, whereas a cDNA for the FSH receptor has been cloned in the *Bothrops jararaca* snake (Bluhm et al., 2004) and in *P. siculus* (Borrelli et al., 2001). In the latter, the FSH receptor is abundantly expressed in previtellogenic follicles (<2 mm), primarily concentrated in small follicular cells, which are responsible for steroid secretion. This receptor responds to mammalian FSH (Motta et al., 1995a,b) and works by stimulating the activity of adenylate cyclase, which is found in the membranes of follicular cells (Borrelli et al., 1997).

3.2. Ovarian hormones

The start of the reproductive activity in the annual cycle, a defining characteristic of the *P. siculus* females, is marked by a dramatic increase in circulating concentrations of sex hormones, as is the case for all other reptiles (Jones, 2024). These hormones include estrogens, progestins, and, to a lesser extent, androgens. The ovary is the endocrine gland primarily responsible for the secretion of these sex steroids; the main estrogen is 17β-estradiol (E2), the main progestin is progesterone (P4), and the third class of steroids, the androgens, is mainly represented by testosterone (T). It plays a crucial role as a precursor to estrogen E2. Although the presence of androgen receptors (AR) in *P. siculus* females has not been documented, in other female reptiles the presence of ARs in various tissues and significant circulating levels of T suggest that androgens have a broader biological significance in females (Staub and De Beer, 1997).

The role of estrogen in oviparous vertebrates is widely studied and well known. Estrogen is the primary factor responsible for the vitellogenic process, i.e. the accumulation of yolk in growing ovarian follicles, which involves the synthesis of vitellogenin (VTG) by the liver and its subsequent transport into the oocytes where it is processed to form yolk platelets (Wallace, 1985). Experimental administration of E2 or xenoestrogenic substances induces VTG overexpression in females, as well as the expression of the *VTG* silent gene and the synthesis of VTG protein in the liver of males (Verderame et al., 2011).

Progesterone, primarily produced by the corpus luteum, is generally believed to inhibit estrogen-induced vitellogenesis, likely by directly influencing the liver (Callard et al., 1990). The increasing levels of this hormone during the periovulatory phase may add up to halt vitellogenesis. It has been suggested that ovarian progesterone, whether of follicular or luteal origin, played a crucial role in the evolution of viviparity. This is because it inhibited myometrial contractions, creating a primary condition for egg retention in the oviducts and viviparity. Additionally, it inhibited estrogen-induced hepatic vitellogenin synthesis, both in normal oviparous cycles and as a concomitant of placental evolution (Callard et al., 1990, 1991). In *P. siculus*, progesterone administration leads to an increase in the number of germ cells in the germinal bed, including both oogonia and primary oocytes in leptotene, zygotene-pachytene, and early diplotene. If the administration occurs just before the breeding season, a significant increase in the number of middle and late previtellogenic follicles is observed, along with an acceleration in egg deposition, despite a moderate reduction in the size of laid eggs (Motta et al., 2020). During the resting period, no significant differences in the number of prefollicular germ cells were observed between control and progesterone-treated ovaries. However, an increase in middle, but not late, previtellogenic follicles was recorded after progesterone treatment. Indeed, progesterone administration does not trigger apoptosis in pyriform cells (Motta et al., 2020), which is a clear sign of the onset of vitellogenic follicular growth (Filosa, 1973).

The *P. siculus* ovary synthesizes molecules beyond steroid hormones, such as prostaglandins F (PGF) and E (PGE), and corticosterone (Gobbetti et al., 1995). As observed in other reptiles, these molecules

may play a role in promoting vitellogenesis and ovulation, as well as influencing the onset of reproductive behaviors (Whittier and Crews, 1986). In *P. siculus*, these molecules are produced by both growing follicles and corpora lutea. In particular, PGF release was highest in mature follicles ready for ovulation, while PGE was highest in early-vitellogenic follicles and in corpora lutea. Corticosterone synthesis is regulated by prostaglandins; specifically, PGF boosts corticosterone production in the ovary and adrenal gland, while PGE has an inhibitory effect on corticosterone production (Gobbetti et al., 1995). Furthermore, beta-endorphin (β-EP)-like immunoreactive cells were also found in lizard ovaries; the immunoresponse was most pronounced during the winter season. In vitro studies have demonstrated that even extremely low (picomolar) amounts of β-EP can stimulate follicular production of estradiol-17 beta during both the reproductive phase and winter stasis, albeit to a lesser extent (Polzonetti-Magni et al., 1994).

4. Ovarian morphology

P. siculus shares with other oviparous vertebrates the typical hollow sac ovary, a small, clustered organ. During reproductive cycles, the paired ovaries grow and develop grape-shaped follicles in distinct stages (previtellogenic, vitellogenic) (Fig. 1A) from a specialized area called the germinal bed, forming a hierarchy of sizes, with the largest closest to the release point, ready for ovulation.

The cortical area is made up of many follicles at different stages of growth, the medulla is made up of connective tissue and blood vessels (Fig. 1B). The median dorsal line of the ovary is occupied by the germinal bed (Fig. 2), divided in two sides by the hilum, through which blood vessels and nerves pass and spread throughout the ovary. Growing follicles are arranged in a stepwise size hierarchy, with the largest follicles being positioned more ventrally. The proliferating oogonia, prefollicular oocytes and prefollicular stromal cells are gathered in two small germinal beds, as in most temperate lizards (Jones et al., 1982), located on the dorsal surface of ovaries, becoming distinguishable quite early during ovarian development.

5. Ovarian follicles

In the ovary, oogonia proliferate forming small clusters, of 8–16 cells, which remain connected by intercellular bridges (Filosa and Taddei, 1976; Andreuccetti et al., 1978). These connections promote uniform distribution of nutrients, including RNAs, and allow a synchronous differentiation up to the early diplotene stage (Andreuccetti et al., 1990), at the beginning of meiosis (Fig. 2). At this stage, somatic cells envelop the oocytes with thin cytoplasmic extensions that cause the interruption of intercellular bridges. Only rarely do cytoplasmatic filaments envelop an entire cluster, leading to the formation of polynucleated follicles. The disruption of the bridges connecting the oocytes

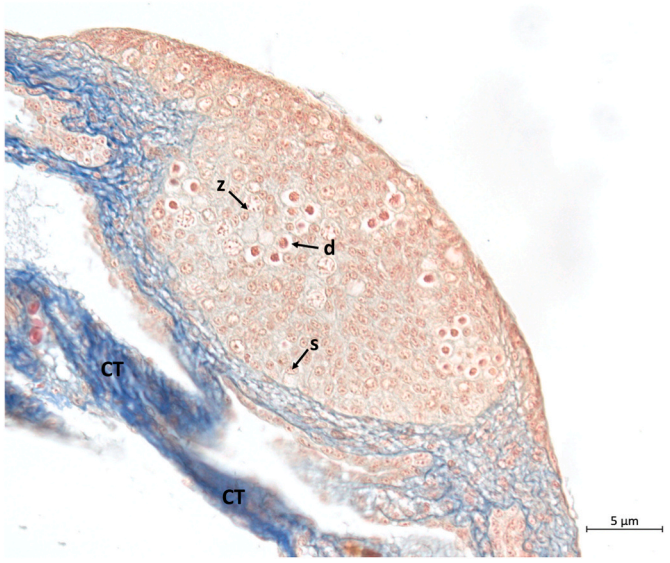

Fig. 2. Cellular morphology of the *P. siculus* germinal bed. Germ cells at different phases of early meiotic prophase (z, zigopachitene; d, diplotene) are evident, dispersed between somatic stroma cells (S). CT, connective tissue. Mallory's trichrome staining, scale bars: 5 µm.

in diplotene marks the beginning of their growth. It has therefore been postulated that the interaction established by bridges and/or the prefollicular cells may play a role in regulating the onset of this process (Filosa and Taddei, 1976). In particular, bridges may facilitate a uniform distribution of transcription blocking factors in the cluster, thereby inhibiting the intense protein synthesis required for growth: when the bridges are broken, the block is removed and the diplotene oocytes start growth. At this stage, the single oocytes, now surrounded by a thin layer of specialized somatic cells, called follicular cells, begin to differentiate independently. These structures, the primary follicles, emerge from the germinal beds, too small to contain them, and migrate ventrally along the ovarian wall (Filosa, 1973). The onset of oocyte growth may be also stimulated by paracrine factors secreted by the follicular cells (Limatola et al., 2002; Cruz-Cano et al., 2023).

In sexually mature females, at the beginning of the ovulatory cycle, in April, the germinal bed contains approximately 150–200 prefollicular oocytes, of which only 13 at most are ovulated. It has been estimated that about 91 % of oocytes that begin differentiation undergo degeneration (Filosa, 1973). Interestingly, this remarkable level of degeneration affects only the early meiotic oocytes and stops after the diplotene phase; in fact, all formed primary follicles will mature. A mechanism that controls oocyte number in the early stage of meiotic differentiation,

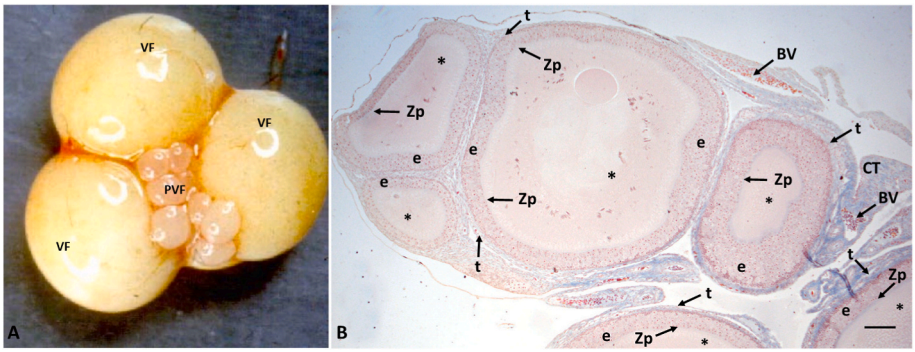

Fig. 1. *Podarcis siculus* ovary. A) Whole ovary observed under a stereoscopic microscope. VF, vitellogenic follicles; PVF, previtellogenic follicles. B), Histological section of the ovary observed under a light microscope, stained with Mallory's trichrome. *, oocytes with regular cytoplasm; zp, zona pellucida; t, theca; e, epithelium; CT, connective tissue; BV, blood vessel. Scale bars: 50 µm.

prior the oocyte growth, may be advantageous in relatively small animals that produce macrolecithal eggs.

5.1. Pre-vitellogenic follicles

The epithelium of the primary follicles, which has a diameter of approximately 100 μm, is composed of a monolayer of small stem cells that proliferate rapidly, assuming a cuboidal shape. Junctions are evident between the germ cells and the differentiating follicular cells (Andreuccetti et al., 1978). The primary follicles are progressively enveloped by a basal lamina and a theca. In parallel, asynchronous cell divisions lead to the formation of two subpopulations. The cells belonging to the first remain in proximity to the external connective tissue, continue to proliferate and are defined as small cells (Filosa et al., 1979) (Fig. 3); the cells belonging to the second increase in size, as does the nucleus, which present very dispersed chromosomes, and the nucleolus. These cells become polarized, with the cytoplasm approaching the oocyte until it comes into contact with it via a thin cytoplasmic extension that ends in an intercellular bridge with the oocyte, crossing the zona pellucida surrounding the oocyte (Filosa and Taddei, 1976). Due to their shape, this cell population is called pyriform cells (Taddei, 1972) (Fig. 3).

The bridge is structurally well organized, with a cytoskeleton made of bundles of microtubule supporting it (Maurizii et al., 1997); electron microscopy images showed the passage of vesicles and organelles towards the oocyte (Andreuccetti et al., 1978). Consequently, it can be stated that pyriform cells will contribute significantly to the oocyte growth by synthesizing and transferring cytoplasm, RNA molecules and organelles to the oocyte via the bridge (Motta et al., 1995a,b).

Follicular cells contribute greatly to the growth of the oocyte before the beginning of the vitellogenic phase. Within a few weeks, the oocyte reaches a diameter of 1.700 mm. The nourishing cells that form the follicular epithelium are huge in number, about 30 thousand per oocyte, arranged in regular layers around the oocyte (Filosa, 1973; Filosa et al., 1979); at this stage, three different types of follicular cells are morphologically recognizable: small round cells, intermediate cells, slightly larger than the previous ones, and pyriforms (Fig. 3 A). The small cells represent the stem cells, the pyriform cells are the nourishing cells of the oocyte, the intermediate cells are immature pyriform cells. All together, they form the granulosa, like that of mammalian ovarian follicles. This same type of organization has also been described in a class of vertebrates phylogenetically distant from Sauropsida, a clade including Reptilia and Aves, in the female of cartilaginous fish, which, like Sauropsida, is characterized by the production of eggs particularly rich in yolk (Callard et al., 1991; Andreuccetti et al., 1999; Prisco et al., 2002).

In this phase of follicular maturation, the oocyte is also very active. The nucleus presents the typical lampbrush chromosomes that are highly transcriptionally active, which ensure a high amplification of RNA molecules (Motta et al., 1991).

The nucleolus of the oocyte undergoes significant changes during follicular growth. In 100–200 μm oocytes (with nuclei in early diplotene), a prominent nucleolus was commonly observed in the nucleus, with well-defined fibrillar and granular compartments (Fig. 4 A), that, as seen through autoradiography with tritiated uridine, actively synthesized rRNA (Tammaro et al., 1998). During oocyte growth, the nucleolus underwent fragmentation: in oocytes of about 400 μm spherical bodies can be observed, that are electron-dense at the transmission electron microscope, do not contain RNAs and are digested by pronase (Taddei and Andreuccetti, 1990; Tammaro et al., 1998) (Fig. 4 B). In oocytes larger than 700 μm, the nucleoplasm contained a large number of small and round structures with fibrillo-granular organization, uridine-incorporating, that should be regarded as micronucleolus-like structures (Tammaro et al., 1998) (Fig. 4 C and insert).

The oocyte cytoplasm accumulates proteins, messenger RNAs and ribosomes; in previtellogenic oocytes, during the non-reproductive period, these molecules crystallize to form what have been defined as ribosomal bodies (RB) (Taddei and Filosa, 1976; Unwin and Taddei,

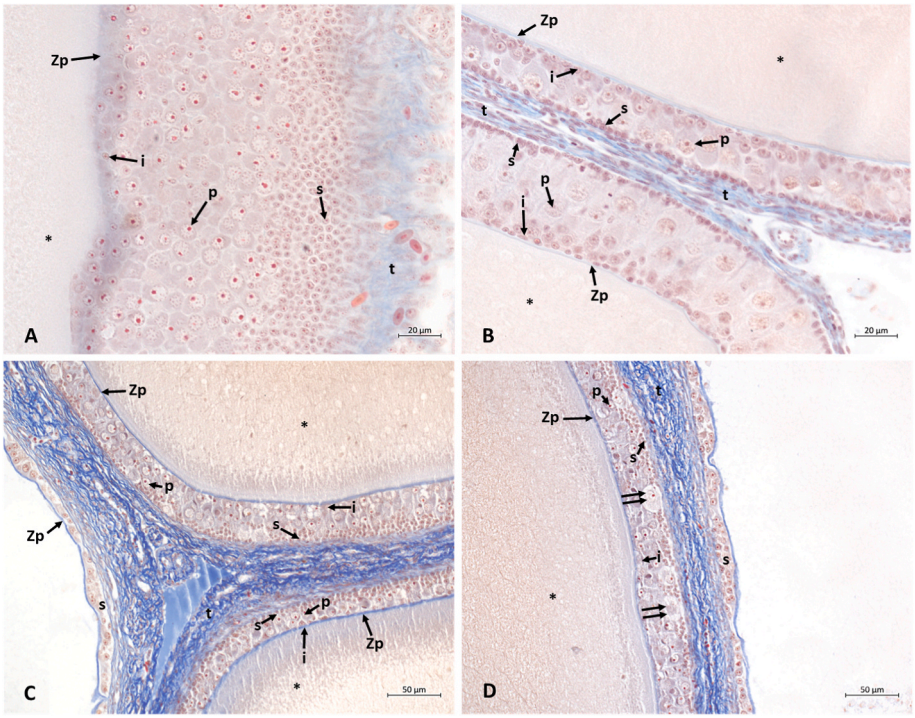

Fig. 3. Cellular morphology of *P. siculus* ovarian follicles at different stages of differentiation. A, previtellogenic follicle, showing the typical polymorphic epithelium composed of small (s), pyriform (p), and intermediate (i) cells; B, C, D, vitellogenic follicles, showing the regression of follicular epithelium; note in D, on the right, the follicular epithelium composed of only small cell. Connectival theca (t); apoptotic cells (double arrow); oocyte cytoplasm (asterisk); zona pellucida (Zp). Mallory's trichrome staining; scale bars: (A, B) 20 μm; (C, D) 50 μm.

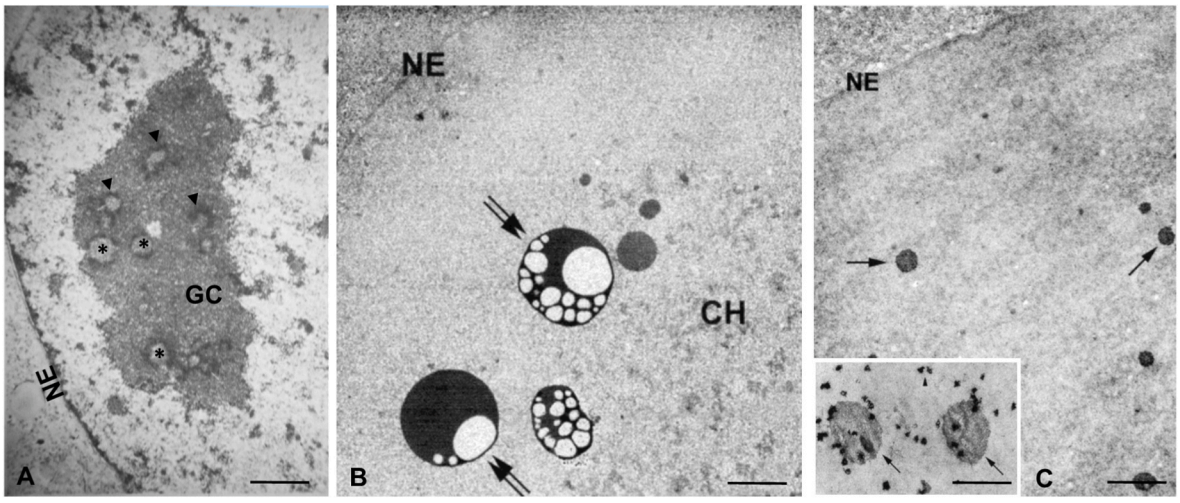

Fig. 4. Nuclear ultrastructure of *P. siculus* oocyte by transmission electron microscopy. A) in 200 μm oocyte, nucleolus is evident, fibrillar (asterisk), densofibrillar (arrowheads) and granular compartments (GC) are well defined; B) in 400 μm oocyte, chromosomes (CH) are localized in the nucleus center, no nucleolus is recognizable while electro-dense spherical bodies are visible (double arrows); C) fibrogranular microstructures (arrows) are dispersed in the nucleoplasm and are positive to uridine incorporation (insert). NE = nuclear envelope. Scale bars: A = 2 μm, B = 5 μm, C = 3 μm, insert = 1 μm *(B and C, modified by* Tammaro et al., 1998*)*.

1977). Although RBs are active in endogenous protein synthesis in a cell-free system in vitro, in vivo they appear to be completely inactive in protein synthesis, suggesting that they represent a regulatory mechanism of protein synthesis, activated when the oocyte is in a quiescent phase (Taddei et al., 1973). *P. siculus* oocyte RBs are similar to germ granules, membrane-less organelles formed through the condensation of RNA and proteins, identified in germ cells across species, and involved in certain aspects of RNA regulation, such as storage, translational control, and RNA processing (Pham-Bui and Lee, 2025). Indeed, RBs also resemble stress granules, cytoplasmic structures dynamically assembled in response to adverse environmental conditions experienced by both somatic and germ cells, including heat shock, oxidative and osmotic stress, UV damage, and viral infection (Schisa, 2012; Protter and Parker, 2016).

Interestingly, once the follicles reach a diameter of about 2 mm, the follicular cells surrounding the oocyte begin to degenerate: as vitellogenesis approaches, the epithelium gradually regresses towards a homomorphic condition, similar to that of the primary follicles, which persists throughout vitellogenetic phase (Filosa, 1973) (Fig. 3C and D). The mechanism of degeneration of intermediate and pyriform cells has been extensively studied. Results obtained by morphological, biochemical and molecular approaches have demonstrated that the epithelial remodeling occurring in large previtellogenic follicles involves apoptotic pathways. The pyriform cells, still connected to the oocyte by intercellular bridges when they undergo apoptosis, release most of the cytoplasm and organelles into the oocyte. Ultrastructural observations clearly showed that during regression, the volume of the pyriform cells was significantly reduced while the intercellular bridges remained open and filled with vesicles, functional mitochondria and other organelles (Andreuccetti et al., 1979; Andreuccetti, 1992; Motta et al., 1995a; Tammaro et al., 2007). Nucleic acids have a different fate: RNA molecules are directly transferred in oocyte (Motta et al., 1995a); vesicles containing pyknotic chromatin and fragments of nuclear membrane are detectable in the small cells, that become the only constituents of the follicular epithelium during vitellogenesis. However, small DNA fragments, probably derived from apoptotic DNA laddering, have also been identified in oocyte yolk platelets (De Caro et al., 1998; Motta et al., 2001).

5.2. *Vitellogenic follicles*

At the beginning of the reproductive period, in late spring, estradiol produced by follicular cells induces hepatocytes to synthesize and secrete vitellogenin, thus determining the formation of vitellogenic follicles. All follicular cells have steroidogenic activity; however, the small cells are primarily responsible for hormone secretion (Motta et., 1995). Plasma vitellogenin is internalized by the oocyte via micropinocytosis. Vitellogenic growth of oocytes lasts 20–30 days and they rapidly increase in diameter from 2 to 9 mm; the increase in size of vitellogenic follicles is due entirely to the oocyte (Wallace, 1985).

Beginning with oocytes larger than 2 mm, the oocyte plasma membrane presents microvilli and invaginations that facilitate micropinocytosis of yolk precursors (Ghiara et al., 1968, 1970), thereby increasing the surface area containing vitellogenin receptors. In this regard, starting from the total RNA prepared from the ovaries of *P. siculus* in the reproductive period, a cDNA fragment encoding a 69 amino acid polypeptide was identified, which shares a high identity with the corresponding region of the VTG-receptor (i.e., very low-density lipoprotein receptor-related protein 8) present in sauropsids (Verderame et al., 2016).

The study of the enzymatic activity of the ovary of *P. siculus* has shown that the intraoocytic processing of the internalized VTG is mediated by two different proteases, both belonging to the aspartic protease family: one is Cathepsin D, a protease ubiquitously expressed in tissues, particularly abundant and active in lizard ovary in June, coinciding with the formation of the yolk platelets (De et al., 1999); the second is Nothepsin, an estrogen-dependent enzyme. The latter, identified for the first time in the liver of Antarctic fish (Capasso et al., 1998), from which it takes its name, is expressed under the action of estrogens in the maternal liver of oviparous vertebrates (Riggio et al., 2000; Zheng et al., 2018). From here, it migrates, along with VTG, into the oocyte, where it participates in the proteolytic cleavage of the same, providing nourishment to the embryo during development (Knoll-Gellida et al., 2006; Mann and Mann, 2008; Bourin et al., 2012).

In the ovary of many sauropsids, follicular atresia of the developing follicles, both previtellogenic and vitellogenic, is a common occurrence. Follicular atresia is thought to serve several functions, such as contributing to the development of follicular hierarchies and limiting clutch size. Excessive rates of follicular atresia have been associated with pathological conditions, such as fasting or exposure to pollutants

(Dervas et al., 2024; Ru et al., 2024). Interestingly, in the ovary of *P. siculus*, under natural conditions, no atretic follicles are detected: the pre-vitellogenetic follicles are blocked; then, at the beginning of the breeding period, some are recruited and undergo the modifications previously described, becoming vitellogenic follicles. All recruited follicles complete their maturation and ovulate without showing atretic phenomena (Andreuccetti et al., 1990); only after ovulation does the follicle undergo atresia and transform into a corpus luteum.

6. Clutch size in *Podarcis siculus*

The absence of atresia of the preovulatory follicles implies that the fecundity rate in this species is regulated in advance, during the follicular recruitment phase, stimulated by favorable light and temperature conditions. In *P. siculus*, prefollicular oocytes are present throughout the year in a small and very predictable number, varying from a minimum of 13 in winter to a maximum of 23 in April, before the first ovulatory wave (Filosa, 1973). However, of all the follicles formed, approximately 13 per ovary undergo growth and ovulation (Motta et al., 2004). Interestingly, this value is not exceeded in case of overstimulation with exogenous FSH administration, exposure to more favorable temperatures and/or duration of daily light and darkness (photoperiod) (Borrelli et al., 2000). Experiments involving unilateral ovariectomy (Motta et al., 2004) have revealed that these numbers are predetermined, and a compensatory mechanism is in place. Indeed, after removing an ovary, the remaining contralateral one consistently showed a gradual but significant increase in follicle count; notably, if the experiment was conducted in winter, the number of follicles rose to an average of 23–24 from the single ovary, a figure that closely resembles the combined count of the two gonads and is typically found in a single gonad only at the onset of the reproductive period. All these follicles, as per the reproductive cycle, are smaller than 2 mm and in the previtellogenesis stage. When the ovariectomy is performed in April, the number of follicles in the remaining ovary exceeds the maximum of 23 typically found during the reproductive period under physiological conditions, with around 10 supernumerary follicles forming. This compensatory event ensures that ovariectomized females produce a batch of eggs comparable to that observed in intact animals (15–20 eggs), potentially slightly larger than usual (Motta et al., 2004).

Based on evidence of crosstalk between gonads, which controls clutch size, researchers (Sica et al., 2001; Motta et al., 2004) have hypothesized the presence of diffusible factors responsible for both the recruitment of oogonia to the germ beds to form previtellogenic follicles, and for the inhibition of the transformation of all previtellogenic follicles into follicles destined for ovulation. The nature of these factors and whether diffusion occurs in a paracrine or endocrine manner remains unclear (Limatola et al., 2002).

7. The toxic effects of environmental contaminants on the ovaries of *P. siculus*

Podarcis siculus is a resilient species that, over the years, has adapted to living in highly anthropized areas, such as city parks and agricultural fields, following the consumption of pristine rural areas by human activity. This has exposed and continues to expose these animals to emerging soil contaminants, such as heavy metals from gasoline and industrial waste, as well as a wide range of pesticides used in agricultural practices.

Studies have revealed a wide range of effects on lizard tissues, resulting from indirect and/or direct exposure to contaminants through various routes, such as dermal exposure, inhalation, and ingestion of contaminated food (Scudiero et al., 2025). Numerous studies have also explored the reproductive system and reproductive fitness of lizards exposed to contaminants. The testis has been extensively studied, given its high proliferative rate of spermatogonia, making it particularly sensitive to the effects of toxic substances that can alter mitotic activity and damage DNA (Rosati et al., 2022). The analysis of plasma and testes in males also confirmed the xenoestrogenic activity of certain contaminants, including alkylphenols and glyphosate (Cardone et al., 2008; Cardone, 2012, 2015; Verderame and Scudiero, 2017; Verderame et al., 2022).

In females, the impact of metals and pesticides on offspring has been a focus of research. This has involved investigating the potential for maternal transfer of contaminants into eggs (Simoniello et al., 2013), as well as analyzing the damage caused to embryo development when incubated in contaminated soil (Simoniello et al., 2011, 2014). The effects of the cadmium (Cd) ions and the herbicide glyphosate have been thoroughly investigated in the context of oogenesis and folliculogenesis.

7.1. The toxic effects of cadmium ions

In the ovaries of *P. siculus* females exposed to Cd during the breeding season, an increase in oocyte recruitment from the oogonial pool was observed (Simoniello et al., 2010, 2013). Given that oogonial proliferation and oocyte recruitment are effects typically exerted by FSH (Motta et al., 1995a,b), it has been suggested that Cd, in addition to causing morphological and biochemical changes in the ovary, also act as an endocrine disruptor, mimicking the effect of gonadotropins (Simoniello et al., 2010). However, the number of primary follicles remained unchanged, and the number of growing follicles decreased due to the occurrence of follicular atresia, resulting in a significant reduction in clutch size (from 13 to 14 eggs observed under natural conditions to 5–6) (Simoniello et al., 2013). Cd contamination significantly altered the morphology of both oocytes and somatic follicular cells. The oocytes exhibited cytoplasmic vesicles containing transparent or filamentous material, as well as small carbohydrate granules; additionally, the oocyte cytoplasm displayed small blebs protruding into the follicular epithelium (Simoniello et al., 2013). The latter was characterized by thickenings and interruptions, resulting in the oocyte membrane directly contacting the theca at certain points. In exposed animals, apoptotic pyriform cells were very frequent; apoptosis occurred in cells of primary and early previtellogenic follicles where cellular regression is normally absent, leading to the presence of atretic follicles, generally absent in control ovaries (Andreuccetti et al., 1990). Finally, the zona pellucida, a protein membrane composed of glycoproteins, was found to be affected by Cd contamination. This membrane is interposed between the oocyte membrane and the follicular cells and is interrupted under normal conditions only by intercellular bridges connecting the cytoplasm of pyriform cells to that of the oocytes (Andreuccetti et al., 1978). Following cadmium exposure, the zona pellucida showed the presence of small vesicles and disorganized areas. It has been suggested that changes in the carbohydrate composition of the zona pellucida may be responsible for the observed effects (Simoniello et al., 2013).

7.2. The toxic effects of the herbicide glyphosate

Glyphosate is the most widely used herbicide in agriculture, but its use for drying cereal crops and in urban areas has been banned in Italy (Gazzetta Ufficiale, 2016). *P. siculus* specimens living in agricultural areas may be exposed to this pesticide through inhalation and ingestion of contaminated food, primarily invertebrates. Research has shown that experimental exposure to glyphosate caused severe fibrosis and oxidative stress in the liver of these lizards (Verderame and Scudiero, 2019). The herbicide significantly altered testicular morphology, impacted spermatogenesis, and modified the localization of estrogen receptors in germ cells, likely as a result of its xenoestrogenic effects (Verderame et al., 2022).

In the ovary, the herbicide triggered the recruitment of oocytes from the germinal beds and the formation of primary follicles (Rosati et al., 2023). At the same time, it facilitated the apoptotic regression of pyriform cells, leading to the early maturation of follicles (Rosati et al., 2023). It also triggered collagen deposits in the follicular epithelium,

altering the oocyte cytoplasm and the composition of the zona pellucida, whose proteins exhibited changes in carbohydrates. Xenoestrogenic activity was also observed in females, where glyphosate induced an overexpression of estrogen receptors (Rosati et al., 2023). Several of these effects are comparable to those observed in the ovaries of lizards exposed to cadmium. This is quite intriguing, as the two substances are distinct molecules, employing distinct pathways to enter cells, and should consequently influence distinct cellular mechanisms. The similarity in response to various contaminants may be due to indirect effects mediated by the liver, an organ particularly affected by toxic substances and crucial for oocyte growth, especially in oviparous vertebrates. Further studies will help clarify the validity of this hypothesis.

8. Conclusions

The numerous studies collected and summarized in this review reveal interesting aspects of oogenesis in *Podarcis*, and consequently, in oviparous terrestrial vertebrates. The most interesting aspect to emerge from these studies is the key role that follicular cells play during oocyte maturation. The follicular epithelium is a dynamic structure that interacts with the oocyte and changes during its different phases. Initially, it consists of a single layer of cells, but by the end of the previtellogenic stage, it becomes multistratified, comprising three different cell types. By the end of the maturation process, it once again consists of a single cell type. Follicular cells not only form a protective lining epithelium but also actively participate in oocyte recruitment and growth. The typical steroidogenic function of follicular cells is accompanied by the production of a diffusible protein factor involved in the recruitment of immature oocytes. The function of the nourishing cells of the growing oocyte, performed by the follicular pyriform cells, is to provide the growing oocyte with functioning cytoplasmic organelles, such as mitochondria, ribosomal RNAs, and DNA fragments.

The crosstalk between somatic and germ cells also extends to the gonadal level, allowing one gonad to recognize the state of the contralateral one. This enables it to respond with a compensatory mechanism to any loss of gonadal functionality, while still ensuring a good clutch size.

Another interesting aspect of the reproductive cycle of *Podarcis* is the partial autumn resumption of gonadal activity, which occurs synchronously in both males and females. This could indicate an ancient biennial reproductive cycle linked to the climate change experienced by this species. A tempting hypothesis is that the biannual cycle could be restored if warmer weather continues into autumn. On the one hand, this could be positive for increasing the lizard populations, which in recent years have been continuously subjected to unfavorable events such as habitat destruction, food scarcity, soil pollution; on the other hand, such an event would be indicative of climate change whose long-term effects remain elusive.

CRediT authorship contribution statement

Rosaria Scudiero: Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation, Conceptualization. **Teresa Chianese:** Writing – original draft, Data curation. **Marina Prisco:** Writing – review & editing, Data curation. **Luigi Rosati:** Writing – review & editing, Validation, Supervision, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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