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Review

The idiosyncrasies of oocytes

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Animal oocytes face extreme challenges. They remain dormant in the body for long periods of time. To support offspring development and health, they need to store genetic material and maternal factors stably and at the same time manage cellular damage in a reliable manner. Recent studies have provided new insights on how oocytes cope with such challenges. This review discusses the many unusual or idiosyncratic nature of oocytes and how understanding oocyte biology can help us address issues of reproduction and intergenerational inheritance.

Highlights

Oocytes perform essential functions in reproduction and intergenerational inheritance.

They face huge challenges to stay dormant, manage cellular damage, and ensure informational storage.

Regulation of protein translation and mitochondrial activity plays important roles in maintaining quality of immature and mature oocytes.

Storage of RNA in 'arrested' condensates and proteins in cytoplasmic lattices in mature oocytes ensures reliable information transfer to the offspring.

The unique oocyte

Animal oocytes perform an essential function, which is to ensure the continuity of a species. To support early development of the embryos, oocytes are technically the largest cells in the body, and they are endowed with maternal factors made throughout oogenesis. Early oocyte development involves a conserved phenomenon that requires the formation of interconnected germline cells called **cysts** (see Glossary) [1,2]. Within these cysts, nurse or sister cells supply important factors such as organelles, proteins, and RNA to the growing oocytes [3–5]. Depending on the organisms, these early or primary oocytes continue to develop into mature oocytes through different mechanisms. *Drosophila* or fruit flies use a system of **nurse cell polyploidy** to support oocyte growth within a short period of a few days [6]. Furthermore, in species such as *Xenopus*, when oocyte growth spans a few months, the oocyte autonomously transcribes all the RNA needed by maximizing the rate of transcription, leading to the formation of giant **lampbrush chromosome loops** [7].

Mammals are unique because they are born with a fixed number of primary oocytes arrested at meiosis I. These oocytes remain dormant in the primordial follicles for months in mice to decades in humans, constituting the ovarian reserve [8]. Upon activation of phosphatidylinositol 3 kinase (PI3K) and the mechanistic target of rapamycin complex 1 (mTORC1) pathways, primary oocytes are activated and start to grow and mature into preovulatory oocytes [9,10]. This process happens after the ovarian reserve has been established and continues until the age of 45–55 when the ovarian reserve is depleted [11]. Besides entering follicular development, some primordial follicles also undergo senescence and loss, contributing to reproductive decline [12]. Therefore, the maintenance of primary oocyte quality during long-term dormancy is essential for reproductive success. After follicle activation, folliculogenesis occurs under the control of hormones to form mature full-size preovulatory oocytes. Mature oocytes cease transcription and store accumulated proteins and mRNAs produced during growth [13,14]. As zygotic transcription only starts during the two-cell (mouse) and four-cell (human) stage, the maternal pool of proteins and RNAs are essential to support early development [15].

Although this review focuses on the unique biology of oocytes, it is important to acknowledge that oocytes are not entirely cell autonomous and indeed require the nearby somatic cells to function. In both *Drosophila* and mice, oocyte biology is regulated by somatic cells via bidirectional communication or signaling. In *Drosophila*, oocyte-somatic follicle cell interaction and signaling regulate oocyte development and polarity [16–18]. Furthermore, in mammals, oocyte and

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granulosa cells communicate to promote growth and development of the follicle and ensure oocyte competence by supplying essential metabolites through the transzonal projects, gap junctions, and oocyte-derived mushroom-like microvilli [19–21].

The task of making an oocyte is daunting, that is, the need to make a large cell that serves as a functional storage of information over a long period of time. But how do long-lived oocytes preserve their genetic materials and maternal factors (including mitochondria) to ensure that they are reliably passed down to the offspring? Recent studies have provided important insights into the seemingly idiosyncratic nature that oocytes adopt to stay dormant, manage damage, and ensure informational storage (Figure 1). Understanding how oocytes cope with these challenges has huge implications for fertility and intergenerational inheritance. This review summarizes the latest findings in *Drosophila*, zebrafish, *Xenopus*, mice, and humans and highlights specific emerging areas of interest that influence our current thinking of oocyte biology. In particular, this review focuses on how immature and mature oocytes use unique mechanisms to store RNAs and proteins, manage protein aggregation and mitochondrial stress, and maintain quality during aging.

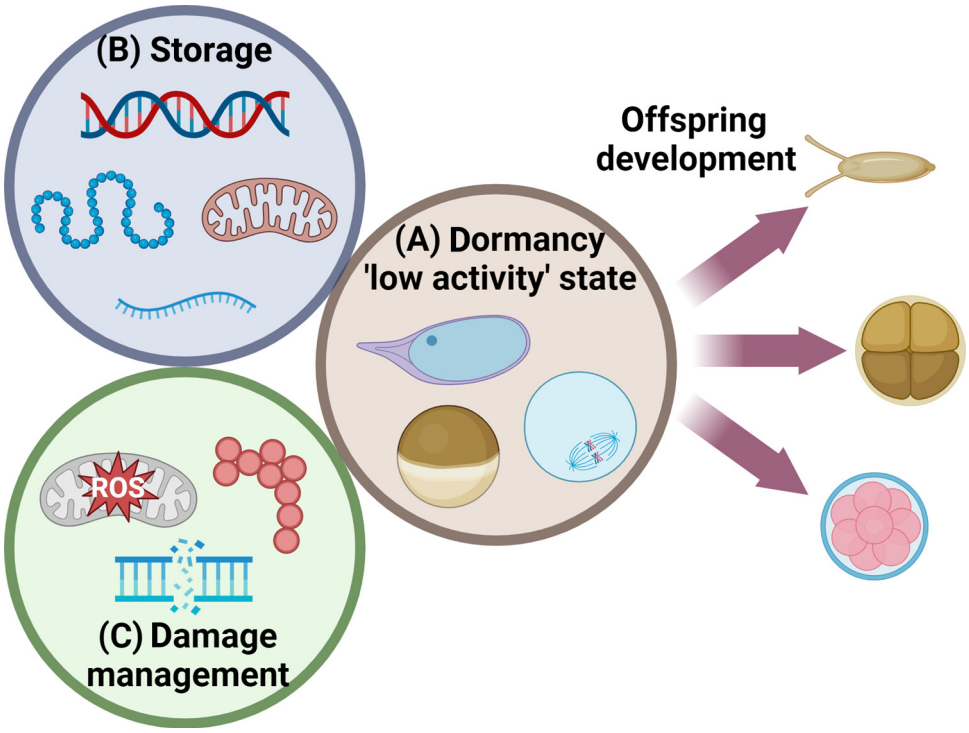


Figure 1. The three major interlinked challenges animal oocytes have to overcome. (A) First, the ability to stay dormant in a 'low-activity' state for long periods of time in the body. Mammalian primary oocytes stay dormant in the primordial follicles for months or decades in mice and humans, respectively. However, *Drosophila* and vertebrates (including *Xenopus* and mammals) produce mature oocytes or eggs that are transcriptionally quiescent and are stored for an extended period of time before ovulation and fertilization occur. (B) Second, the ability to store information such as DNA, RNA, proteins, and organelles reliably. The core function of oocytes is to produce offspring. Thus, oocytes have evolved mechanisms to ensure that they pass down genetic materials and cellular factors (such as mitochondria and mRNAs) accurately even though they have been stored for a long time. The ability to store and transmit such information is crucial for the survival of the species. (C) Third, the ability to minimize cellular damage and cope with *de novo* damage. Because the quality of the maternal factors is important for offspring development, oocytes minimize the production of damage inducing agents such as reactive oxygen species (ROS). Should damage occur, oocytes respond and manage it effectively so as not to compromise the quality of the mature oocytes. Figure created with BioRender (biorender.com).

Glossary

Autophagosome: a double-membrane vesicle formed during autophagy, which engulfs cellular organelles and other cytoplasmic contents and brings them to the lysosomes for degradation.
Balbiani body: a membrane-less structure consisting of mitochondria, endoplasmic reticulum (ER), Golgi apparatus, RNA, and specific proteins, which is found only in dormant oocytes in both vertebrates and invertebrates. During oocyte activation, the Balbiani body disassembles and releases its contents into the cytoplasm. The function of the Balbiani body is unknown, but it is suggested to function in the maintenance of the dormant oocytes by regulating mitochondrial quality and sequestering RNA and proteins important for oocyte activation.
Cysts: interconnected germline cells derived from the same progenitor cell via cell division with incomplete cytokinesis.
Integrated stress response: a signaling pathway in response to stress stimuli that restores cellular homeostasis. It functions by decreasing the translation of global protein and activating specific genes.
Lampbrush chromosome loops: sites of active transcription from the giant lampbrush chromosome during meiotic prophase in oocytes of vertebrates such as frogs, chicken, and salamanders.
Mitochondrial membrane potential: a proton gradient across the mitochondrial inner membrane, which is required to generate ATP via oxidative phosphorylation.
Mitophagy: a process to degrade damaged mitochondria via autophagy during damage or stress.
Nurse cell: a cell that is connected to, and supplies proteins, RNA, and organelles to, the developing oocyte.
P bodies: nonmembranous cytoplasmic granules consisting of mRNA and ribonucleoproteins, which are sites of translation repression.
Phase transition: the process when a substance changes from one state to another (e.g., between liquid and solid states).
Pole cells: the first germline cells that are formed at the posterior pole of some insect eggs.
Poleplasm: a region of the egg that contains specialized germ cell determinants.
Polyploidy: a cell state that contains more than one pair of chromosomes.

mRNA storage in 'arrested' condensates

Drosophila maturation and mature oocytes

In *Drosophila*, the location of the germline cells of the offspring are already determined in the mothers' oocytes. During oogenesis, *oskar* mRNA is transported from the nurse cells to the posterior pole of the oocyte [22]. Upon localizing to the posterior pole, translation of the Oskar protein occurs, and Oskar protein induces the process of **poleplasm** assembly [23–25]. During embryogenesis, the poleplasm is necessary and sufficient in specifying **pole cell** formation.

A study showed that *oskar* mRNA sequentially binds Bruno, Hrp48, and polypyrimidine tract binding protein (PTB) during trafficking from nurse cells to the posterior pole of the oocyte [26]. It was previously shown that the *oskar* 3′ untranslated region (UTR) can dimerize, and Bruno and PTB can form oligomers with the *oskar* 3′ UTR in higher-order complexes [27–29]. The new study showed that the binding of Bruno to the *oskar* 3′ UTR led to granule condensate formation that quickly transits from a liquid to solid state (Figure 2A). The solid state of *oskar* granules is important for proper posterior localization and timely translation of *oskar* mRNA, the failing of which results in defects in both pole cell formation and embryonic patterning. The mechanical stability of solid *oskar* granules may be essential to protect *oskar* mRNA during the long-distance transport from nurse cells to oocytes. As prolonged presence of *oskar* mRNA is toxic to pole cells, it can also prevent mixing of *oskar* granules with germ granules, which will have detrimental effects on germline development [30].

In mature *Drosophila* oocytes, processing bodies **(P bodies)** are in a similar 'arrested' state, whereby they store maternal mRNAs stably until egg activation. A study examined two known P body RNA-binding proteins maternal expression at 31B (Me31B) and Trailer Hitch (Tral) and found that they formed condensates that were immobile in mature oocytes [31] (Figure 2B). These P bodies contain *bicoid* mRNA for storage and translation repression. During egg activation, the P bodies disperse, regain mobility, and release *bicoid* mRNA into the cytoplasm for translation. *Bicoid* is a maternal effect gene, and early translation of maternally loaded *bicoid* mRNA is important for the production of Bicoid protein, which functions as a morphogen to pattern the embryo by defining the anterior–posterior axis.

Mature mouse oocytes

Mouse mature oocytes also contain a similar type of 'arrested' cytoplasmic body known as mitochondria-associated ribonucleoprotein domain (MARDO) [32] (Figure 3A). MARDO contains typical P body components DDX6 (fly Me31B) and LSM14B (fly Tral) on top of other RNA-binding proteins ZAR1, YBX2, and 4E-T. It forms a hydrogel-like matrix sequestering specific mRNA for storage and translation repression. During oocyte meiotic maturation, MARDO dissolves and translation ensues for meiotic progression. The release of translationally repressed stored mRNAs is important for effective oocyte maturation and zygotic development. Mutant oocytes that affect MARDO formation do not store mRNAs and exhibit defects such as spindle disassembly, chromosome misalignment, and cell cycle abnormalities [32]. One unique characteristic of MARDO is its association with mitochondria. The assembly of MARDO requires **mitochondrial membrane potential** during oocyte growth. However, the biological significance of MARDO-mitochondria association remains to be discovered.

It appears that oocytes make use of the **phase transition** of RNA-binding proteins to control the solubility of maternal mRNA in order to protect them from decay [33]. Evidence in vertebrate oocytes had also provided insights into the regulation of oocyte mRNA via Xvelo1 (in *Xenopus*) and Bucky Ball (in zebrafish). Xvelo (homolog of Bucky Ball) can self-assemble into an amyloid-like matrix that holds the mitochondria together in the **Balbiani body** [34] (Figure 4). This phenomenon

Previtellogenic arrest: a checkpoint before the insect ovarian follicle undergoes growth and maturation into a mature oocyte.
Proteasome: a protein complex that functions to degrade intracellular proteins, usually damaged or not needed, by a process called proteolysis.
Stable intronic sequence (sis)RNA: cellular RNA derived from noncoding intronic sequences that are not actively degraded and thus have longer half-lives than other intronic RNA.
VDAC1: voltage-dependent anion-selective channel 1 is a transmembrane protein that functions as an ion channel in the outer mitochondrial membrane and allows transport of ATP from the mitochondrion to the cytoplasm.

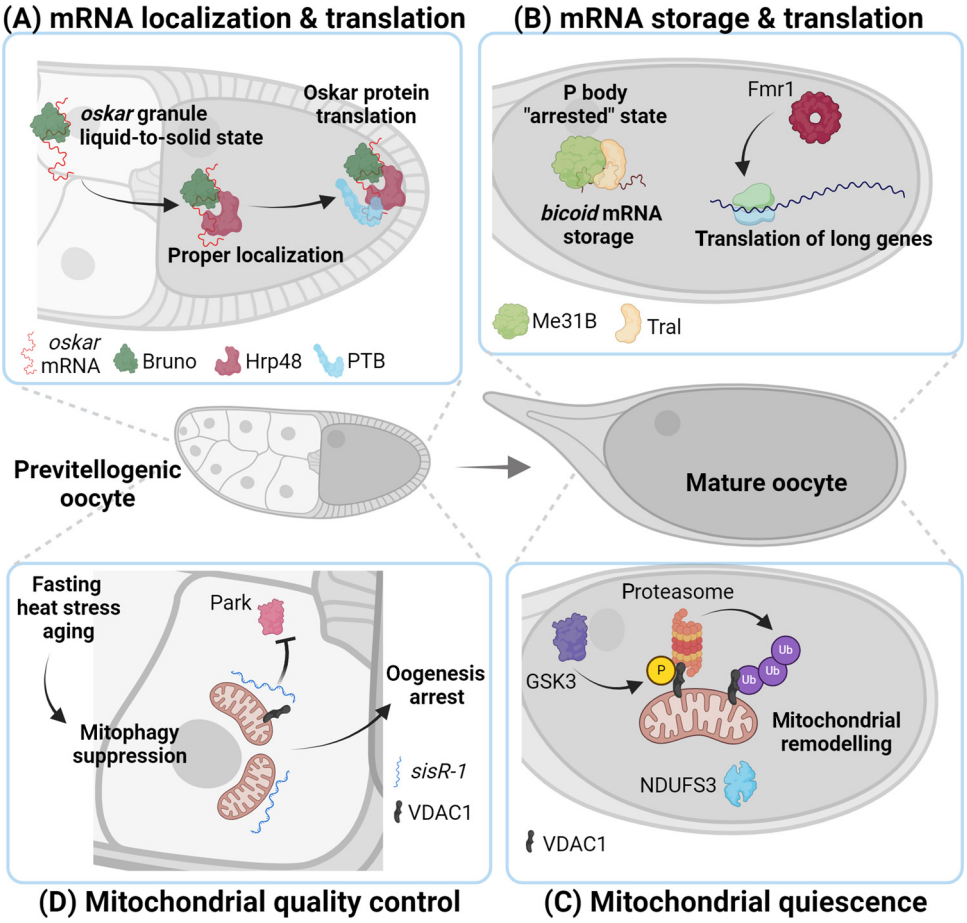


Figure 2. Different mechanisms for regulating localization and translation of mRNA and mitochondria in previtellogenic egg chambers and mature oocytes in *Drosophila*. (A) During oogenesis, *oskar* granules undergo a liquid-to-solid state transition, which is required for effective transport to the posterior pole of the oocyte and Oskar protein translation. The sequential binding of *oskar* RNA to Bruno, Hrp48, and PTB promotes liquid-to-solid phase transition. The solid phase of *oskar* granules promotes Oskar translation and poleplasm assembly in the maturing oocyte. (B) In mature oocytes, maternal mRNA including *bicoid* mRNA are stored in arrested P bodies. This ensures that *bicoid* mRNA is being stored in a translationally repressed state and subsequently released into the cytoplasm for active translation during early development for embryonic patterning. Furthermore, a basal level of translation of long genes is still maintained by Fmr1 in stored oocytes. These genes often encode large proteins needed for neurodevelopment and have human homologs associated with autism spectrum disorders. (C) In mature oocytes, mitochondria undergo respiratory quiescence by remodeling of mitochondrial proteins. Glycogen synthase kinase 3 (GSK3) promotes the recruitment of the proteasome to VDAC1 via phosphorylation. Upon recruitment to mitochondria, VDAC1 is polyubiquitinated and degraded. In addition, complex I protein NDUFS3 is also excluded from the remodeled mitochondria. These processes lead to the storage of low-activity mitochondria in mature oocytes. (D) Upon nutrient and heat stress, and aging, damaged mitochondria are not cleared by mitophagy via the accumulation of *sisR-1* with mitochondria. *sisR-1* inhibits the polyubiquitination of VDAC1 by Park, leading to mitochondrial clumping and oogenesis arrest. When nutrients are available, *sisR-1* is degraded by Clu, and mitophagy resumes, which is coupled with oocyte maturation. Figure created with BioRender (biorender.com).

is remarkably similar to MARDO in mice, whereby storage of RNA in arrested cytoplasmic bodies is closely linked to mitochondria [32]. Similar observations were also made a few decades ago in *Drosophila* mature oocytes where germ granules closely associate with mitochondria [35,36]. The functional relationship between the conserved associations between RNA, RNA-binding proteins, and mitochondria remains an intriguing area of investigation for the future.

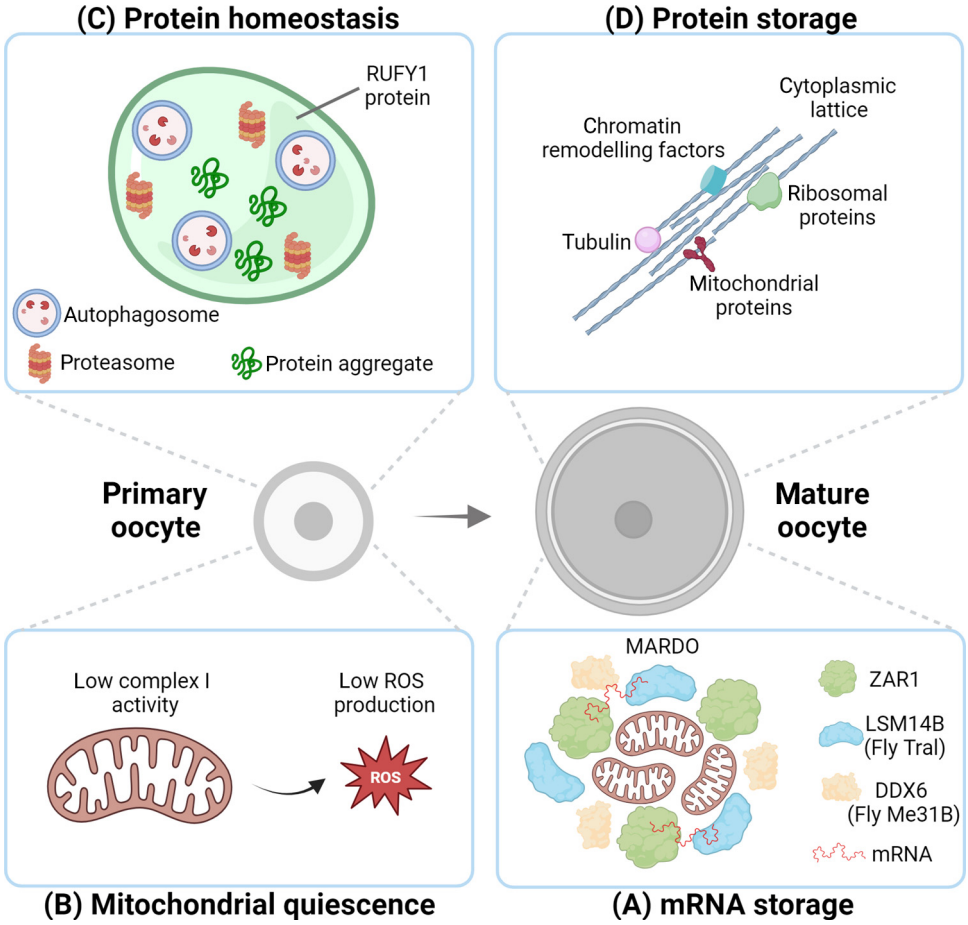


Figure 3. Different mechanisms for regulating storage of mRNA, mitochondria, and proteins in primary and mature oocytes in mammals. (A) Mature oocytes store mRNAs in cytoplasmic bodies called mitochondria-associated ribonucleoprotein domain (MARDO), which contain P body-related proteins LSM14B and DDX6. MARDO stores mRNAs important for oocyte maturation after fertilization and early zygotic development. (B) In primary oocytes, mitochondria maintain low rates of reactive oxygen species (ROS) production by bypassing the requirement for complex I. This mechanism helps to minimize damage to the primary oocytes, which remain dormant for months and years in mice and humans, respectively. (C) Protein aggregates are stored in cytoplasmic bodies called endolysosomal vesicular assemblies (ELVAs) in immature oocytes. These bodies also contain autophagosomes and proteasomes that are brought together with a protein 'glue' known as RUFY1. In this way, immature oocytes keep protein aggregates in check but do not degrade them. Only upon maturation are ELVAs disassembled, and the protein aggregates are cleared for robust embryonic development. (D) Mature oocytes store proteins on stable cytoplasmic lattices. These proteins (containing chromatin remodeling factors, tubulin, and ribosomal and mitochondrial proteins) are kept immobile and sequestered away from their normal locations. This mechanism ensures that proteins are stably maintained and are only released during zygotic development for immediate functions. Figure created with BioRender (biorender.com).

Translation maintenance in mature *Drosophila* oocytes

In some organisms such as zebrafish and *Xenopus*, mature eggs shut down translation and store dormant ribosomes for future embryonic development [37] (Figure 4). However, studies in mature *Drosophila* oocytes suggest that a basal level of translation is needed to maintain oocyte quality during prolonged storage [38] (Figure 2B). Fragile X mental retardation 1 (Fmr1), a protein commonly known to mediate translation repression, is required to promote translation of long proteins in mature *Drosophila* oocytes [39]. Many of these long proteins such as Poe (human Ubr4), Bruce (human BIRC6), Dom (human SRCAP), and Nf1 (human Nf1), which are downregulated in

	'Arrested' condensates	Translation regulation	Mitochondrial remodeling	sisRNAs
Drosophila	Oskar granule P body (mature oocytes)	Regulated by Fmr1 (mature oocytes)	Respiratory quiescence, lack of Porin & NDUFS3 (mature oocytes)	Nutrient, age-dependent regulation of mitophagy (immature oocytes)
Xenopus	Xvela1 in Balbiani body (immature oocytes)	Ribosome dormancy (mature oocytes)	Lack of complex I (immature oocytes)	sisRNAs of unknown function (immature & mature oocytes)
Mouse	MARDO (mature oocytes)	Ribosomes stored at lattices (mature oocytes)	Lack of complex I (immature oocytes)	Presence not known in oocytes

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Figure 4. Conservation of mechanisms and phenomena in *Drosophila*, *Xenopus*, and mice. A summary table on the comparisons of the different phenomena involving 'arrested' condensates, translation regulation, mitochondrial remodeling, and stable intronic sequence RNAs (sisRNAs) between *Drosophila*, *Xenopus*, and mice. Some phenomena exhibit a high degree of similarity even between invertebrates and vertebrates, suggesting that there may be 'universal' mechanisms or common principles in oocyte biology. Figure created with BioRender (biorender.com). Abbreviation: MARDO, mitochondria-associated ribonucleoprotein domain.

Fmr1-mutant oocytes, have been implicated in dominant intellectual disability and autism spectrum disorder [39]. Consistent with the downregulation of maternally loaded proteins important for neurodevelopment, aged oocytes mutant for *Fmr1* did not complete embryonic development and exhibited neuronal defects. It was later also shown that in mice, the FMR1 encoded FMRP also promotes translation of long protein in the brain. *Fmr1*-knockout mouse cortex has a reduction in translation of the *Auts2* gene, implicated in autosomal dominant autism spectrum disorder [40]. These studies suggest that the translation-activating role of Fmr1 is highly conserved and important for expression of neurodevelopmental genes.

In a related study, it was found that overall translation is also downregulated during prolonged storage in wild-type mature oocytes, which has negative consequences on meiotic spindle maintenance [38]. During aging, translation of Fmr1 is also downregulated in oocytes, suggesting a possible link between oocyte age and offspring neurodevelopment. Thus, translation is a highly regulated process in mature *Drosophila* oocytes, and understanding this process has profound implications on reproductive aging and intergenerational inheritance of neurodevelopmental syndromes including autism spectrum disorder.

Mitochondrial respiratory quiescence

Mature *Drosophila* oocytes

An early study suggested that *Drosophila* and zebrafish oocytes contain mitochondria that are simpler in morphology, less active, and thus produce lower reactive oxygen species (ROS) than sperm and somatic cells [41]. This adaptation could potentially protect the mitochondrial DNA from damage, thus preserving the quality of oocytes throughout the lifetime. Recent studies have provided more in-depth mechanisms on the process of mitochondrial remodeling when they enter respiratory quiescence in the oocytes [42,43] (Figure 2C). As oocytes mature, insulin signaling is downregulated, triggering the activation of the AKT target glycogen synthase kinase 3 (GSK3). Phosphorylation of **VDAC1** (or Porin) by GSK3 promotes **proteasome** recruitment and subsequent turnover of VDAC1 and other outer mitochondrial membrane proteins, contributing to mitochondrial respiratory quiescence. Furthermore, in mature oocytes, complexes I and V are significantly reduced, but not complex IV. Complex I component NDUFS3 is excluded from mitochondria, and complex V becomes disassembled in mature oocytes, suggesting that mitochondrial

remodeling also involves disassembly of respiratory components and subsequent storage in the cytoplasm. Failure to enter mitochondrial respiratory quiescence leads to persistent mitochondrial activity, accompanied by a reduction in glycogen storage and consequently a lower developmental competency of the embryos.

Xenopus and immature human oocytes

Evidence from *Xenopus* and human immature oocytes suggests that ROS production is suppressed via the elimination of complex I [44] (Figures 3B and 4). The lack of complex I activity is coupled with a low-energy state of primary oocytes, which remain dormant in the body for years. Immature oocytes also contain Balbiani bodies, which are amyloid-like bodies that sequester mitochondria [34]. One can imagine that the immobile state of Balbiani bodies may be essential for storing and keeping mitochondria in a quiescent state over long periods of time. Inability to maintain mitochondrial respiratory quiescence may lead to accumulation of ROS over time, leading to higher oxidative damage. Such an event may damage cellular organelles and genetic materials and trigger senescence, resulting in lower-quality oocytes and reduction in ovarian reserve, respectively.

Mitochondrial quality control

Previtellogenic *Drosophila* oocytes

Animals inherit their mitochondria exclusively from their mothers. An endowment of quality mitochondria supports embryonic development and has consequences in the offspring metabolic health. Thus, during oogenesis, mitochondria undergo various steps of selection and quality control [45]. It is known that nutritional stress induces **previtellogenic arrest** of egg chambers at stage 8/9 of oogenesis in *Drosophila* [46]. This is accompanied by the clumping of mitochondria around the nurse cell nucleus, which is often associated with unhealthy mitochondria [47,48]. Upon refeeding, these mitochondria are cleared away by **mitophagy**, and oocyte quality improves [49] (Figure 2D). These observations suggest that suppression of mitophagy during fasting leads to an accumulation of defective mitochondria.

The observation that mitophagy is suppressed during nutritional stress appears to be counterintuitive as various reports have shown that fasting promotes mitophagy [45]. However, this strategy may be beneficial in the context of oogenesis where vitellogenesis is coupled with nutrient availability. Under fasting conditions, egg chambers arrested at the previtellogenic stage may be poised to accumulate damaged mitochondria only to be degraded when they enter vitellogenesis. Coupling mitophagy to oocyte maturation may be a strategy to meet energy demands.

The suppression of mitophagy is mediated by a stable intron *sisR-1*. Under well-fed conditions, *sisR-1* levels are suppressed by two RNA-binding proteins [nuclear DIP1 and cytoplasmic Clueless (Clu)], and both promote the destabilization of *sisR-1* [49,50]. When flies undergo fasting, DIP1 is downregulated, and Clu cytoplasmic bodies disassemble, contributing to the upregulation of *sisR-1*, which localizes to the mitochondria [51]. *sisR-1* further inhibits the polyubiquitination of VDAC1 (by Parkin) and therefore suppresses p62 [or Ref(2)-P]-mediated mitophagy [52,53]. Following refeeding, the mitochondrion localized *sisR-1* is destabilized by Clu, allowing VDAC1 to be polyubiquitinated by Parkin and subsequently cleared away via mitophagy. The molecular mechanism by which *sisR-1* localizes to mitochondria and inhibits VDAC1 polyubiquitination is unclear and requires further investigation. However, *sisR-1* appears to only inhibit mitophagy but not general autophagy during nutrient stress, consistent with published reports that autophagy is activated by starvation during oogenesis in *Drosophila* [47,49,54].

In addition to nutrient deprivation conditions, *sisR-1* is also upregulated in ovaries during aging, concomitant with an increase in mitochondrial clumps and a decrease in mature egg production.

These observations suggest that *sisR-1*-mediated clumping of mitochondria may induce previtellogenic arrest, leading to reduced egg production. In support of this model, knockdown of *sisR-1* alleviates mitochondrial clumping and improves egg production in aged females [49]. Hence, the reduction in mature oocyte production during aging may be in part caused by upregulation of *sisR-1* expression.

Stable introns or **stable intronic sequence (sisRNAs)** were first identified in *Xenopus* oocyte nuclei, and a few had been shown to mediate maternal inheritance in *Drosophila* oocytes [7,55–61]. So far sisRNAs have not been reported in mammalian oocytes, although they have been identified in somatic cells in mammals, including mice and humans [62–64] (Figure 4). Hence, further investigation in stable intron functions may reveal more unique biology of oocytes.

Protein aggregate management

Immature mammalian oocytes

Mammalian oocytes contain a pool of long-lived proteins that may be important for the maintenance of reproductive capacity during the lifetime [65]. A study in mouse immature oocytes identified non-membrane-bound compartments named endolysosomal vesicular assemblies (ELVAs) [66] (Figure 3C). ELVAs contain **autophagosomes**, proteasomes, and aggregates of TAR DNA-binding protein 43 and KIT. Although protein aggregates are sequestered in close proximity to autophagosomes, lysosomes, and proteasomes, they are not degraded. The integrity of ELVAs is maintained by the RUN and FYVE domain-containing protein 1 (RUFY1), which functions as a 'protein glue' to hold the components together. The oocyte only starts to degrade the protein aggregates during maturation. ELVAs are transported to the cortex via an actin-dependent mechanism and subsequently dissolve. The molecular mechanism that controls the timing of degradation is currently unclear.

RUFY1 is highly expressed in oocytes compared with somatic cells. It contains an intrinsically disordered domain and a coiled-coil domain. In oocytes, RUFY1 self-assembles in a manner that is dependent on its coiled-coil domain. When overexpressed in somatic cells, it can lead to the formation of ELVA-like compartments containing autophagosomes and lysosomes but not proteosomes, suggesting that some additional factors in oocytes are needed for full ELVA formation. Although ELVAs are only found in oocytes, the phenomenon of protein aggregate storage is also seen in hematopoietic stem cells, neural stem cells, and neurons, suggesting that other cell types also manage protein aggregates in a similar manner [67–70].

This phenomenon of having immature oocytes store damaged proteins is reminiscent of how *Drosophila* stores damaged mitochondria in previtellogenic egg chambers during nutritional stress (as described earlier). The ability of immature oocytes to persist despite accumulation of damaged macromolecules and organelles may be conserved in both invertebrates and vertebrates. One would imagine that cellular damage needs to be cleared or removed quickly for the cell to survive. However, the oocyte has chosen to manage the damage by 'safekeeping' it temporarily. By learning how oocytes handle cellular damage effectively, one may develop novel strategies to improve cellular health during aging or stress.

Protein storage

Mature mammalian oocytes

In mature mammalian oocytes, proteins are stabilized on cytoplasmic lattices that were first described by scientists in the 1960s [71,72]. Cytoplasmic lattices consist of oocyte-specific maternal peptidylarginine deiminase 6 (PADI6) and subcortical maternal complex (SCMC) proteins, which are immobile, thus, providing a stable platform for proteins to anchor [73]

(Figure 3D). Cytoplasmic lattices appear to store essential proteins in a nonsoluble state, which can confer longer term stability. Many of these stored proteins consist of chromatin remodeling factors, ribosomal proteins, tubulin, and mitochondrial proteins that are important for the development of early embryos. For example, cytoplasmic lattices are required for the storage of proteins such as UHRF1 and KDM2B, which are required for epigenetic reprogramming in early embryos. In addition, as premature localization of UHRF1 into the oocyte nucleus results in hypermethylation of the genome, cytoplasmic sequestration of UHRF1 by lattices may allow for the passive demethylation of the maternal genome after fertilization [74]. Maternal mutations in *Padi6* or SCMC genes result in developmental arrest during the preimplantation stage in mice. Human mutations in *PADI6* and SCMC genes result in infertility and often lead to embryonic arrest, abnormal embryonic structures, and offspring with imprinting disorders [75].

In addition, storing maternal mitochondrial and ribosomal proteins on cytoplasmic lattices may facilitate maintenance of mitochondria respiratory quiescence and ribosome dormancy in mature oocytes. Thus, immobilization of proteins on cytoplasmic lattices may be a general mechanism for sequestrating proteins from their normal active sites, which contributes to the unique characteristics of mature oocytes. So far, cytoplasmic lattices have only been observed in mammalian oocytes, suggesting a specialized mechanism in controlling protein stability and localization.

Concluding remarks

Oocytes face extreme challenges and hence have evolved extreme strategies. It is this recognition of idiosyncrasies that allows us to discover novel mechanisms that are not possibly revealed by somatic cells. Indeed, past lessons have taught us repeatedly that learning from extreme biology helped us to understand common principles; one such example is how amplification of extrachromosomal ribosomal DNA in frog oocytes subsequently provided insights that led to the discovery of telomeric DNA sequences and the development of *in situ* hybridization [76,77].

One continues to wonder what other unknown mechanisms remain to be discovered in oocytes [78] (see Outstanding questions). We have learned how primary oocytes manage to store damaged mitochondria and protein aggregates only to be degraded later when development resumes. Studies in mice and humans have suggested the hyperactive state of the **integrated stress response** in these oocytes, suggesting that they are under chronic stress [79,80]. The lack of transcription in mature oocytes suggests that they rely entirely on post-transcriptional mechanisms, which makes long-term homeostasis inherently difficult to maintain. Similarly, they store mRNAs and proteins in specialized structures that are stable over long periods of time. Could these characteristics account for age-related deterioration, or oocytes that may have evolved specific mechanisms to achieve long-term homeostasis? Future research will provide more insights on oocyte biology and how this knowledge can be harnessed in biomedical science.

Outstanding questions

What are the mechanisms that couple oocyte biology to its metabolic state?

How do oocytes store protein aggregates and damaged mitochondria while they remain viable at the same time?

How do mature oocytes maintain homeostasis without transcription?

What other unique molecular and cellular characteristics do oocytes possess to maintain dormancy?

What is the functional relationship between the associations between RNA, RNA-binding proteins, and mitochondria in oocytes?

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Declaration of interests

The author declares no competing interests.

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