Metabolic hubs in reproduction: The regulatory network of lipid droplets in gamete and embryo physiology (Review)

LIUZHU PAN*, ZONGZHUANG WEN* and YI JIN

Metabolism and Disease Research Centre, Research Center of Basic Medicine, Central Hospital Affiliated to Shandong First Medical University, Jinan, Shandong 250013, P.R. China

Received December 25, 2025; Accepted February 3, 2026

DOI: 10.3892/ijmm.2026.5770

Abstract. Lipid droplets (LDs) are dynamic organelles that extend beyond lipid storage to regulate diverse aspects of reproductive physiology. In both mammals and *Caenorhabditis elegans*, LDs support gamete maturation, fertilization, embryogenesis and steroidogenesis by modulating lipid mobilization, signaling pathways, protein quality control and hormone production. The present review highlights the roles of LDs in oocytes, sperm, Sertoli and granulosa cells, embryonic stem cells and early embryos. Key regulatory molecules, including perilipins, adipose triglyceride lipase, Hormone-Sensitive Lipase (HSL), Diacylglycerol O-acyltransferases and seipin, as well as lipophagy, are discussed in the context of reproductive cell function. *C. elegans* demonstrates conserved genetic pathways linking LD metabolism with gamete quality and embryonic viability. The present review aimed to discuss emerging technologies such as lipidomics, high-resolution imaging, Clustered Regularly Interspaced Short Palindromic Repeats screening and single-cell sequencing that enable deeper investigation into LD dynamics. Finally, the present review aimed to examine how LD dysfunction contributes to reproductive disorders including infertility, polycystic ovary syndrome and metabolic syndrome. Understanding LD biology offers promising avenues for improving reproductive health and gamete and embryonic developmental potential.

Correspondence to: Professor Yi Jin, Metabolism and Disease Research Centre, Research Center of Basic Medicine, Central Hospital Affiliated to Shandong First Medical University, 105 Jiefang Road, Jinan, Shandong 250013, P.R. China
E-mail: jinhongyi@mail.hzau.edu.cn

*Contributed equally

Key words: lipid droplet, reproduction, gametogenesis, embryonic development, steroidogenesis

Contents

1. Introduction

Lipid droplets (LDs), typically considered inert reservoirs of neutral lipids, are recognized as dynamic and metabolically active organelles central to cell energy balance, lipid metabolism, proteostasis and stress adaptation (1,2). Structurally, LDs consist of a hydrophobic core enriched in triacylglycerols (TAGs) and cholesteryl esters (CEs), encased by a phospholipid monolayer that is uniquely enriched in proteins such as perilipin (PLIN), lipase and endoplasmic reticulum (ER)-associated scaffolding proteins (3). The formation of LDs begins at specific subdomains of the ER, where neutral lipid phase separation is initiated and nucleated by key regulatory proteins including seipin (SEIP-1) (4,5).

While extensively studied in metabolically active tissue such as adipocytes and hepatocytes, LDs have garnered growing attention in non-adipose cells where their functions extend beyond energy storage (2,6,7). In the central nervous system, immune cells and particularly in reproductive cells, LDs regulate cell signaling, redox homeostasis, steroidogenesis and embryonic morphogenesis (8-10). Reproductive cells exhibit notable plasticity in energy demand and metabolic activity, particularly during oocyte maturation, fertilization and preimplantation embryo development, periods marked by high biosynthetic and proliferative requirements.

Oocytes accumulate substantial quantities of LDs during proliferation and maturation, forming lipid-rich stores that support the metabolic needs of the embryo during early cleavage divisions (11,12). In lipid-rich species such as pigs,

cows and humans, this cytoplasmic lipid reserve provides energy via β-oxidation and supports membrane biogenesis and redox buffering (13). Dysregulation of LD content in oocytes, either excessive or deficient, is linked to impaired maturation, fertilization failure and reduced developmental competence (14).

By contrast, mature spermatozoa are devoid of prominent LDs, but their development is dependent on lipid mobilization and LD dynamics in precursor germ and Sertoli cells (15). Sertoli cells exhibit cyclic changes in LD number and composition, reflecting their roles in nutrient provision, phagocytosis of residual bodies and energy buffering during spermatogenesis (16,17). Testicular Leydig cells also use LDs as platforms for storing and mobilizing cholesterol esters in response to luteinizing hormone (LH) stimulation, enabling rapid testosterone synthesis (18,19).

Granulosa and luteal cells in the ovary similarly use LDs for estrogen and progesterone production (20). These cells respond to follicle-stimulating hormone (FSH) or LH by activating hormone-sensitive lipase (HSL) to hydrolyze CE within LDs, liberating free cholesterol for steroidogenesis within mitochondria (21,22). Proteomic studies have identified key steroidogenic enzymes, such as CYP11A1 and 3β-hydroxysteroid dehydrogenase, localizing to LDs in these cells, suggesting that LDs not only serve as storage platforms but also scaffold sites for enzymatic reactions (20,23,24).

The nematode *Caenorhabditis elegans* is a powerful genetic model for studying LD function in reproduction. Its transparency, short generation time and well-mapped reproductive system enable *in vivo* tracking of LD dynamics during gametogenesis and embryogenesis (25). In *C. elegans*, SEIP-1 regulates a subpopulation of LDs that contribute to lipid layer assembly in the embryonic eggshell, which is key for embryo viability (25). Mutants lacking SEIP-1 exhibit disrupted permeability barriers and embryonic lethality, phenotypes that can be partially rescued by modulating PLIN-1 or Ras-related protein Rab-18 function, revealing parallel compensatory pathways (25,26).

Despite these advances, major questions remain unresolved. The temporal coordination of LD biogenesis and degradation during fertilization or implantation requires further elucidation. Molecular cues that determine LD targeting by lipophagy in reproductive cells remain to be identified. LD imbalance contributes to reproductive pathologies such as infertility or polycystic ovary syndrome (PCOS) (27-30), however the mechanisms that warrant deeper exploration. Understanding these questions is key given the metabolic sensitivity of reproductive cells and their susceptibility to lipid imbalance.

Coherent anti-Stokes Raman scattering (CARS) and stimulated Raman scattering (SRS) microscopy enable label-free, real-time imaging of LD dynamics in living oocytes and embryos (31,32). Lipidomics and metabolomics, even at single-embryo resolution, have uncovered lipid profile shifts associated with *in vitro* maturation or developmental arrest (33). Genome editing tools such as clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated protein 9 (CRISPR-Cas9) and RNA interference (RNAi) screens in *C. elegans* or mammalian systems have revealed novel regulators of LD size, turnover and localization (34,35). Additionally, single-cell transcriptomics has revealed cell type-specific expression of LD-associated genes [PLIN2, Diacylglycerol O-acyltransferase DGAT2, adipose triglyceride lipase (ATGL) across the testis, ovary and early embryo (36).

LD dysfunction is increasingly linked to reproductive disorder (28,37). Obesity and metabolic syndrome alter lipid composition and increase oxidative stress in oocytes and sperm, decreasing fertility and embryo quality (38,39). In PCOS, altered lipid metabolism in granulosa cells impairs steroid hormone production, oocyte competence and follicular development (30). Genetic disorders affecting LD regulators, such as mutations in SEIP-1, the protein encoded by Berardinelli-Seip congenital lipodystrophy 2, in congenital lipodystrophy, typically involve hypogonadism and infertility (40).

The present review aimed to summarize the roles of LDs in reproduction across species and cell types, including oocytes, sperm and early embryos, and how supporting somatic Sertoli, Leydig, granulosa and luteal cells use LDs for metabolic coordination and hormonal output, as well as findings from *C. elegans* that uncover conserved regulatory mechanisms. The present review aimed to highlight key proteins such as ATGL, HSL, PLIN, DGATs, SEIP-1 and lipophagy-associated factors and assess how cutting-edge technologies are advancing the study of LD biology in reproductive physiology and how LD dysfunction contributes to reproductive disease.

2. Biological landscape and core functions of LDs in reproduction

Lipid availability in reproductive systems is heterogeneous, varying across cell types, developmental stages, and species. Oocytes, particularly in lipid-rich species such as pigs, cows and humans, accumulate abundant LDs during growth, whereas mature spermatozoa contain few if any visible lipid stores. By contrast, reproductive somatic cells, including Sertoli, Leydig, granulosa, and luteal cells, display dynamic LD populations that fluctuate in response to developmental cues and hormonal stimulation (24,41-43).

Beyond spatial heterogeneity, LDs also exhibit notable temporal dynamics. Their abundance increases during oocyte maturation and steroidogenic activation, is remodeled following fertilization and progressively declines during early embryonic development as stored lipids are mobilized (37,41,44). These spatial and temporal patterns establish the foundational context in which LDs serve not only as energy reserves, but as platforms that support metabolic coordination and signaling processes (Fig. 1).

Spatial distribution of lipids and LDs in reproductive systems. Lipid availability in reproductive systems exhibits marked heterogeneity, with distinct patterns across germ and somatic cells as well as species-specific adaptations. For instance, while oocytes in lipid-rich species like pigs, cows, and humans amass numerous cytoplasmic LDs that confer opacity and fuel early embryogenesis through β-oxidation and membrane synthesis, murine oocytes maintain lower lipid reserves, highlighting metabolic divergences (9-12). In somatic support cells, LD profiles are tailored to functional demands: Sertoli

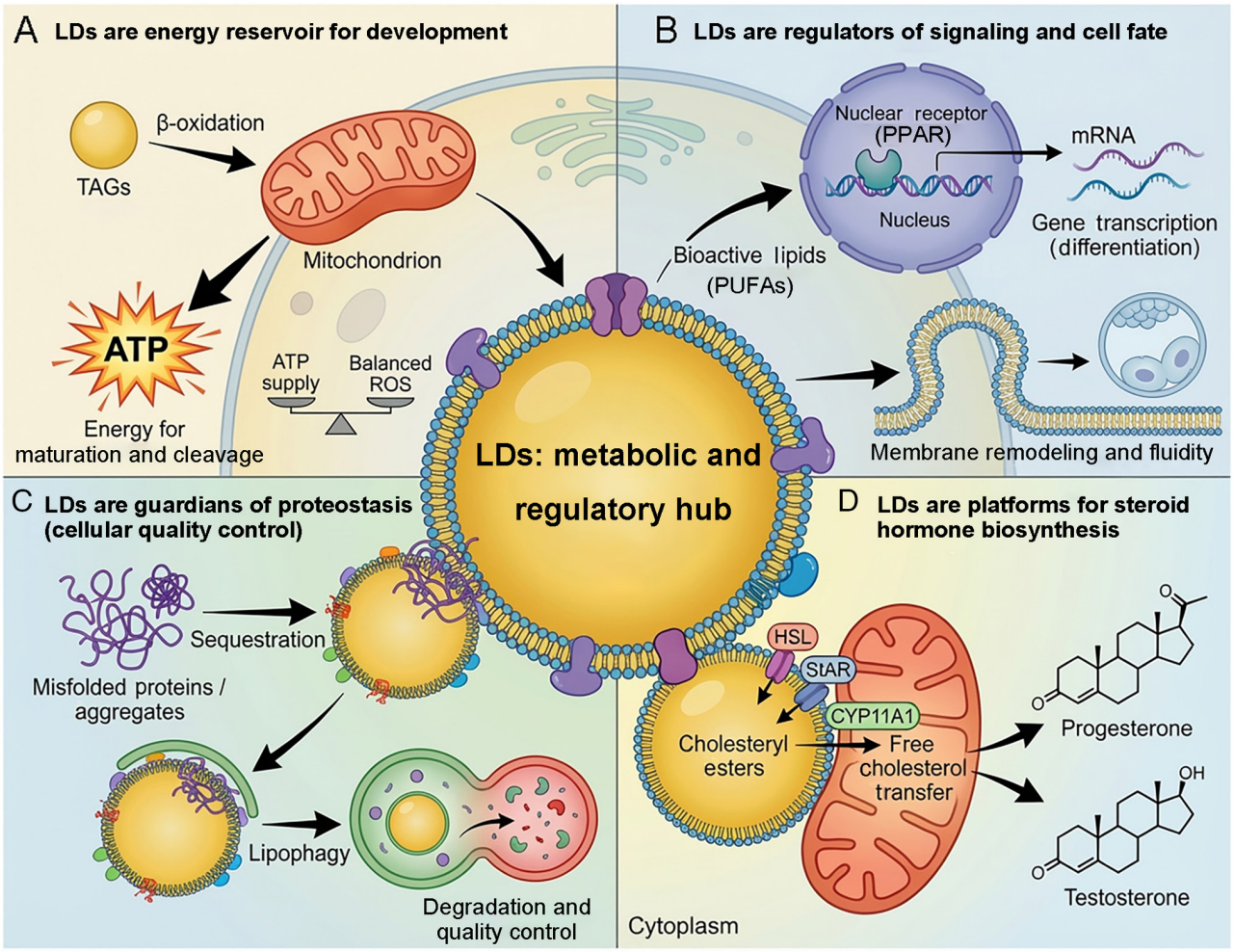

Figure 1. Roles of LDs as metabolic and regulatory hubs in reproductive cells. (A) LDs are energy reservoir for development. LDs store TAGs that are mobilized via lipolysis to provide fatty acids for mitochondrial β-oxidation. This generates ATP, which is key for oocyte maturation, fertilization and early cleavage, while maintaining a balanced redox state (low ROS), which is critical for embryo viability. (B) LDs are regulators of signaling and cell fate. LDs release bioactive lipids (such as PUFAs) that act as signaling ligands for nuclear receptors (such as PPARs) to drive gene transcription and differentiation. LD-derived lipids contribute to membrane remodeling, influencing fluidity and morphogenetic events during cell division. (C) LDs are guardians of proteostasis (cell quality control). LDs function as sequestration sites for misfolded or aggregated proteins, acting as transient detoxification zones. These protein-laden LDs are cleared via lipophagy (autophagic degradation) or lysosomal pathways, which is key for maintaining proteostasis during high-stress periods such as spermatogenesis. (D) LDs are platforms for steroid hormone biosynthesis. In steroidogenic cells (Leydig, granulosa and luteal cells), LDs store cholesteryl esters. Following hormonal stimulation, these esters are hydrolyzed to free cholesterol, which is transported to mitochondria (facilitated by proteins such as StAR and HSL at the LD-mitochondria interface) to serve as the substrate for the synthesis of steroid hormones such as progesterone and testosterone. HSL, hormone-sensitive lipase; LD, lipid droplet; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; StAR, steroidogenic acute regulatory protein; TAG, triacylglycerol.

cells show cyclic LD accumulation tied to phagocytosis and spermatogenic cycles (15-17), whereas granulosa and luteal cells prioritize cholesteryl ester storage for sustained steroidogenesis under hormonal regulation (20-22).

Temporal dynamics of LDs across reproductive stages. In addition to spatial heterogeneity, LDs exhibit notable temporal regulation throughout reproductive processes. During oocyte growth, LD content increases as neutral lipids are synthesized or imported and stored in preparation for fertilization and early embryonic development (11,12). Following fertilization, maternally inherited LDs undergo redistribution and partial consumption during cleavage divisions, reflecting a shift from lipid storage to utilization (13,31).

Similar temporal patterns are evident in reproductive somatic cells: In Sertoli cells, LD abundance fluctuates across the spermatogenic cycle, increasing during periods of active germ cell turnover and phagocytosis of residual bodies (16,17,45,46). In granulosa cells, LD accumulation intensifies during follicular maturation and peaks following luteinization, coinciding with maximal steroidogenic activity (24,47,48). These dynamic changes indicate that LDs are not static lipid depots but responsive organelles whose formation and turnover are associated with developmental timing and hormonal cues.

Metabolic use of stored lipids in reproductive cells. Once accumulated, lipids stored within LDs serve as key metabolic substrates. Triacylglycerols can be hydrolyzed to release fatty acids (FAs) that fuel mitochondrial β-oxidation, providing ATP during energetically demanding processes such as oocyte maturation, early embryonic cleavage and spermatogenic

support by Sertoli cells (11,13,49). In parallel, LD-derived lipids contribute to membrane biogenesis, ensuring sufficient phospholipid supply during rapid cell division and cellular remodeling (50).

The balance between lipid storage and mobilization is regulated. Excessive lipid accumulation leads to lipotoxicity and oxidative stress, whereas insufficient lipid reserves compromise energy availability and developmental competence (14,51). Reproductive cells therefore rely on coordinated control of lipid synthesis, lipolysis and oxidation to maintain metabolic homeostasis across fluctuating physiological demands (49,50).

LDs as regulatory and signaling hubs. Beyond their metabolic roles, LDs integrate lipid metabolism with signaling and regulatory pathways. The controlled release of bioactive lipid species from LDs influences nuclear receptor activation, including peroxisome proliferator-activated receptors (PPARs), thereby modulating transcriptional programs associated with cell differentiation and developmental progression (52,53). In steroidogenic cells, LDs store cholesteryl esters that are rapidly mobilized in response to gonadotropic stimulation, coupling lipid storage directly to hormone biosynthesis (20-22).

LDs also engage in notable physical and functional interactions with other organelles. Increasing evidence supports the existence of membrane contact sites between LDs and mitochondria or the ER, enabling efficient lipid transfer, metabolic channeling and coordination of redox homeostasis (54,55). Ultrastructural evidence supports the concept of LDs as metabolic hubs: Electron microscopy studies have revealed tight membrane contact sites between LDs and mitochondria or the ER, indicating that these organelles are physically connected rather than randomly juxtaposed (54-57). Such contacts are hypothesized to facilitate efficient lipid transfer, metabolic channeling and coordinated regulation of energy production and lipid metabolism, providing a structural basis for the functional interactions illustrated in schematic models (58,59). Through these interactions, LDs serve not merely as passive reservoirs but as dynamic hubs that synchronize energy metabolism, signaling and cell adaptation during reproduction (2,10).

Accumulating evidence indicates that the LD-mitochondria interface represents a physically tethered unit rather than a transient or stochastic association (58,60). Ultrastructural analyses have revealed well-defined membrane contact sites that anchor LDs to mitochondria, thereby establishing stable platforms for lipid transfer and metabolic coordination (54,55,61,62). These contact sites are mediated by specific tethering proteins that physically link the organelles. Among these, PLIN5 is a LD-associated protein that promotes sustained LD-mitochondria coupling and facilitates the channeling of FAs from LDs to mitochondria for β-oxidation. In parallel, mitoguardin 2, a mitochondrial outer membrane protein, forms physical bridges between mitochondria and LDs, coordinating lipid trafficking and mitochondrial energy metabolism (54,63,64). Together, these tethering mechanisms support a model in which LDs and mitochondria serve as integrated metabolic units, providing a structural and molecular basis for the metabolic hub concept in reproductive cells.

The diverse and sometimes contradictory functions of LDs can be reconciled by viewing them as organelles with multiphase activities that are dynamically regulated across developmental and physiological contexts. In a storage phase, LDs primarily accumulate neutral lipids, serving as reservoirs that buffer energy availability and protect cells from lipid overload. During metabolic phases, LDs undergo controlled lipolysis, releasing FAs that fuel mitochondrial β-oxidation and support membrane biosynthesis. In signaling phases, LD-derived lipid species serve as bioactive molecules that engage nuclear receptors, such as PPARs, thereby influencing transcriptional programs associated with cell fate decisions and developmental progression (2,60,65).

The transition between these phases is not fixed but context-dependent, shaped by developmental timing, hormonal cues and cellular energy demands. This multiphase framework provides a conceptual basis for understanding how the same LD population alternately serves as a protective storage depot, a metabolic fuel source or a signaling platform during reproduction (2,41,48,66).

3. LDs in oocyte maturation and competence

The oocyte is a metabolically unique cell, characterized by large size, prolonged growth phase and dependence on stored reserves to sustain early embryogenesis. Among these reserves, LDs serve a key role in determining oocyte quality and developmental competence (37,41,49). While their role as energy depots is well-established, evidence highlights a broader regulatory role for LDs in shaping the oocyte redox balance, signaling landscape and cytoplasmic remodeling capacity, which are indispensable for meiotic progression and post-fertilization events (67-69) (Fig. 2).

LD accumulation is temporally regulated during oocyte growth. LD biogenesis in oocytes is a tightly orchestrated process that coincides with folliculogenesis. Throughout the growing phase, oocytes accumulate neutral lipids via both *de novo* synthesis and uptake of exogenous FAs, which are esterified and stored in LDs (37,68). During oocyte growth, LDs primarily operate in a storage phase, ensuring sufficient lipid reserves for subsequent developmental transitions. In large antral follicles, LDs become prominent cytoplasmic features (68). Their abundance and distribution vary across species: Porcine and bovine oocytes are lipid-rich and visibly opaque, whereas murine and human oocytes have fewer LDs and a clearer cytoplasm (41,42,70,71). These differences reflect fundamental differences in lipid metabolism, sensitivity to *in vitro* conditions and developmental strategies (49,72). For example, lipid-rich oocytes in porcine and bovine species rely heavily on β-oxidation of stored lipids for energy during early embryogenesis, as shown by reduced developmental rates when β-oxidation inhibitors are applied in culture (11). In contrast, murine oocytes exhibit greater dependence on glycolysis, making them less sensitive to lipid perturbations but more vulnerable to glucose fluctuations *in vitro* (73). Human oocytes, while lipid-moderate, show intermediate sensitivity, with *in vitro* maturation success influenced by media supplements that mitigate oxidative stress from lipid peroxidation (74). These variations underscore species-specific

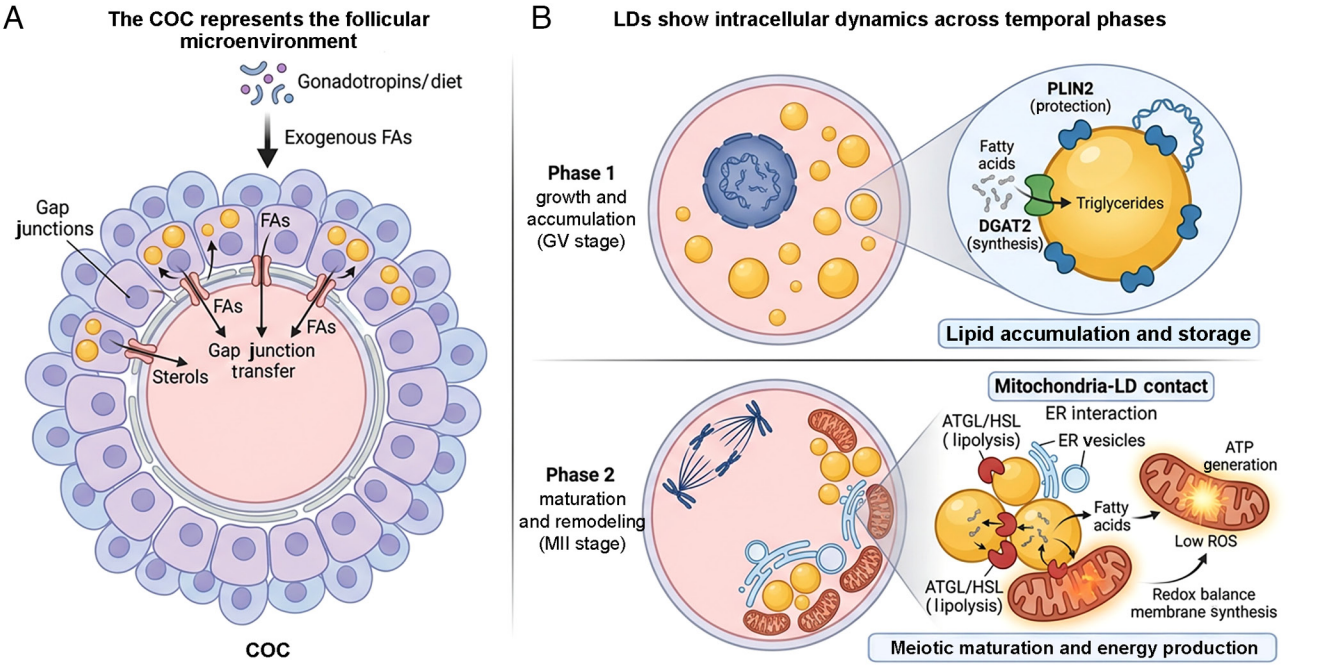

Figure 2. LD dynamics and regulation during oocyte maturation. (A) COC (the follicular microenvironment). The oocyte is surrounded by cumulus cells, forming the COC. Cumulus cells modulate the oocyte lipid profile by transferring FAs and sterols through gap junctions. This supply chain is influenced by external factors such as gonadotropins and dietary intake (exogenous FAs). Cumulus cells maintain their own LD reserves to support this metabolic coupling. (B) LDs show intracellular dynamics across temporal phases. During the GV stage, the oocyte actively synthesizes and stores lipids. DGAT2 catalyzes triacylglycerol synthesis and PLIN2 facilitates coating of the LD surface to promote stability and prevent premature lipolysis, resulting in the accumulation of dispersed LDs. Following meiotic resumption (MII transition), LDs undergo spatial reorganization and functional activation. At mitochondria-LD contact sites, lipolytic enzymes (ATGL/HSL) mobilize stored lipids. The released FAs are directed into mitochondria for β-oxidation, generating ATP while maintaining redox balance (low ROS) and supporting membrane synthesis essential for meiotic progression and fertilization competence. COC, cumulus-oocyte complex; DGAT2, diacylglycerol acyltransferase 2; ER, endoplasmic reticulum; GV, germinal vesicle; HSL, hormone-sensitive lipase; MII, metaphase II; PLIN2, perilipin 2; ROS, reactive oxygen species; FA, fatty acid; LD, lipid droplet; ATGL, adipose triglyceride lipase.

reproductive adaptations, where lipid-rich strategies buffer against nutrient scarcity post-fertilization, whereas lipid-poor ones prioritize rapid external nutrient uptake (49).

Oocyte capacity to accumulate and mobilize LDs is associated with the ability to resume meiosis and support embryo development (72,75). Disruptions in LD formation, either through inhibition of DGAT1/2 or alterations in FA composition, impair nuclear maturation and decrease blastocyst yield, underscoring the role of LDs in establishing developmental competence (49,69,76).

LD dynamics and cytoplasmic remodeling. LDs undergo dynamic spatial reorganization during meiotic maturation. In many species, LDs are dispersed throughout the oocyte cytoplasm at the germinal vesicle (GV) stage, then undergo clustering or partial consumption during GV breakdown and metaphase II transition (31,37,49,77). These changes may reflect a metabolic switch: As the oocyte transitions from quiescence to a highly active biosynthetic state, lipid oxidation increases, supported by mitochondrial redistribution and enhanced FA flux (67,68).

Moreover, LD remodeling is typically coordinated with organelle positioning. In mammalian oocytes, LDs have been observed in proximity to mitochondria and ER-derived vesicles, suggesting metabolic crosstalk and potential transfer of lipid species (54,55,61,62). These interactions may be key for shaping mitochondrial function, as lipid overload or misdistribution is associated with increased ROS production and mitochondrial dysfunction, which are detrimental to fertilization and embryo cleavage (63,64,71).

Regulatory mechanisms: Enzymes and LD-coating proteins. The functional integrity of LDs in oocytes is governed by a tightly regulated network of enzymes and structural proteins (37,69). DGAT2, which catalyzes TAG synthesis, is enriched in growing oocytes, and its inhibition leads to decreased lipid storage and impaired oocyte maturation (69,76). Similarly, the LD surface protein PLIN2 is abundantly expressed in lipid-rich oocytes, and is hypothesized to stabilize LDs by preventing premature lipolysis (78-80). Knockdown or pharmacological interference with PLIN2 results in dysregulated lipid metabolism and altered oocyte developmental trajectories (69,81).

In addition to synthesis and stabilization, lipid mobilization is precisely timed. Lipolytic enzymes such as ATGL and HSL are activated in peri-ovulatory periods, allowing controlled release of FAs for β-oxidation and membrane synthesis (82-85). An imbalance in this process, either via excessive lipid accumulation or hyperactive lipolysis, compromises oocyte viability (86).

Paracrine influences and somatic-oocyte interaction. LD content and composition in the oocyte are not solely determined by intrinsic metabolic programs. Surrounding cumulus and granulosa cells contribute to the oocyte lipid profile through paracrine signaling and metabolite transfer (41,87,88).

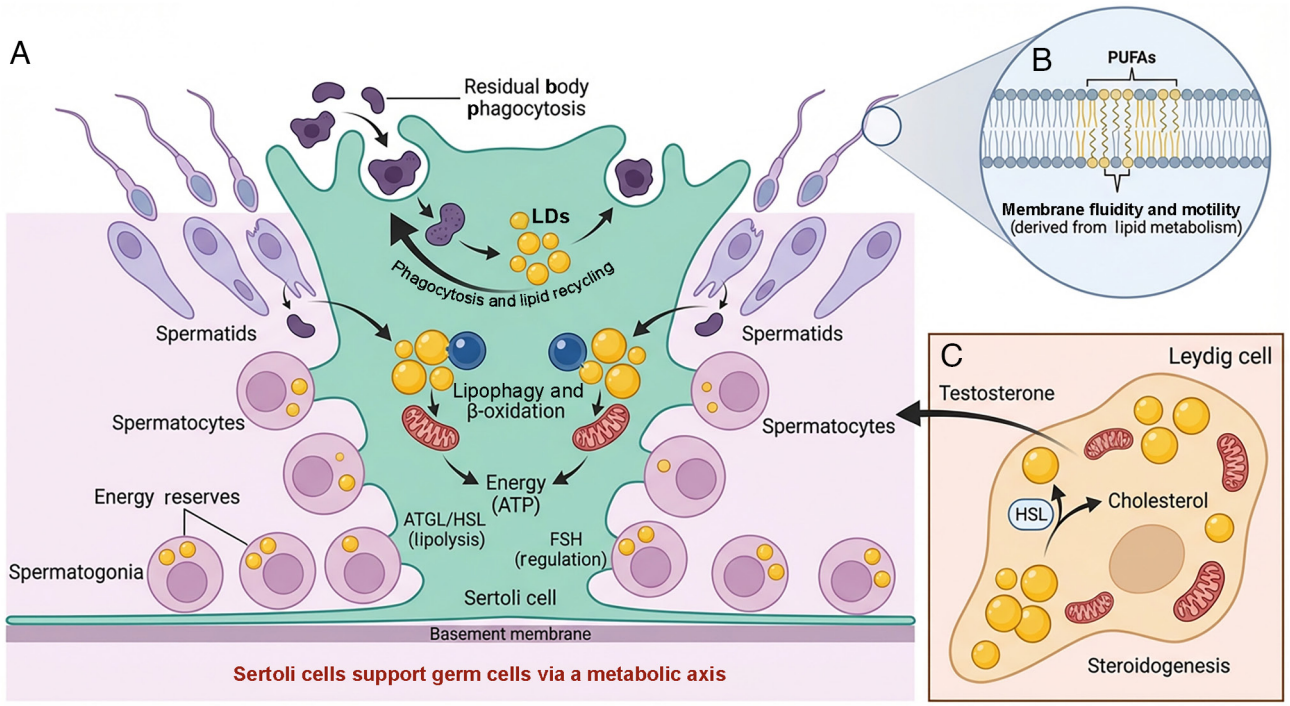

Figure 3. LD dynamics and metabolic crosstalk in the testis. (A) Sertoli cells support germ cells via a metabolic axis. Within the seminiferous tubule, Sertoli cells support the developing germ cells. As spermatids elongate, they shed excess cytoplasm as residual bodies, which are phagocytosed by Sertoli cells. These lipid-rich remnants are sequestered into LDs (phagocytosis and lipid recycling). Stored LDs in Sertoli cells are catabolized via lipophagy (lysosomal degradation) and mitochondrial β-oxidation to generate ATP, fueling the high energy demands of spermatogenesis. Early germ cells (spermatogonia/cytes) contain transient LDs as energy reserves, which decline as cells differentiate into mature spermatozoa. (B) Sperm undergo membrane remodeling. Although mature spermatozoa lack LDs, their plasma membranes are enriched with PUFAs derived from upstream lipid metabolism. Integration of PUFAs into the sperm membrane is a critical factor for maintaining membrane fluidity, motility and fertilization capacity. FSH, follicle-stimulating hormone; HSL, hormone-sensitive lipase; LD, lipid droplet; PUFA, polyunsaturated fatty acid. (C) Leydig cells regulate interstitial processes. In the interstitial space, Leydig cells use LDs as reservoirs for cholesteryl esters. Under the regulation of LH, HSL mobilizes cholesterol from these LDs to synthesize Testosterone, which is key for maintaining spermatogenesis.

Cumulus-oocyte complexes exhibit extensive gap junction communication, allowing transfer of small lipophilic molecules such as FAs and sterols (89-92). Cumulus cells express lipoprotein receptors, FA transporters and lipogenic enzymes, and can modulate the lipid environment of the oocyte in response to gonadotropic stimulation or dietary lipid availability (41,91,93).

Alterations in cumulus cell metabolism, such as those seen in high-fat diet models or PCOS, lead to excessive lipid accumulation in oocytes and are associated with lower fertilization and blastocyst rates (71,77,93). These findings emphasize that LD metabolism in the oocyte must be understood in the context of the follicular microenvironment (41,87,88).

LD metabolism as a marker and modulator of oocyte quality. Because LD content reflects metabolic history and readiness for fertilization, it is increasingly studied as a biomarker of oocyte competence (31,94,95). Non-invasive imaging modalities, such as CARS microscopy, have made it possible to quantify LD content in live oocytes and demonstrate its association with subsequent embryo development (31,96-99). Moreover, interventions aimed at modifying LD metabolism through culture media supplementation with oleic acid or antioxidants have shown potential to rescue poor-quality oocytes by rebalancing lipid profiles (96-99).

Altogether, LDs in oocytes serve as more than static energy stores; they are dynamic organelles whose content, composition and spatial behavior are critical determinants of oocyte maturation and developmental success (37,69). Their regulation is multifactorial, involving intrinsic enzyme systems, extrinsic paracrine input and inter-organelle coordination. Understanding and manipulating LD biology in the oocyte may thus represent a promising avenue for improving assisted reproduction outcomes (96,100,101).

4. LDs in spermatogenesis and sperm function

Spermatogenesis is a complex, highly regulated process that requires precise coordination of energy metabolism, membrane remodeling and quality control. While mature spermatozoa lack prominent LDs, increasing evidence suggests that LDs play key upstream roles during the earlier stages of germ cell development and in the metabolic crosstalk between developing spermatogenic cells and their supporting Sertoli cells (15,43,102) (Fig. 3).

LDs in early germ cells and spermatogenic progression. During the early phases of spermatogenesis, including in spermatogonia and early spermatocytes, LDs are readily observed and serve as temporary energy reserves and platforms for lipid remodeling (15,102,103). As germ cells differentiate toward the elongated spermatid stage, LD content typically declines, which is associated with cytoplasmic condensation and organelle removal (15,102). However, disturbances in lipid storage

Table I. Conserved and divergent roles of LDs in reproduction.

Biological process	*C. elegans*	Mammals	Conservation	(Refs.)
LD biogenesis	Regulated by SEIP-1 at ER-LD junctions	Conserved role of SEIP-1 in LD formation	Conserved	(215,216)
LD spatial distribution	Prominent LDs in germline and early embryos	LD-rich oocytes and steroidogenic cells	Conserved	(217,218)
Role in embryogenesis	SEIP-1-dependent LDs support eggshell lipid barrier formation	LDs support early embryonic energy supply and membrane biosynthesis	Functionally conserved	(37,219)
Steroidogenesis	Absent	LDs store cholesteryl esters for steroid hormone synthesis	Divergent	(220,221)
LD-mitochondria interaction	Functional coupling inferred genetically	Physical tethering via PLIN5/MIGA2-mediated contact sites	Partially conserved	(222,223)
Lipid mobilization	Lipolysis supports embryonic viability	β-oxidation fuels oocyte maturation and embryo development	Conserved	(215,224,225)
Regulatory signaling	Genetic pathways linking LDs to development	Nuclear receptor signaling (PPARs) linked to LD-derived lipids	Divergent	(215,226)
Clinical relevance	Model for conserved mechanisms	Direct relevance to infertility and ART outcomes	Divergent	(35,219)

LD, lipid droplet; SEIP-1, seipin; ER, endoplasmic reticulum; PLIN, perilipin; MIGA, mitofusin-γ-interacting ankyrin; ART, assisted reproductive technology.

and LD homeostasis during these early stages impair germ cell differentiation and decrease sperm output (43,104,105).

Model organisms such as *Drosophila* and *C. elegans* are key in dissecting LD function during spermatogenesis (43). For example, the *Drosophila* homolog of ATGL, Brummer, localizes to LDs in testicular germ cells and its deletion results in massive LD accumulation and spermatogenic arrest (43). Similarly, in mammals, ATGL and HSL are functionally important in lipid mobilization during spermatogenic progression (43,106). Deficiency in these enzymes leads to abnormal lipid accumulation, disrupted spermatid elongation and reduced fertility (106).

While studies in *C. elegans* have uncovered genetically conserved roles of LD in embryonic integrity (25,107,108), mammalian systems exhibit additional layers of complexity, particularly in steroidogenesis and hormonal regulation. For instance, LDs in mammalian reproductive cells integrate with hormone-responsive lipases to mobilize cholesterol for steroid hormone synthesis and interact with organelles such as mitochondria for enhanced metabolic channeling, features modulated by endocrine signals absent in simpler models (Table I).

Sertoli cell-LD axis in supporting spermatogenesis. Sertoli cells provide structural and metabolic support to developing germ cells (46,109-111). Sertoli cells contain abundant LDs, the composition and abundance of which fluctuate in response to the spermatogenic cycle and phagocytic activity (45,46,110). One notable source of LDs in Sertoli cells is the engulfment of residual bodies (cytoplasmic fragments shed by spermatids during final maturation) (17,46,110,112). Lipid-rich components of these residual bodies are internalized and sequestered into LDs within Sertoli cells, where they may be catabolized via β-oxidation or lipophagy to fuel Sertoli cell metabolism (15,17,46).

The dynamic balance between LD formation and degradation in Sertoli cells is key for maintaining testicular homeostasis (103,113,114). Exposure to toxicants such as lead or cadmium disrupts lysosomal and autophagic pathways in Sertoli cells, leading to impaired LD clearance, lipid overload and testicular dysfunction (113). Furthermore, hormonal regulation, particularly by FSH, modulates LD content in Sertoli cells by stimulating lipid uptake and lipogenic gene expression (109). This endocrine-metabolic axis ensures that Sertoli cells are metabolically equipped to support the rapid turnover of lipids during active spermatogenesis (109,111,114).

While rodent models have provided insights into the metabolic coupling between Sertoli and germ cells, key differences exist between human and rodent spermatogenesis (115,116). Human spermatogenesis is characterized by a longer developmental timeline, distinct seminiferous epithelial organization and differences in hormonal regulation and metabolic demands compared with commonly used rodent models (117,118). Moreover, the dynamics of lipid metabolism and LD turnover in human Sertoli cells are less well characterized, in part due to limited access to human testicular tissue (115,117,119).

These species-specific features suggest that, although core principles of Sertoli-germ cell metabolic support are

potentially conserved, direct extrapolation from rodent studies to human reproductive physiology should be approached with caution. Integrating findings from human tissue analyses, organoid systems and single-cell profiling is key to define the relevance of LD-mediated mechanisms in human spermatogenesis (120-123).

Lipids and membrane remodeling in sperm maturation. Although mature spermatozoa lack classical LDs (typical cytoplasmic organelles characterized by a hydrophobic core of neutral lipids encased in a phospholipid monolayer), lipid metabolism is key for their structural and functional integrity (43,124). The plasma membrane of sperm is rich in polyunsaturated FAs (PUFAs), which provide membrane fluidity necessary for motility and capacitation (124-130). The composition of these lipids is tightly regulated during epididymal maturation and influenced by prior LD metabolism in germ and Sertoli cells (43,103,124,131).

Enzymes such as acyl-CoA synthetase long-chain family members, which participate in FA activation and incorporation into complex lipids, are key for proper sperm development (75). Genetic disruption of these enzymes leads to altered lipid composition and defective sperm morphology (75). These findings suggest that early LD metabolism indirectly shapes sperm functionality by controlling the availability and remodeling of lipid precursors (43, 75,124).

LD-associated defects and male infertility. Aberrant lipid metabolism in the testis is increasingly implicated in male reproductive disorder (43,104,105,132). In both mouse and rat models and human patients, disturbances in lipid homeostasis, manifested as altered LD dynamics, defective lipolysis or accumulation of cholesteryl esters, are associated with low sperm count, impaired motility and hormonal imbalance (43,104-106,132). Notably, mouse models with HSL knockout exhibit lipid-laden Leydig cells, decreased testosterone levels and oligospermia, underscoring the importance of intact LD mobilization for androgen synthesis and spermatogenic support (106,133,134).

Lipidomics and histological analyses of human testicular biopsies have revealed elevated LD accumulation in Sertoli and Leydig cells of infertile patients, often accompanied by disrupted mitochondrial morphology and increased oxidative stress markers (119,135-137). These observations further reinforce the idea that LD dysregulation contributes to male infertility not only through energy imbalance, but also by disrupting redox homeostasis, membrane remodeling and hormone production (43,104,106,132,138).

5. LDs in reproductive support cells

Reproductive support cells (Sertoli cells in the testis and granulosa cells in the ovary) serve key roles in nurturing germ cells and regulating the hormonal environment of the gonads (139). Both cell types are metabolically active, highly responsive to hormonal cues and rely on tightly regulated lipid metabolism to perform their functions (140). LDs within these cells serve as key metabolic and regulatory hubs, participating not only in lipid storage and mobilization but also in steroidogenesis, phagocytic recycling and paracrine signaling (6) (Fig. 4).

LDs in Sertoli cells: Nutrient buffering and phagocytic recycling. Sertoli cells are the central architectural and metabolic support for spermatogenesis, forming the blood-testis barrier, providing nutrients to developing germ cells and clearing apoptotic or senescent spermatocytes (139). These cells contain prominent LDs, particularly during periods of active spermatogenic turnover or high phagocytic activity (15).

A notable source of lipids for LD formation in Sertoli cells is the internalization of residual bodies and degenerating germ cells (17). These engulfed materials, rich in membrane and cytoplasmic lipids, are processed in lysosomes, with a portion of the liberated FAs and sterols re-esterified and stored in LDs. These droplets are mobilized for energy production via β-oxidation, allowing Sertoli cells to meet their metabolic demands while supporting adjacent spermatogenic cells (141).

The degradation of LDs in Sertoli cells involves not only cytosolic lipases (HSL) but also selective autophagy of LDs, known as lipophagy (142). This process is regulated by nutrient availability and endocrine factors. Under physiological stress or toxicant exposure (lead, cadmium), lysosomal dysfunction or autophagy impairment leads to LD accumulation, disrupted lipid homeostasis and impaired Sertoli cell function, contributing to testicular atrophy and infertility (143).

Furthermore, hormonal regulation serves a key role in LD dynamics. FSH promotes lipid uptake and storage in Sertoli cells by upregulating lipoprotein receptors and lipogenic gene expression. This hormonally mediated lipid buffering ensures an adequate energy reserve during active spermatogenesis and facilitates metabolic synchronization between Sertoli and germ cells (109,144-146).

LDs in granulosa and luteal cells: Platforms for steroidogenesis. Granulosa cells, which surround and support the developing oocyte, undergo extensive metabolic reprogramming as follicles mature (147). In the pre-ovulatory phase, these cells proliferate, increase steroidogenic activity and accumulate LDs rich in cholesteryl esters (49). Following ovulation, granulosa cells differentiate into luteal cells, which are among the most steroidogenically active cells in the body (147). In both phases, LDs serve as central platforms for steroid hormone biosynthesis (148).

LDs in granulosa and luteal cells store cholesteryl esters that serve as substrates for estrogen and progesterone synthesis, respectively (149). Upon gonadotropin (FSH or LH) stimulation, HSL is activated and hydrolyzes cholesteryl esters into free cholesterol (148). The cholesterol is transported to mitochondria via steroidogenic acute regulatory protein, where it is converted to pregnenolone by CYP11A1, initiating the steroidogenic cascade (149).

Several studies have demonstrated that LD content and associated enzyme expression levels vary depending on follicular stage and endocrine environment (150-153). For example, mature preovulatory granulosa cells contain larger and more numerous LDs than their early antral counterparts, consistent with enhanced steroidogenic readiness (23). Disruption of lipid mobilization pathways via HSL inhibition, PLIN dysregulation or excessive lipid accumulation impairs estrogen and progesterone synthesis, follicular rupture and corpus luteum formation (150).

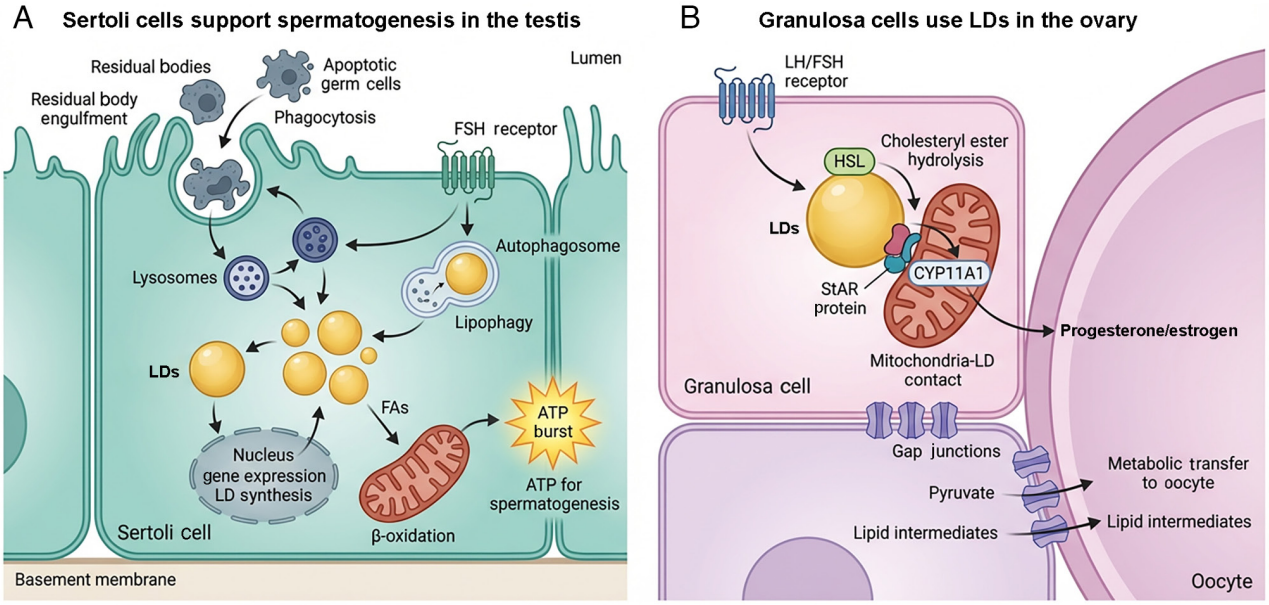

Figure 4. Comparative functions of LDs in reproductive support cells. (A) In the seminiferous epithelium, Sertoli cells support spermatogenesis through a recycling mechanism. Sertoli cells engulf residual bodies (cytoplasmic remnants) and apoptotic germ cells via phagocytosis. These internalized materials are processed in lysosomes and their lipid content is recycled into LDs. Stored lipids are subsequently mobilized via lipophagy (autophagic degradation) and mitochondrial β-oxidation to generate ATP, providing the energy required for Sertoli cell metabolism and germ cell support. This process is regulated by FSH, which stimulates lipid uptake and storage gene expression. (B) In the ovarian follicle, granulosa cells use LDs primarily as substrate reservoirs for hormone synthesis. Upon stimulation by gonadotropins (LH/FSH), HSL hydrolyzes stored cholesteryl esters into free cholesterol. Cholesterol is transported to mitochondria via the StAR protein at LD-mitochondria contact sites. Inside the mitochondria, CYP11A1 initiates the conversion of cholesterol into steroid hormones (progesterone/estrogen). Granulosa cells also metabolically support the oocyte by transferring pyruvate and lipid intermediates through gap junctions, a process associated with the metabolic status of their own LDs. CYP11A1, cytochrome P450 family 11 subfamily A member 1; FSH, follicle-stimulating hormone; HSL, hormone-sensitive lipase; LD, lipid droplet; LH, luteinizing hormone; StAR, steroidogenic acute regulatory protein; FA, fatty acid.

Proteomic and lipidomic profiling of granulosa cell LDs has identified key components of the steroid biosynthetic machinery localized to or enriched around LDs, including enzymes of the P450 family and mitochondrial contact proteins (90). These findings suggest that LDs are not passive lipid depots, but serve as biochemical scaffolds that facilitate rapid and localized hormone production (148).

LD-oocyte communication: The somatic-germ cell interface. Beyond their intrinsic functions, support cell LDs also influence germ cell development through metabolic coupling and paracrine interactions (154). Cumulus granulosa cells, which form the innermost layer of follicular somatic cells directly surrounding the oocyte, are metabolically connected to the oocyte via transzonal projections and gap junctions (155). These cells actively metabolize glucose and FAs, generating pyruvate, amino acids and lipid intermediates that are transferred to the oocyte to support growth and maturation (28,154).

LDs within cumulus cells reflect this metabolic activity (156). Their number and size increase with gonadotropin stimulation and they show dynamic responses to oxidative stress, FA exposure and endocrine disruption (157). Excess accumulation of saturated FAs in cumulus cell LDs, such as under high-fat diet or PCOS, alter oocyte lipid composition, increase ER stress and reduce developmental competence (156).

Therefore, somatic cell LDs contribute indirectly to oocyte quality by modulating the follicular lipid environment, buffering toxic lipid species and fine-tuning substrate availability for oocyte maturation (157). Disruption of these functions leads to broader metabolic dysfunction and subfertility, highlighting the need to consider support cell lipid metabolism in the assessment of reproductive health (89).

6. LDs in early embryo development and pluripotency

Early embryonic development is an energy-intensive process that depends on maternally derived reserves, since transcriptional activity is minimal until zygotic genome activation (37). Among the maternally supplied nutrients, LDs serve as critical reservoirs of neutral lipids and bioactive lipids that sustain cleavage division, lineage specification and metabolic reprogramming (69). Beyond their role as passive energy stores, LDs are increasingly recognized as dynamic organelles that integrate metabolic and signaling pathways, influencing not only embryo viability but also the maintenance of pluripotency (37,69,75,158) (Fig. 5).

LD inheritance and remodeling post-fertilization. Upon fertilization, the zygote inherits LDs from the oocyte, which vary in size, number and lipid composition across species (72). Following fertilization, LDs transition toward a metabolic phase characterized by enhanced lipolysis and FA oxidation (FAO). In lipid-rich species such as pigs and cows, zygotes contain abundant LDs that are readily visualized by light microscopy, while in mice and humans LDs are smaller (159). These maternal LDs are progressively redistributed during the first cleavage divisions (42). Time-lapse imaging studies reveal that LDs undergo dynamic clustering, dispersion and partial lipolysis in synchrony with cell cycle progression (158,160-162). This

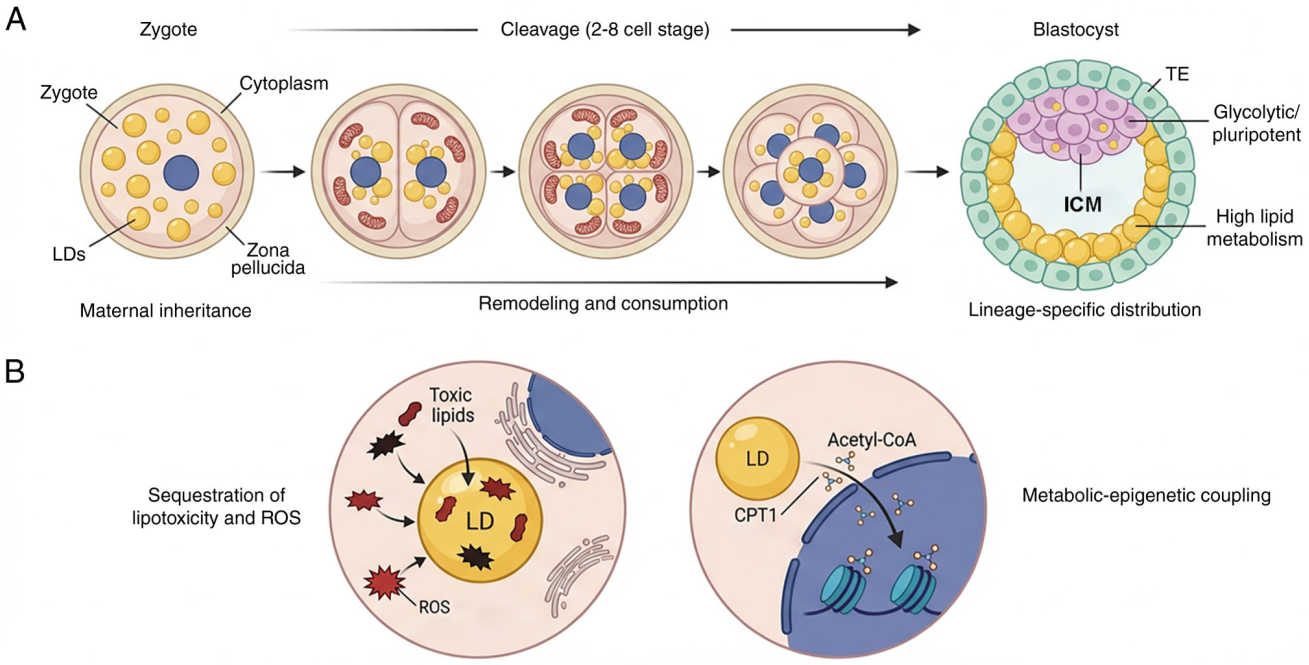

Figure 5. Spatiotemporal dynamics and functional roles of LDs during preimplantation development. (A) Developmental timeline (zygote to blastocyst). Following fertilization, the zygote inherits a pool of maternal LDs. During early cleavage divisions, LDs undergo dynamic clustering (typically perinuclear) and partial lipolysis. They interact with mitochondria to provide fatty acids for β-oxidation, fueling the energy-intensive process of rapid cell division. At the blastocyst stage, LDs exhibit asymmetric distribution. TE cells (outer layer) contain larger and more numerous LDs, supporting their high lipid metabolic needs for implantation and steroidogenesis. By contrast, the ICM (inner cluster) contains fewer LDs, consistent with a glycolytic, pluripotent metabolic state. (B) Functional mechanisms. LDs act as detoxification sinks by sequestering toxic saturated fatty acids and peroxidized lipids, thereby protecting the embryo from lipotoxicity and oxidative stress (ROS) when antioxidant defenses are developing. In pluripotent cells, LD-derived acetyl-CoA enters the nucleus to serve as a substrate for histone acetylation. This metabolic-epigenetic link influences chromatin structure and gene expression, thereby regulating the maintenance of pluripotency and stem cell fate decisions. ICM, inner cell mass; LD, lipid droplet; ROS, reactive oxygen species; TE, trophectoderm; CPT, carnitine palmitoyltransferase.

remodeling reflects a shift from maternal lipid storage toward active use, enabling the embryo to meet energetic demands of rapid mitosis (31). Beyond serving as lipid reservoirs, LDs in early embryos also participate in the storage and regulation of non-lipid macromolecules. Johnson *et al* (126) demonstrated that LDs in early embryos serve as storage depots for maternal histones and selectively recruit RNA-binding proteins involved in post-transcriptional regulation. Through this mechanism, LDs contribute to the temporal control of mRNA translation during early embryogenesis, a developmental window characterized by limited zygotic transcription. These findings expand the functional scope of LDs beyond energy metabolism, positioning them as organizational platforms that coordinate lipid storage with proteostasis and translational control in the early embryo.

The extent of LD remodeling is sensitive to culture conditions and external nutrient availability (163). Embryos cultured *in vitro* often display altered LD number and distribution compared with *in vivo* counterparts, which has been linked to reduced developmental potential (164). These findings highlight LDs as sensitive indicators of embryo metabolic state (71).

LD metabolism and early energy supply. During cleavage, embryos rely primarily on pyruvate and lactate metabolism, but FAO becomes increasingly important as development proceeds to the blastocyst stage (49). LDs provide a readily accessible pool of FAs through controlled lipolysis (165). Inhibition of FAO enzymes such as carnitine palmitoyltransferase 1 (CPT1) leads to developmental arrest, underscoring the importance of LD-derived FAs in sustaining blastocyst formation (166).

Mitochondrial-LD interactions are central to this process (37). In mouse and bovine embryos, LDs are typically found close to mitochondria, facilitating efficient FA transfer and oxidation (13). This spatial proximity suggests that LDs and mitochondria form functional units that coordinate energy production and redox regulation during early development (167).

An additional context in which LD-mitochondria interactions may be relevant is ovarian aging. Advanced maternal age is associated with progressive mitochondrial dysfunction in oocytes, including decreased oxidative capacity, altered mitochondrial dynamics and increased oxidative stress (168,169). Emerging evidence suggests that aged oocytes often display abnormal LD accumulation and altered lipid distribution, raising the possibility that impaired mitochondrial FA utilization contributes to LD dysregulation during aging (69,170,171).

Whether aberrant LD accumulation in aged oocytes represents a compensatory response to mitochondrial insufficiency or a maladaptive process that compromises oocyte quality remains unresolved. Clarifying how mitochondrial dysfunction intersects with LD storage, mobilization and oxidative stress control during ovarian aging is key for understanding age-associated declines in oocyte competence and embryo developmental potential.

In addition to their roles in energy metabolism and signaling, LDs have recently been implicated in protecting embryos from lipid peroxidation and ferroptotic cell death (172-174). PUFAs, while essential for membrane synthesis and developmental signaling, are susceptible to oxidative damage. Sequestration of PUFAs within LDs limits their availability for uncontrolled lipid peroxidation, thereby decreasing oxidative stress and ferroptosis during early embryonic development (174-177).

Recent studies have highlighted LDs as key buffers that spatially compartmentalize PUFAs away from pro-oxidant environments, particularly under conditions of heightened mitochondrial activity and reactive oxygen species production (175,176,178). This protective function may be key during early embryogenesis, when antioxidant capacity is limited and metabolic demands rapidly increase. Together, these findings position LDs not only as metabolic hubs but also as key guardians of redox homeostasis and embryo survival.

Carnitine shuttle system as the rate-limiting step of LD-derived FAO. While FA β-oxidation is a notable pathway through which LD-derived lipids support reproductive processes, its flux is constrained by a rate-limiting step: The transport of long-chain FAs into mitochondria (179-181). This process is mediated by the carnitine shuttle system, which consists of CPT1 on the outer mitochondrial membrane and CPT2 on the inner membrane (2,179,182,183). CPT1 catalyzes the conversion of long-chain acyl-CoAs into acyl-carnitines, enabling their translocation across the mitochondrial membranes, whereas CPT2 reconverts acyl-carnitines into acyl-CoAs within the mitochondrial matrix for β-oxidation (180,184-186).

In oocytes and early embryos where mitochondrial oxidative capacity is tightly coupled with developmental competence, disruption of carnitine-dependent FA transport leads to impaired energy production and developmental arrest, underscoring the importance of this regulatory checkpoint in lipid utilization (49,166). Notably, supplementation with L-carnitine or acetyl-L-carnitine improves mitochondrial function, enhances FAO and increases blastocyst yield in multiple assisted reproduction settings (187,188). These findings suggest that the carnitine shuttle not only represents a biochemical bottleneck of LD-derived energy metabolism, but also constitutes a clinically actionable node linking LD biology to gamete quality and embryo developmental outcomes.

LDs as regulators of redox homeostasis and stress responses. Beyond energy supply, LDs also protect early embryos from lipotoxicity and oxidative stress (2). Excess accumulation of saturated FAs in culture or maternal metabolic disorders can trigger ER stress and apoptosis in embryos (69). By sequestering potentially toxic lipids into LDs, embryos buffer against lipotoxic insult (189). Moreover, LDs can serve as sinks for peroxidized lipids, thereby limiting propagation of oxidative damage (190). This detoxification role is key during preimplantation, when embryonic antioxidant defenses are developing (161).

LD dynamics and lineage specification. As embryos reach the blastocyst stage, LD distribution becomes asymmetric between inner cell mass (ICM) and trophectoderm (TE) (42). TE cells, which contribute to the placenta, contain more and larger LDs than ICM cells, suggesting lineage-specific metabolic requirements (42,158,191). This differential LD allocation may reflect the TE role in steroidogenesis, nutrient transport and implantation, which demand robust lipid metabolism (158).

In pluripotent ICM cells, LDs are fewer but metabolically active, supporting a glycolysis-dominant phenotype typical of stem cells (192). Manipulating LD metabolism *in vitro* influences stem cell fate: Pharmacological activation of lipolysis promotes differentiation, while stabilizing LDs maintains pluripotency (193). These findings position LDs as regulators of cell fate transitions in the embryo (194).

Implications for assisted reproduction and stem cell biology. Understanding LD biology in embryos has practical implications (72). In assisted reproductive technology, embryo selection is typically based on morphology, yet LD content and dynamics may provide more sensitive biomarkers of viability (31). Non-invasive imaging techniques such as CARS microscopy have been applied to quantify LDs in live embryos, revealing an association between lipid distribution and implantation success (160).

In stem cell biology, insights into LD regulation in early embryos inform strategies to maintain pluripotency *in vitro* and direct differentiation (49). For example, modulating lipid availability or LD turnover influences epigenetic programming, since acetyl-CoA and lipid-derived metabolites serve as cofactors for chromatin-modifying enzymes. Thus, LDs not only support metabolic needs but also contribute to epigenetic landscapes that govern developmental trajectories (195).

7. Key regulators of LD biology in reproductive cells

The biology of LDs in reproductive systems is orchestrated by a complex network of enzymes, structural proteins, transcriptional factors and signaling pathways (6). These regulators not only govern LD biogenesis and turnover but also link lipid metabolism to the unique demands of gametogenesis, steroidogenesis and embryogenesis (49). Their coordinated activity ensures that lipid reserves are properly balanced between storage and mobilization, safeguarding reproductive success (69) (Fig. 6).

Enzymes of neutral lipid synthesis. LD biogenesis begins with the synthesis of neutral lipids within the ER, a process primarily mediated by enzymes such as DGAT1 and DGAT2 for triacylglycerols and acyl-CoA cholesterol acyltransferases (ACATs) for cholesteryl esters (140). In reproductive cells, these enzymes facilitate metabolic readiness: In oocytes, DGAT2 activity underlies the accumulation of lipid stores necessary for meiotic progression (196), while in granulosa and luteal cells, ACAT-mediated cholesterol esterification establishes a pool of precursors for steroid hormone synthesis (149). Disruption of these synthetic pathways reduces oocyte competence and compromises hormone production, highlighting their key role in reproductive physiology (150).

LD-coating and stabilizing proteins. Once formed, LDs are stabilized and functionally tuned by coat proteins, most prominently the PLIN family (197). PLIN2, highly abundant

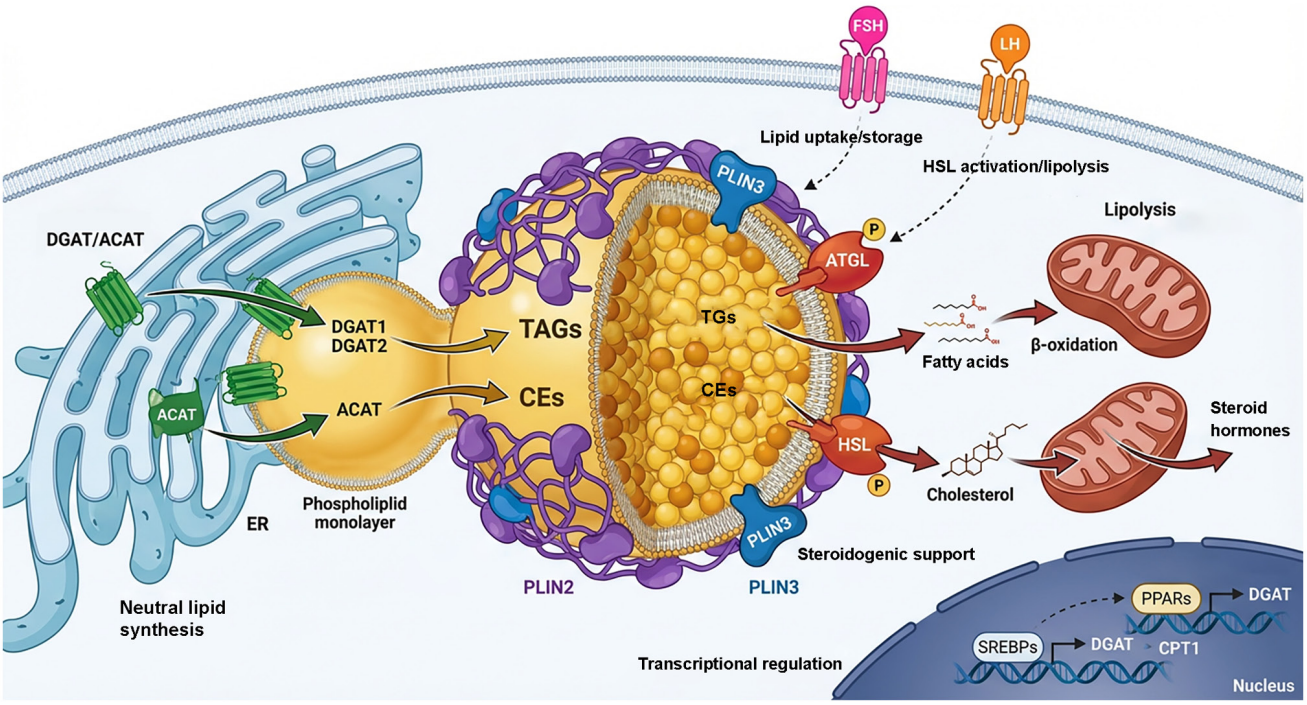

Figure 6. Molecular landscape of LD regulation in reproductive cells. Integrated network of enzymes, structural proteins and signaling pathways orchestrate LD biology, ensuring the balance between lipid storage and utilization. LD formation originates at the ER. DGAT1/2 catalyze the synthesis of TAGs, while ACATs synthesize CEs. These neutral lipids are packaged into the nascent LD core, establishing the metabolic reserves required for gametogenesis and steroidogenesis. The LD surface is coated by PLIN family proteins. PLIN2 stabilizes the LD by preventing uncontrolled lipolysis (crucial for oocyte lipid retention), while PLIN3 supports cholesterol storage in steroidogenic cells. These proteins serve as gatekeepers, regulating access to the lipid core. Controlled lipid breakdown is mediated by lipases. ATGL initiates TAG hydrolysis to release fatty acids for mitochondrial β-oxidation. HSL, activated via phosphorylation, hydrolyzes TAGs and CEs, liberating cholesterol for steroid hormone synthesis. The entire system is governed by upstream regulators. Hormones such as FSH promote lipid uptake/storage, whereas LH triggers lipolysis by activating HSL. At the nuclear level, transcription factors SREBP and PPAR modulate the expression of lipogenic and oxidative genes, respectively, adapting cell metabolism to developmental demands. ACAT, acyl-CoA cholesterol acyltransferase; ATGL, adipose triglyceride lipase; DGAT, diacylglycerol acyltransferase; ER, endoplasmic reticulum; FSH, follicle-stimulating hormone; HSL, hormone-sensitive lipase; LH, luteinizing hormone; PLIN, perilipin; PPAR, peroxisome proliferator-activated receptor; SREBP, sterol regulatory element-binding protein; LD, lipid droplet; TAG, triacylglycerol; CPT, carnitine palmitoyltransferase; CE, cholesteryl Ester.

in lipid-rich oocytes and granulosa cells, prevents uncontrolled lipolysis and ensures lipids remain available for developmental cues (37,48,68). PLIN3, enriched in steroidogenic cells, contributes to cholesterol storage and supports rapid progesterone synthesis following LH stimulation (22,24,47). These surface proteins not only regulate LD size and stability but also serve as molecular scaffolds that recruit lipases or tether LDs to partner organelles, integrating storage with utilization (2).

Lipolytic enzymes. Mobilization of LD lipids is mediated by lipolytic enzymes, whose activity is coupled to reproductive events (148). ATGL initiates triacylglycerol breakdown, providing FAs for mitochondrial β-oxidation, which is key for oocyte maturation and embryonic cleavage (166). HSL plays a dual role, hydrolyzing both TAGs and cholesteryl esters. In luteal cells, LH-induced phosphorylation of HSL rapidly liberates cholesterol for progesterone synthesis, directly linking lipolysis to endocrine function (147). Failure of these pathways, as seen in mouse knockout models of ATGL or HSL deficiency, results in lipid accumulation, impaired gametogenesis and subfertility (106,133).

Transcriptional and hormonal regulators. The transcriptional and hormonal control of LD regulators provides another layer of coordination (143). Sterol regulatory element-binding proteins activate the expression of lipogenic enzymes, ensuring reproductive cells adapt to energy demand and steroidogenic flux (198). PPARs fine-tune lipid storage and oxidation, with PPARγ promoting lipid accumulation in granulosa cells and PPARα enhancing FA use in embryos (199). Endocrine signals, particularly FSH and LH, further dictate LD dynamics: FSH promotes lipid uptake and storage in Sertoli and granulosa cells, while LH triggers lipolysis and cholesterol mobilization, exemplifying how systemic hormonal cues converge on LD regulation (20,109,200).

8. LD dysfunction and reproductive disorders

The regulation of LD biology is key for reproductive competence and its disruption is increasingly recognized as a pathogenic factor in infertility and reproductive disease (6,37,41). Aberrant LD accumulation, altered lipid composition or defective mobilization disturb gametogenesis, hormone production and embryonic development, ultimately compromising reproductive outcomes (49) (Fig. 7).

Excessive lipid storage or impaired lipid utilization is associated with ovarian pathologies (150). Patients with PCOS, one of the most common causes of infertility, display abnormal LD accumulation and dysregulated lipid metabolism in granulosa cells (156). This metabolic imbalance alters

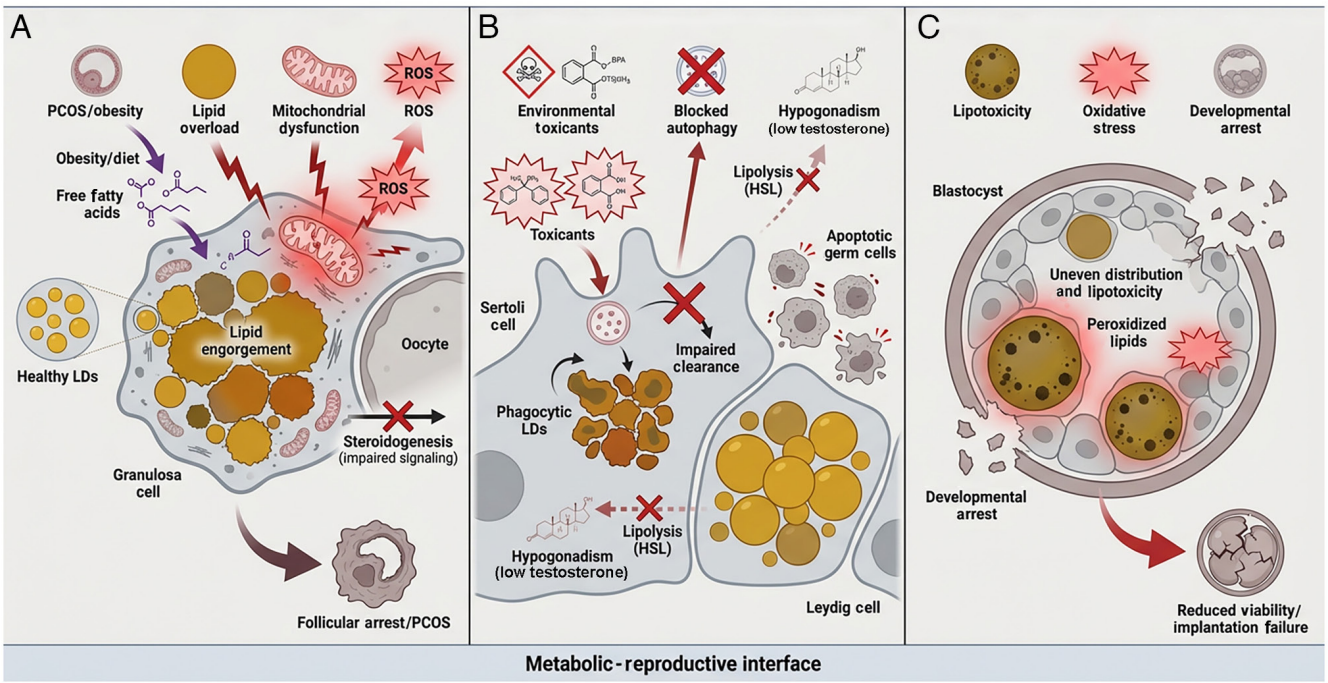

Figure 7. LD dysfunction as a driver of reproductive pathology. (A) Obesity causes lipid overload in granulosa cells and oocytes. Under conditions of obesity or dietary excess, high levels of free fatty acids cause lipid overload in granulosa cells and oocytes. This leads to mitochondrial dysfunction and the generation of ROS. The resulting metabolic stress impairs steroidogenic signaling and disrupts follicle development, culminating in follicular arrest and phenotypes associated with PCOS. (B) Toxicants disrupt LD homeostasis in the testis. Exposure to environmental toxicants (BPA, phthalates) disrupts LD homeostasis in the testis. In Sertoli cells, toxicants block lysosomal/autophagic pathways, preventing the clearance of phagocytosed lipids. This leads to the accumulation of phagocytic LDs and impairs the nutritional support provided to germ cells. In Leydig cells, disruption of lipolysis (HSL inhibition) prevents cholesterol mobilization, resulting in decreased testosterone synthesis (hypogonadism) and germ cell apoptosis. (C) Lipotoxicity leads to developmental arrest in embryos. In the context of IVF or maternal metabolic disorder, embryos may exhibit uneven distribution of LDs. The accumulation of peroxidized lipids creates a state of lipotoxicity and oxidative stress. These cell insults compromise blastocyst quality, leading to developmental arrest, decreased viability and implantation failure. BPA, bisphenol A; HSL, hormone-sensitive lipase; IVF, *in vitro* fertilization; LD, lipid droplet; PCOS, polycystic ovary syndrome; ROS, reactive oxygen species.

steroidogenic signaling, impairs follicle development and reduces oocyte competence (89). Similarly, maternal obesity and diabetes are associated with excessive LD deposition in oocytes and embryos, resulting in lipotoxicity, mitochondrial dysfunction and decreased embryo viability (201). These findings suggest that LD mismanagement contributes to the metabolic-reproductive interface that underlies certain female infertility syndromes (38).

In the male gonad, LD dysfunction also exerts notable effects (143). Sertoli cells, which provide structural and metabolic support for spermatogenesis, rely on LD turnover to supply energy substrates to developing germ cells (139). Disruption of lipolysis or autophagic clearance in these cells leads to LD accumulation, impaired nutrient transfer and defective sperm maturation (141). Leydig cells depend on LDs for cholesterol ester storage and rapid mobilization following LD stimulation; defects in this system decrease testosterone synthesis, contributing to hypogonadism and subfertility (202). Moreover, environmental toxicants such as phthalates and bisphenol A perturb LD homeostasis in testicular cells, linking lipid dysregulation to environmentally induced reproductive disorder (203).

Beyond the gonads, LD abnormality influences early developmental competence (69). *In vitro* fertilization studies reveal that embryo with excessive or uneven LD distribution exhibit lower developmental potential, potentially due to oxidative stress and impaired energy regulation (31,41,69,204). Defects in LD-associated proteins, including PLIN and SEIP-1, cause embryonic lethality or reduced implantation success, underscoring the importance of regulated LD dynamics for reproductive success (205).

Together, these findings position LD dysfunction as both a biomarker and a mechanistic driver of reproductive pathology (2). By disrupting lipid homeostasis, LD abnormality compromises gamete quality, hormone production and embryo viability (37). Clarifying the molecular underpinnings of LD dysfunction in reproductive disorders holds promise not only for understanding infertility but also for identifying novel diagnostic markers and therapeutic targets (206).

9. Technological advances in studying LDs in reproduction

The study of LDs in reproductive biology has benefited from technological innovations that allow improved resolution, sensitivity and functional insight (6). Traditional staining approaches, such as Oil Red O and BODIPY dyes, provided the first visualization of LDs in oocytes and embryos (207), but advances in imaging and molecular profiling permit dynamic and quantitative analyses of LD biology within reproductive contexts (69).

High-resolution microscopy has been key to these advances (13). Confocal and two-photon microscopy enable three-dimensional imaging of LD distribution in intact oocytes and embryos (31), while super-resolution techniques

such as stimulated emission depletion and structured illumination microscopy reveal nanoscale details of LD-organelle interactions. Live-cell imaging with fluorescently tagged LD-associated proteins makes it possible to track LD dynamics during meiotic maturation, fertilization and early embryogenesis, providing functional insight into how LD turnover couples with developmental transition (160).

Complementing imaging, mass spectrometry-based lipidomics has transformed the characterization of LD composition in reproductive tissue (208). Shotgun and targeted lipidomics approaches identify neutral lipid species, cholesterol esters and signaling lipids within LDs, enabling the detection of metabolic alterations in pathological states such as PCOS or maternal obesity. Single-cell and spatial lipidomics approaches have been applied to oocytes and embryos, resolving metabolic heterogeneity that underlies differences in developmental competence (209-212).

Genetic and molecular tools have also advanced functional studies (37,213,214). CRISPR-Cas9 editing in mice and *C. elegans* allows precise manipulation of LD-associated genes, demonstrating their roles in gametogenesis and embryonic development (205). Fluorescent reporters, such as PLIN or SEIP-1 fusion proteins, permit *in vivo* visualization of LD subsets and their dynamic responses to hormonal or metabolic cues (196). In parallel, optogenetic and inducible systems are powerful approaches to manipulate LD formation or lipolysis in real time, offering a causal understanding of LD function in reproductive processes (167).

Finally, integrative approaches that combine imaging, lipidomics and systems biology are beginning to redefine the landscape of LD research in reproduction (2). Spatial multi-omics platforms map LDs in the context of transcriptional and metabolic states (42), while computational models help predict how LD dysfunction develops into cell stress and developmental failure (192). Such integrative technologies not only provide mechanistic understanding but also hold promise for translational applications, such as developing LD-based biomarkers of oocyte quality or embryo viability in assisted reproductive technology (89).

In sum, methodological advances have propelled LD research from descriptive observations to mechanistic and translational insight (49). By coupling dynamic visualization with molecular profiling and functional manipulation, these technologies reshape understanding of how LDs support reproductive success and how their dysfunction contributes to infertility (150).

10. Conclusion

LDs are multifaceted organelles that are key for reproductive physiology. Beyond their traditional role as passive lipid stores, LDs serve as dynamic hubs integrating energy supply, membrane biosynthesis, steroidogenesis and stress adaptation. From oocyte maturation to early embryonic development, their regulated formation, turnover and organelle interactions ensure reproductive success. Dysregulation of LD biology, conversely, contributes to a number of disorders including PCOS, male infertility, and embryonic developmental defects, underscoring their centrality to reproductive health.

Mechanistically, it is not fully understood how LD subpopulations are formed or differentiated (based on size, lipid composition or functional specialization) in reproductive cells and how their interactions with mitochondria, ER and lysosomes are spatiotemporally regulated. The contribution of lipid signaling molecules released from LDs to epigenetic programming and lineage specification during early embryogenesis also remains largely unexplored. Moreover, the interplay between systemic metabolic disorders, such as obesity and diabetes, and LD dysfunction in gametes and embryos requires investigation to explain the intergenerational transmission of reproductive risk.

Future research may benefit from continued integration of cutting-edge technologies. Advances in live-cell super-resolution microscopy, spatial and single-cell lipidomics and CRISPR-based gene editing provide powerful opportunities to dissect LD biology. LD-based biomarkers hold promise for assessing oocyte and embryo quality in assisted reproductive technology, while therapeutic strategies targeting LD metabolism may emerge as novel approaches to treat infertility associated with metabolic or endocrine dysfunction. Importantly, comparative studies across species, from *C. elegans* and mice to humans, may demonstrate the evolutionary conservation and divergence of LD functions in reproduction.

In conclusion, LDs represent a dynamic interface between lipid metabolism and reproductive biology. By bridging basic mechanistic insights with clinical applications, LD research may deepen understanding of fundamental cell biology but also to transform reproductive medicine.

Acknowledgements

Not applicable.

Funding

The present study was supported by Shandong Provincial Medical and Health Science and Technology Project (grant no. 202402081168), Ji Nan Health High-Caliber Talent Project (grant no. 202512), Science and Technology Development Plan Project of Jinan Municipal Health Commission (grant no. 2024302002), the National Natural Science Foundation of China (grant no. 82401009), Shandong Provincial Natural Science Foundation (grant no. ZR2025MS1456), Science and Technology Development Program of Jinan Municipal Health Commission (grant no. 2024202001) and the Research Start-up Fee for Introducing Talents to Jinan Central Hospital (grant nos. YJRC2023001 and YJRC2023005).

Availability of data and materials

Not applicable.

Authors' contributions

LP conducted the literature review and wrote the manuscript. ZW constructed figures. YJ wrote the manuscript and provided supervision. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the authors used artificial intelligence-assisted tools (including Grok) to improve the readability and language of the manuscript, to draft the cover letter and to propose a running title. No artificial intelligence tool was used to generate scientific content, analyse or interpret data, draw scientific conclusions or create figures. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

1. Farese RV Jr and Walther TC: Lipid droplets finally get a little R-E-S-P-E-C-T. Cell 139: 855-860, 2009.
2. Olzmann JA and Carvalho P: Dynamics and functions of lipid droplets. Nat Rev Mol Cell Biol 20: 137-155, 2019.
3. Walther TC, Chung J and Farese RV Jr: Lipid droplet biogenesis. Annu Rev Cell Dev Biol 33: 491-510, 2017.
4. Salo VT, Belevich I, Li S, Karhinen L, Vihinen H, Vigouroux C, Magré J, Thiele C, Hölttä-Vuori M, Jokitalo E and Ikonen E: Seipin regulates ER-lipid droplet contacts and cargo delivery. EMBO J 35: 2699-2716, 2016.
5. Cartwright BR and Goodman JM: Seipin: From human disease to molecular mechanism. J Lipid Res 53: 1042-1055, 2012.
6. Welte MA and Gould AP: Lipid droplet functions beyond energy storage. Biochim Biophys Acta Mol Cell Biol Lipids 1862: 1260-1272, 2017.
7. Bosch M, Sanchez-Alvarez M, Fajardo A, Kapetanovic R, Steiner B, Dutra F, Moreira L, López JA, Campo R, Marí M, *et al*: Mammalian lipid droplets are innate immune hubs integrating cell metabolism and host defense. Science 370: eaay8085, 2020.
8. Lass A, Zimmermann R, Oberer M and Zechner R: Lipolysis-a highly regulated multi-enzyme complex mediates the catabolism of cellular fat stores. Prog Lipid Res 50: 14-27, 2011.
9. Cruz ALS, Barreto EA, Fazolini NPB, Viola JPB and Bozza PT: Lipid droplets: Platforms with multiple functions in cancer hallmarks. Cell Death Dis 11: 105, 2020.
10. Henne WM, Reese ML and Goodman JM: The assembly of lipid droplets and their roles in challenged cells. EMBO J 37: e98947, 2018.
11. Sturmey RG, Reis A, Leese HJ and McEvoy TG: Role of fatty acids in energy provision during oocyte maturation and early embryo development. Reprod Domest Anim 44 (Suppl 3): S50-S58, 2009.
12. Brusentsev EY, Mokrousova VI, Igonina TN, Rozhkova IN and Amstislavsky SY: Role of lipid droplets in the development of oocytes and preimplantation embryos in mammals. Russ J Dev Biol 50: 230-237, 2019.
13. Bradley J and Swann K: Mitochondria and lipid metabolism in mammalian oocytes and early embryos. Int J Dev Biol 63: 93-103, 2019.
14. Aardema H, Vos PL, Lolicato F, Roelen BA, Knijn HM, Vaandrager AB, Helms JB and Gadella BM: Oleic acid prevents detrimental effects of saturated fatty acids on bovine oocyte developmental competence. Biol Reprod 85: 62-69, 2011.
15. Ahmed N, Liu Y, Chen H, Yang P, Waqas Y, Liu T, Gandahi JA, Huang Y, Wang L, Song X, *et al*: Novel cellular evidence of lipophagy within the Sertoli cells during spermatogenesis in the turtle. Aging (Albany NY) 9: 41-51, 2016.
16. Staggenborg S, Koch R, Rode K, Hüneke H, Tiedje L, Wirth G, Langeheine M, Blume I, Rohn K, Wrede C, *et al*: Connexin43 represents an important regulator for Sertoli cell morphology, Sertoli cell nuclear ultrastructure, and Sertoli cell maturation. Sci Rep 12: 12898, 2022.
17. Wang H, Wang H, Xiong W, Chen Y, Ma Q, Ma J, Ge Y and Han D: Evaluation on the phagocytosis of apoptotic spermatogenic cells by Sertoli cells in vitro through detecting lipid droplet formation by Oil Red O staining. Reproduction 132: 485-492, 2006.
18. Yamaguchi T, Fujikawa N, Nimura S, Tokuoka Y, Tsuda S, Aiuchi T, Kato R, Obama T and Itabe H: Characterization of lipid droplets in steroidogenic MLTC-1 Leydig cells: Protein profiles and the morphological change induced by hormone stimulation. Biochim Biophys Acta 1851: 1285-1295, 2015.
19. Gao F, Li G, Liu C, Gao H, Wang H, Liu W, Chen M, Shang Y, Wang L, Shi J, *et al*: Autophagy regulates testosterone synthesis by facilitating cholesterol uptake in Leydig cells. J Cell Biol 217: 2103-2119, 2018.
20. Plewes MR, Talbott HA, Saviola AJ, Woods NT, Schott MB and Davis JS: Luteal lipid droplets: A novel platform for steroid synthesis. Endocrinology 164: bqad124, 2023.
21. Przygrodzka E, Hou X, Zhang P, Plewes MR, Franco R and Davis JS: PKA and AMPK signaling pathways differentially regulate luteal steroidogenesis. Endocrinology 162: bqab015, 2021.
22. Plewes MR, Krause C, Talbott HA, Przygrodzka E, Wood JR, Cupp AS and Davis JS: Trafficking of cholesterol from lipid droplets to mitochondria in bovine luteal cells: Acute control of progesterone synthesis. FASEB J 34: 10731-10750, 2020.
23. Khor VK, Ahrends R, Lin Y, Shen WJ, Adams CM, Roseman AN, Cortez Y, Teruel MN, Azhar S and Kraemer FB: The proteome of cholesteryl-ester-enriched versus triacylglycerol-enriched lipid droplets. PLoS One 9: e105047, 2014.
24. Shen WJ, Azhar S and Kraemer FB: Lipid droplets and steroidogenic cells. Exp Cell Res 340: 209-214, 2016.
25. Cao Z, Fung CW and Mak HY: A flexible network of lipid droplet associated proteins support embryonic integrity of C. elegans. Front Cell Dev Biol 10: 856474, 2022.
26. Bai X, Huang LJ, Chen SW, Nebenfuehr B, Wysolmerski B, Wu JC, Olson SK, Golden A and Wang CW: Loss of the seipin gene perturbs eggshell formation in Caenorhabditiselegans. Development 147: dev192997, 2020.
27. Tao A, Wu T, Han X, Niu D and Feng X: Lipidomics reveals common mechanisms in polycystic ovarian syndrome, recurrent spontaneous abortion, and infertility: A genetic-based analysis. Int J Womens Health 17: 1055-1065, 2025.
28. Raviv S, Hantisteanu S, Sharon SM, Atzmon Y, Michaeli M and Shalom-Paz E: Lipid droplets in granulosa cells are correlated with reduced pregnancy rates. J Ovarian Res 13: 4, 2020.
29. Liu Q, Xie YJ, Qu LH, Zhang MX and Mo ZC: Dyslipidemia involvement in the development of polycystic ovary syndrome. Taiwan J Obstet Gynecol 58: 447-453, 2019.
30. Zhang CH, Liu XY and Wang J: Essential role of granulosa cell glucose and lipid metabolism on oocytes and the potential metabolic imbalance in polycystic ovary Syndrome. Int J Mol Sci 24: 16247, 2023.
31. Bradley J, Pope I, Masia F, Sanusi R, Langbein W, Swann K and Borri P: Quantitative imaging of lipids in live mouse oocytes and early embryos using CARS microscopy. Development 143: 2238-2247, 2016.
32. Zhang C: Coherent Raman scattering microscopy of lipid droplets in cells and tissues. J Raman Spectrosc 54: 988-1000, 2023.
33. Inoue N, Nishida Y, Harada E, Sakai K and Narahara H: GC-MS/MS analysis of metabolites derived from a single human blastocyst. Metabolomics 17: 17, 2021.
34. Schwartz HT and Sternberg PW: A sequencing-based screening method identifies regulators of EGFR signaling from nonviable mutants in Caenorhabditis elegans. Sci Signal 18: eadp9377, 2025.
35. An L, Fu X, Chen J and Ma J: Application of caenorhabditis elegans in lipid metabolism research. Int J Mol Sci 24: 1173, 2023.

36. Wamaitha SE, Nie X, Pandolfi EC, Wang X, Yang Y, Stukenborg JB, Cairns BR, Guo J and Clark AT: Single-cell analysis of the developing human ovary defines distinct insights into ovarian somatic and germline progenitors. Dev Cell 58: 2097-2111 e3, 2023.
37. Ibayashi M, Aizawa R, Mitsui J and Tsukamoto S: Homeostatic regulation of lipid droplet content in mammalian oocytes and embryos. Reproduction 162: R99-R109, 2021.
38. Purcell SH and Moley KH: The impact of obesity on egg quality. J Assist Reprod Genet 28: 517-524, 2011.
39. Leary C, Leese HJ and Sturmey RG: Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. Hum Reprod 30: 122-132, 2015.
40. Jiang M, Gao M, Wu C, He H, Guo X, Zhou Z, Yang H, Xiao X, Liu G and Sha J: Lack of testicular seipin causes teratozoospermia syndrome in men. Proc Natl Acad Sci USA 111: 7054-7059, 2014.
41. Khan R, Jiang X, Hameed U and Shi Q: Role of lipid metabolism and signaling in mammalian oocyte maturation, quality, and acquisition of competence. Front Cell Dev Biol 9: 639704, 2021.
42. Lipinska P, Pawlak P and Warzych E: Species and embryo genome origin affect lipid droplets in preimplantation embryos. Front Cell Dev Biol 11: 1187832, 2023.
43. Chao CF, Pesch YY, Yu H, Wang C, Aristizabal MJ, Huan T, Tanentzapf G and Rideout E: An important role for triglyceride in regulating spermatogenesis. Elife 12: RP87523, 2024.
44. Aizawa R, Ibayashi M, Mitsui J and Tsukamoto S: Lipid droplet formation is spatiotemporally regulated in oocytes during follicular development in mice. J Reprod Dev 70: 18-24, 2024.
45. Kerr JB and De Kretser DM: Cyclic variations in Sertoli cell lipid content throughout the spermatogenic cycle in the rat. J Reprod Fertil 43: 1-8, 1975.
46. Regueira M, Gorga A, Rindone GM, Pellizzari EH, Cigorraga SB, Galardo MN, Riera MF and Meroni SB: Apoptotic germ cells regulate Sertoli cell lipid storage and fatty acid oxidation. Reproduction 156: 515-525, 2018.
47. Talbott HA, Plewes MR, Krause C, Hou X, Zhang P, Rizzo WB, Wood JR, Cupp AS and Davis JS: Formation and characterization of lipid droplets of the bovine corpus luteum. Sci Rep 10: 11287, 2020.
48. Plewes MR, Talbott HA, Schott MB, Wood JR, Cupp AS and Davis JS: Unraveling the role of lipid droplets and perilipin 2 in bovine luteal cells. FASEB J 38: e23710, 2024.
49. Dunning KR, Russell DL and Robker RL: Lipids and oocyte developmental competence: The role of fatty acids and beta-oxidation. Reproduction 148: R15-R27, 2014.
50. Schindler M, Pendzialek M, Grybel KJ, Seeling T, Gürke J, Fischer B and Navarrete Santos A: Adiponectin stimulates lipid metabolism via AMPK in rabbit blastocysts. Hum Reprod 32: 1382-1392, 2017.
51. Ma W, Yang X and Liang X: Obesity does not aggravate vitrification injury in mouse embryos: A prospective study. Reprod Biol Endocrinol 10: 68, 2012.
52. Hallberg M, Morganstein DL, Kiskinis E, Shah K, Kralli A, Dilworth SM, White R, Parker MG and Christian M: A functional interaction between RIP140 and PGC-1alpha regulates the expression of the lipid droplet protein CIDEA. Mol Cell Biol 28: 6785-6795, 2008.
53. Ning Z, Deng X, Li L, Feng J, Du X, Amevor FK, Tian Y, Li L, Rao Y, Yi Z, *et al*: miR-128-3p regulates chicken granulosa cell function via 14-3-3β/FoxO and PPAR-γ/LPL signaling pathways. Int J Biol Macromol 241: 124654, 2023.
54. Cui L and Liu P: Two types of contact between lipid droplets and mitochondria. Front Cell Dev Biol 8: 618322, 2020.
55. Ma X, Qian H, Chen A, Ni HM and Ding WX: Perspectives on mitochondria-ER and mitochondria-lipid droplet contact in hepatocytes and hepatic lipid metabolism. Cells 10: 2273, 2021.
56. Latchman NR, Stevens TL, Bedi KC, Prosser BL, Margulies KB and Elrod JW: Ultrastructure analysis of mitochondria, lipid droplet and sarcoplasmic reticulum apposition in human heart failure. J Mol Cell Cardiol Plus 13: 100461, 2025.
57. Liu L, Yang S, Liu Y, Li X, Hu J, Xiao L and Xu T: DeepContact: High-throughput quantification of membrane contact sites based on electron microscopy imaging. J Cell Biol 221: e202106190, 2022.
58. Benador IY, Veliova M, Liesa M and Shirihai OS: Mitochondria bound to lipid droplets: Where mitochondrial dynamics regulate lipid storage and utilization. Cell Metab 29: 827-835, 2019.
59. Freyre CAC, Rauher PC, Ejsing CS and Klemm RW: MIGA2 links mitochondria, the ER, and lipid droplets and promotes de novo lipogenesis in adipocytes. Mol Cell 76: 811-825 e14, 2019.
60. Herker E, Vieyres G, Beller M, Krahmer N and Bohnert M: Lipid droplet contact sites in health and disease. Trends Cell Biol 31: 345-358, 2021.
61. Fan H and Tan Y: Lipid droplet-mitochondria contacts in health and disease. Int J Mol Sci 25: 6878, 2024.
62. Monteiro-Cardoso VF and Giordano F: Emerging functions of the mitochondria-ER-lipid droplet three-way junction in coordinating lipid transfer, metabolism, and storage in cells. FEBS Lett 598: 1252-1273, 2024.
63. Benador IY, Veliova M, Mahdaviani K, Petcherski A, Wikstrom JD, Assali EA, Acín-Pérez R, Shum M, Oliveira MF, Cinti S, *et al*: Mitochondria bound to lipid droplets have unique bioenergetics, composition, and dynamics that support lipid droplet expansion. Cell Metab 27: 869-885 e6, 2018.
64. Talari NK, Mattam U, Meher NK, Paripati AK, Mahadev K, Krishnamoorthy T and Sepuri NBV: Lipid-droplet associated mitochondria promote fatty-acid oxidation through a distinct bioenergetic pattern in male Wistar rats. Nat Commun 14: 766, 2023.
65. Flores-Romero H, Ros U and Garcia-Saez AJ: A lipid perspective on regulated cell death. Int Rev Cell Mol Biol 351: 197-236, 2020.
66. Danielsen ET, Moeller ME, Yamanaka N, Ou Q, Laursen JM, Soenderholm C, Zhuo R, Phelps B, Tang K, Zeng J, *et al*: A *Drosophila* genome-wide screen identifies regulators of steroid hormone production and developmental timing. Dev Cell 37: 558-570, 2016.
67. Prates EG, Nunes JT and Pereira RM: A role of lipid metabolism during cumulus-oocyte complex maturation: impact of lipid modulators to improve embryo production. Mediators Inflamm 2014: 692067, 2014.
68. Liu T, Qu J, Tian M, Yang R, Song X, Li R, Yan J and Qiao J: Lipid metabolic process involved in oocyte maturation during folliculogenesis. Front Cell Dev Biol 10: 806890, 2022.
69. Li T, Jin Y, Wu J and Ren Z: Beyond energy provider: Multifunction of lipid droplets in embryonic development. Biol Res 56: 38, 2023.
70. Kajdasz A, Warzych E, Derebecka N, Madeja ZE, Lechniak D, Wesoly J and Pawlak P: Lipid stores and lipid metabolism associated gene expression in porcine and bovine parthenogenetic embryos revealed by fluorescent staining and RNA-seq. Int J Mol Sci 21: 6488, 2020.
71. de Andrade Melo-Sterza F and Poehland R: Lipid metabolism in bovine oocytes and early embryos under in vivo, in vitro, and stress conditions. Int J Mol Sci 22: 3421, 2021.
72. Arena R, Bisogno S, Gasior L, Rudnicka J, Bernhardt L, Haaf T, Zacchini F, Bochenek M, Fic K, Bik E, *et al*: Lipid droplets in mammalian eggs are utilized during embryonic diapause. Proc Natl Acad Sci USA 118: e2018362118, 2021.
73. Downs SM: Nutrient pathways regulating the nuclear maturation of mammalian oocytes. Reprod Fertil Dev 27: 572-582, 2015.
74. Agarwal A, Gupta S and Sharma R: Oxidative stress and its implications in female infertility-a clinician's perspective. Reprod Biomed Online 11: 641-650, 2005.
75. Aizawa R, Ibayashi M, Tatsumi T, Yamamoto A, Kokubo T, Miyasaka N, Sato K, Ikeda S, Minami N and Tsukamoto S: Synthesis and maintenance of lipid droplets are essential for mouse preimplantation embryonic development. Development 146: dev181925, 2019.
76. Zhang JF, Choi SH, Li Q, Wang Y, Sun B, Tang L, Wang EZ, Hua H and Li XZ: Overexpression of DGAT2 stimulates lipid droplet formation and triacylglycerol accumulation in bovine satellite cells. Animals (Basel) 12: 1847, 2022.
77. Malyszka N, Pawlak P, Cieslak A, Szkudelska K and Lechniak D: Distinct dynamics of lipid accumulation by porcine cumulus cells during in vitro maturation with follicular fluid of low and high fatty acid contents. Theriogenology 195: 93-102, 2023.
78. Zhang RN, Fu XW, Jia BY, Liu C, Cheng KR and Zhu SE: Expression of perilipin 2 (PLIN2) in porcine oocytes during maturation. Reprod Domest Anim 49: 875-880, 2014.
79. Sowinska N, Lechtanska J, Greczka K, Lechniak D and Pawlak P: Feline cumulus cells and oocytes show massive accumulation of lipid droplets and upregulation of PLIN2 expression after in vitro maturation. Theriogenology 232: 70-78, 2025.
80. Monks J, Orlicky DJ, Libby AE, Dzieciatkowska M, Ladinsky MS and McManaman JL: Perilipin-2 promotes lipid droplet-plasma membrane interactions that facilitate apocrine lipid secretion in secretory epithelial cells of the mouse mammary gland. Front Cell Dev Biol 10: 958566, 2022.
81. Xiang X, Chen J and Che L: Emerging roles and therapeutic implications of lipid droplet protein perilipin 2 in liver disease. Genes Dis 13: 101712, 2025.

82. Morak M, Schmidinger H, Riesenhuber G, Rechberger GN, Kollroser M, Haemmerle G, Zechner R, Kronenberg F and Hermetter A: Adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) deficiencies affect expression of lipolytic activities in mouse adipose tissues. Mol Cell Proteomics 11: 1777-1789, 2012.
83. Miyoshi H, Perfield JW II, Obin MS and Greenberg AS: Adipose triglyceride lipase regulates basal lipolysis and lipid droplet size in adipocytes. J Cell Biochem 105: 1430-1436, 2008.
84. Schweiger M, Schreiber R, Haemmerle G, Lass A, Fledelius C, Jacobsen P, Tornqvist H, Zechner R and Zimmermann R: Adipose triglyceride lipase and hormone-sensitive lipase are the major enzymes in adipose tissue triacylglycerol catabolism. J Biol Chem 281: 40236-40241, 2006.
85. Lass A, Zimmermann R, Haemmerle G, Riederer M, Schoiswohl G, Schweiger M, Kienesberger P, Strauss JG, Gorkiewicz G and Zechner R: Adipose triglyceride lipase-mediated lipolysis of cellular fat stores is activated by CGI-58 and defective in Chanarin-Dorfman Syndrome. Cell Metab 3: 309-319, 2006.
86. Gaidhu MP, Anthony NM, Patel P, Hawke TJ and Ceddia RB: Dysregulation of lipolysis and lipid metabolism in visceral and subcutaneous adipocytes by high-fat diet: role of ATGL, HSL, and AMPK. Am J Physiol Cell Physiol 298: C961-C971, 2010.
87. Turathum B, Gao EM and Chian RC: The function of cumulus cells in oocyte growth and maturation and in subsequent ovulation and fertilization. Cells 10: 2292, 2021.
88. Richani D, Poljak A, Wang B, Mahbub SB, Biazik J, Campbell JM, Habibalahi A, Stocker WA, Marinova MB, Nixon B, *et al*: Oocyte and cumulus cell cooperativity and metabolic plasticity under the direction of oocyte paracrine factors. Am J Physiol Endocrinol Metab 326: E366-E381, 2024.
89. Dumesic DA, Meldrum DR, Katz-Jaffe MG, Krisher RL and Schoolcraft WB: Oocyte environment: Follicular fluid and cumulus cells are critical for oocyte health. Fertil Steril 103: 303-316, 2015.
90. Xie J, Xu X and Liu S: Intercellular communication in the cumulus-oocyte complex during folliculogenesis: A review. Front Cell Dev Biol 11: 1087612, 2023.
91. Uhde K, van Tol HTA, Stout TAE and Roelen BAJ: Metabolomic profiles of bovine cumulus cells and cumulus-oocyte-complex-conditioned medium during maturation in vitro. Sci Rep 8: 9477, 2018.
92. Russell DL, Gilchrist RB, Brown HM and Thompson JG: Bidirectional communication between cumulus cells and the oocyte: Old hands and new players? Theriogenology 86: 62-68, 2016.
93. Chen M, Yang W, Guo Y, Hou X, Zhu S, Sun H, Guo X, Chen M and Wang Q: Multi-omics reveal the metabolic patterns in mouse cumulus cells during oocyte maturation. J Ovarian Res 16: 156, 2023.
94. Lawson GLG: Composition of Lipid Droplets and Vesicles and their Relation to Oocyte Development Competency. Reader K (ed). BBiomedSc (Hons), University of Otago, 2023.
95. Ordonez-Leon EA, Merchant H, Medrano A, Kjelland M and Romo S: Lipid droplet analysis using in vitro bovine oocytes and embryos. Reprod Domest Anim 49: 306-314, 2014.
96. Budani MC and Tiboni GM: Effects of supplementation with natural antioxidants on oocytes and preimplantation embryos. Antioxidants (Basel) 9: 612, 2020.
97. Fayezi S, Leroy JLMR, Ghaffari Novin M and Darabi M: Oleic acid in the modulation of oocyte and preimplantation embryo development. Zygote 26: 1-13, 2018.
98. Rakha SI, Elmetwally MA, El-Sheikh Ali H, Balboula A, Mahmoud AM and Zaabel SM: Importance of antioxidant supplementation during in vitro maturation of mammalian oocytes. Vet Sci 9: 439, 2022.
99. Guseva O, Kan N, Chekmareva V, Kokorev D, Ilyasov P and Zhu YQ: The impact of antioxidant supplements on oocytes and preimplantation embryos of humans and mammals, and their potential application for mitigating the consequences of oxidative stress in vitro: A review. Reproductive and Developmental Medicine 8: 252-263, 2024.
100. Dubeibe Marin DF, da Costa NN, di Paula Bessa Santana P, de Souza EB and Ohashi OM: Importance of lipid metabolism on oocyte maturation and early embryo development: Can we apply what we know to buffalo? Anim Reprod Sci 211: 106220, 2019.
101. Catandi GD, LiPuma L, Obeidat YM, Maclellan LJ, Broeckling CD, Chen T, Chicco AJ and Carnevale EM: Oocyte metabolic function, lipid composition, and developmental potential are altered by diet in older mares. Reproduction 163: 183-198, 2022.
102. Chen H, Huang Y, Yang P, Shi Y, Ahmed N, Liu T, Bai X, Haseeb A and Chen Q: Autophagy enhances lipid droplet development during spermiogenesis in Chinese soft-shelled turtle, Pelodiscus sinensis. Theriogenology 147: 154-165, 2020.
103. Oresti GM, Ayuza Aresti PL, Gigola G, Reyes LE and Aveldano MI: Sequential depletion of rat testicular lipids with long-chain and very long-chain polyenoic fatty acids after X-ray-induced interruption of spermatogenesis. J Lipid Res 51: 2600-2610, 2010.
104. Liu M, Qi L, Zeng Y, Yang Y, Bi Y, Shi X, Zhu H, Zhou Z and Sha J: Transient scrotal hyperthermia induces lipid droplet accumulation and reveals a different ADFP expression pattern between the testes and liver in mice. PLoS One 7: e45694, 2012.
105. Furland NE, Luquez JM, Oresti GM and Aveldano MI: Mild testicular hyperthermia transiently increases lipid droplet accumulation and modifies sphingolipid and glycerophospholipid acyl chains in the rat testis. Lipids 46: 443-454, 2011.
106. Osuga J, Ishibashi S, Oka T, Yagyu H, Tozawa R, Fujimoto A, Shionoiri F, Yahagi N, Kraemer FB, Tsutsumi O and Yamada N: Targeted disruption of hormone-sensitive lipase results in male sterility and adipocyte hypertrophy, but not in obesity. Proc Natl Acad Sci USA 97: 787-792, 2000.
107. Zhang J, Hu Y, Wang Y, Fu L, Xu X, Li C, Xu J, Li C, Zhang L, Yang R, *et al*: mmBCFA C17iso ensures endoplasmic reticulum integrity for lipid droplet growth. J Cell Biol 220: e202102122, 2021.
108. Wang C, Wang B, Pandey T, Long Y, Zhang J, Oh F, Sima J, Guo R, Liu Y, Zhang C, *et al*: A conserved megaprotein-based molecular bridge critical for lipid trafficking and cold resilience. Nat Commun 13: 6805, 2022.
109. Dasso ME, Centola CL, Galardo MN, Riera MF and Meroni SB: FSH increases lipid droplet content by regulating the expression of genes related to lipid storage in Rat Sertoli cells. Mol Cell Endocrinol 595: 112403, 2025.
110. Gorga A, Rindone GM, Regueira M, Pellizzari EH, Camberos MC, Cigorraga SB, Riera MF, Galardo MN and Meroni SB: PPARγ activation regulates lipid droplet formation and lactate production in rat Sertoli cells. Cell Tissue Res 369: 611-624, 2017.
111. Chen ZF, Shen YF, Gao DW, Lin DF, Ma WZ and Chang DG: Metabolic pathways and male fertility: Exploring the role of Sertoli cells in energy homeostasis and spermatogenesis. Am J Physiol Endocrinol Metab 329: E160-E178, 2025.
112. Breucker H, Schafer E and Holstein AF: Morphogenesis and fate of the residual body in human spermiogenesis. Cell Tissue Res 240: 303-309, 1985.
113. Guo C, Wang L, Cui K, Zhang G, Tan Y, Chen W, Wang Y, Liu J, Liu W, Zhang G and Zhou Z: Lead causes lipid droplet accumulation by impairing lysosomal function and autophagic flux in testicular sertoli cells. Toxics 13: 175, 2025.
114. Rindone GM, Dasso ME, Centola CL, Pellizzari EH, Camberos MDC, Toneatto J, Galardo MN, Meroni SB and Riera MF: Sertoli cell adaptation to glucose deprivation: Potential role of AMPK in the regulation of lipid metabolism. J Cell Biochem 124: 716-730, 2023.
115. Bush SJ, Nikola R, Han S, Suzuki S, Yoshida S, Simons BD and Goriely A: Adult human, but not rodent, spermatogonial stem cells retain states with a foetal-like signature. Cells 13: 742, 2024.
116. Wang J, Chen M, Yao Y, Zhu M, Jiang Y, Duan J, Yuan Y, Li L, Chen M and Sha J: Characterization of metabolic patterns in mouse spermatogenesis and its clinical implications in humans. Int J Mol Sci 26: 1001, 2025.
117. Plant TM and Marshall GR: The functional significance of FSH in spermatogenesis and the control of its secretion in male primates. Endocr Rev 22: 764-786, 2001.
118. Guo J, Grow EJ, Mlcochova H, Maher GJ, Lindskog C, Nie X, Guo Y, Takei Y, Yun J, Cai L, *et al*: The adult human testis transcriptional cell atlas. Cell Res 28: 1141-1157, 2018.
119. Paniagua R, Nistal M, Saez FJ and Fraile B: Ultrastructure of the aging human testis. J Electron Microsc Tech 19: 241-260, 1991.

120. Li N, Mruk DD, Mok KW, Li MW, Wong CK, Lee WM, Han D, Silvestrini B and Cheng CY: Connexin 43 reboots meiosis and reseals blood-testis barrier following toxicant-mediated aspermatogenesis and barrier disruption. FASEB J 30: 1436-1452, 2016.
121. Vo BT, Morton D Jr, Komaragiri S, Millena AC, Leath C and Khan SA: TGF-beta effects on prostate cancer cell migration and invasion are mediated by PGE2 through activation of PI3K/AKT/mTOR pathway. Endocrinology 154: 1768-1779, 2013.
122. Sahin MB, Schwartz RE, Buckley SM, Heremans Y, Chase L, Hu WS and Verfaillie CM: Isolation and characterization of a novel population of progenitor cells from unmanipulated rat liver. Liver Transpl 14: 333-345, 2008.
123. Richburg JH, Myers JL and Bratton SB: The role of E3 ligases in the ubiquitin-dependent regulation of spermatogenesis. Semin Cell Dev Biol 30: 27-35, 2014.
124. Zalata AA, Christophe AB, Depuydt CE, Schoonjans F and Comhaire FH: The fatty acid composition of phospholipids of spermatozoa from infertile patients. Mol Hum Reprod 4: 111-118, 1998.
125. Fusaro I, Parrillo S, Buonaiuto G, Prasinou P, Gramenzi A, Bucci R, Cavallini D, Carosi A, Carluccio A and De Amicis I: Effects of hemp-based polyunsaturated fatty acid supplementation on membrane lipid profiles and reproductive performance in Martina Franca jacks. Front Vet Sci 12: 1553218, 2025.
126. Johnson MR, Stephenson RA, Ghaemmaghami S and Welte MA: Developmentally regulated H2Av buffering via dynamic sequestration to lipid droplets in *Drosophila* embryos. Elife 7: e36021, 2018.
127. Byrne CJ, Fair S, English AM, Holden SA, Dick JR, Lonergan P and Kenny DA: Dietary polyunsaturated fatty acid supplementation of young post-pubertal dairy bulls alters the fatty acid composition of seminal plasma and spermatozoa but has no effect on semen volume or sperm quality. Theriogenology 90: 289-300, 2017.
128. Prochowska S, Bonarska-Kujawa D, Bobak L, Eberhardt M and Nizanski W: Fatty acid composition and biophysical characteristics of the cell membrane of feline spermatozoa. Sci Rep 14: 10214, 2024.
129. Liu Q, Zhou YF, Duan RJ, Wei HK, Peng J and Jiang SW: Dietary n-6:n-3 ratio and Vitamin E improve motility characteristics in association with membrane properties of boar spermatozoa. Asian J Androl 19: 223-229, 2017.
130. Tran LV, Malla BA, Sharma AN, Kumar S, Tyagi N and Tyagi AK: Effect of omega-3 and omega-6 polyunsaturated fatty acid enriched diet on plasma IGF-1 and testosterone concentration, puberty and semen quality in male buffalo. Anim Reprod Sci 173: 63-72, 2016.
131. Schlegel RA, Hammerstedt R, Cofer GP, Kozarsky K, Freidus D and Williamson P: Changes in the organization of the lipid bilayer of the plasma membrane during spermatogenesis and epididymal maturation. Biol Reprod 34: 379-391, 1986.
132. Jabarineitapeh M, Naderi N, Tavalaee M and Nasr-Esfahani MH: Effects of L-carnitine over-supplementation on spermatogenesis and sperm function in healthy NMRI mice. Tissue Cell 96: 103014, 2025.
133. Casado ME, Huerta L, Marcos-Diaz A, Ortiz AI, Kraemer FB, Lasunción MA, Busto R and Martín-Hidalgo A: Hormone-sensitive lipase deficiency affects the expression of SR-BI, LDLr, and ABCA1 receptors/transporters involved in cellular cholesterol uptake and efflux and disturbs fertility in mouse testis. Biochim Biophys Acta Mol Cell Biol Lipids 1866: 159043, 2021.
134. Casado ME, Huerta L, Ortiz AI, Pérez-Crespo M, Gutiérrez-Adán A, Kraemer FB, Lasunción MÁ, Busto R and Martín-Hidalgo A: HSL-knockout mouse testis exhibits class B scavenger receptor upregulation and disrupted lipid raft microdomains. J Lipid Res 53: 2586-2597, 2012.
135. Nistal M, Jimenez F and Paniagua R: Sertoli cell types in the Sertoli-cell-only syndrome: Relationships between Sertoli cell morphology and aetiology. Histopathology 16: 173-180, 1990.
136. Chung KW and Hamilton JB: Testicular lipids in mice with testicular feminization. Cell Tissue Res 160: 69-80, 1975.
137. Weinbauer GF, Respondek M, Themann H and Nieschlag E: Reversibility of long-term effects of GnRH agonist administration on testicular histology and sperm production in the nonhuman primate. J Androl 8: 319-329, 1987.
138. Wang T, Xiao Y, Hu Z, Gu J, Hua R, Hai Z, Chen X, Zhang JV, Yu Z, Wu T, *et al*: MFN2 deficiency impairs mitochondrial functions and PPAR pathway during spermatogenesis and meiosis in mice. Front Cell Dev Biol 10: 862506, 2022.
139. Griswold MD: The central role of Sertoli cells in spermatogenesis. Semin Cell Dev Biol 9: 411-416, 1998.
140. Walther TC and Farese RV Jr: Lipid droplets and cellular lipid metabolism. Annu Rev Biochem 81: 687-714, 2012.
141. Hermo L, Pelletier RM, Cyr DG and Smith CE: Surfing the wave, cycle, life history, and genes/proteins expressed by testicular germ cells. Part 1: Background to spermatogenesis, spermatogonia, and spermatocytes. Microsc Res Tech 73: 241-278, 2010.
142. Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM and Czaja MJ: Autophagy regulates lipid metabolism. Nature 458: 1131-1135, 2009.
143. Rato L, Alves MG, Socorro S, Duarte AI, Cavaco JE and Oliveira PF: Metabolic regulation is important for spermatogenesis. Nat Rev Urol 9: 330-338, 2012.
144. Regueira M, Riera MF, Galardo MN, Camberos Mdel C, Pellizzari EH, Cigorraga SB and Meroni SB: FSH and bFGF regulate the expression of genes involved in Sertoli cell energetic metabolism. Gen Comp Endocrinol 222: 124-133, 2015.
145. Shi JF, Li YK, Ren K, Xie YJ, Yin WD and Mo ZC: Characterization of cholesterol metabolism in Sertoli cells and spermatogenesis (Review). Mol Med Rep 17: 705-713, 2018.
146. Guma FC, Wagner M, Martini LH and Bernard EA: Effect of FSH and insulin on lipogenesis in cultures of Sertoli cells from immature rats. Braz J Med Biol Res 30: 591-597, 1997.
147. Stocco C: Aromatase expression in the ovary: hormonal and molecular regulation. Steroids 73: 473-487, 2008.
148. Kraemer FB and Shen WJ: Hormone-sensitive lipase: control of intracellular tri-(di-)acylglycerol and cholesteryl ester hydrolysis. J Lipid Res 43: 1585-1594, 2002.
149. Miller WL and Auchus RJ: The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev 32: 81-151, 2011.
150. Wu LL, Dunning KR, Yang X, Russell DL, Lane M, Norman RJ and Robker RL: High-fat diet causes lipotoxicity responses in cumulus-oocyte complexes and decreased fertilization rates. Endocrinology 151: 5438-5445, 2010.
151. Yuan X, Zhang X, Lin Y, Xie H, Wang Z, Hu X, Hu S, Li L, Liu H, He H, *et al*: Proteome of granulosa cells lipid droplets reveals mechanisms regulating lipid metabolism at hierarchical and pre-hierarchical follicle in goose. Front Vet Sci 12: 1544718, 2025.
152. Ibayashi M and Tsukamoto S: Lipid droplet biogenesis in the ovary. Reprod Med Biol 23: e12618, 2024.
153. Gao S, Gan X, He H, Hu S, Deng Y, Chen X, Li L, Hu J, Li L and Wang J: Dynamic characteristics of lipid metabolism in cultured granulosa cells from geese follicles at different developmental stages. Biosci Rep 39: BSR20192188, 2019.
154. Su YQ, Sugiura K and Eppig JJ: Mouse oocyte control of granulosa cell development and function: Paracrine regulation of cumulus cell metabolism. Semin Reprod Med 27: 32-42, 2009.
155. Kidder GM and Vanderhyden BC: Bidirectional communication between oocytes and follicle cells: Ensuring oocyte developmental competence. Can J Physiol Pharmacol 88: 399-413, 2010.
156. Robker RL, Wu LL and Yang X: Inflammatory pathways linking obesity and ovarian dysfunction. J Reprod Immunol 88: 142-148, 2011.
157. Russell DL and Robker RL: Molecular mechanisms of ovulation: Co-ordination through the cumulus complex. Hum Reprod Update 13: 289-312, 2007.
158. Mau KHT, Karimlou D, Barneda D, Brochard V, Royer C, Leeke B, de Souza RA, Pailles M, Percharde M, Srinivas S, *et al*: Dynamic enlargement and mobilization of lipid droplets in pluripotent cells coordinate morphogenesis during mouse peri-implantation development. Nat Commun 13: 3861, 2022.
159. Kikuchi K, Ekwall H, Tienthai P, Kawai Y, Noguchi J, Kaneko H and Rodriguez-Martinez H: Morphological features of lipid droplet transition during porcine oocyte fertilisation and early embryonic development to blastocyst in vivo and in vitro. Zygote 10: 355-366, 2002.
160. Watanabe T, Thayil A, Jesacher A, Grieve K, Debarre D, Wilson T, Booth M and Srinivas S: Characterisation of the dynamic behaviour of lipid droplets in the early mouse embryo using adaptive harmonic generation microscopy. BMC Cell Biol 11: 38, 2010.
161. Welte MA: As the fat flies: The dynamic lipid droplets of *Drosophila* embryos. Biochim Biophys Acta 1851: 1156-1185, 2015.
162. Li Z, Thiel K, Thul PJ, Beller M, Kuhnlein RP and Welte MA: Lipid droplets control the maternal histone supply of *Drosophila* embryos. Curr Biol 22: 2104-2113, 2012.

163. Crocco MC, Kelmansky DM and Mariano MI: Does serum cause lipid-droplet accumulation in bovine embryos produced in vitro, during developmental days 1 to 4? J Assist Reprod Genet 30: 1377-1388, 2013.
164. Abe H, Yamashita S, Satoh T and Hoshi H: Accumulation of cytoplasmic lipid droplets in bovine embryos and cryotolerance of embryos developed in different culture systems using serum-free or serum-containing media. Mol Reprod Dev 61: 57-66, 2002.
165. van der Weijden VA, Stotzel M, Iyer DP, Fauler B, Gralinska E, Shahraz M, Meierhofer D, Vingron M, Rulands S, Alexandrov T, *et al*: FOXO1-mediated lipid metabolism maintains mammalian embryos in dormancy. Nat Cell Biol 26: 181-193, 2024.
166. Dunning KR, Cashman K, Russell DL, Thompson JG, Norman RJ and Robker RL: Beta-oxidation is essential for mouse oocyte developmental competence and early embryo development. Biol Reprod 83: 909-918, 2010.
167. Herms A, Bosch M, Reddy BJ, Schieber NL, Fajardo A, Rupérez C, Fernández-Vidal A, Ferguson C, Rentero C, Tebar F, *et al*: AMPK activation promotes lipid droplet dispersion on detyrosinated microtubules to increase mitochondrial fatty acid oxidation. Nat Commun 6: 7176, 2015.
168. Babayev E and Seli E: Oocyte mitochondrial function and reproduction. Curr Opin Obstet Gynecol 27: 175-181, 2015.
169. May-Panloup P, Boucret L, Chao de la Barca JM, Desquiret-Dumas V, Ferré-L'Hotellier V, Morinière C, Descamps P, Procaccio V and Reynier P: Ovarian ageing: The role of mitochondria in oocytes and follicles. Hum Reprod Update 22: 725-743, 2016.
170. Steinhauser CB, Askelson K, Lambo CA, Hobbs KC, Bazer FW and Satterfield MC: Lipid metabolism is altered in maternal, placental, and fetal tissues of ewes with small for gestational age fetusesdagger. Biol Reprod 104: 170-180, 2021.
171. Wu LL, Russell DL, Wong SL, Chen M, Tsai TS, St John JC, Norman RJ, Febbraio MA, Carroll J and Robker RL: Mitochondrial dysfunction in oocytes of obese mothers: Transmission to offspring and reversal by pharmacological endoplasmic reticulum stress inhibitors. Development 142: 681-691, 2015.
172. Naowarojna N, Wu TW, Pan Z, Li M, Han JR and Zou Y: Dynamic regulation of ferroptosis by lipid metabolism. Antioxid Redox Signal 39: 59-78, 2023.
173. Motamedi S, Ravoet N, Dehairs J, Vanderhoydonc F, Escamilla-Ayala A, Sliwinska MA, Wang S, Idkowiak J, Soenen S, Agostinis P, *et al*: AMP-activated protein kinase-driven lipid droplet dynamics govern melanoma sensitivity to polyunsaturated fatty acid and iron-induced ferroptosis. Nat Commun 16: 11252, 2025.
174. Lange M, Wolk M, Li VW, Doubravsky CE, Hendricks JM, Kato S, Otoki Y, Styler B, Johnson SL, Harris CA, *et al*: FSP1-mediated lipid droplet quality control prevents neutral lipid peroxidation and ferroptosis. Nat Cell Biol 27: 1902-1913, 2025.
175. Danielli M, Perne L, Jarc Jovicic E and Petan T: Lipid droplets and polyunsaturated fatty acid trafficking: Balancing life and death. Front Cell Dev Biol 11: 1104725, 2023.
176. Lee H, Horbath A, Kondiparthi L, Meena JK, Lei G, Dasgupta S, Liu X, Zhuang L, Koppula P, Li M, *et al*: Cell cycle arrest induces lipid droplet formation and confers ferroptosis resistance. Nat Commun 15: 79, 2024.
177. Obaseki E, Adebayo D, Bandyopadhyay S and Hariri H: Lipid droplets and fatty acid-induced lipotoxicity: In a nutshell. FEBS Lett 598: 1207-1214, 2024.
178. Chen Z, Ho IL, Soeung M, Yen EY, Liu J, Yan L, Rose JL, Srinivasan S, Jiang S, Edward Chang Q, *et al*: Ether phospholipids are required for mitochondrial reactive oxygen species homeostasis. Nat Commun 14: 2194, 2023.
179. Virmani A, Pinto L, Bauermann O, Zerelli S, Diedenhofen A, Binienda ZK, Ali SF and van der Leij FR: The carnitine palmitoyl transferase (CPT) system and possible relevance for neuropsychiatric and neurological conditions. Mol Neurobiol 52: 826-836, 2015.
180. Qu Q, Zeng F, Liu X, Wang QJ and Deng F: Fatty acid oxidation and carnitine palmitoyltransferase I: Emerging therapeutic targets in cancer. Cell Death Dis 7: e2226, 2016.
181. De Paula IF, Santos-Araujo S, Majerowicz D, Ramos I and Gondim KC: Knockdown of carnitine palmitoyltransferase I (CPT1) reduces fat body lipid mobilization and resistance to starvation in the insect vector Rhodnius prolixus. Front Physiol 14: 1201670, 2023.
182. Choi J, Smith DM, Scafidi S, Riddle RC and Wolfgang MJ: Carnitine palmitoyltransferase 1 facilitates fatty acid oxidation in a non-cell-autonomous manner. Cell Rep 43: 115006, 2024.
183. Dissanayake LV, Smith BA, Zietara A, Levchenko V, Lowe M, Kravtsova O, Shapiro A, Upadhyay G, Halade GV, Geurts AM, *et al*: The role of carnitine palmitoyl transferase 2 in the progression of salt-sensitive hypertension. Am J Physiol Cell Physiol 329: C1188-C1202, 2025.
184. Xiang F, Zhang Z, Xie J, Xiong S, Yang C, Liao D, Xia B and Lin L: Comprehensive review of the expanding roles of the carnitine pool in metabolic physiology: Beyond fatty acid oxidation. J Transl Med 23: 324, 2025.
185. Liang K: Mitochondrial CPT1A: Insights into structure, function, and basis for drug development. Front Pharmacol 14: 1160440, 2023.
186. Knottnerus SJG, Bleeker JC, Wust RCI, Ferdinandusse S, IJlst L, Wijburg FA, Wanders RJA, Visser G and Houtkooper RH: Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuttle. Rev Endocr Metab Disord 19: 93-106, 2018.
187. Reader KL, Cox NR, Stanton JA and Juengel JL: Effects of acetyl-L-carnitine on lamb oocyte blastocyst rate, ultrastructure, and mitochondrial DNA copy number. Theriogenology 83: 1484-1492, 2015.
188. Knitlova D, Hulinska P, Jeseta M, Hanzalova K, Kempisty B and Machatkova M: Supplementation of l-carnitine during in vitro maturation improves embryo development from less competent bovine oocytes. Theriogenology 102: 16-22, 2017.
189. Kilwein MD, Dao TK and Welte MA: *Drosophila* embryos allocate lipid droplets to specific lineages to ensure punctual development and redox homeostasis. PLoS Genet 19: e1010875, 2023.
190. Bailey AP, Koster G, Guillermier C, Hirst EM, MacRae JI, Lechene CP, Postle AD and Gould AP: Antioxidant role for lipid droplets in a stem cell niche of *Drosophila*. Cell 163: 340-353, 2015.
191. Kim K, Park S and Roh S: Lipid-rich blastomeres in the two-cell stage of porcine parthenotes show bias toward contributing to the embryonic part. Anim Reprod Sci 130: 91-98, 2012.
192. Zhang J, Khvorostov I, Hong JS, Oktay Y, Vergnes L, Nuebel E, Wahjudi PN, Setoguchi K, Wang G, Do A, *et al*: UCP2 regulates energy metabolism and differentiation potential of human pluripotent stem cells. EMBO J 30: 4860-4873, 2011.
193. Folmes CD, Nelson TJ, Martinez-Fernandez A, Arrell DK, Lindor JZ, Dzeja PP, Ikeda Y, Perez-Terzic C and Terzic A: Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. Cell Metab 14: 264-271, 2011.
194. Yanes O, Clark J, Wong DM, Patti GJ, Sánchez-Ruiz A, Benton HP, Trauger SA, Desponts C, Ding S and Siuzdak G: Metabolic oxidation regulates embryonic stem cell differentiation. Nat Chem Biol 6: 411-417, 2010.
195. Shiraki N, Shiraki Y, Tsuyama T, Obata F, Miura M, Nagae G, Aburatani H, Kume K, Endo F and Kume S: Methionine metabolism regulates maintenance and differentiation of human pluripotent stem cells. Cell Metab 19: 780-794, 2014.
196. Dunning KR, Anastasi MR, Zhang VJ, Russell DL and Robker RL: Regulation of fatty acid oxidation in mouse cumulus-oocyte complexes during maturation and modulation by PPAR agonists. PLoS One 9: e87327, 2014.
197. Brasaemle DL: Thematic review series: Adipocyte biology. The perilipin family of structural lipid droplet proteins: Stabilization of lipid droplets and control of lipolysis. J Lipid Res 48: 2547-2559, 2007.
198. Horton JD, Goldstein JL and Brown MS: SREBPs: Activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest 109: 1125-1131, 2002.
199. Fan W and Evans R: PPARs and ERRs: Molecular mediators of mitochondrial metabolism. Curr Opin Cell Biol 33: 49-54, 2015.
200. Sayers NS, Anujan P, Yu HN, Palmer SS, Nautiyal J, Franks S and Hanyaloglu AC: Follicle-stimulating hormone induces lipid droplets via Galphai/o and β-Arrestin in an endometrial cancer cell line. Front Endocrinol (Lausanne) 12: 798866, 2021.
201. Igosheva N, Abramov AY, Poston L, Eckert JJ, Fleming TP, Duchen MR and McConnell J: Maternal diet-induced obesity alters mitochondrial activity and redox status in mouse oocytes and zygotes. PLoS One 5: e10074, 2010.
202. Shen WJ, Patel S, Natu V, Hong R, Wang J, Azhar S and Kraemer FB: Interaction of hormone-sensitive lipase with steroidogenic acute regulatory protein: Facilitation of cholesterol transfer in adrenal. J Biol Chem 278: 43870-43876, 2003.

203. Ludovic, Le, Corre, *et al*: Bisphenol A disrupts the intestinal lipid metabolism. Toxicology Letters 211: S210, 2012.
204. Vit FF, Sangalli JR, Fiorenza MF, de Almeida Saraiva HFR, Ferst JG, Perecin F, Meirelles FV, de la Torre LG and da Silveira JC: Dynamic microdevice culture during bovine oocyte maturation decreases lipid accumulation and improve blastocyst cell numbers. Sci Rep 16: 232, 2025.
205. Zhu J, Lam SM, Yang L, Liang J, Ding M, Shui G and Huang X: Reduced phosphatidylcholine synthesis suppresses the embryonic lethality of seipin deficiency. Life Metab 1: 175-189, 2022.
206. Dumesic DA, Padmanabhan V and Abbott DH: Polycystic ovary syndrome and oocyte developmental competence. Obstet Gynecol Surv 63: 39-48, 2008.
207. Sturmey RG and Leese HJ: Energy metabolism in pig oocytes and early embryos. Reproduction 126: 197-204, 2003.
208. Horn PJ, Ledbetter NR, James CN, Hoffman WD, Case CR, Verbeck GF and Chapman KD: Visualization of lipid droplet composition by direct organelle mass spectrometry. J Biol Chem 286: 3298-3306, 2011.
209. Ding Y, Jiang Y, Zhu M, Zhu Q, He Y, Lu Y, Wang Y, Qi J, Feng Y, Huang R, *et al*: Follicular fluid lipidomic profiling reveals potential biomarkers of polycystic ovary syndrome: A pilot study. Front Endocrinol (Lausanne) 13: 960274, 2022.
210. Zhang M, Wang Y, Di J, Zhang X, Liu Y, Zhang Y, Li B, Qi S, Cao X, Liu L, *et al*: High coverage of targeted lipidomics revealed lipid changes in the follicular fluid of patients with insulin-resistant polycystic ovary syndrome and a positive correlation between plasmalogens and oocyte quality. Front Endocrinol (Lausanne) 15: 1414289, 2024.
211. Ruebel ML, Piccolo BD, Mercer KE, Pack L, Moutos D, Shankar K and Andres A: Obesity leads to distinct metabolomic signatures in follicular fluid of women undergoing in vitro fertilization. Am J Physiol Endocrinol Metab 316: E383-E396, 2019.
212. Gao J, Liu M, Liu J, Shi P, Cui H, Zhao S, Zhang X and Tao C: Effect of high-fat diet on the lipid profile of ovarian granulosa cells and female reproduction in mice. PLoS One 18: e0287534, 2023.
213. Cao Z, Hao Y, Fung CW, Lee YY, Wang P, Li X, Xie K, Lam WJ, Qiu Y, Tang BZ, *et al*: Dietary fatty acids promote lipid droplet diversity through seipin enrichment in an ER subdomain. Nat Commun 10: 2902, 2019.
214. Schmiedel JM, Klemm SL, Zheng Y, Sahay A, Blüthgen N, Marks DS and van Oudenaarden A: Gene expression. MicroRNA control of protein expression noise. Science 348: 128-132, 2015.
215. Mak HY: Lipid droplets as fat storage organelles in Caenorhabditis elegans: Thematic review series: Lipid droplet synthesis and metabolism: From Yeast To Man. J Lipid Res 53: 28-33, 2012.
216. Kumari RM, Khatri A, Chaudhary R and Choudhary V: Concept of lipid droplet biogenesis. Eur J Cell Biol 102: 151362, 2023.
217. Meister P, Towbin BD, Pike BL, Ponti A and Gasser SM: The spatial dynamics of tissue-specific promoters during C. elegans development. Genes Dev 24: 766-782, 2010.
218. Frezal L and Felix MA: C. elegans outside the Petri dish. Elife 4: e05849, 2015.
219. Schmokel V, Memar N, Wiekenberg A, Trotzmuller M, Schnabel R and Doring F: Genetics of lipid-storage management in caenorhabditis elegans embryos. Genetics 202: 1071-1083, 2016.
220. Vrablik TL, Petyuk VA, Larson EM, Smith RD and Watts JL: Lipidomic and proteomic analysis of Caenorhabditis elegans lipid droplets and identification of ACS-4 as a lipid droplet-associated protein. Biochim Biophys Acta 1851: 1337-1345, 2015.
221. Liu Y, Xu S, Zhang C, Zhu X, Hammad MA, Zhang X, Christian M, Zhang H and Liu P: Hydroxysteroid dehydrogenase family proteins on lipid droplets through bacteria, C. elegans, and mammals. Biochim Biophys Acta Mol Cell Biol Lipids 1863: 881-894, 2018.
222. Mondal M, Scifo E, Ciliberti RE, Wischhof L, Abbariki TN, Jackson J, Menegatou IM, Zeisler-Diehl V, Riemer J, Jussila B, *et al*: Dietary lipid content modifies wah-1/AIFM1-associated phenotypes via LRK-1 and DRP-1 expression in C. elegans. Nat Commun 16: 10817, 2025.
223. Campbell D and Zuryn S: The mechanisms and roles of mitochondrial dynamics in C. elegans. Semin Cell Dev Biol 156: 266-275, 2024.
224. Mullaney BC and Ashrafi K: C. elegans fat storage and metabolic regulation. Biochim Biophys Acta 1791: 474-478, 2009.
225. Lynn DA, Dalton HM, Sowa JN, Wang MC, Soukas AA and Curran SP: Omega-3 and -6 fatty acids allocate somatic and germline lipids to ensure fitness during nutrient and oxidative stress in Caenorhabditis elegans. Proc Natl Acad Sci USA 112: 15378-15383, 2015.
226. Li Q, Zhou X, Zhang X, Zhang C and Zhang SO: Nuclear receptor signaling regulates compartmentalized phosphatidylcholine remodeling to facilitate thermosensitive lipid droplet fusion. Nat Commun 16: 3955, 2025.