Stem Cells and Cloning: Advances and Applications

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REVIEW

# The Mammalian Oocyte: A Central Hub for Cellular Reprogramming and Stemness

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**Abstract:** The mammalian oocyte is pivotal in reproductive biology, acting as a central hub for cellular reprogramming and stemness. It uniquely contributes half of the zygotic nuclear genome and the entirety of the mitochondrial genome, ensuring individual development and health. Oocyte-mediated reprogramming, exemplified by nuclear transfer, resets somatic cell identity to achieve pluripotency and has transformative potential in regenerative medicine. This process is critical for understanding cellular differentiation, improving assisted reproductive technologies, and advancing cloning and stem cell research. During fertilization, the maternal-zygotic transition shifts developmental control from maternal factors to zygotic genome activation, establishing totipotency. Oocytes also harbor reprogramming factors that guide nuclear remodeling, epigenetic modifications, and metabolic reprogramming, enabling early embryogenesis. Structures like mitochondria, lipid droplets, and cytoplasmic lattices contribute to energy production, molecular regulation, and cellular organization. Recent insights into oocyte components, such as ooplasmic nanovesicles and endolysosomal vesicular assemblies (ELVAS), highlight their roles in maintaining cellular homeostasis, protein synthesis, and reprogramming efficiency. By unraveling the reprogramming mechanisms inherent in oocytes, we advance our understanding of cloning, cell differentiation, and stem cell therapy, highlighting their valuable significance in developmental biology and regenerative medicine.
**Keywords:** reprogramming, oocytes, genome activation, epigenetics

## Introduction

Cellular reprogramming represents a cornerstone in developmental biology and regenerative medicine, offering profound insights into the processes that govern cell identity and fate.[1] Totipotency and pluripotency are central concepts in this field, defining the developmental potential of cells. Totipotency refers to the capacity of a single cell, such as a zygote or a blastomere, to develop into an entire organism, including both embryonic and extraembryonic tissues.[2] Pluripotency, on the other hand, denotes the ability of cells to differentiate into all three germ layers but excludes the potential to form extraembryonic structures, such as placenta.[3] These fundamental states underpin the remarkable ability of oocytes to reprogram somatic nuclei and restore developmental potential, positioning them as unparalleled models for understanding cellular differentiation and plasticity.[4]

Understanding the feasibility and functional capacity of the mammalian oocytes is crucial, as it plays a fundamental role in ensuring successful fertilization and subsequent normal embryonic development. Gaining insight into oocyte quality, maturation processes, and their ability to support the complex molecular and cellular events required for the formation of a viable embryo is essential for advancing reproductive biology and improving assisted reproductive technologies. The mammalian oocyte, with its intrinsic reprogramming machinery, plays a pivotal role in achieving totipotency and pluripotency. This is exemplified by somatic cell nuclear transfer (SCNT), a process that reprograms a differentiated nucleus into a totipotent state within the oocyte cytoplasm. SCNT has been applied to generate several mammalian species such as sheep,[1] dogs,[5] pigs,[6] monkeys,[7] and buffalos,[8] as well as to generate human embryonic stem

Received: 7 January 2025
Accepted: 13 February 2025
Published: 18 February 2025

cells.[9] In SCNT, the nucleus of a somatic cell is transferred into an enucleated oocyte (an oocyte with its nucleus removed). The oocyte's cytoplasm contains a unique molecular environment rich in reprogramming factors, such as transcription factors, histone-modifying enzymes, and RNA molecules. These factors work together to erase the somatic epigenetic marks from the transferred nucleus and re-establish a totipotent or pluripotent state. This reprogramming process involves resetting DNA methylation patterns, chromatin remodeling, and reactivating genes critical for early embryonic development (Figure 1). Even though the reprogramming machinery in oocytes is superior for generating totipotency, the work to generate induced totipotent or pluripotent stem cells requires additional tuning to increase the efficiency and safety of unwanted cell behaviors such as tumor formation.[10–13] Therefore, simulating what happens during the oocyte reprogramming machinery would pave the way for induced totipotency and pluripotency.[14] This extraordinary reprogramming capacity of the oocyte underpins the success of cloning experiments, such as the birth of "Dolly the sheep[1]" and provides invaluable insights into cellular plasticity, epigenetics, and developmental biology. Understanding the mechanisms driving this reprogramming, erasure of somatic epigenetic marks, and re-establishing embryonic gene expression programs, oocytes offer transformative potential for therapeutic applications such as the generation of patient-specific stem cells and the study of early embryonic development. Furthermore, the maternal-zygotic transition (MZT) during fertilization, wherein developmental control shifts from maternally deposited factors to the zygotic genome, underscores the oocyte's critical role in initiating and sustaining early development. This prospect has important medical promise for affected patients with degenerative human diseases. However, progress toward this goal has been slowed by legal and social considerations.[15]

Despite these advances, significant gaps remain in our understanding of oocyte reprogramming mechanisms. For instance, the molecular events driving epigenetic remodeling—such as DNA demethylation, histone modifications, and chromatin reorganization—are not yet fully elucidated. Similarly, the metabolic shifts and the role of oocyte-specific factors, including maternal mRNAs, proteins, and vesicles like intra-ooplasmic nanovesicles and endolysosomal assemblies, require further investigation. Addressing these gaps is crucial for enhancing the efficiency of reprogramming techniques and advancing therapeutic cloning and regenerative medicine. In addition, the low efficiency of SCNT, the risk of aberrant reprogramming leading to developmental anomalies, and societal concerns about cloning underscore the need for comprehensive research. Furthermore, the variability in reprogramming efficiency across species highlights the importance of species-specific studies to refine existing models and approaches.[16,17]

This review aims to provide an in-depth analysis of the critical components of the oocyte and their roles in reprogramming and early embryogenesis. By synthesizing current knowledge, we seek to identify the unfilled gaps in

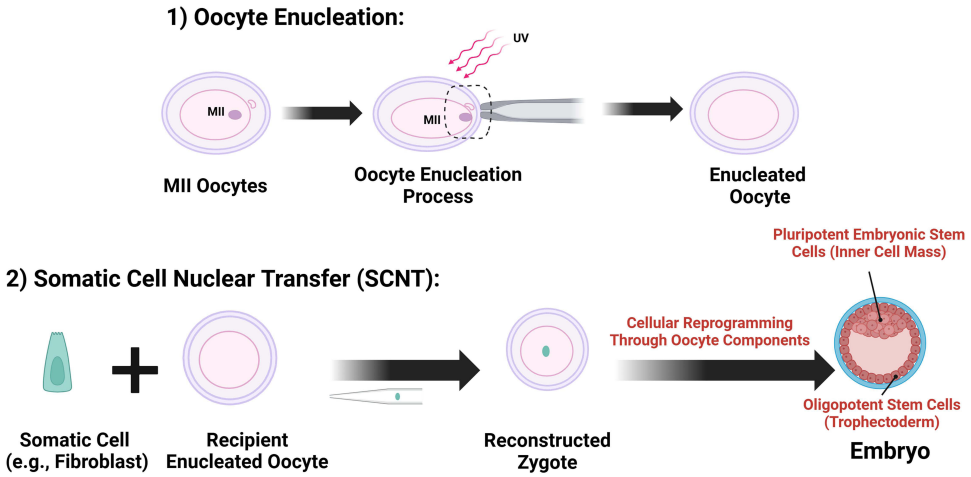


**Figure 1** Oocyte Enucleation and Somatic Cell Nuclear Transfer (SCNT). This illustration outlines the procedure for generating embryonic stem cells via oocyte enucleation and SCNT. (1) Oocyte Enucleation: Mature metaphase II (MII) oocytes are transiently exposed to UV light to aspirate the MII plate. (2) Somatic cell fusion: An enucleated oocyte is combined with a donor cell (eg, a fibroblast) nucleus through a precise fusion process. (3) Artificial Activation: The reconstituted oocyte, now containing the somatic nucleus, is activated using specific transcription factors, initiating the reprogramming process. (4) Embryonic Stem Cell Formation: This reprogramming leads to the development of embryonic stem cells, which can further differentiate into an embryo. This technique demonstrates the potential of SCNT in generating pluripotent cells for research and therapeutic purposes.

oocyte reprogramming machinery and propose future directions for research. A deeper understanding of these processes will not only enhance our ability to harness the reprogramming power of oocytes but also pave the way for novel applications in reproductive and regenerative medicine.

## Reprogramming Concepts

The concept of cell reprogramming in germ cells refers to the unique ability of the oocyte to reset the identity of a differentiated somatic cell nucleus, restoring its pluripotency and enabling it to develop into a complete organism. Oocytes provide 50% and 100% of the nuclear and mitochondrial genomes of the embryo, respectively.[18] The reprogramming of sperm and oocyte genomes is a highly orchestrated process essential for the formation of a totipotent zygote. Upon fertilization, the paternal genome delivered by the sperm undergoes protamine-histone exchange and extensive epigenetic remodeling to integrate with the maternal genome. Simultaneously, the maternal oocyte cytoplasm provides essential reprogramming factors, including transcriptional activators and chromatin remodelers, that reset both parental genomes to a totipotent state. After fertilization, a process called the maternal-zygotic transition (MZT) or oocyte-to-embryo transition occurs, during which control of cellular development shifts from the oocyte to the zygote. This reprogramming involves the erasure and re-establishment of epigenetic makeup of DNA methylation and histone modifications, allowing the zygotic genome to initiate transcriptional activity.[19] The coordinated activation of maternal-zygotic transition further ensures the shift from maternal mRNA and protein reliance to the autonomous control of embryonic development by the newly formed zygotic genome. This process activates totipotency and initiates early embryogenesis which transitions the full transcriptional activation of the zygotic genome, early embryogenesis, and the development of all cell lineages.[20] Pluripotent stem cells have been successfully isolated from all stages of preimplantation embryos, across many mammalian species, including primates. These cells typical of primate embryonic stem cells. Notably, these cells exhibit normal karyotypes, elevated telomerase activity, express surface markers, and maintained their developmental potential even after proliferating in an undifferentiated state for 4 to 5 months in vitro, demonstrating the capacity to form trophoblasts and derivatives of all three embryonic germ layers: endoderm, mesoderm, and ectoderm.[21]

## Reprogramming Mechanisms

Reprogramming factors in oocytes are crucial in the field of regenerative medicine and developmental biology. Oocytes in general have a unique power to reprogram somatic cells into pluripotent cells. The matter enables their use in cloning, cell differentiation, and stem cell therapy. Herein, different mechanisms for reprogramming occur in the oocyte:[18]

### Nuclear Reprogramming

Nuclear reprogramming of oocytes is a cutting-edge area in regenerative medicine and reproductive biology. It involves the genetic modification of oocytes to promote its developmental potential. The matter has huge applications in the fields of infertility treatment, cloning, and regenerative medicine. Cellular reprogramming is mediated by intra-ooplasmic components of mature oocytes.[22] The induction of pluripotent stem cells is based mainly on many maternal transcription factors that promote totipotency.[23] During spermiogenesis, the paternal genome undergoes a significant transformation where histones, the proteins that help package DNA, are largely replaced by protamines.[24] This exchange is crucial for the condensation of the genetic material into a compact form necessary for sperm formation. However, upon fertilization, this process is rapidly and powerfully reversed.[25]

The histones are reintroduced to the paternal genome, a key step that is essential for reprogramming the parental genome and activating the zygote's developmental processes.[26] A splicing kinase SRPK1 proceeds this event by catalyzing site-specific phosphorylation of protamine, the way that triggers the protamine-to-histone exchange[27] (Figure 2). It was approved that human metaphase II oocyte extract cultured with mesenchymal stromal cells was able to induce genetic programming of stromal cells into embryonic phenotypic cells.[28]

Furthermore, H3.3 is involved in the establishment and maintenance of open chromatin states that are essential for the activation of pluripotency-associated genes.[29] Unlike canonical histones, H3.3 is incorporated into chromatin throughout the cell cycle, particularly during transcriptional activation and developmental transitions. This dynamic incorporation

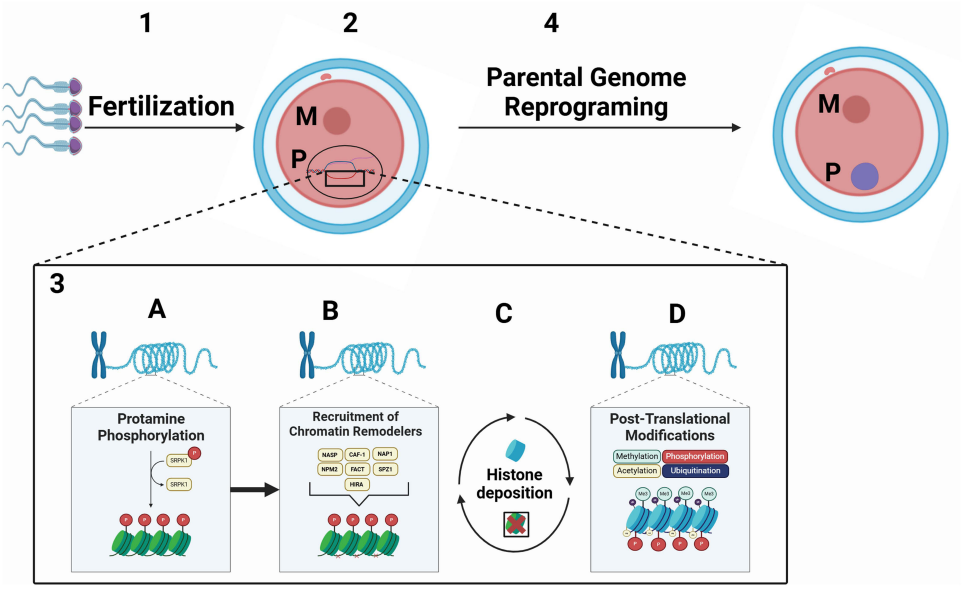


**Figure 2** SRPK1-Mediated Protamine Phosphorylation and Histone Exchange During Parental Genome Reprogramming. 1) Fertilization: The schematic begins with the fertilization process, where spermatozoa deliver paternal genetic material (**P**) to the oocyte. 2) Pronuclear Formation: Following fertilization, the zygote displays both maternal (**M**) and paternal (**P**) pronuclei, indicating the presence of both parental genomes. 3) SRPK1-Catalyzed Protamine Phosphorylation and Protamine-to-Histone Exchange: Panel A illustrates the activity of the splicing kinase SRPK1, which catalyzes the site-specific phosphorylation of protamine molecules within the paternal chromatin. This phosphorylation event is critical for initiating the chromatin remodeling process necessary for subsequent histone incorporation. The role of chromatin remodelers like NASP, NPM2, CAF-1, FACT, and HIRA in facilitating protamine removal and histone deposition is illustrated in Panel B. This is combined with sequential progression from protamine phosphorylation by SRPK1 to histone deposition as in Panel C. Post-translational modifications (PTMs) such as methylation (Me), acetylation (Ac), phosphorylation (**P**), and ubiquitination (Ub) are shown in Panel D. 4) Parental Genome Reprogramming: The final stage depicts the reprogramming of the paternal genome, now organized with histones, enabling the activation of embryonic gene expression and the initiation of developmental processes.

facilitates the remodeling of chromatin architecture, which is critical for cellular identity changes. By promoting an open chromatin environment, H3.3 enhances the plasticity of somatic cells, enabling them to acquire pluripotency or adopt alternative cell fates.[30]

In SCNT, H3.3 plays a crucial role in nuclear reprogramming. During the transfer of somatic cell nuclei into enucleated oocytes, H3.3 aids in the rapid re-establishment of a chromatin landscape that supports embryonic development. The incorporation of H3.3 into the transferred somatic cell nucleus is essential for the activation of embryonic genes and the silencing of somatic cell-specific genes, thus promoting the successful reprogramming of the nucleus. The proper deposition of H3.3 at key genomic loci is critical for ensuring the developmental competence of the reconstructed nucleus. By facilitating the conversion of a somatic nucleus into a totipotent state, H3.3 is instrumental in enabling the oocyte to support embryonic development and the subsequent stages of growth.[31,32] Overall, histone variant H3.3's unique ability to be incorporated into chromatin throughout the cell cycle, its role in establishing and maintaining an open chromatin configuration, and its involvement in epigenetic reprogramming make it a key factor in both cell reprogramming and SCNT. Its dynamic action on chromatin remodeling is fundamental to cellular plasticity, the activation of pluripotency, and the successful reprogramming of somatic cells.[33]

The genetic reprogramming methods used to reset histone modifications[34] serve as a crucial tool for generating pluripotent stem cells. These methods typically involve the use of transcription factors such as Oct4, Sox2, Klf4, c-Myc, Nanog, and others,[35,36] which are employed to generate induced pluripotent stem cells (iPSCs).[14] This mechanism is conserved across different species, despite variations in homology with human transcription factors (Table 1), and exhibits notable species-specific differences (Supplementary Figure 1). For example, Nanog in rats shares 84.4% homology with the mouse counterpart but shows less than 50% homology with the human version.[37,38] Paradoxically, Nanog was found to be unnecessary for generating mouse iPSCs.[39]

In the last decade, CRISPR/Cas9, a genome editing technology, was applied as a tool for the genetic reprogramming of oocytes because it allows precise alterations of DNA sequences within oocytes for targeted genetic reprogramming. CRISPR/Cas9 system was used to generate semi-cloned mice carrying multiple genetic modifications, as well as in

**Table 1** BLAST Comparison Between Homology of the Major Transcription Factors in Human and the Other Species

| Scientific Name | Common Name | Oct4 homology % | KLF4 homology % | Sox2 homology % | c-MYC Homology % | Nanog Homology % |
|---|---|---|---|---|---|---|
| Homo sapiens | Human | 100 | 100 | 100 | 100 | 100 |
| Pan troglodytes | Chimpanzee | 99.93 | 99.35 | 99.25 | 99.71 | 99.19 |
| Macaca mulatta | Rhesus monkey | 98.15 | 97.06 | 97.29 | 97.88 | 94.86 |
| Sus scrofa | Pig | 89.32 | 91.79 | 94.38 | 88.81 | 81.93 |
| Bos taurus | Domestic cattle | 89.3 | 88.74 | 94.72 | 86.11 | 78.86 |
| Mus musculus | House mouse | 82.5 | 85.67 | 88.71 | 82.16 | 75.36 |
| Oryctolagus cuniculus | Rabbit | 85.57 | 89.77 | 91.88 | 91.69 | 78.44 |
| Rattus norvegicus | Norway rat | 82.54 | 86.22 | 88.45 | 81.94 | NA |

**Abbreviations**: NA, Negligible homology percentage; Oct4, Octamer-binding transcription factor 4; KLF4, Krüppel-like factor 4; SOX2, SRY-Box Transcription Factor 2; c-MYC, Cellular myelocytomatosis oncogene.

mutagenic screening.[40] This system was involved also in the production of mammalian haploid embryonic stem cells.[41] Also, it was involved in the production of genetically engineered sheep and goats.[42]

Another tool to regulate gene expression during oocyte reprogramming is induced by targeting MicroRNAs (miRNAs). Editing of miRNA precursors may lead to elimination of the selected miRNA and overall reprogramming of miRNA activity the matter which affects the development of preimplanted embryos.[43] Their role in maternal-to-zygotic reprogramming and promoting pluripotency has been established since 2010.[44] The miRNA processing machinery has been involved in the growth and maturation of mammalian oocytes, early development of embryos, stem cell implantation, and differentiation.[45] A few years ago, miRNAs were elucidated to play a pivotal role in the development and reprogramming of human oocytes through activation of their expression in oocytes.[46] bta-miR-183 for example significantly improved the SCNT embryos in terms of cleavage, blastocyst formation, apoptotic index, and trophoblast ratio.[47] miR-449b derived from sperms has been approved to influence epigenetic reprogramming of SCNT embryos in bovine.[48] On the other way, inhibition of miR-145 enhances blastocyst formation rate in bovine.[49] While overexpression of miR-29b improves quality of blastocyst derived SCNT in cattle through decreasing the expression of DNA Methyltransferases.[50]

## Epigenetic Reprogramming

After nuclear transfer of somatic nuclei, histone acetylation is very important for the process of its reprogramming, it has been demonstrated that hyperacetylation of histones at this stage is more important than their deacetylation moreover, hyperacetylation is the main factor for epigenetic reprogramming of somatic nuclei.[51] Oocytes have a great capacity for epigenetic reprogramming. They can facilitate the remodeling and modification of epigenetic markers, such as DNA methylation and histone modifications. Many tools are involved in the epigenetic reprogramming of oocytes like TET enzymes, Histone Deacetylases (HDACs), and DNA methyltransferase.[52] TET Enzymes (Ten-Eleven Translocation) enzymes consisting of oocytes catalyze the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, playing a pivotal role in DNA demethylation and facilitating cell reprogramming and embryonic genome activation.[53] A recent study approved that the auto-suppression of TET dioxygenases could protect mouse oocytes from demethylation matter which confirms the role of these enzymes in the methylome reprogramming of oocytes.[54] TET methylcytosine dioxygenase activation is approved to be involved also in the female germ cell development and zygote genome reprogramming leading to elongation of the female reproductive period.[55] Finally, methylation and demethylation dynamics during oocyte growth played a crucial role in the development of embryos, zygote reprogramming, and improved the overall events that will present the embryos' epigenome.[56–58]

On the other hand, Histone Deacetylases (HDACs) play a pivotal role in the epigenetic reprogramming of oocytes, it was approved that inhibition of HDACs produced a significant improvement in the quality of blastocysts,[59] promoted DNA double strands break repair and so increased the development of SCNT embryos,[60] and affected germ cell specification reprogramming.[61] HDAC6 inhibitors, for example, enhanced the cleavage of blastocyst of nuclear transfer embryos in pigs, this means that HDAC6 restricted the reprogramming of SCNT.[62]

HDAC1/2 contributes to the epigenetic reprogramming of donor nuclei. Specifically, HDAC1/2 is implicated in the removal of donor cell-specific epigenetic marks, facilitating the re-establishment of a totipotent state that is critical for embryonic development. Studies have shown that the inhibition of HDAC activity can improve reprogramming efficiency during SCNT.[63] For instance, HDAC inhibitors like trichostatin A (TSA) and scriptaid enhance developmental outcomes by relaxing chromatin structure, allowing for the activation of genes essential for early embryonic development.[64] In porcine SCNT, scriptaid has been observed to increase blastocyst formation rates and the total number of cells in blastocysts, likely by downregulating HDAC2 expression, which modulates chromatin remodeling and transcription activation. These findings highlight HDAC1/2 as critical targets for improving cloning efficiency. Modulating their activity through inhibitors not only facilitates nuclear reprogramming but also improves developmental competence, making them essential for advancing animal cloning and therapeutic applications.[65,66]

Recently another process known as histone lactylation has emerged as a novel epigenetic modification involved in the regulation of multiple cellular processes. It is approved also to be changed dynamically during embryogenesis in mice, lactylation could be induced by 10 mm of sodium lactate this amount can impact the transcription of the glycolytic gene revealing an improve in oocyte maturation and embryo quality.[67]

## Metabolic Reprogramming

It is well-known that the oocyte is a highly specialized cell. It undergoes metabolic reprogramming to support its need for energy and biosynthetic molecules, which are crucial for its maturation, fertilization as well as embryo development. These metabolic pathways are regulated distinctly from those in somatic cells to balance energy needs and biomolecule synthesis for cellular maintenance and formation of a new organism.[68]

### Glycolysis and Oxidative Phosphorylation

There is a continuous interplay between glycolysis and oxidative phosphorylation (OXPH) in oocytes during their maturation. OXPH is the primary source for ATP production which is needed for spindle formation, chromatin organization, and cytokinesis during meiosis. Herein the mitochondrial DNA copies are noticed to be increased. On the other hand, glycolysis also becomes active during oocyte maturation, providing very important intermediates essential for nucleotide and lipids formation which by the way are important in oocyte maturation and embryogenesis. Glycolysis in general is important around the cumulus as it supplies oocytes by lactate and pyruvate the two products are very important to maintain mitochondrial functions.[69] Studies approved the association of mitochondrial energy metabolism (OXPH) and cell plasticity and embryonic development.[70] Phosphoglycerate mutase as a member of glycolytic enzymes has to maintain oocyte quality via mitochondrial dynamic rearrangement.[71] Moreover, shifting the metabolism towards glycolysis in oocytes improves the efficiency of SCNT and the survival of embryos.[72]

### Lipids Metabolism

Oocyte depends on lipids metabolism for ATP production particularly when nutrient supply is deficient. Lipids stored in the form of droplets in the cytoplasm are mobilized to mitochondria for energy production through $\beta - oxidation$. Inhibition of $\beta - oxidation$. has been shown to impair oocyte maturation and embryo development.[73,74] Now, there are several studies approve the great link between lipid metabolism and oocyte quality in general,[75] and its maturation and embryo development in a special manner.[76] Furthermore, lipids play a crucial role in the synthesis of membrane lipids and other signaling molecules (eg sphingolipids).[77,78] Lipids have been involved in the metabolic reprogramming of oocytes, they improve the pluripotency and reprogramming in procaine.[79] Interestingly, proteomic analysis studies approved the great role of lipids in oocyte metabolic reprogramming.[80]

### Amino Acids Metabolism

Amino acids perform a pivotal role in oocytes, they are the building blocks for proteins, acting as regulatory factors for many signaling pathways, and antioxidant synthesis (eg glutathione) and are involved in redox balance (eg glycine).[81] The metabolic disorders in amino acids metabolism will directly decrease oocyte quality and potentiality.[82] Furthermore, the intrafollicular amino acids concentration directly affects the oocyte maturation, fertilization, and preimplantation development.[83] On the other hand, the enhancement of branched-chain amino acids metabolism improves mitochondrial metabolic processes and so improves age-related reproduction.[84] Amino acids also, have a great role in the energy provision needed for oocyte maturation, early development of embryos,[85] and blastocyst formation.[86] Glutamine for example is abundant in follicular fluid and considered an important source of energy required for oocyte maturation; to increase its stability, glycine-glutamine is replaced by glutamine the matter which reduces its degradation to ammonia and pyrrolidone carboxylic acid and promotes more development of embryos.[87] In addition to their role as biosynthetic and energy-producing molecules as previously mentioned, amino acids also were incorporated in the epigenetic regulation during histone deacetylations and methylations modifications reactions. For instance, histone 3 methylated at Arginine 17 or lysine 27, 4 are pivotal for reprogramming of zygotic paternal genome.[34,88–90] In the same way, Histone 2 deubiquitinating at lysine 119 is an important prerequisite for zygote genome activation.[91] Moreover, acetylation of histone 4 at lysine 16 is an important process for zygotic gene activation.[19,92]

### Oocyte Components

The oocyte cargo and components are critical for embryogenesis development and zygote outcome by the transition from oocyte to fertilized oocytes involving many changes, including protein synthesis, protein and RNA degradation, and organelle remodeling in the meiotic divisions.[93,94] The largest portion of the cytoplasmic contents is contributed by the oocyte: maternal mRNA and proteins stored during oocyte growth serve as crucial templates before the activation of the embryonic genome. Additionally, mitochondria provide energy for the embryo, lipid droplets supply metabolic reserves and cytoskeletal components are essential for various inter- and intracellular processes.[95] The cytoskeleton components in oocytes disturbances the function of embryo development and blastocyst stage which can result in aneuploidy. The combined occurrence of meiotic and mitotic aneuploidies contributes to the arrest of human embryos in vitro, as development becomes increasingly dependent on embryonic gene expression by the blastocyst stage.[96] Centrosome and microtubule dysfunctions are closely linked to aneuploidy in this context.[97]

## Vesicles

Oocyte vesicles have been demonstrated and described in different mammalian oocyte species including humans,[98] sheep,[99] pigs,[100] mice, and possums.[101] Vesicles, membranous structures enclosed by lipid bilayers, play crucial roles in cellular processes by mediating transport and communication within and between cells.[102] The dynamic nature of vesicles allows for the precise regulation of intracellular conditions, which is essential for maintaining oocyte viability and developmental competence.[103]

### Ooplasmic Nanovesicles

We first identified the intra-ooplasmic vesicles (IOVs) which displayed spherical lipid bilayer with diameters ranging from 63–624 nm (average: 186.3 nm).[104] Mass spectrometry of these IOVs identified 411 proteins among 1,498 proteins detected overall in oocytes. Bioinformatic analysis revealed that IOV proteins were enriched in biological processes like catabolism, carboxylic acid metabolism, and protein folding. Cellular components included cytosol and proteasome complexes, while molecular functions involved protein and isomerase binding. Hub genes SOD1 and HSPA9 emerged as critical, with network analysis highlighting proteasome and RNA degradation pathways.

### Endolysosomal Vesicular Assemblies (ELVAS)

ELVAs play a crucial role in various aspects of oocyte development, fertilization, and early embryogenesis.[105] ELVAs are non-membrane-bound compartments made up of endolysosomes, autophagosomes, and proteasomes, held together by a protein matrix formed by RUFY1. Functional assays have shown that in immature oocytes, ELVAs sequester aggregated proteins, such as TDP-43, and degrade them during oocyte maturation. Inhibiting the degradative activity of ELVAs results in the

accumulation of protein aggregates in the embryo, which negatively impacts embryo survival.[106] Furthermore, ELVAs preserve endosomal-lysosomal activity in a dormant state in oocytes, ensuring timely activation during early development.[107] Additionally, lysosomes may influence porcine oocyte maturation and subsequent developmental potential, partly by regulating chromosome organization, cytoskeleton assembly, and the autophagy-apoptosis pathways.[108]

### Functions of IOVs and ELVAS in Oocyte Development and Reprogramming

IOVs and ELVAS are pivotal in oocyte development, contributing to processes such as protein synthesis, folding, transport, cellular organization, and maturation. They facilitate the localization and translation of maternal mRNAs, ensuring proper protein synthesis and folding required for oocyte growth and function.[109]

When cultured somatic cells were treated with IOVs, cell aggregates formed, and pluripotency and trophoblast markers (OCT4, CDX2) increased significantly. Real-time PCR showed and elevated expression of reprogramming factors such as KLF4, SOX2, OCT4, and SALL4), trophectoderm marker CDX2, and genes like YBX3 and ZEB2, demonstrating IOVs' potential in cellular reprogramming.[104]

Furthermore, ELVAS plays a critical role in the transport of proteins and other macromolecules between the oocyte and its surrounding cells, thereby maintaining cellular organization and promoting oocyte maturation.[110] The involvement of ELVAS in genetic, epigenetic, and metabolic reprogramming within oocytes is profound. ELVAS mediate the transfer of DNA, RNA, and proteins that induce genetic and epigenetic modifications necessary for oocyte reprogramming and subsequent embryonic development.[111] These vesicles also participate in metabolic reprogramming by transporting metabolites and enzymes that modulate the metabolic state of the oocyte, thereby optimizing the cellular environment for development.[112] Upon fertilization, the composition, and function of ELVAS undergo significant changes, impacting early embryonic development and cellular differentiation. The vesicles facilitate the delivery of paternal RNAs and proteins to the oocyte, which are critical for zygote formation and early developmental processes.[113] These dynamic changes in ELVAS are essential for the reprogramming of the oocyte to a totipotent state, enabling the proper progression of embryogenesis.[113]

### Applications and Future Directions

Research on IOVs and ELVAS holds substantial potential for applications in SCNT, artificial gametes (haploidization), and iPSCs.[114] Understanding the mechanisms of ELVAS-mediated reprogramming could enhance the efficiency and outcomes of SCNT by improving the delivery of reprogramming factors to somatic nuclei.[115] Vesicles can be used to deliver reprogramming factors, improving the efficiency of SCNT and enhancing the developmental potential of reconstructed embryos.[116] Additionally, the molecular cargo of vesicles can be harnessed to improve iPSC generation, providing insights into cellular reprogramming and offering potential therapeutic applications.[117]

## Cytoplasmic Lattices (CPLs)

Lattices, defined as regular, repeating three-dimensional structures, play crucial roles in various cellular processes due to their ability to provide scaffolding and organize intracellular components.[118] Within the context of oocyte biology, lattices are particularly significant as they contribute to the structural integrity and functional regulation of these cells.[119] These intricate cytoplasmic lattices are instrumental in organizing the oocyte internal architecture, ensuring proper positioning and functioning of organelles and molecular complexes vital for oocyte maturation and embryonic development.[120] Cytoplasmic lattices are utilized as storage in oocytes for associated proteins.[120,121] Furthermore, cytoplasmic lattices concentrate maternally provided proteins to prevent their premature degradation and loss of cellular activity, thereby supporting early mammalian development.[122] The lattices used to store peptidyl arginine deiminase 6 (PADI6) or subcortical maternal complex (SCMC) proteins for successful embryonic development.[122] PADI6 is a maternal factor that is vital for early embryonic development.[123] Additionally, embryonic genome activation is impaired in Padi6-arrested embryos at the 2-cell stage. These findings indicate that, in mammals, Padi6 is stored in the oocyte cytoplasmic lattices and is essential for protein translation during early development.[124] Other studies have indicated that rRNAs are significantly reduced in Padi6 knockout (KO) oocytes, and mRNAs, potentially complexed with MSY2 and PADI6, are bound to the cytoplasmic lattices. These mRNAs may play a role in anchoring the mRNA-MSY2

complex to the cytoplasmic lattices Further evidence highlighting the critical role of the homozygous PADI6$^{R132C}$ variant in embryonic development suggests that it could lead to cleavage-stage embryonic arrest in female patients.[125,126] A case report reveals that a complex heterozygous mutation in the PADI6 gene resulted in embryos being arrested at the 1- or 2-cell stage.[127] In addition, the mutational spectrum of PADI6 and transducin-like enhancer of split 6 (TLE6) is associated with embryonic developmental arrest with ART failure.[128] However, these findings enhance our understanding of the genetic basis of human early embryonic arrest, a largely overlooked Mendelian phenotype, caused by mutations in PADI6 that lead to early embryonic arrest.[129] In murine oocytes, PADI6, and MATER are required for cytoplasmic lattices formation and play an essential role in controlling the processes of the oocyte-to-embryo transition.[130] Another study demonstrated that PADI6 regulates both nuclear and cytoplasmic oocyte processes that are essential for preimplantation epigenetic reprogramming and zygotic genome activation.[131]

## Functions of Lattices in Oocyte Development and Reprogramming

The functions of lattices in oocyte development are manifold, involving the maintenance of cellular structure, stability, and facilitating crucial developmental processes. Cytoplasmic lattices, for instance, are integral to the organization of the cytoskeleton, which provides structural support and coordinates intracellular transport mechanisms.[121] These lattices also play a vital role in ribosomal storage and protein synthesis, which are critical during the maternal-to-embryonic transition, ensuring the proper development of the early embryo.[124] Furthermore, the stable platforms provided by flat clathrin lattices facilitate the recruitment and organization of endocytic cargo, thereby regulating membrane dynamics during cell division and differentiation.[132] Lattices are deeply involved in the reprogramming mechanisms within oocytes, influencing genetic, epigenetic, and metabolic processes essential for cellular development and differentiation. Cytoplasmic lattices are known to store ribosomal components and regulatory proteins that are pivotal during the early stages of embryogenesis, thereby facilitating the necessary genetic and epigenetic modifications required for the transition from oocyte to embryo.[133]

These lattices also contribute to the metabolic reprogramming by regulating the synthesis and distribution of metabolic enzymes and substrates, thus ensuring that the metabolic needs of the developing embryo are met.[131] Moreover, lattice structures are implicated in the stabilization and localization of mRNAs, which are critical for the post-transcriptional control of gene expression during oocyte maturation and early embryonic development.[121]

Upon fertilization, the composition, and function of oocyte lattices undergo significant changes that are crucial for early embryonic development and cellular differentiation. The CPLs, for example, experience a reorganization that facilitates the activation of the embryonic genome and the initiation of protein synthesis, which are essential for the progression beyond the two-cell stage.[124] The dynamic nature of these lattices ensures that the necessary molecular components are appropriately distributed and activated in response to fertilization cues.[134] Moreover, the rearrangement of lattice structures during early development supports cellular differentiation processes by providing the scaffold necessary for the establishment of cellular polarity and tissue organization.[135]

## Mitochondria

Mitochondria are the most crucial organelle for oocyte developmental competence, playing an essential role in ATP production as well as the regulation of $Ca^{2+}$ and redox homeostasis in the oocyte.[136,137] The decreased ATP content may be linked to fertilization failure, halted division, and abnormal embryonic development.[138] Evidence suggests that a specific number, distribution pattern, and morphology of mitochondria are necessary for the metabolic shift involved in successful reprogramming.[139–141]

Mitochondria in oocytes have unstructured cristae with a limited capacity for energy production.[142] A similar pattern was observed in the embryonic stem cells, and during the iPSC reprogramming. Undifferentiated embryonic stem cells (ESCs) are characterized by a limited number of mitochondria, which display underdeveloped cristae and are predominantly located near the nucleus. Additionally, ESCs have a low mtDNA copy number, which rises as the cells undergo differentiation and their mitochondria mature.[143,144]

Importantly, studies highlighted the crucial role of mitochondrial electron transport chain (ETC) Complex I (ETC CI) in facilitating cell reprogramming to a pluripotent state.[145] Continuous inhibition of ETC CI function throughout the

reprogramming process significantly suppresses the generation of iPSCs. Notably, mitochondrial content in iPSC precursors peaks on day 3 before declining sharply by day 6, indicating substantial mitochondrial network reorganization during the transition from somatic to pluripotent states. This aligns with the findings that mitophagy occurs during reprogramming and that oxidative phosphorylation capacity reaches its maximum by days 2–3 of reprogramming. Furthermore, mitochondrial superoxide anion (SOA) and total reactive oxygen species (ROS) levels also peak in iPSC precursors on day 3 before decreasing by days 6 and 10, mirroring mitochondrial dynamics during these stages. ROS generated by ETC CI inactivation during the first 3 days are well-tolerated and support reprogramming. However, inhibiting CI at later stages severely impairs the process. These findings suggest that mitochondria-generated ROS during early reprogramming stages play a pivotal role in the success of cell reprogramming.[145]

Mitochondrial distribution has been associated with developmental competence, as they shift from a peripheral location to a more uniform distribution throughout the oocyte cytoplasm during maturation.[99,146] These mitochondria appear to play a role in blastocyst differentiation, expansion, and hatching, with their morphological changes reflecting heightened cellular activity.[147] This distribution of mitochondria plays a crucial role in cleavage, ensuring that each blastomere receives an adequate supply of mitochondria. High levels of ATP and $Ca^{2+}$ signaling are essential for survival during early embryogenesis.[148,149] Competent embryos up to the 16-cell stage displayed intermediate levels of activity (16–50%), but this activity decreased as development progressed toward the blastocyst stage. Non-competent embryos exhibited low levels of activity (1–15%) at all stages, supporting the idea that mitochondria regulate the potential competence required to reach the blastocyst stage.[150]

## Ooplasmic Lipid Droplets

Oocytes contain large stores of lipids, with the relative abundance of lipids being species-specific. Ultrastructural studies have also shown a high number of lipid droplets in the ooplasm.[100] Oocyte fatty acids serve as a source of metabolites for energy production, as shown by the inhibition of β-oxidation during oocyte maturation, which resulted in decreased embryo viability in pigs, cows, and mice. Additionally, oocytes contain phospholipids and cholesterol, which are essential for the formation of membranes required for the repeated cell divisions needed to form an embryo.[74,151–153] Ooplasmic droplets, also known as lipid droplets (LDs), are intracellular organelles primarily composed of neutral lipids such as triacylglycerols and cholesteryl esters, enclosed by a phospholipid monolayer.[154] These droplets are ubiquitous and process multifunctions such as energy storage and metabolic regulation. In oocyte biology, LDs store essential nutrients and energy reserves that are mobilized during periods of high metabolic demand, such as oocyte maturation and early embryogenesis.[154,155] The presence and distribution of these droplets within oocytes are indicative of the cell's metabolic state and are crucial for proper cellular function.[156]

## Types of Ooplasmic Lipid Droplets in Oocytes

Ooplasmic droplets in oocytes can be classified into several types based on their structure, composition, and function. The primary types include alpha yolk spheres and beta yolk spheres. Alpha yolk spheres are rich in proteins and unsaturated lipids, whereas beta yolk spheres contain polysaccharides and more saturated lipids.[157] In addition to these, lipid droplets associated with endoplasmic reticulum (ER) and mitochondria have been observed, indicating their involvement in lipid metabolism and energy production.[158] The structure and composition of these droplets vary during different stages of oocyte development, reflecting their dynamic roles in oocyte maturation and initial blastomeres divisions.[159]

## Ooplasmic Lipid Droplets and Reprogramming Mechanisms

Ooplasmic droplets are actively involved in the reprogramming of genetic, epigenetic, and metabolic states within oocytes. These droplets provide a lipid-rich environment that supports the reorganization of chromatin and the establishment of epigenetic marks necessary for early developmental stages.[158] Metabolically, they supply fatty acids and other lipid derivatives that are crucial for membrane synthesis and function during cellular reprogramming.[157] Additionally, ooplasmic droplets contribute to the regulation of mitochondrial dynamics and bioenergetics, which are essential for the successful reprogramming of somatic cells into pluripotent states.[160]

Specifically, the Wnt pathway is essential for maintaining stem cell pluripotency and guiding cell fate during embryonic development, influencing processes like axis formation and organogenesis. This pathway involves Wnt ligands, Frizzled receptors, and LDL-related co-receptors. Monounsaturated fatty acids (MUFAs) activate this pathway, which regulates lipid synthesis through SREBP isoforms, particularly SREBP1c for fatty acid (FA) production and SREBP2 for cholesterol synthesis. The enzyme SCD1, integral to FA metabolism, promotes the formation of lipid droplets, vital for embryo development. Saturated FAs hinder this process, underscoring SCD1's role in early embryogenesis.[161] Similarly, The AMPK pathway is vital for energy regulation during embryonic development. Composed of α, β, and γ subunits, AMPK is activated by elevated AMP/ATP ratios, leading to decreased lipid synthesis and increased fatty acid oxidation. It phosphorylates acetyl coenzyme A carboxylase (ACC), reducing FA synthesis while promoting CPT1 expression for FA oxidation. ACC and CPT1 support lipid droplet formation and energy storage. Additionally, the PI3K/AKT pathway modulates lipid metabolism via SREBP1C and FASN, driving lipid synthesis and storage in response to sugar levels during embryogenesis.[161,162] Moreover, fatty acid oxidation affects cellular transitions like endothelial-to-mesenchymal changes by modulating SMAD7 stability.[163] Enhanced de novo lipogenesis reduces acetyl-CoA levels, and considered critical for stem cell pluripotency, and facilitates somatic cell reprogramming via promoting mitochondrial fission through acetylation-dependent FIS1 degradation.[164]

Additionally, the interaction between lipid droplets and other organelles, such as mitochondria and ER, becomes more pronounced, facilitating efficient metabolic regulation and signaling necessary for reprogramming and embryonic development.[155]

## Ooplasmic Transcriptome and Proteome

Utilizing the latest Affymetrix Human GeneChip, 5,331 transcripts were identified as being highly expressed in human oocytes, including well-known genes such as FIGLA, STELLA, VASA, DAZL, GDF9, ZP1, ZP2, MOS, OCT4, NPM2, NALP5/MATER, ZAR1, and H1FOO. Notably, 1,430 of these up-regulated genes have unknown functions, highlighting the need for further research to understand their functional roles in the human oocyte and reprogramming.[165] The ooplasmic transcriptome is instrumental in maintaining the transcriptional silence observed during the late stages of oocyte maturation, thereby ensuring that the stored maternal RNAs are readily available for immediate translation post-fertilization.[166] The stored maternal RNAs are translated into proteins that facilitate cellular processes and different signaling processes for successful reprogramming.[167]

Ooplasmic proteins are a group of proteins found within the cytoplasm of oocytes, and are the components of the reprogrammome.[80] Ooplasmic proteins play a pivotal role in cellular functions, particularly in the development and maturation of oocytes. These proteins encompass a wide range of functional categories, including enzymes, structural proteins, and regulatory molecules that contribute to cellular homeostasis and metabolic processes.[168] Ooplasmic proteins are crucial for the synthesis, folding, and modification of other proteins within the endoplasmic reticulum, ensuring that oocytes are equipped with the necessary components for subsequent developmental stages.[169] These proteins are essential for various aspects of oocyte development, fertilization, and early embryonic development.[170]

On the other hand, the roles of histone chaperones in somatic cell reprogramming were also elucidated in iPSCs reprogramming, however, its role in SCNT and oocyte reprogramming machinery was not tested. For instance, ASF1A, associated with H3K56ac modification; is essential for pluripotency and reprogramming in humans[171] but not yet tested in somatic cell nuclear transfer (SCNT). Moreover, CAF1 is linked to H3K56ac, H4K20me3, and H3K9me3 modifications and its downregulation improves reprogramming efficiency in mice,[172] though its role in SCNT remains untested.

## Ooplasmic Transcripts/RNAs and Proteins and Reprogramming Mechanisms

Genetic reprogramming is facilitated through the selective degradation and stabilization of specific mRNAs, ensuring that only the necessary transcripts are available for translation at crucial developmental stages.[173] Epigenetic modifications, mediated by lncRNAs and miRNAs, regulate chromatin structure and gene expression patterns, thereby influencing cellular differentiation and development.[174]

Key molecular components of ooplasmic proteins include various enzymes and regulatory factors that interact synergistically to maintain cellular homeostasis. For instance, the protein disulfide isomerases (PDIs) family members are crucial for oxidative protein folding and maintaining redox balance within the endoplasmic reticulum.[175] Additionally, glucose-regulated proteins such as GRP78 and GRP94 function as molecular chaperones, facilitating the proper folding and assembly of nascent proteins and mitigating stress responses.[176] The interplay between these components ensures the functionality and stability of the oocyte's proteome, highlighting their significance in reproductive biology.[177]

The involvement of ooplasmic proteins in genetic, epigenetic, and metabolic reprogramming is a key aspect of their function in oocytes. These proteins influence the chromatin structure and gene expression patterns necessary for the transition from a differentiated oocyte to a totipotent zygote (Lin et al, 2019). Epigenetic reprogramming involves modifications such as DNA methylation and histone acetylation, which are mediated by specific ooplasmic proteins to reset the genomic landscape for embryonic development.[178] Metabolically, ooplasmic proteins regulate the nutrient and energy flux within the oocyte, ensuring that it can support the initial stages of embryogenesis.[179] This reprogramming capacity underscores the pivotal role of ooplasmic proteins in the early developmental processes.

We previously mentioned the functions and roles of pluripotency transcription factors, and there are more oocyte gene products crucial for both SCNT and cell reprogramming. For instance, TBP2 is a transcription factor essential for SCNT; not yet tested in iPSCs.[180] Moreover, GLIS1 is Critical for bovine ZGA and embryonic development; supports iPSC reprogramming and substitutes cMYC in mice.[181,182] Furthermore, some proteins are crucial for cell reprogramming, such as Tet3, which facilitates 5mC demethylation, reactivating Oct4 in SCNT and pluripotency genes in iPSC reprogramming.[183] Additionally, RPB1 is a subunit of polymerase II that replaces somatic counterparts during somatic cell nuclear transfer (SCNT), but it has not yet been tested in induced pluripotent stem cells (iPSCs).[14,180]

Additionally, there are candidate oocyte-enriched miRNA families essential for iPSC reprogramming. For example; miR-125b is critical for bovine somatic cell cloning,[184] miR-21, miR-130a in mice are associated with iPSCs differentiation into endothelium, miR-93 enhances the generation of iPSC, miR-184, miR-10a, miR-100, miR-125a inhibit pluripotency by promoting lineage-specific differentiation, as well as downregulation of miR-29a, miR-21, miR-30d, miR-320a support cellular reprogramming, and self-renewal.[185] Therefore, fine-tuning miRNA networks is vital for optimizing reprogramming strategies.[186,187]

Moreover, the roles of lncRNA in pluripotency have been evidenced in several reports. Lin et al identified 20 lncRNA candidates with particular involvement in maintaining the pluripotency such as TUNA/MEGAMIND which activates transcription of Nanog, Sox2, and Fgf4 and maintains the pluripotency.[188] Furthermore, Linc-RoR is considered the "regulator of reprogrammation" and supports human pluripotent stem cell's self-renewal and promotes reprogramming through inhibiting miR-145 and activation of Oct4, Nanog, and Sox2 expression.[189,190]

**Table 2** Oocyte Components and Their Functions

| Major Components | Description | Roles | Ref. |
|---|---|---|---|
| Vesicles | Bilipid layered nanovesicles | Conversion of somatic cells to stem-like cells | [104] |
| Endolysosomal vesicular assemblies (ELVAs) | Protein aggregates in liquid-like compartments | Harbor endolysosomes, autophagosomes, proteasomes and degrade upon oocyte maturation to promote healthy embryogenesis | [192] |
| Cytoplasmic lattices | Periodic protein filaments enriched in PADI6 | - protein synthesis machinery - Regulation of microtubule dynamics – Epigenetic reprogramming of early embryo | [118,119,122,124,193] |

**Abbreviation**: PADI6, peptidylarginine deiminase 6.

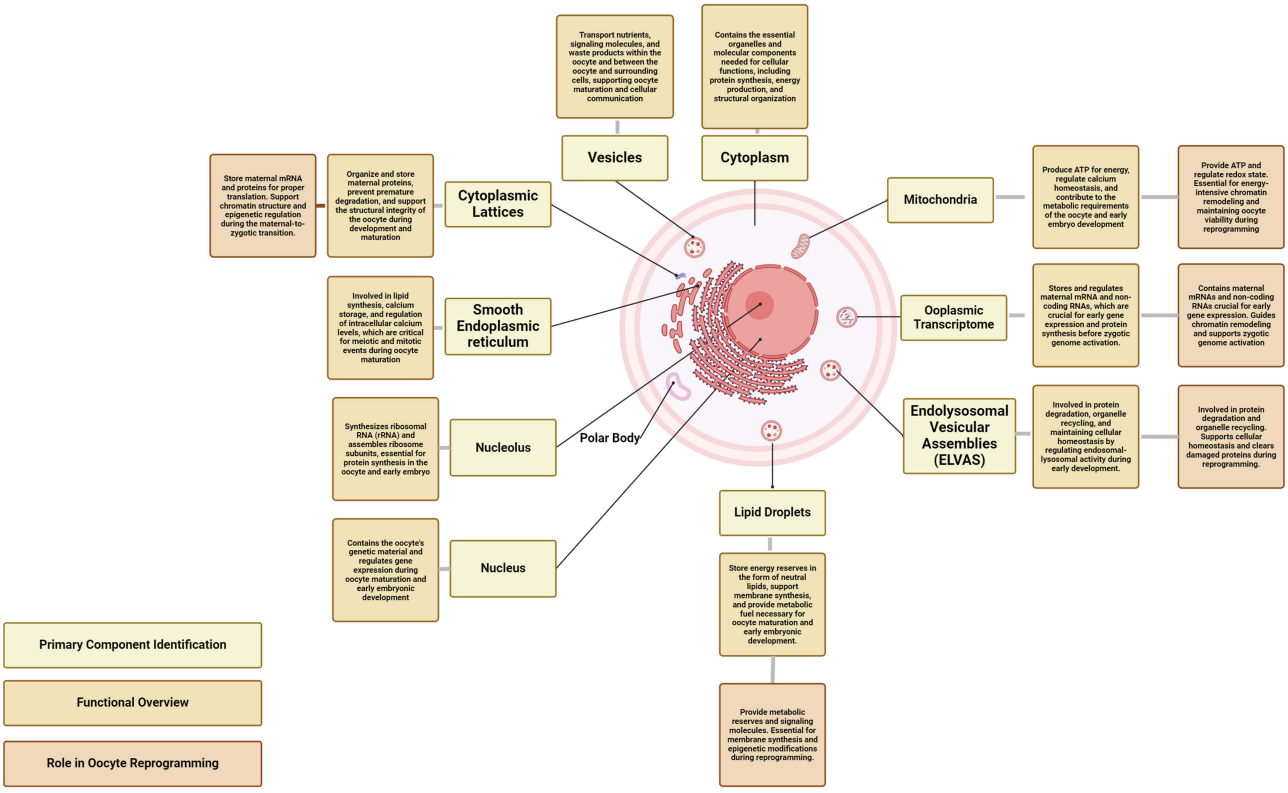


**Figure 3** Comprehensive Overview of Oocyte Components and Their Roles in Reprogramming and Early Embryonic Development. This figure illustrates the structural and functional components of the oocyte, highlighting their roles in reprogramming and supporting early embryogenesis. The oocyte contains various organelles and molecular structures that are crucial for its developmental competence. (1) Cytoplasmic Lattices: Organize and store maternal mRNA and proteins, supporting early gene expression and chromatin remodeling during the transition to an embryo. (2) Mitochondria: Provide ATP and regulate cellular redox state, essential for energy-intensive processes like chromatin restructuring and maintaining oocyte viability. (3) Ooplasmic Transcriptome: Contains maternal RNAs necessary for protein synthesis and gene regulation, playing a vital role in the maternal-to-zygotic transition. (4) Endolysosomal Vesicular Assemblies (ELVAS): Facilitate the degradation and recycling of proteins and organelles, maintaining cellular homeostasis during reprogramming. (5) Lipid Droplets: Serve as metabolic reserves, providing energy and signaling molecules required for reprogramming and cellular differentiation. The illustration uses a color-coded key to differentiate levels of information: Level 1 identifies primary components, Level 2 explains their basic functions, and Level 3 details their roles in reprogramming and development.

Conversely, lincRNA-p21 is induced by p53 and prevents somatic cell reprogramming by maintaining the methylation of H3K9me3 and/or CpG at the promotors of the pluripotency gene.[191]

## Conclusion

This review illustrates the critical components of the oocyte and their collective roles in supporting cellular integrity, energy production, and molecular regulation essential for reprogramming and early embryogenesis. Key structures, such as mitochondria, the nucleus, and cytoplasmic lattices, work synergistically to ensure proper gene expression, energy supply, and structural organization. Reprogramming is highlighted as a central function, driven by unique features like the ooplasmic transcriptome and endolysosomal vesicular assemblies (ELVAS), which regulate gene expression, chromatin remodeling, and cellular homeostasis. Together, these components enable the oocyte to transition into a totipotent state, underscoring their pivotal role in developmental biology and advancing reproductive and regenerative medicine (Table 2, Figure 3). Gaining further insight into the oocyte components and compartments is important for determining oocyte competence and may open new possibilities for enhancing the outcomes of both natural and ART as well as improving the generation of totipotent and pluripotent stem cells. The evidence presented in this review highlights the importance of studying oocyte components, especially the unfertilized metaphase II oocyte, to deepen our understanding of how somatic cells can be reprogrammed to achieve pluripotency. With the advent of advanced genomic, transcriptomic, metabolomic, and proteomic technologies, we now have the opportunity to revisit fundamental questions regarding the mechanisms and key regulators by which


https://doi.org/10.2147/SCCAA.S513982

the oocyte cytosol influences the nucleus. This opens an exciting new era for exploring cellular reprogramming with precise temporal control and high-resolution insights. These advancements will soon help us tackle critical questions while paving the way for new research in areas like aging, developmental origins of disease, and cancer.

## Acknowledgment

The authors are thankful to the Deanship of Graduate Studies and Scientific Research at University of Bisha for supporting this work through the Fast-Track Research Support Program.

## Disclosure

The authors report no conflicts of interest in this work.

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