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Epigenetic Codes of Cumulus Oophorus Extracellular Vesicles in Oocyte Sufficiency: Programming of Oocyte Peripheral Memory and Determination of Embryonic Developmental Potential

Oosit Yeterliliğinde Cumulus Oophorus Hücre Dışı Veziküllerinin Epigenetik Kodları: Oosit Çevresel Hafıza Programlanması ve Embriyonik Gelişim Potansiyelinin Belirlenmesi

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Abstract

Aim and Significance: Oocyte developmental competence is closely associated with bidirectional communication between the oocyte and the surrounding cumulus oophorus cells. Extracellular vesicles (EVs) play an important role in this communication by transferring proteins, microRNAs (miRNAs), and other bioactive molecules. This review aims to evaluate the roles of cumulus cell-derived EVs in the epigenetic regulation of oocyte developmental competence and embryonic developmental potential, as well as their possible clinical applications.

Materials and Methods: This narrative review examines findings of the literature on the molecular cargo of cumulus cell- and follicular fluid-derived EVs, their effects on oocyte developmental competence, and their potential applications in assisted reproductive technologies.

Findings: The reviewed studies indicate that EVs may influence oocyte developmental competence through three principal mechanisms: miRNA-mediated regulation of gene expression, metabolic and antioxidant support, and modulation of cellular signaling pathways including MAPK signaling. Small and large EV subpopulations exhibit differences in their molecular cargo and biological functions. Furthermore, alterations in EV cargo associated with aging and conditions such as polycystic ovary syndrome may provide molecular indicators related to oocyte quality.

Conclusion: Cumulus cell-derived EVs may contribute to intercellular communication and epigenetic regulatory processes influencing oocyte developmental competence. Characterizing EV cargo as potential biomarkers and using it in in vitro oocyte maturation systems may offer promising applications in assisted reproductive technologies. However, further research is required to establish their clinical effectiveness.

Keywords: *Cumulus Cells; Extracellular Vesicles; Oocytes; Epigenesis; Genetic.*

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Özet

Araştırmanın Amacı ve Önemi: Oositin gelişimsel yeterliliği, çevresindeki kumulus ooforus hücreleri ile kurduğu çift yönlü iletişimle yakından ilişkilidir. Hücre dışı veziküller (EV'ler), proteinler, mikroRNA'lar (miRNA'lar) ve diğer biyoaktif molekülleri taşıyarak bu iletişimde önemli rol oynamaktadır. Bu derlemenin amacı, kumulus hücreleri kaynaklı EV'lerin oosit gelişimsel yeterliliğinin epigenetik düzenlenmesindeki rollerini, embriyonik gelişim potansiyeli üzerindeki etkilerini ve olası klinik uygulamalarını değerlendirmektir.

Gereç ve Yöntem: Bu derlemede, kumulus hücreleri ve foliküler sıvı kaynaklı EV'lerin moleküler içerikleri, oosit gelişimsel yeterliliği üzerindeki etkileri ve yardımcı üreme teknolojilerindeki potansiyel kullanımlarına ilişkin literatürde bildirilen bulgular ele alınmıştır.

Bulgular: İncelenen çalışmalar, EV'lerin oosit gelişimsel yeterliliğini başlıca üç mekanizma aracılığıyla etkileyebileceğini göstermektedir: miRNA aracılı gen ekspresyonunun düzenlenmesi, metabolik ve antioksidan desteğin sağlanması ve MAPK gibi hücresel sinyal yolaklarının modülasyonu. Küçük ve büyük EV alt popülasyonlarının moleküler içerikleri ve biyolojik işlevleri farklılık gösterir. Ayrıca yaşlanma ve polikistik over sendromu gibi durumlarda EV içeriklerinde meydana gelen değişiklikler, oosit kalitesiyle ilişkili olabilecek moleküler göstergeler sunmaktadır.

Sonuç: Kumulus hücrelerinden kaynaklı EV'ler, oositin gelişimsel yeterliliğini etkileyen hücreler arası iletişim ve epigenetik düzenleme süreçlerinde önemli rol oynayabilir. EV içeriklerinin biyobelirteç olarak değerlendirilmesi ve in vitro oosit olgunlaştırma ortamlarında kullanılması, yardımcı üreme teknolojileri açısından potansiyel uygulamalar sunmaktadır. Bununla birlikte, klinik etkinliklerinin belirlenmesi için ileri araştırmalara ihtiyaç bulunmaktadır.

Anahtar Kelimeler: *Kumulus hücreleri; Hücre dışı veziküller; Oositler; Epigenetik düzenleme.*

1. Introduction

Cumulus oophorus cells (COCs) are specialized granulosa cells that surround the oocyte and directly influence its development, maturation, and fertilization potential. Cumulus granulosa cells regulate the restart of meiosis, direct steroidogenesis by supplying metabolic substrates, and expand the extracellular matrix, generating clinical, non-invasive biomarkers for embryo viability. Through bidirectional signaling, oocyte-secreted factors (such as GDF9 and BMP15) control cumulus cell differentiation, while granulosa cells provide regulatory metabolites and cyclic GMP to maintain the meiotic pause until the LH surge (Rouhollahi Varnosfaderani, S., 2020). Furthermore, through metabolic cooperation, cumulus-granulosa cells metabolize glucose via glycolysis and redirect pyruvate and amino acids to the oocyte because the oocyte has limited glycolytic capacity (Huang, Z. & Wells, D. 2010). Gonadotropins trigger hyaluronic acid synthesis, matrix stabilization, and cumulus expansion, all essential for successful ovulation and readiness for fertilization. In clinical practice, gene expression profiling and biomarkers, assessed through transcriptomic analysis of cumulus cells (e.g. SERPINE2, ADAMTS1, or extended gene classifiers), help predict fertilization (Turathum B., 2021). Apoptotic cell death and mitochondrial dysfunction grade blastocyst development and IVF success. High rates of apoptotic cell death or mitochondrial dysfunction in cumulus cells are associated with poor oocyte quality and reduced implantation potential. Bidirectional communication (crosstalk) between COCs and

oocytes underpins folliculogenesis and the acquisition of oocyte competence (Voros et al., 2025). Disruption of this communication between somatic cells and the oocyte during folliculogenesis, which involves oocyte development and maturation, can lead to significant reproductive health problems such as infertility. In recent years, extracellular vesicles (EVs) have emerged as key mediators of this communication (Pan et al., 2025). EVs are defined as very small structures released from cells that carry bioactive molecules such as proteins, mRNAs, and especially microRNAs (miRNAs). Recent studies on female reproductive organs suggest that EVs may play an active role in this system; however, no studies have linked this mechanism to epigenetics (Voros et al., 2025). This review will address the relationship between COC-oocyte cross-communication and EVs.

EVs are defined as cargo vesicles secreted by eukaryotic cells to facilitate communication with nearby and distant cells. These vesicles, measuring 30-100 nm, have a double-layered lipid structure and cannot divide. Beyond communication, protection, and the transfer of genetic information (proteins, lipids, DNA, mRNA, miRNA, lncRNA, etc.) between cells, they also help remove unnecessary and toxic products from the cell, reducing internal and external stress. Furthermore, they can carry a wide variety of molecules such as cytokines, inflammatory mediators, and miRNAs, which are crucial for maintaining homeostasis, inducing/reducing inflammation, and promoting repair (Pan et al., 2025; Bazzan et al., 2021; Somuncu et al., 2023; Varik et al., 2025).

Recent studies in various mammalian species have revealed the presence of EVs in follicular fluid (FF), and EVs are indicated as important mediators in COC-oocyte communication. (da Silveira et al., 2012; Hung et al., 2015; Matsuno et al., 2017; Rodrigues et al., 2019; Rooda et al., 2020; Santonocito et al., 2014; Sohel et al., 2013) EVs, which are abundant in FF, facilitate communication between oocytes and somatic cells in the follicular microenvironment, regulating critical processes such as follicle growth, oocyte competence, and metabolic homeostasis. In a study on small and large EVs in human FF, it was determined that small EVs (SEVs) were rich in miRNAs involved in the differentiation of granulosa cells, while large EVs (LEVs) were rich in piRNAs involved in maintaining genomic stability. Furthermore, it was determined that extensive changes, including transcription, TGF-β signaling, extracellular matrix remodeling, and cell cycle regulation, occur in SEVs in the Human Granulosa Cell Tumor Cell Line (KGN), whereas LEVs show limited transcriptional changes, with modulation of genes related to immune regulation and oxidative stress defense. Extensive studies have shown that FF-EVs are not a single homogeneous population; rather, SEV and LEV subpopulations differ significantly in both molecular content and functional effects on granulosa cells (Varik et al., 2025).

Recent research has revealed that the role of EVs in folliculogenesis goes beyond being merely a physiological communication medium. Current literature shows that FF EVs can be a strong biomarker of cargo content, oocyte quality, and in vitro fertilization (IVF) success (Muraoka et al., 2024). Extracellular vesicles (EVs) originating from the cumulus oophorus play a crucial role in shaping the oocyte's epigenetic code and determining its embryonic developmental potential. Current studies have shown that the EV cargo (especially miRNA, mRNA, and proteins) plays a key role in programming the oocyte's environmental memory and in epigenetic regulation (Brazzale et al., 2025; Fiorentino et al., 2024; De Ávila et al., 2019).

Physiological Role of EVs and Mechanisms Affecting Oocyte Quality

EVs establish a bidirectional communication network among cells within the follicular microenvironment. Recent studies have focused on three main mechanisms that affect oocyte competence: miRNA-mediated gene regulation, metabolic synergy, and energy-supported modulation of signaling pathways.

A study in a mouse model showed that EVs released from cumulus cells can cross the zona pellucida and

ooplasm, carrying 74 distinct miRNAs. Some of these miRNAs regulate 71 target genes involved in processes such as restarting oocyte meiosis, follicle growth, and acquisition of developmental competence. In particular, miRNAs such as miR-28c stand out as markers of oocyte developmental competence [Fiorentino et al., 2024; Zuccotti et al., 2024].

According to a study on cattle, the miRNA content of EVs isolated from FF varied by follicular stage during the estrous cycle, and these EVs were shown to modulate gene expression and biological processes in cumulus cells. EVs obtained from follicles with low progesterone levels have been shown to upregulate genes affecting oocyte development, immune responses, and Notch signaling pathways (Mendes de Ávila et al., 2019).

As maternal age increases, miRNA expression in COCs changes, reducing the quality of cargo transferred to the oocyte via EVs. Age-related changes in miRNA profiles can disrupt the regulation of genes that negatively affect oocyte developmental capacity (Dell'Aversana et al., 2021). This may reflect age-related epigenetic programming.

In human and animal models, miRNAs carried by EVs have been shown to improve oocyte competence and embryo quality by regulating epigenetic and metabolic pathways such as PI3K-AKT, ERK1/2, and TGF-β/SMAD (Voros et al., 2025).

Table 1. Follicular Fluid Extracellular Vesicle (FF-EV) Subtypes and Clinical Potential

Vesicle / Condition Type	Molecular Content & Characteristics	Cellular & Clinical Implication	References
Small Extracellular Vesicles (sEVs)	Rich in miRNAs associated with glycolysis and TGF-β signaling.	Granulosa cell differentiation, cell cycle regulation, and ECM remodeling.	Varik et al., 2025
Large Extracellular Vesicles (LEVs)	Rich in miRNAs that maintain genomic stability.	Modulation of immune regulation and oxidative stress defense genes.	Varik et al., 2025
Maternal Aging	Altered miRNA profile with reduced quality.	Adverse effects on oocyte developmental competence and epigenetic programming disorders.	Dell'Aversana et al., 2021

2. Metabolic Synergy and Energy Support

The effects of EVs on oocyte and embryo development depend on the type and quantity of cargo molecules they carry. Follicular fluid EVs obtained from competent oocytes increase blastocyst rates, and this effect is thought to occur particularly through specific miRNAs such as miR-143 (Esposito et al., 2025). In addition, EVs support energy metabolism by increasing oocyte mitochondrial function and antioxidant capacity, which positively affects embryo development quality (Lipińska et al., 2025).

The oocyte meets a large part of its energy needs by taking up glucose metabolites (especially pyruvate and lactate) from the surrounding COC. EVs play a critical role in transferring these metabolic molecules. CC-EVs regulate glycolysis in the COC by carrying growth factors such as GDF9 and BMP15, which activate the transcription of glycolytic genes in the oocyte (Xiong & Li, 2024).

In addition, EVs can increase oocyte resistance to oxidative stress by transferring molecules that regulate mitochondrial membrane potential and reduce reactive oxygen species (ROS) production, especially in senescent oocytes. EVs improve oocyte quality by carrying proteins or nucleic acids that regulate oocyte mitochondrial function. In senescent oocytes, EV supplementation has been observed to re-regulate mitochondrial membrane potential and reduce ROS production (Ezzati et al., 2025; Lipinska et al., 2025). Repair of the mitochondrial membrane and a reduction in ROS levels can be considered an indication that EVs increase the oocyte's resistance to oxidative stress.

3. Modulation of Signaling Pathways

EVs modulate signaling pathways in the COC-oocyte complex, enabling the oocyte to adapt to environmental conditions. Studies show that the mitogen-activated protein kinase (MAPK) signaling pathway and gap junction communication via connexin play a significant role in this context.

The MAPK signaling pathway is vital for COC expansion and cytoplasmic/nuclear maturation of the oocyte. EVs obtained from follicular fluid support COC expansion by carrying molecules that activate the MAPK signaling pathway [Gabryś et al., 2024]. This expansion is a critical step for the oocyte to separate from the follicle and be collected for fertilization.

EVs can indirectly affect gap junction communication between COC and connexin through connexin communication. For example, luteinizing hormone (LH) release activates MAPK, increasing Connexin 43 (Cx43) phosphorylation. EVs contribute to the regulation of this signaling, optimizing the ability of COCs to transport nutrients and signaling molecules to the oocyte (Del Bianco & Coticchio, 2024).

EVs carry miRNAs and proteins that influence mechanisms such as histone modifications, DNA methylation, and chromatin rearrangement in the programming of the oocyte's epigenetic memory. In particular, miRNAs such as miR-21, miR-34c, and miR-143-3p shape the oocyte's epigenetic code by regulating the cell cycle, apoptosis, glycolysis, and mitochondrial functions (Voros et al., 2025; Benedetti et al., 2024). In addition, proteins carried by EVs also increase the developmental potential of the oocyte by activating signaling pathways such as ERK/MAPK, PI3K/AKT, and mTOR (Voros et al., 2025).

Analysis of small non-coding RNAs (sncRNAs) in FF EVs offers the potential to predict oocyte quality non-invasively (Ezzati et al., 2025).

It has been experimentally shown that abnormal changes in the cargo content of FF EVs lead to mitochondrial and spindle dysfunction in oocytes, thereby reducing oocyte quality and causing reproductive disorders such as Polycystic Ovary Syndrome (PCOS) (Zhao et al., 2025). These findings make EVs attractive targets for both diagnostic and therapeutic approaches. In addition to these studies, therapeutic applications such as enhancing oocyte quality by supplementing EVs to in-vitro maturation (IVM) media and providing antioxidant protection in aged oocytes with stem cell-derived EVs (hucMSCs-Exos) indicate promising developments in this field (Zhao et al., 2025; Pakniyat et al., 2025).

Table 2. Functional roles, cargo contents, and clinical implications of extracellular vesicles (EVs) in the follicular microenvironment and oocyte-cumulus crosstalk.

Mechanism	Cargo / Mediators	Discovered Effects on Oocyte & Embryo	References
miRNA-Mediated Gene Regulation	74 different miRNAs (e.g., miR-28c, miR-143)	Resumption of meiosis, follicle growth, and acquisition of developmental competence.	Fiorentino et al., 2024; Zuccotti et al., 2024; Esposito et al., 2025
Metabolic Synergy & Energy Support	GDF9 and BMP15 growth factors, pyruvate, lactate, and antioxidant molecules	Activation of glycolysis in cumulus cells, enhancement of oocyte mitochondrial function, and resistance to oxidative stress.	Lipińska et al., 2025; Xiong & Li, 2024
Modulation of Signaling Pathways	Specific miRNA and protein contents	Improvement of embryo quality through the regulation of PI3K-AKT, ERK1/2, and TGF-β/SMAD pathways.	Voros et al., 2025
IVF Biomarker Potential	Specific miRNAs, mRNAs, and proteins that program environmental memory.	Assessment of oocyte quality, prediction of blastocyst rates, and IVF success.	Muraoka et al., 2024; Brazzale et al., 2025

4. Conclusion

EVs derived from the cumulus oophorus play a significant role in shaping the oocyte's epigenetic code and determining its embryonic developmental potential. EVs influence oocyte quality through multiple mechanisms, including regulating gene expression via miRNA transfer within the COC, supplying metabolic substrates and antioxidants, and modulating critical signaling pathways. Whereas SEVs primarily affect GC differentiation and growth pathways (TGF-β, ECM, miRNA), LEVs are more specifically associated with androgen production (testosterone) and genomic/immune stress defense pathways. A thorough understanding of these mechanisms enables the use of EVs as targetable molecular tools to enhance oocyte competence and improve success rates in infertility treatments.

Detailed profiling and functional analyses of EV cargo will enable the development of novel biomarkers and therapeutic strategies in assisted reproductive technologies (Varik et al., 2025; Voros et al., 2025). In conclusion, Cumulus Oophorus-derived Extracellular Vesicles (COC-EVs) are not only mediators of bidirectional communication between oocytes and somatic cells but also central epigenetic modulators that program oocyte developmental competence and embryonic developmental potential (Voros et al., 2025; Pan et al., 2025). Their multifaceted functions, such as regulating gene expression through miRNAs they carry (e.g. miR-28c & miR-143-3p), maintaining mitochondrial health by providing metabolic substrates and antioxidants (Esposito et al., 2025; Lipińska et al., 2025), and modulating critical signaling pathways (MAPK, PI3K/AKT) (Voros et al., 2025; Del Bianco & Coticchio, 2024), have been investigated in line with current literature. The fact that EV subpopulations (SEV and LEV) exhibit different cargo contents and functional effects (Varik et

al., 2025) highlights the complexity and regulatory role of the follicular microenvironment. Age-related (Dell'Aversana et al., 2021) or pathological (PCOS) changes in the FF-EV cargo profile directly affect oocyte quality (Zhao et al., 2025), making EVs powerful non-invasive biomarkers for infertility diagnosis and prognosis. In the future, supplementing in vitro maturation (IVM) environments with EVs or using stem cell-derived EVs therapeutically will open the door to novel, targeted strategies to enhance oocyte competence and improve Assisted Reproductive Technology (ART) success rates (Zhao et al., 2025; Pakniyat et al., 2025). A complete elucidation of these mechanisms at the molecular level is critical for developing personalized treatment approaches in reproductive medicine.

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