Review

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The Importance of Exosomes in Gynecological Diseases

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ABSTRACT

Exosomes play significant roles in key functions of the female reproductive system, such as oogenesis, implantation success, embryo development, and proper fertilization. Functional connectivity between cells is essential for the viability, development, and coordination of the female reproductive system. It has been demonstrated that the information carried by exosomes is crucial for these cooperative biological mechanisms.

Exosomes are formed and encapsulate biological molecules from the cells of origin. They contribute both to the reorganization of cellular functions and to the collective functioning of cell populations. In addition the content of exosomes may be used to monitor the diagnostic and therapeutic processes of various gynecological diseases. They contain genetic and proteomic data that can be used as biomarkers or therapeutic targets in gynecological cancers and pregnancy-related disorders.

This article will review the roles of exosomes in major female reproductive disorders, including endometriosis, premature ovarian failure, polycystic ovary syndrome, Asherman syndrome, endometrial cancer, cervical cancer, ovarian cancer, and preeclampsia.

Keywords: Exosomes, infertility. women's reproductive diseases

INTRODUCTION

Exosomes are extracellular vesicles secreted by cells and possess a double-layered lipid membrane.[1-3] These vesicles typically measure between 30-150 nm in diameter.[4] Their contents include RNA molecules, proteins, lipids, and occasionally DNA.[5-7] These components regulate various cellular functions mediated by exosomes.[8] Based on size, surface markers, biogenesis, and content, three major types of extracellular vesicles are recognized: apoptotic bodies, microvesicles, and exosomes.[9,10] Exosomes are effective paracrine regulators of intercellular communication. In recent years, they have been shown to participate in biological functions including metabolic regulation, cell proliferation, apoptosis, angiogenesis, antigen presentation, inflammation, tumor pathogenesis, tissue repair, and reproduction.[11-13] Exosomes are produced through the inward budding of endosomal membranes, forming multivesicular bodies, which later fuse with the plasma membrane to release exosomes.[14] They interact with target cells via ligand-receptor binding or endocytosis.[15] Following this interaction, vesicles are internalized by phagocytosis.[2,16] Functional protein groups found in exosomes include β-actin, GPI-anchored proteins, heat shock proteins (HSP8, HSP90), tubulin, and tetraspanins such as CD9, CD63, and CD8.[17] Under both physiological and pathological conditions, exosomes reflect the molecular characteristics of their donor cells. This makes them valuable prognostic and diagnostic biomarkers.[18,19] Exosomes are be secreted from various tissues of the female reproductive system, including the fallopian tube epithelium, follicular fluid, endometrium, uterus, and placenta.[20-23] Proper reproductive function and successful pregnancy rely heavily on effective intercellular communication. Oogenesis, follicular development, implantation, fertilization, and embryo development are closely tied to maternal-embryo cellular interaction during pregnancy.[13,24,25] Studies have confirmed both direct and indirect roles of exosomes in cellular communication.[26-28]

Exosomes communicate with recipient cells through delivery of the exosomal contents.[29-31] Once exosomes are internalized, they initiate physiological processes by

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delivering bioactive molecules such as coding and non-coding RNAs, proteins, and lipids. These molecules modulate the functions of the recipient cells.[32-34] Studies in human and animal models have demonstrated that exosomes are involved in follicular development, oocyte maturation, and embryo formation. They are also known to carry microRNAs (miRNAs) involved in meiotic resumption and ovulation signaling pathways.[35] miRNAs are non-coding RNAs composed of 21-24 nucleotides and participate in various biological processes. They regulate oocyte development, follicular growth, implantation, and embryo development by targeting key genes.[36] The most common signaling pathways by miRNAs include Wnt (Wingless), neurotrophin, epidermal growth factor receptor (EGFR), and transforming growth factor-beta (TGF-β) pathways.[37-39] Research into the roles of exosomes in reproductive disorders is expanding rapidly. Due to their diagnostic and therapeutic potential, exosomes are anticipated to play an increasingly significant role in future gynecological disease management.[40] This review focuses on the implications in polycystic ovary syndrome (PCOS), premature ovarian failure (POF), Asherman syndrome, endometriosis, endometrial cancer, cervical cancer, ovarian cancer, and preeclampsia.

Polycystic Ovary Syndrome

PCOS is an endocrine disorder characterized by ovulatory dysfunction and hyperandrogenism. Affecting 6-8% of women globally, PCOS is associated with infertility, obesity, insulin resistance, dyslipidemia, type 2 diabetes, and cardiovascular diseases.[41-45] Follicular fluid analyses from PCOS patients revealed increased expression levels of miR-25-3p, miR-126-3p, miR-143-3p, miR-146a-5p, miR-193b-3p, miR-199a-5p, miR-199a-3p, miR-199b-3p, miR-629-5p, miR-4532, miR-4745-3p, and miR-6087. In addition, elevated levels of miR-10a-5p, miR-18a-3p, miR-20b-5p, miR-23b-3p, miR-98-5p, miR-106a-5p, miR-141-3p, miR-200a-3p, miR-200c-3p, miR-382-5p, miR-483-5p, miR-483-3p, and miR-3911 were observed. Changes in tRNA and piRNA expression patterns were also noted in exosomes derived from PCOS patients.[46-48] These miRNA alterations are implicated in the mitogen-activated protein kinase signaling pathway, circadian rhythm regulation, endocytosis, and overall PCOS risk.[46-48]Another study reported increased expression of S100-A9 in the exosomes of PCOS patients.[49] S100-A9, a calcium-binding protein secreted by ovarian, granulosa, and immune cells, is involved in cell cycle regulation, proliferation, and inflammation.[50,51] These exosomes were shown to activate the NF-κB signaling pathway in granulosa-like tumor cells and elevate pro-inflammatory factor expression.[49] This inflammatory mechanism may underlie reproductive dysfunction in PCOS.[41,49] In addition to their diagnostic value, exosomes may offer therapeutic benefits. For instance, exosomes derived from adipose mesenchymal stem cells (MSCs) alleviated PCOS symptoms by inhibiting apoptosis via miR-323-3p and altering PDCD4 expression.[52]

Premature Ovarian Failure

POF is an infertility disorder characterized by hypergonadotropism, amenorrhea, and estrogen deficiency due to follicular dysfunction. It affects approximately 1% of women aged 30-39 years.[53-55] While its etiology remains unclear, POF is considered a heterogeneous condition influenced by both genetic and environmental factors.[56] Recent studies have investigated the therapeutic potential of exosomes in POF. For example, exosomes derived from placenta-derived (PD)-MSCs increased the expression of antioxidant enzymes such as catalase and peroxiredoxin (PRDX1) in ovariectomized rats, improving ovarian function and reducing mitochondrial reactive oxygen species levels. Similarly, human amniotic epithelial cell-derived exosomes containing miR-1246 were found to restore ovarian function in POF mice via modulation of apoptosis- and phosphatidylinositol-related pathways.[57] Exosomes derived from various MSCs also improved follicular morphology and suppressed apoptosis through miR-664-5p, targeting p53.[58] Another study demonstrated that bone marrow-derived MSC (BMSC) exosomes containing miR-144-5p targeted PTEN, inhibited apoptosis, and improved ovarian function in POF rats.[59] Collectively, these studies suggest that exosome-based therapy could represent a promising approach for the treatment of POF.

Asherman Syndrome

Asherman syndrome is characterized by intrauterine adhesions caused by trauma, leading to hypomenorrhea and infertility.[60] These scar tissues obstruct blastocyst implantation and result in infertility. Although surgical intervention is commonly used to treat this condition, alternative therapeutic strategies are still required.[61,62] Recent studies suggest that exosomal therapy could be beneficial in Asherman syndrome. In a rat model, MSC-derived exosomes were shown to reduce fibrosis and promote proliferation and vascularization in uterine tissue. Following exosome application, gene expression levels of matrix metalloproteinases MMP-2 and MMP-9, proliferating cell nuclear antigen, CD31, and vascular EGFR were increased, while tissue inhibitor of metalloproteinase-2 levels decreased. These findings suggest that exosomes could be promising biomolecules for treating Asherman syndrome.

Endometriosis

Endometriosis is a multifactorial, estrogen-dependent disorder characterized by the presence of endometrial tissue outside the uterine cavity. The main clinical manifestations include pelvic pain and infertility.[64-66] Currently, no definitive treatment ensures the complete resolution of symptoms or long-term remission.[67,68] Exosomes have emerged as both therapeutic agents and biomarkers for understanding the pathophysiology of endometriosis. Some studies have identified novel diagnostic targets, while others suggest therapeutic roles for exosomes.

Exosomes derived from the endometrium have contributed significantly to elucidating the underlying mechanisms of endometriosis. In one study, exosomes isolated from peritoneal fluid samples of patients with endometriosis contained histone type 2-C, PRDX1, inter-α-trypsin inhibitor heavy chain H4, annexin A2, and tubulin α-chain.[69] Another study examining tissue and plasma-derived exosomes from endometriosis patients reported significant differences in miRNA and lncRNA profiles. Decreased expression was noted in lncRNAs LINC00293, LINC00929, MEG8, SNHG25, and RP5-898J17.1, while increased expression was observed in LINC00998, NEAT1, PVT1, H19, and RP4-561L24.3. These RNA molecules influence signaling pathways associated with angiogenesis and inflammation.[70] Exosomal miRNAs, including miR-130b, miR-145, miR-342, miR-365, miR-425, miR-432, miR-451a, miR-486-5p, miR-505, miR-1908, miR-4488, and miR-6508 have shown significant associations with inflammatory processes in endometriosis.[71] A recent study proposed that elevated serum levels of exosomal miR-22-3p and miR-320a could serve as diagnostic markers for endometriosis.[72] These findings highlight the potential of exosomes in improving diagnostic accuracy and developing novel treatment approaches. Another essential feature of exosomes is their therapeutic potential. Exosomes from healthy endometrial epithelial cells carry molecules important for embryo-endometrial interaction during implantation.[72] Application of these exosomes in endometriosis models has shown beneficial effects in modulating the ectopic endometrial environment.[73-76] Proteins such as focal adhesion kinase and various surface receptors have been shown to influence the adhesive and migratory capacities of trophoblast cells via exosomal signaling.[77] miRNAs, including miR-17, miR-30d, miR-106a, and miR-200c were found to play critical roles in implantation success when transferred by exosomes.[29,78,80] M2 macrophage-derived exosomes exhibit regenerative properties that may reduce endometriotic lesions. These exosomes, which are underrepresented or altered in patients with endometriosis, contribute to macrophage activation mediated by miR-223.[81,82] Wu et al.[83] demonstrated that miR-214 suppresses fibrosis and promotes lesion regression. Collectively, these studies suggest that exosomes may modulate immune escape, cell proliferation, angiogenesis, and lesion invasion in endometriosis. Exosomes derived from ectopic or shed endometrial tissue might also induce metaplasia or tissue repair in recipient cells through the miRNAs and specialized proteins they carry.[84]

Endometrial Cancers

Endometrial cancer is the fourth most common malignancy of the female reproductive system.[85] While most cases are diagnosed early due to postmenopausal bleeding, approximately 20% are identified at an advanced stage.[86,87] Surgical procedures, radiotherapy, and chemotherapy are commonly employed in treatment, but these approaches are often insufficient. Therefore, identifying new molecular targets and biomarkers is important for more effective disease management. Exosomes play important roles in the pathogenesis, progression, diagnosis, and potential treatment of endometrial cancer. Communication between endometrial fibroblasts and cancer cells via exosomes has been proposed.[88] In one study, exosomes derived from cancer-associated fibroblasts lacked miR-148b, contributing to tumor progression. Under normal conditions, miR-148b suppresses DNA (cytosine-5)-methyltransferase 1, a protein involved in metastasis by promoting epithelial-mesenchymal transition.[89] The absence of miR-148b in CAF-derived exosomes is believed to drive endometrial cancer progression through this mechanism. Furthermore, exosomes isolated from the plasma of endometrial cancer patients were shown to promote angiogenesis in human umbilical vein endothelial cells by activating the PI3K/AKT/VEGFA signaling pathway.[90] miR-320a, which targets hypoxia-inducible factor 1-alpha, normally suppresses VEGFA expression and cell proliferation. However, reduced levels of miR-320a in CAF-derived exosomes may facilitate malignancy in endometrial cancer.[91] Exosomes from the serum of PCOS patients have been reported to enhance the migration and invasion of endometrial cancer cells via upregulation of miR-27a-5p, which targets SADM4.[92] In another study, 114 dysregulated miRNAs were identified in exosomes isolated from peritoneal lavage fluid of endometrial cancer patients. Notable miRNAs included miR-10b-5p, miR-34b-3p, miR-34c-5p, miR-34c-3p, miR-449b-5p, miR-200b-3p, miR-383-5p, and miR-2110, all of which were proposed as novel biomarkers.[93] These studies suggest the potential importance of exosome-derived data in endometrial cancer research. Furthermore, they indicate that the sample type and cellular origin of exosomes may be critical for accurate diagnosis and effective therapeutic targeting. The biological source of exosomes may influence tumor behavior, highlighting the need for careful evaluation of exosome origin in both research and clinical applications.

Cervical Cancer

Cervical cancer originates from squamocolumnar junction cells of the cervix and is closely associated with human papillomavirus infection.[94,95] Early diagnosis, as in many cancers, is important for preventing disease progression and improving outcomes.[96] Consequently, identifying novel biomarkers for early detection is of great clinical significance. Exosomal miRNAs have been shown to be associated with the progression of cervical cancer. Increased expression levels of miR-21, miR-146a, miR-221-3p, miR-222, let-7d-3p, and miR-30d-5p were found in cervical lavage samples and cell lines, while plasma levels of miR-125a-5p were decreased in cervical cancer patients.[97-102] Among these, miR-221-3p has been identified as a key regulator of angiogenesis through its modulation of the *thrombospondin-2* gene.[103] These findings support the use of exosomal miRNAs and other molecules as potential diagnostic and therapeutic biomarkers for cervical cancer. Moreover, exosomes derived from cervical cancer cell lines have been found to carry high levels of miRNAs targeting Hedgehog signaling pathway components such as PTCH1, smoothened, frizzled family receptor, sonic hedgehog signaling molecule, Indian hedgehog signaling molecule. This

pathway is implicated in cervical cancer growth, metastasis, invasion, and drug resistanc.[104] Exosome-based analysis of this pathway may help identify novel therapeutic agents that can inhibit Hedgehog signaling and halt disease progression. Ongoing research has also demonstrated the potential of exosomes as therapeutic agents. For example, exosomes enriched with miR-22 have shown a positive effect on radiotherapy efficacy by downregulating c-Myc binding protein (MYCBP) and human telomerase reverse transcriptase (hTERT) gene expression.[105] Given the molecular cargo carried by exosomes, they may hold potential for contributing to both diagnosis and therapy in the management of cervical cancer.

Ovarian Cancer

Ovarian cancer is the most lethal gynecological malignancy and ranks among the most prevalent cancers affecting the female reproductive system.[106] More than 50% of patients are diagnosed at an advanced stage, contributing to a five-year survival rate of less than 50%.[85,107] The poor prognosis and quality of life among ovarian cancer patients are partly attributed to the absence of effective early diagnostic tools. Thus, the development of novel diagnostic and therapeutic strategies will be beneficial for identifying cases earlier and improving outcomes.[108] Exosomes secreted by ovarian cancer cells have been shown to play significant roles in tumor progression, metastasis, and invasion. Exosomal proteins such as TSG101, CD9, CD24, CD44, and CD63 contribute to the development of ovarian cancer by facilitating intercellular communication. Molecules like HSP27, HSP70, and HSP90 are highly expressed in ovarian cancer patients and are involved in disease pathogenesis.[109-113] Enzymes, such as aldehyde reductase, phosphoglycerate isomerase, fatty acid synthase, and PRDX1, together with major histocompatibility complex class I and II have also been associated with tumor development and metastasis[108,114]. In addition to their roles in tumor biology, exosomal proteins are involved in drug resistance. Elevated levels of annexin A3 in exosomes has been linked to increased platinum resistance in ovarian cancer cells.[115] Exosomal miRNAs including miR-106a, miR-130a, miR-221, miR-222, miR-433, and miR-591 have also been associated with drug resistance mechanisms.[116-120] Exosome-associated miRNAs miR-21, miR-184, miR-193b, miR-200a, miR-200b, miR-200c, miR-203, miR-214, and miR-215 have shown potential as diagnostic biomarkers for ovarian cancer.[112,114,121-123] Additional miRNAs including miR-25, miR-29b, miR-100, miR-105, miR-150, miR-187, miR-221, and miR-335 are implicated in the development of malignant ovarian tumors.[112,114,124] Notably, miR-21 has emerged as a critical player in oncogenesis and metastasis in serous ovarian carcinoma, functioning as an oncomiR.[125] Moreover, exosome-delivered molecules have therapeutic potential. For instance, miR-29c, miR-101, miR-128, miR-182, miR-506, and miR-520d-3p are under investigation as possible treatment targets for ovarian cancer.[126] Together, these studies suggest that non-coding RNAs and proteins delivered via exosomes may play important roles in the biology, diagnosis, and treatment of ovarian cancer. Gaining a better understanding of the mechanisms through which exosomes influence ovarian cancer progression could potentially contribute to the development of more effective therapies and improved disease management.

Preeclampsia

Preeclampsia is a hypertensive disorder of pregnancy responsible for 10-15% of all fetal deaths. It is associated with significant maternal and fetal morbidity and typically occurs after the 20th week of gestation. The condition is often characterized by placental hypoxia.[127-130] Despite considerable research, the molecular mechanisms underlying preeclampsia remain unclea.[131-133] Recent evidence suggests that exosomes released by placental trophoblasts into maternal circulation may contribute to the pathogenesis of preeclampsia.[134] Hypoxic conditions in the placenta are known to increase the release of exosomes from the syncytiotrophoblast layer.[135,136] Therefore, analyzing the contents of PD exosomes may help to understand disease pathogenesis and improve diagnostic capabilities. Increased levels of syncytin a protein involved in the differentiation of syncytiotrophoblasts from villous trophoblasts, have been found in the exosomes of preeclamptic patients. These trophoblasts play a key role in remodeling maternal spiral arteries and differentiating vascular endothelial and smooth muscle cells.[137-139] Exosomal profiling in preeclamptic patients revealed that miR-23a-3p, miR-125b-2-3p, miR-144-3p, miR-192-5p, miR-205-5p, miR-208a-3p, miR-335-5p, miR-451a, miR-518a-3p, and miR-542-3p were downregulated. In contrast, miR-7a-5p, miR-17-5p, miR-26a-5p, miR-30c-3p, miR-141-3p, miR-199a-3p, miR-221-3p, miR-584-5p, miR-744-5p, and miR-6724-5p were upregulated.[140-143]

Safety of Exosomes

Exosomes have been shown to distribute into all body compartments bypassing blood-brain barrier, blood testis barrier and blood follicle barriers.[144-146] This suggests a novel use for exosomes as drug delivery agents. This is in addition to their potential as diagnostic agents in different diseases and direct use as therapeutic agents. Specific tissue cell culture exosomes were classified as enhanced exosomes while natural *in vivo* produced exosomes from stem cells can be classified as naive exosomes.[147] Naive exosomes are mostly obtained from human umblical cord stem cells, human umblical cord blood stem cells, human and human induced pluripotent stem cell derived MSCs.[148] Exosomes were not reported to cause immunologic reactions and can be applied to the area of inflamation.[149] Exosomes were not shown to form teratomas in contrast to some stem cell therapie.[150]

Advences in technology are driving progress in the diagnostic and therapeutic strategies for gynecological diseases. However, new approaches are still needed to address the complexities of these conditions. Research suggests that exosomes offer promising potential in gynecological disorders by providing new mechanisms for diagnosis, treatment, and disease monitoring. Exosome-based studies are expected to make substantial

contributions to understanding and managing gynecological diseases, particularly through the identification of novel diagnostic markers and therapeutic targets, and improved patient monitoring strategies.

Footnote

Authorship Contributions

Literature Search: N.Ç., H.S., Writing: N.Ç., H.S.

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