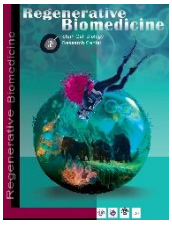

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Review Article

Exosomes: the Future of Stem Cell Therapy in the Female Reproductive System

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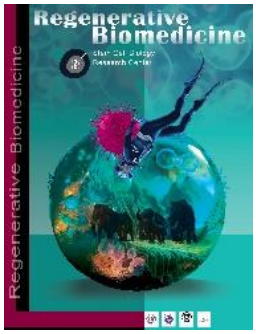
Abstract

Exosomes (Exos) are extracellular nanovesicles that are released from almost all cells. Events such as disposal of waste proteins, antigen supply, immune response, angiogenesis, inflammation, metastasis, spread of pathogens and many other activities, including the roles of these vesicles, depend on their content in the body. The growth and function of multicellular tissue requires intercellular communication, so Exos are one of the strategies for cellular cross-talk. Recent studies have shown that during implantation, Exos can participate in the complex dialogue between the embryo and maternal tissues. Here, we review the state of research on exosomes in diseases related to the female reproductive tract, focusing on their biological role in follicogenesis, early embryonic development, as well as the implantation process. Isolation and use of Exos compared to cell therapy has significant advantages, such as: increased stability, reduced contamination of the culture medium, non-rejection of cells due to surface markers participating in the immune system, non-tumorigenesis and reduced problems in maintenance, and their displacement has been noticed in recent years.

Keywords: Exosome, Exosome Therapy, Female reproduction, microRNA, Regenerative Medicine



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Introduction

There are different ways for cells to communicate with each other (1). These connections are established through several mechanisms, such as paracrine, juxtacrine, and autocrine methods (1). In recent decades, scientists realized that cells, in addition to secreting soluble factors, produce a series of nanovesicles called Exos, and in this way communicate with nearby and distant cells (2). Exos were first discovered by Pan and Johnstone in 1983, who reported that the release of transferrin into the extracellular space during maturation of sheep retinoblasts was associated with a variety of small vesicles (3). Exos are small vesicles with a phospholipid bilayer membrane, a size of 50 to 150 nm, which are present in almost all body fluids, such as blood, urine, serum, saliva, semen, ... (4, 5). The cargos of EVs are heterogeneous, such as nucleic acids (DNA, mRNA, microRNAs, and long non-coding RNAs), lipids, a variety of proteins, membrane and binding transporters (Annexin, GTPase), tetraspanins (CD6, CD9, CD63, CD81, CD82), and heat shock proteins (Hsp90, Hsp70) (6) (3). Among the nucleic acids, microRNAs are present in a higher proportion in Exos (1). ExoCarta database for EVs has been developed, with more than 8,000 proteins and 195 lipids associated with Exos (5). Some studies related to the application of Exos are listed in Table 1.

The use of Exos in clinical trials is increasing, so researchers are trying to study the behavior and biology of Exos in pathological conditions in various diseases.

The purpose of this review is to summarize the current knowledge about the physiological roles of Exos produced by the tissues of the female reproductive tract and embryo as intercellular messengers in the process of embryo implantation. We have also reviewed how Exos are gradually replacing stem cell therapy in assisted reproductive techniques (ART).

How are Exos biosynthesized?

Exosomes are formed by the cell through a process known as endocytosis .Next, the cell membrane folds inward and forms small pouches within the cell. They grow to become larger receptacles termed endosomes. In the endosomes, more small pouches or vesicles are formed. They are termed multivesicular bodies. Eventually, these bodies merge with the outside membrane of the cell, releasing the small vesicles outside the cell into the surrounding space. These released vesicles are what we call Exos (4).

Exos interaction with the target cell

Generally, Exos can be in contact with the target cell in three ways: Firstly, the membrane proteins of Exos bind to the receptors of the target cell. Secondly, Exos merge into the plasma membrane of the target cell and transfer their contents into the cell (7). Lastly, Exos can enter the cell in two ways: they can be engulfed by the target cell, fuse with endosomes, and be transferred to neighboring cells by transcytosis, or they can enter the endosomes of the target cell and be routed to lysosomes for breakdown (7).

The role of Exos in various biological processes within the female reproductive system

Recent studies have shown that exosomes serve a specific and decisive function at pivotal stages of reproduction, including granulosa cell development, oocyte growth,

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Table 1: Exos Applications .

Reference	Disease models	Exos Applications
Van den Boorn JG, et al, 2013	Alzheimer's disease, heart failure, and inflammation	Carrier of drug factors
Yu B, et al, 2014	Types of cancer and non-cancer diseases	Biomarker and check the treatment of the disease
Yamashita T, 2018	Cardiovascular diseases, bone diseases, renal diseases, metabolic diseases, neural diseases	Exos therapy
Srivastava, et al, 2022	Head and neck cancer, breast cancer, liver cancer, glioblastoma cancer	Carrier of drug factors

follicle growth, ovulation, fertilization, embryogenesis, and implantation. In recent years, due to the advantages of using exosomes, this method has become an alternative to cell therapy. Some studies related to cell therapy are listed in Table 2.

Exos in follicogenesis

According to studies, follicular fluid has provided an important environment for oocyte development due to its composition, including proteins, metabolites, ions, plasma compounds, and types of non-coding and regulatory RNAs.

Exos therapy using granulosa cells is important research considering the presence of several microRNAs associated with fertilization and embryo quality, including miR-21, which positively impacts the growth of the fertilized oocyte, embryo development, and regulation of anti-apoptotic gene expression. For the first time in 2013, Exos were detected in human follicular fluid (FF) by electron microscopy, and several miRNAs were identified (7). Da Silveira and their team gathered Exos from young and old mares and noticed that the expression of certain miRNAs varied depending on the stage of the follicles (8). They also discovered that when older mares had higher levels of miR-181a, miR-375, and miR-513a-3p in their follicular fluid, it affected how oocytes matured. This happened because these miRNAs stopped the TGFβ pathway from working properly, which is a key gene involved in that process (8).

Exos in embryo development and implantation:

In 2017, Pavani and their team did a study where they grew a group of early-stage embryos in a lab setting. They found that signals within and between the embryos, like proteins, growth factors, metabolites, and exosomes, play a role (9). Pavani and their team in 2018 showed that using a medium with bovine serum albumin and extracellular vesicles from conditioned embryo culture medium helped reduce cell death and improve the rate of blastocyst formation (10). It seems clear that Exos, by mediating the dialogue between the endometrium and the embryo, perform a basic role in human implantation (11). Moreover, characterization of their cargo could be useful in embryo selection and information about endometrial receptivity (11). Vilella and their team found that miR-30d was taken up by the trophoblastic cells in mouse embryo tissues from the endometrial fluid. This affected the embryo's genetic activity and how it sticks to

Table 2: cell-based therapy in the female reproductive system

References	Goals	Conclusion
Larry, et al, 1998	To evaluate the effect of autologous endometrial coculture versus conventional medium on pre-implantation embryo development	Increasing the number of blastomeres in the pre-implantation embryo and a decrease in the fragmentation rate
Ling, et al, 2008	Effect of conditioned medium (CM) of mesenchymal stem cells on the in vitro maturation and subsequent development of mouse oocyte	Increasing Production of estrogen C.M. is an effective medium for pre-antral follicle growth, oocyte maturation, and sequential embryo development
Ghadami M et al, 2012	Effect of BMSCs on the POF mouse model	Increasing the number and Estradiol. decreasing FSH
Tan J et al, 2016	Effect of MenSCs on Asherman's syndrome	Increasing the endometrial thickness
Cao Y et al, 2018	Effect of UCSCs on Intrauterine adhesions in humans	Increasing the endometrium thickness and live birth rate
Jafari Atrabi, et al,2019	Formation and activation induction of primordial follicles using granulosa and cumulus cells conditioned medium (CCC.M)	Enhance in vitro activation of primordial follicles, probably through down-regulation of PTEN
Zhang, et al, 2021	Concentrated Exos from menstrual blood-derived stromal cells improves ovarian activity in a rat model of POI	Improved ovarian morphology, follicle numbers, regulated serum hormones, ECM remodeling, restored fertility in POI rats in vivo
Li, et al, 2021	To evaluate the effect of hUCMSC-Exos on Ovarian Function in the POI model	Hormone levels and the number of ovarian follicles returned to nearly normal levels, Improved reproductive outcomes. In vitro, co-culture with Exos improved the proliferation of ovarian GCs

the uterine lining, as shown by lab experiments (12). In 2013, Ng and others used bioinformatics tools to show that microRNAs in exosomes were involved in controlling several KEGG pathways that are important for implantation (13). Some studies investigating exosomal microRNAs are summarized in Table 3.

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Table 3: Exos and miRNA analysis in the female reproductive system

References	Goals	Conclusion
Perrini, et al, 2016	Microvesicles secreted from equine amniotic-derived cells and their potential role in reducing inflammation in endometrial cells in an in vitro model	Decreasing Apoptosis, TNF-α, IL-6, IL-1β, MMP-1, and 13. Increasing anti-inflammatory cytokines, miR-26a-2 , 335, 146a in EV of AMC
Qing et al, 2017	Effects of embryo-derived Exo on the development of bovine cloned embryos	Embryos can secrete Exo into the culture medium during IVC. Exos are essential for blastocyst formation, quality, and following development to term. removal of Exo induced by culture medium replacement impairs embryo development, which can be avoided by non-renewal culture procedure or markedly recovered by Exo supplementation
Giacomini et al,2017	Human pre-implantation embryos at different developmental stages can release EVs during their IVC for ART procedures	The embryonic origin of these EVs has been confirmed by the presence of stemness gene transcripts and their enrichment in HLA-G protein
BlaÂzquez, et al, 2018	Murine embryos exposed to human endometrial MSCs-derived EV	Increasing the blastomere count, embryo hatching
Marinaro, et al, 2019	Characterization of EVs released by menstrual blood-derived enMSCs and unraveling the proteome and microRNAome of these EVs	miR 143-3p, 16-5p, 21-5p, let-7b-5p inhibited IGF1R and induced Proliferation, Survival, Adhesion
Marinaro, et al, 2019	To evaluate the effect of EV-enMSCs on embryo quality in an aged murine model	Enhance embryo quality, Blastomere count, and morphokinetic events
Liu et al., 2020	Let-7 derived from endometrial EV is an important inducer of embryonic diapause in mice	Co-culture study of blastocysts with let-7g-enriched EVs also resulted in prolonged survival of blastocysts by inhibition of both the C-MYC/mTORC signaling pathways
Yang et al, 2020	Human UCMSC-Derived Exo Mitigate the Age-Related Retardation of Fertility in Female Mice	UCMSC-exos as a new approach to mitigate the age-related retardation of fertility in women

Conclusion

Exos have created a new therapeutic observation for the transfer of biological molecules and drugs. One of the main causes of failure during ART procedures is the inability of the embryo to implant. results showing that during IVC for ART human embryos can secrete EVs that can be easily uptaken by the maternal side raise some exciting possibilities regarding their potential therapeutic use as a co-factor for promoting the establishment of a successful pregnancy.

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