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Exosomes: New regulators of reproductive development

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ABSTRACT

Exosomes are a subtype of extracellular vesicles (EVs) with a size range between 30 and 150 nm, which can be released by the majority of cell types and circulate in body fluid. They function as a long-distance cell-to-cell communication mechanism that modulates the gene expression profile and fate of target cells. Increasing evidence has indicated exosomes' central role in regulating various complex reproductive processes. However, to our knowledge, a review that focally and vividly describes the role of exosomes in reproductive development is still lacking. This review highlights our knowledge about the contribution of exosomes to early mammalian reproduction, such as gametogenesis, fertilization, early embryonic development, implantation, placentation and pregnancy. The discussion is primarily drawn from literature pertaining to the mammalian lineage with emphasis on the roles of exosomes in human reproduction and laboratory and livestock models.

1. Introduction

Extracellular vesicles (EVs) are membrane-derived vesicles released by cells into the extracellular space, with important roles in cell-to-cell communication and regulating a range of biological processes [1]. The past decade has witnessed a rapid growth in knowledge of the classes and characteristics of EVs and their physiological and pathological roles. The main classes of EVs are apoptotic bodies, microvesicles and exosomes [2]. Among the three kinds of EVs, exosomes have unique physical and chemical properties, with a diameter of 30–150 nm and a density of 1.13–1.19 g/mL. Exosomes are composed of lipids, proteins, mRNAs, miRNAs and DNAs, which depend on the cell of origin [3]. A large variety of constitutive elements have been identified in exosomes from different cell types, including approximately 4400 proteins, 194 lipids, 1639 mRNAs, and 764 miRNAs [4]. Therefore, exosomes have become one of the ideal targets for developing drug transport carriers due to their nanoscale size, excellent stability, biocompatibility, permeability, low toxicity and low immunogenicity [5,6].

The functions of exosomes depend on the origin of the cell, and are involved in immune response, antigen presentation, programmed cell death, angiogenesis, inflammation, coagulation, and morphogen transporters in the creation of polarity during development and differentiation [7]. Increasing evidence has established a central role of exosomes in reproductive development and reproductive diseases [8,9]. In this paper, we summarized the role of exosomes in the delicate and complex reproductive process from gametogenesis to early pregnancy in human and laboratory and livestock models. Moreover, due to the natural transport medium of biomolecules and the development of a drug delivery platform for exosomes, they participate in intercellular communication and their cargos can be used as diagnostic biomarkers or therapeutic candidates for reproductive diseases.

2. Exosomes

2.1. Exosome genesis and transport

Exosomes released by different cells have similar biosynthesis pathways, all of which originate from endocytosis (Fig. 1). An early secretory endosome is formed by intracellular plasmic membrane invagination, which then buds inward and envelops proteins, nucleic acids and other substances to further mature, forming intracavitary vesicles (ILVs) contained in the endosome, called multivesicular bodies (MVBs). Eventually, ILVs fuse with the plasma membrane as exosomes and are released extracellularly [10]. Therefore, most proteins contained in exosomes are dependent on the endocytosis network, which is the basis of homogenization and standardized identification of exosomes.

Endosomal sorting complex required for transport (ESCRT) is the central molecular mechanism of exosome formation at endosomes [11].

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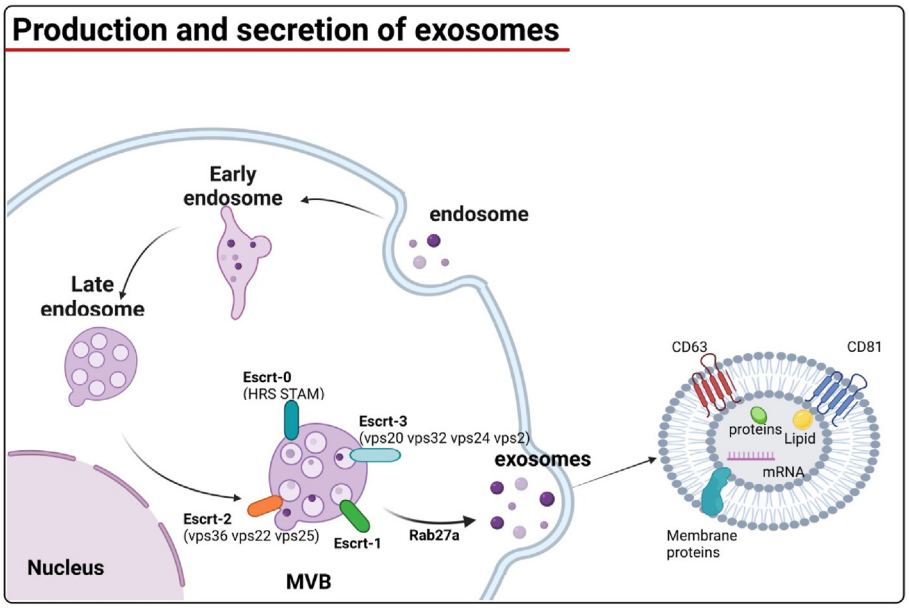

Fig. 1. Production and secretion of exosomes. The production of exosomes involves the double invaginations of plasma membrane and the formation of Intraluminal vesicles (ILVs) and Multivesicular bodies (MVBs). The first invagination of the plasma membrane forms early-sorting endosome (ESE). ESEs develop into mature late-sorting endosomes (LSEs) and eventually form MVBs. MVBs contains multiple ILVs. MVBs are degraded by fusion with lysosomes or autophagosomes, or fuse with plasma membranes to release the contained ILVs as exosomes. The secretion and transport of exosomes are mainly mediated by the Endosomal sorting complex Required for transport (ESCRT) on the MVBs membrane. ESCRT is mainly composed of ESCRT-0, –I, –II and –III complexes. Escrt-0 (HRS and STAM) regulates content aggregation through ubiquitination dependent pathways, ESCRT-I and ESCRT-II (Vps36, Vps22 and double-copy Vps25) induce bud formation. Escrt-III is composed of four core subunits: Vps20, Snf7 (Vps32), Vps24, and Vps2, as well as accessory proteins Did2, Vps60, and Ist1, which mainly promote membrane separation and vesicle cleavage. In addition, Rab27a and Rab27b, members of the Rab family GTPases, act on the docking of MVBs to the plasma membrane. ARF6 is a regulator of ILVs budding and exosome biosynthesis, which can promote the formation of ILVs.

ESCRT mechanism is comprised of approximately thirty proteins arranged into four proteins complexes, i.e., ESCRT-0, –I, –II, and-III, along with associated proteins such as vacuolar protein sorting 4 (VPS4), VPS20 associated 1(VTA1) and ALIX [12]. The ESCRT mechanism is initiated by recognition and sequestration of ubiquitinated proteins to specific domains of the endosomal membrane via ubiquitin-binding subunits of ESCRT-0 [13]. It also recruits complexes ESCRT-I and –II capable of cargo binding. After interaction with the ESCRT-I and –II complexes, the total complex will then combine with ESCRT-III, a protein complex involved in promoting the budding process. Finally, ESCRT-III promotes membrane separation and causes vesicles to break apart, thus forming ILVs [14]. As for the formation process of exosomes, sphingomyelin inhibitor GW4869 has been proven to inhibit the release of exosomes from MVBs by blocking the germination of polyvesicles in macrophages, epithelial cells, interstitial cells and other cells, thus regulating various pathophysiological processes [15,16]. However, some studies have found that GW4869 can promote the secretion of exosomes at doses that do not induce apoptosis, but inhibit the secretion of exosomes only at higher concentrations that induce apoptosis [12]. Therefore, there is also an ESCRT-independent mechanism for the formation of ILVs and MVBs assisted by lipids, amides, tetraspanins or heat shock proteins [17]. In addition, the formation of MVBs is a calcium-dependent mechanism, and dimethyl amiloride (DMA) is also used to inhibit the release of exosomes as a sodium-calcium exchange inhibitor [18]. In reproductive studies, GW4869 was used only as an exosome inhibitor to elucidate the mechanism of exosomes in endometrial matrix injury and early abortion [19,20]. DMA can play a separate role in the regulation of sperm fertilization and oocyte maturation due to its regulation of Na^+, H^+ and Ca^{2+} exchange [21,22]. In a word, GW4869 is the preferred exosome inhibitor in various studies. However, researchers should reevaluate the inhibitory effect of GW4869 in different studies.

Upon formation, exosomes pinch off from the plasma membrane and prime them for secretion, including autocrine, paracrine and endocrine [23]. Once exosomes are released into the extracellular environment, the ability of exosomes to interact with recipient cells and transfer proteins, lipids and nucleic acid contents determines its role in physiological and pathological processes. It has been reported that the membrane proteins transfer during direct cell-to-cell contact [17]. Endocytosis, membrane fusion and receptor-ligand mediated interactions are the three main ways for exosomes to get into the target cells [24,25].

2.2. Isolation and identification of exosomes

Although it is difficult to separate exosomes completely from other EVs, a set of standardized extraction and identification methods for exosomes have been widely accepted and applied by researchers. To date, the most commonly used separation methods in exosome studies are ultrafast centrifugation and exosome extraction kit based on polyethylene glycol (PEG) precipitation. For the identification of exosomes, electron microscopes have been used to observe cup shape, and Nanoparticle Tracking Analysis (NTA) is used to measure particle sizes in the range of 30–150 nm. Western blot was used to detect the high expression of positive marker proteins in exosomes (transmembrane proteins CD63, CD9, CD81, soluble protein TSG101 and Alix) and negative marker proteins in exosomes (endoplasmic reticulum protein Calnexin, nuclear proteins histone and Golgi protein GM130). At present, the international standard is to detect three positive proteins (including exosome transmembrane protein and solute protein) and one negative protein.

3. The role of exosomes in gametogenesis and maturation

In the sexual reproduction of higher organisms, sperm and ovum are bridge of generation alternation and life ring of the continuation of genetic life. The maturation and function of germ cells are critical for future reproductive success. Increasing evidence suggests that exosomes play important roles in the genesis and maturation of sperm and ovum.

3.1. The role of exosomes in spermatogenesis and maturation

3.1.1. Spermatogenesis

Spermatogenesis is a very complex cell differentiation process, which can be divided into four stages: spermatogonial stem cell proliferation and differentiation, spermatogonial meiosis, spermatogenesis and sperm maturation. Sertoli cells, which envelope the developing germ cells during spermatogenesis, coordinating germ cell development and spermatogenesis by offering nutrients and participating in the formation of

the blood-testis barrier. Recent studies suggest that exosomes released by Sertoli cells in the testis can get into the spermatogenic tubules during sperm differentiation (Fig. 2a). However, there are few reports on the role of exosomes in spermatogenesis and maturation in testicular tissue.

3.1.2. Spermioteleosis

Semen consists of spermatozoa and secretions from the accessory gonads (spermatoplasm), in which the total volume of testicular and epididymis secretions is 60%, prostate secretion is about 30%, and other accessory gonads are about 10%. Increasing evidences have reported that these bioactive regulatory molecules carried by exosomes from seminal plasma are involved in the regulation of spermatogenesis, modification and fertilization (Fig. 2b). Sperm produced by testicular spermatogenic tubules are not fertile when they enter the epididymis. Exosomes mediate numerous modifications and gains when sperm leave the testes and enter the epididymis [26–29]. In human, bovine and mouse models, the cargo of epididymosomes derives from epididymal fluid, epididymal cauda and caput have differential cargo loading respectively [30]. In a cat model, epididymal caput, corpus and cauda derived exosomal proteins are related to motility, zona pellucida binding and acrosome reaction, and have been linked to teratospermia [31]. Sperm adhesion molecule 1 (SPAM1) [29,32], glioma pathogenesis-related 1-like protein 1 (GliPr1L1) [33] and metalloproteases [34] play important roles in fertilization. Proto-oncogene tyrosine-protein kinase Src (cSrc) and macrophage migration inhibitory factor (MIF) have an effect on capacitation and motility [35,36]. Liprin α3 is an important component for sperm to undergo the acrosome reaction [37]. Moreover, epididymosomal cargo incorporated into sperm and transported to specific areas of the sperms based on the region of the epididymis from which they are released [38]. These molecules are transported to the fibers of the flagellum and play important roles in sperm motility [39,40]. Molecules bound to the zona pellucida are transported to the plasma membrane and coat the acrosome [41]. The fusion of epididymosomes with sperm and the redistribution of inclusions are mediated by milk fat globule-EGF Factor 8 (MFGE8) [42].

The prostate is the largest accessory gonad in men. Secretions from the prostatic epithelium into the prostatic ducts make up to one-sixth of the ejaculate which then mixes with sperm from the vas deferens. Sperm within the ejaculate is not yet fully functional and must first undergo capacitation, and prostasome can deliver cyclic adenosine monophosphate (cAMP) to stimulate protein kinase C activity, which drives the capacitation [43]. In addition, prostasome also transports cyclic adenosine diphosphate and Ca^{2+} signaling molecules to sperm [28]. Intracellular regulation of Ca^{2+} is critical for sperm motility and

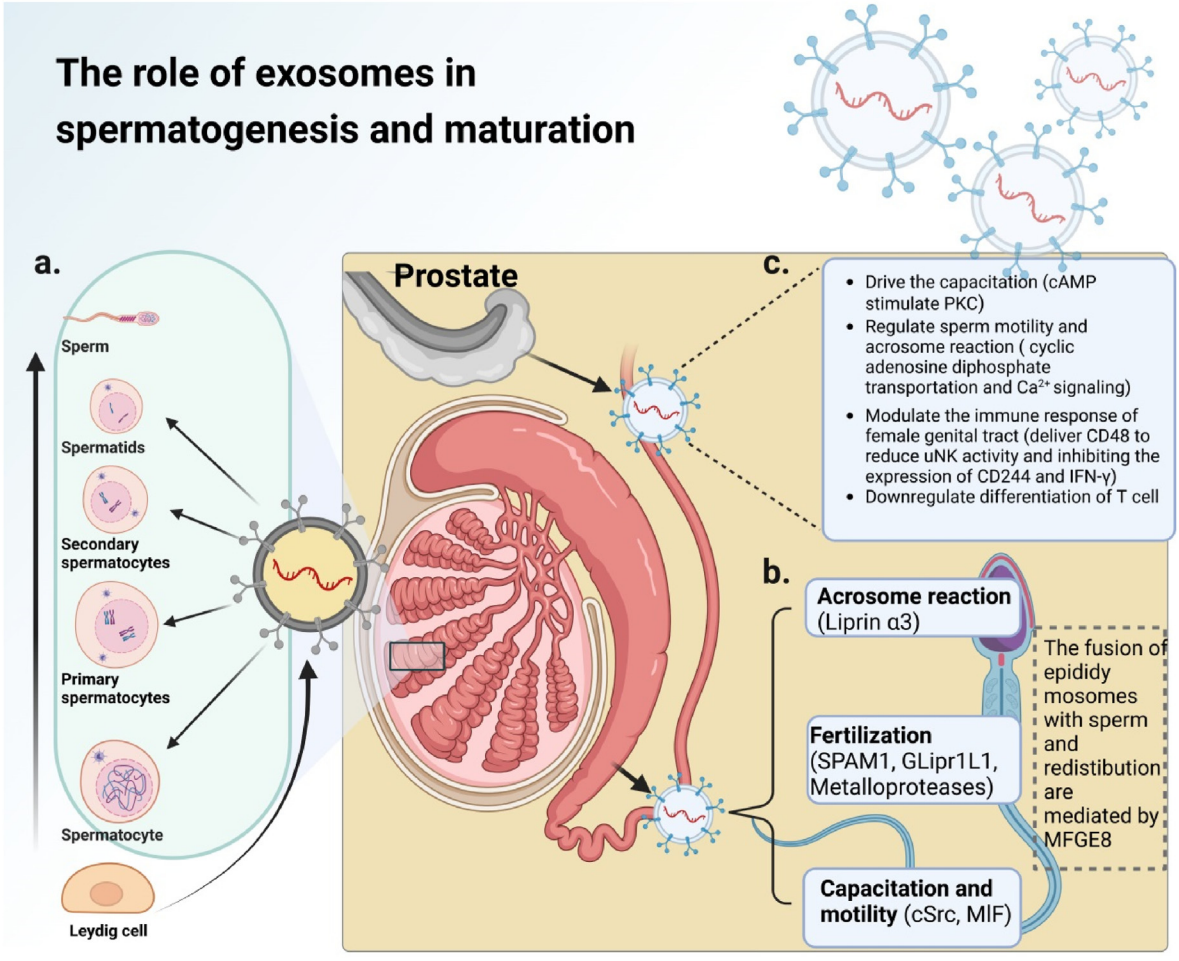

Fig. 2. The role of exosomes in spermatogenesis and maturation. Increasing evidences have reported that exosomes derived from seminal plasma are involved in the regulation of spermatogenesis, modification and fertilization ability. (A) Exosomes secreted by Sertoli cells in the testis can get into the spermatogenic tubules during sperm differentiation. (B) Sperm produced by testicular spermatogenic tubules are not fertile. Exosomes mediate numerous modifications and gains when sperm leave the testes and get into the epididymis [26–29]. The cargo of epididymosomes derives from epididymal fluid, caudal and distal have differential cargo loading [30]. Epididymal caput, corpus and cauda derived exosomal proteins are related to motility (cSrc and MIF), fertilization (SPAM1, GliPr1L1 and Metalloproteases) and acrosome reaction (Liri α3) [31]. (C) Sperm within the ejaculate are not yet fully functional and must first undergo capacitation, and prostasome can drive the capacitation response [43] and modulate the immune response of female genital tract [46].

interaction with oocytes during acrosome reaction [26,28] (Fig. 2c). The interaction of sperm and seminal fluid derived exosomes occurring only after ejaculation means the majority of their association and transfer of cargo occurs in the lower part of female genital tract [44]. Once sperm enter the female genital tract, exosomes derived from seminal fluid persistently modulate and adapt the maternal immune response both to sperm and developing semi-allogenic conceptus [45]. The prostasome expressing CD48 can inhibit the expression of CD244 in uterine natural killer (uNK) and reduce the activity of uNK and the secretion of interferon-γ (IFN-γ) [46]. The combination of these effects may be protective to sperm traversing the female reproductive tract and subsequent embryo implantation. In addition, the prostasome expressing CD48 protects sperm from attack by the complement system of the female genital tract [46]. In a porcine model, exosomes protect spermatozoa in the female genital tract by down-regulating T cell differentiation, while the alteration of inflammatory pathway may be a key aspect to regulate the implantation window of embryos [47].

The male gamete and female genital tract are dynamic in preparation for fertilization and subsequent implantation of embryos. Related studies have found the acid-base environment of the genital reproductive tract affects the binding site of exosomes and sperm. An acidic environment promotes the fusion of exosomes and sperm middle section, and a neutral environment promotes the fusion of exosome and sperm head [28]. In *In vitro* models, spermatozoa can also uptake endometrial cell derived exosomes and increase capacitation potential of sperm [48].

3.2. The role of exosomes in oogenesis

3.2.1. Before ovulation

A mature ovarian follicle contains an oocyte that is surrounded by several cell populations. The closest layer to the oocyte is the Zona pellucida surrounded by corona radiata granulosa cells, cumulus granulosa cells and mural granulosa cells (GCs) that surround the antrum of a follicle filled with follicular fluid (FF). The outermost layer of the follicular cells is theca cells (TCs) with distinctions for the outer and inner layers [49]. The FF of follicular cell secretion contains a variety of components, including proteins, hormones and exosomes [50]. Recent studies have shown that FF derived exosomes play a vital and supportive role in various reproductive processes such as cumulus expansion [51] and meiotic resumption of oocytes [52], ovarian physiology, modulation of the oviduct in preparation for fertilization and embryo development [53]. The above-mentioned processes are affected by the miRNA and mRNA delivered by exosomes, which affect mitogen-activated protein kinase (MAPK), transforming growth factor β (TGF-β), ErbB, Wnt and ubiquitin-mediated pathways [54] (Fig. 3a). For instance, exosomal miR-130b promotes oocyte maturation and the proliferation of cumulus and granulosa cells by targeting Smad family member 5 (*SMAD5*) and mitogen and stress-activated protein kinase 1 (*MSK1*) during the development of bovine oocytes [55]. In porcine models, exosomal miR-146b was significantly upregulated during follicular atresia and increased the apoptosis of ovarian granulosa cells by inhibiting *CYP19A1* [56]. In addition, FF derived exosomes can also protect the oocyte from heat stress [57,58].

3.2.2. After ovulation

Oocytes enter the oviduct after ovulation. Oviduct derived exosomes (Oc-Exo) can improve the physiological state of cumulus cells, including cell density, viability and proliferation and reduce the accumulation of reactive oxygen species and apoptosis rate (Fig. 3b). Oc-Exo can also effectively enhance the physiological state of cumulus cells in the process of GW4869 or gefitinib treatment through epidermal growth factor receptor (EGFR)/MAPK signaling pathway [59]. In addition, communication between the ovarian follicle and the cumulus cells is crucial for follicle maturation, and to produce an oocyte capable of fertilization and supporting subsequent embryonic development [57].

4. Regulation of fertilization by exosomes

4.1. Sperm travel in the female genital tract

Sperm need to pass through the vagina, uterus and fallopian tube before reaching the site of fertilization, and then encounter with oocyte,

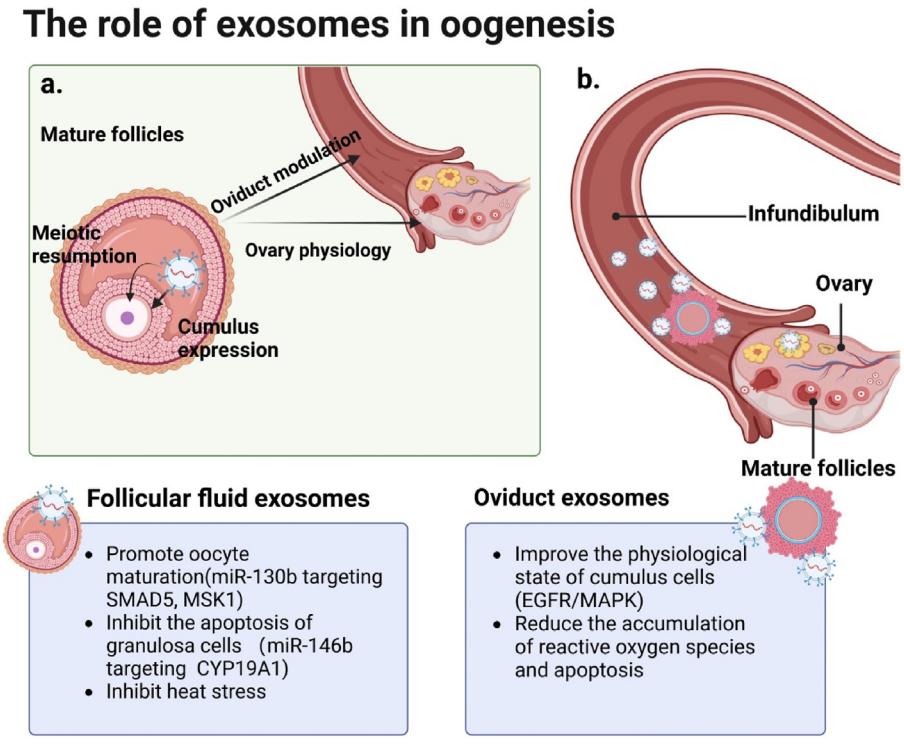

Fig. 3. The role of exosomes in oogenesis. Communication between the ovarian follicle and the cumulus cells is crucial for the follicle maturation, and to produce an oocyte capable of fertilization and supporting subsequent embryonic development. (A) Recent studies have shown that follicular fluid (FF)-derived exosomes play a vital and supportive role in various reproductive processes such as cumulus expansion [51] and meiotic resumption of oocytes [52], ovarian physiology, oviduct modulation in preparation for fertilization and embryonic development [53]. (B) Oviduct exosomes (Oc-Exo) can improve the physiological state of cumulus cells, including cell density, viability and proliferation, and reduce the accumulation of reactive oxygen species and apoptosis [59].

triggering acrosome reaction and vitelline membrane reaction, and finally completing fertilization [60]. Sperm fertilization is an extremely complex regulatory process. Most sperm are stored in the female genital tract, and exosomes derived from female genital tract cells play important roles in maintaining sperm fertilization ability [61]. When sperm passes through the uterus, the uterine cell derived exosomes (uterosomes) carrying transmembrane proteins and glycosyl phosphatidylinositol junction protein (SPAM1), which are essential for sperm fertilization and enhance the ability to cross the cumulus cell [62](Fig. 4a). When sperm passes through the oviduct, Oocyte derived exosomes (Oc-Exo) carrying specific sugar protein membrane Ca^{2+}-ATpase 4 (PMCA4) to the sperm surface and increase resistance to zona pellucida hydrolysis and harden zona pellucida and reduce multiple sperm fertilization and improve sperm motility and prevent premature sperm capacitation [63]. Oc-Exo can also promote sperm capacitation by increasing the induction of tyrosine phosphorylation at appropriate times, thus triggering acrosome reaction [64] (Fig. 4b).

4.2. Sperm-egg fusion

In the process of sperm-egg fusion, human semen derived exosomes participate in the process of sperm-egg fusion through glutathione peroxidase-5 (GPX5), SPAM1, prostate-specific antigen (PSA), kinesin family member 5B (KIF5B), annexin A2 (ANXA2) and kallikrein 2 (KLK2) [65]. Sperm fertilization can be affected by any abnormality in the expression of these proteins [66]. Oocyte derived exosomes (Oo-Exo) have also been shown to play important roles in acrosome reaction that occur when sperm contact with oocytes. Oo-Exo that carries the CD81 is responsible for the transfer of CD9. Both tetraspanins are involved in sperm-egg fusion and act independently of each other [67] (Fig. 4c). To date, there are many unanswered questions about the mechanism by which exosomes regulate gamete/embryo-maternal interactions. Therefore, we suggest that the role of exosomes must be fully elucidated in conjunction with the studies of reproductive hormones.

5. The role of exosomes in early embryonic development

5.1. The embryo that develops and transports in the fallopian tube

The development of the mammalian preimplantation embryos encompasses the period from fertilization to implantation [68]. During the migration of the embryo from the fallopian tube to the uterus, the embryo goes through different stages of development (cleavage, morula, blastula and gastrula). The exosomes mediate two-way trafficking of molecules for embryo-maternal communication (Fig. 5). Labelled *in vivo* exosomes derived from bovine oviduct flushing fluid were internalized by *in vitro* produced embryos [69]. Both *in vivo* exosomes and *in vitro* exosomes isolated from bovine oviduct epithelial cells were shown to exert a positive effect on the development and quality of embryos produced *in vitro* from cattle [59]. Mass spectrometry analyses showed that the protein content of exosomes derived from oviduct flushing fluid and oviduct epithelial cells was significantly different [59]. In *in vitro,* exosomes supplementation altered the transcription of bovine embryos, suggesting a possible role of exosomal miRNA cargos in controlling embryonic development [70]. The addition of oviduct epithelial cells-derived exosomes *in vitro* increased the birthrate of transplanted mice due to the decrease in apoptosis rate and the improvement of embryonic cell differentiation [71].

5.2. Communication between the embryo and the uterus before implantation

When embryos go through the blastula stage and enter the uterus, the hatching blastula is composed of three cell types: the outer epithelial trophectoderm (Tr), the primitive endoderm (PE) and the pluripotent inner cell mass (ICM) [72]. The connection between the blastula and the uterus is strengthened to enable subsequent implantation. For example, miR-661 derived from human blastula was up-taken by endometrial epithelial cells and inhibits the adhesion of blastula adhesion and

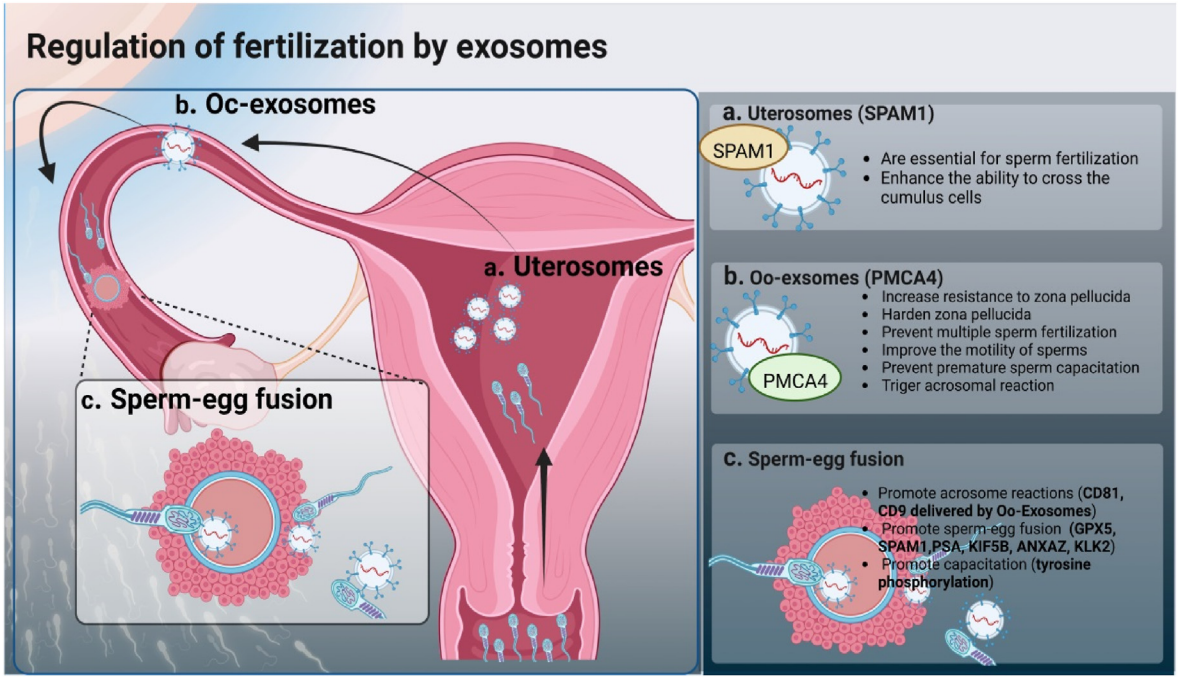

Fig. 4. Regulation of fertilization by exosomes. Sperm need to pass through the vagina, uterus and fallopian tube to reach the site of fertilization, exosomes derived from female genital tract cells play important roles in maintaining sperm fertilization ability. (A) When sperm passes through the uterus, the utero-derived exosomes (uterosomes) are essential for sperm fertilization, and enhance their ability to cross the cumulus cells [62]. (B) When sperm passes through the oviduct, Oocyte exosomes (Oc-Exo) carrying specific sugar protein membrane Ca^{2+}-ATpase 4 (PMCA4) to the sperm surface, increases resistance to zona pellucida hydrolysis, hardens zona pellucida, reduces multiple sperm fertilization, improves sperm motility and prevents premature sperm capacitation [63]. (C) In the process of sperm-egg fusion, semen-derived exosomes and Oocyte exosomes (Oo-Exo) have been shown to plays an important role in acrosome reaction [65].

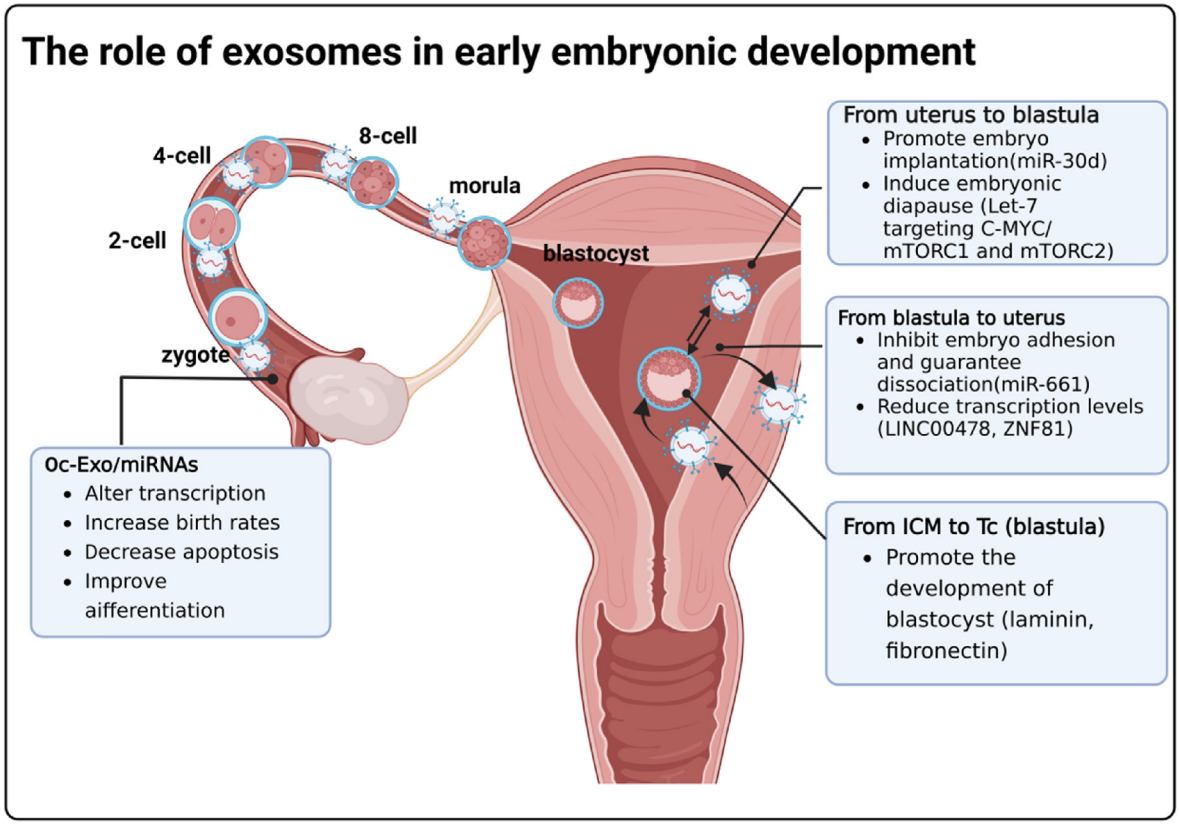

Fig. 5. The role of exosomes in early embryonic development. The development of the mammalian preimplantation embryo encompasses the period from fertilization to implantation [68]. During embryo migration from the oviduct to the uterus, the embryo undergoes distinct metabolic stages (cleavage, morula, blastula and gastrula). Exosomes derived from oviduct exert a positive effect on development of embryos [121]. Uterine exosomes can promote embryo implantation (miR-30d) and induce embryonic diapause (Let-7 transportation and targeting C-MYC/mTORC1 and mTORC2). Blastula exosomes can inhibit embryo adhesion and guarantee dissociation (miR-661 transportation) and reduce transcription levels (LINC00478 and ZNF81 transportation). In addition, ICM exosomes can also promote the development of blastocyst (laminin and fibronectin transportation).

guarantees dissociation until the blastula reaches the appropriate attachment site [73]. An *in vitro* study of co-culture of human trophoblast spheroids and human endometrial epithelial cells (hEECs) showed that exosomes package and transport specific RNAs (*LINC00478* and *ZNF81*) from trophoblast to endometrial cells, and resulted in decreased levels of transcripts of endometrial cells. In *in vitro* and *in vivo* studies have reported that exosomal miRNAs also shuttle from endometrium to embryos. During the window of implantation, human endometrium epithelium-derived exosomes carry specific miRNAs. Among them, miR-30d was observed to be encapsulated in exosomes, released by human endometrial epithelial primary cells and transferred to the trophectoderm of murine embryos by regulating genes that related to embryonic adhesion and embryonic implantation [74]. In addition, in a murine model of dormant embryo, endometrium epithelium-derived exosomal let-7 is an important inducer of embryonic diapause by inhibiting the C-MYC/mTORC1 and mTORC2 signaling pathways [75]. At the same time, the component cells of blastula also regulate their own function and development by means of exosomes transportation. Exposure of somatic cell nuclear transfers (SCNT) embryos to exosomes derived from other SCNT embryos increases the blastocyst rate [76]. In mice, laminin and fibronectin are present in exosomes derived from the preimplantation blastocyst ICM and interact with integrins on the cell surface of trophectoderm cells (TE), increasing the efficiency of blastocyst implantation [77].

6. The role of exosomes in embryo implantation

6.1. Endometrial receptivity establishment

Embryo implantation can be divided into three processes: endometrial receptivity establishment, endometrial decidualization and trophoblast invasion [78]. Endometrial reactivity and readiness for embryo implantation also result from the participation of exosomes in the communication process originating from endometrium and embryo [79,80]. One study reported that the presence of uterine fluid-derived exosomes during the preimplantation stage contains a higher abundance of proteins involved in cell apoptosis, while the uterine fluid-derived exosomes in the implantation stage had a higher abundance of proteins involved in cell adhesion [81]. Moreover, the highest number of exosomes are observed in the uterine fluid during the luteal phase of the menstrual cycle [82,83]. The abundant cargo of exosomes includes proteins like fibulin1 (FBLN1), cysteine-rich 61 (CYR61), complement decay-accelerating factor (CD55) and heparan sulfate proteoglycan 2 (HSPG2) which have specific roles in embryo implantation [84]. The immune environment of the uterus plays an important in ensuring the success of embryo implantation. For example, bovine uterine flushing fluids (UFs)-derived exosomal bta-miR-98 negatively regulates several immune system-related genes and promotes the attachment of conceptus to the endometrial epithelium during the periimplantation period, such as cathepsin C (*CTSC*), Interleukin-6 (IL6), Caspase-4 (CASP4) and IKBKE [85].

6.2. Embryo implantation

A subsequent study showed that endometrial-derived exosomes promote implantation by modulating the proliferation and adhesion of trophoblast cells (Fig. 6). The enhanced adhesive capability of trophoblast cells in response to endometrial epithelial cells (EECs)-derived exosomes is also associated with a significant increase in the expression and phosphorylation of focal adhesion kinase and higher fibronectin production [84]. Several studies have suggested that maternal miRNAs might act as a transcriptomic modifier of the preimplantation embryo. In an *in vitro* model, exosomal hsa-miR-30d was internalized by the trophectoderm of mouse embryos, resulting in an indirect overexpression of genes encoding for certain molecules involved in the murine embryonic adhesion, such as integrin subunit beta3 (*ITGβ3*), integrin subunit alpha 7 (*ITGα7*) and *CDH5* [86]. In addition, another study reported that EECs-derived exosomes influence the physiology of uterus and regulate embryo implantation in an autocrine manner. Exosomal miRNAs are predicted to modulate endometrial receptivity and embryo implantation by targeting the members of the junctional protein family, extracellular matrix (*ECM*), vascular endothelial growth factor (*VEGF*), JAK-STAT and Toll-like receptor signaling pathways [87]. A proteomic analysis confirmed that exosomes derived from uterine fluid of fertile women versus infertile women carry known predictors of embryo implantation (PRDX2 and IDHC), endometrial receptivity (S100A4, FGB, SERPING1, CLU and ANXA2) and implantation success (CAT, YWHAE and PPIA) [88]. At the same time, embryo-derived exosomes are also detected in the uterine fluid of ewes during the implantation stage which traverse through the ZP and then are released into the surrounding culture medium [89]. Exosomes are detected in the cultured fluid of embryonic stem cells and *in vitro* cultured embryos from various species [80,90–92]. An *in vitro* study demonstrated that exosomal laminin and fibronectin derived from ICM interact with integrins along the surfaces of the trophoblasts and stimulate the migration of trophoblast cells by triggering the activation of Jun N-terminal kinase (JNK) and focal adhesion kinase (FAK) [80]. In conclusion, a variety of proteins and miRNAs contained in the exosomes are associated with biological processes such as endometrial receptivity and embryo implantation, and have become new biomarkers to modulate endometrial receptivity and embryo implantation (Table 1).

7. The role of exosomes in placentation

7.1. Role of exosomes derived from placental trophoblast cells in placentation

Placenta is a temporary organ for the exchange of nutrients between the fetus and the mother, and the invasive migration of placental trophoblast cells is the basic element of placentation and pregnancy maintenance. During pregnancy, placenta-derived exosomes (p-Exo) are secreted by various types of placental cells are rich in various growth factors, DNA fragments, miRNA and mRNA, which are involved in regulating the physiological function of maternal uterus and fetal development [93] (Fig. 7a). The release of p-Exo continuously increases in maternal circulation over the first trimester of pregnancy. p-Exo can be detected in maternal blood as early as 6 weeks after gestation, and its levels increase with gestational age. A proteomic analysis demonstrated that 282 exosomal proteins were isolated from trophoblast cells, of which 147 proteins were not in the exosomes but expressed on the plasma membrane of microvesicles [94] p-Exo reflects the changes of blood vessels during pregnancy, as well as the placental function and fetal growth [95].

Trophoblast cells-derived exosomes (Tc-Exo) can promote the invasion of trophoblast cells outside the villus by activating the related signaling pathways mediated by MMPs and MAPK [96]. Placental microvascular endothelial cells-derived exosomal miR-486–5p regulates the proliferation and invasion of trophoblast cells by targeting insulin-like growth factor 1(*IGF1*) [97]. p-Exo can induce angiogenesis through a variety of mechanisms in the presence of hypoxia during early

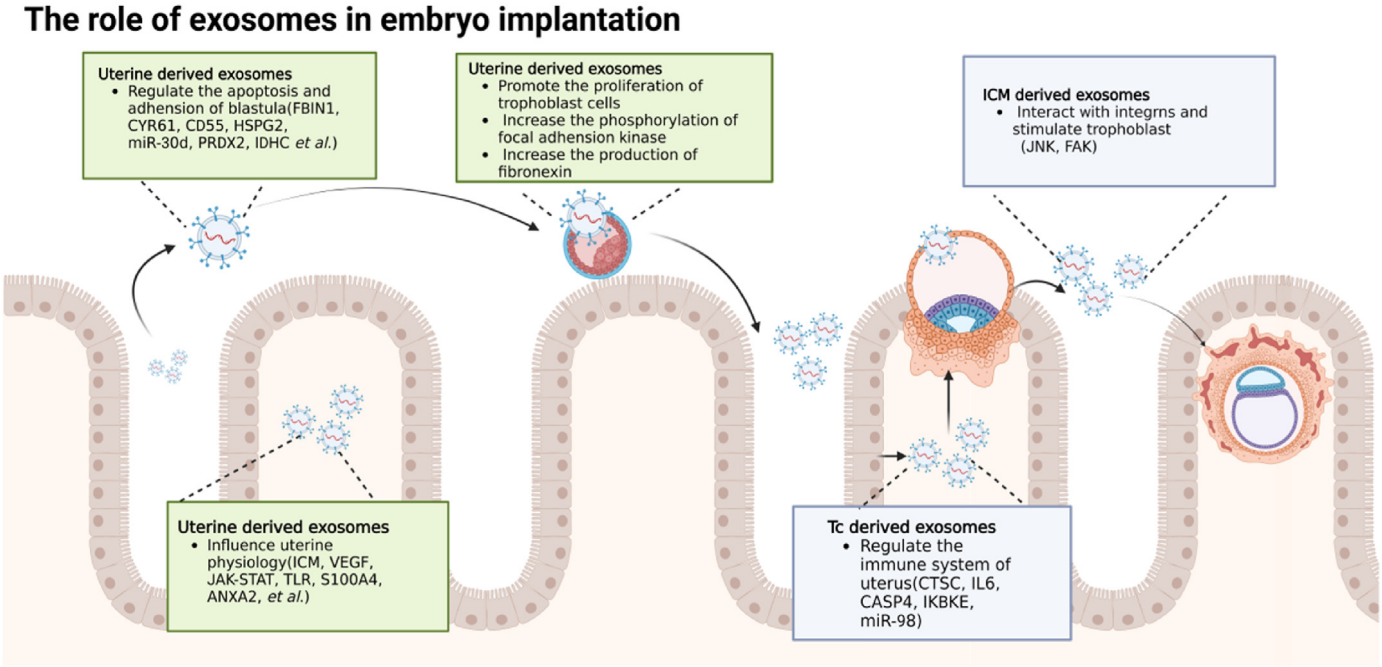

Fig. 6. The role of exosomes in embryo implantation. The implantation of the embryo in the uterus depends mainly on the proper communication between the endometrium and the blastula. A blastula is composed of the ICM and the trophoblast cells (Tc). A subsequent study showed that endometrial-derived exosomes regulate the apoptosis and adhesion of blastula (Transporting FBlN1, CYR61, CD55, HSPG2, miR-30d, PRDX2, IDHC et al.), influence uterine physiology (Transporting ICM, VEGF, JAK-STAT, TLR, S100A4, ANXA2 et al.), promote the proliferation of trophoblast cells and increase the phosphorylation of focal adhesion kinase and the production of fibronexin. At the same time, embryo-derived exosomes interact with integrns and stimulate trophoblast (JNK and FAK transportation) and regulate the immune system of uterus (CTCS, IL6, CASP4, IKBKE and miR-98 transportation) [89].

Table 1
Related functions of exosomes and their cargos in different stages of reproductive activity.

Reproductive stage	Species	Biomarkers	Related function/pathway	Reference
oogenesis	Human	miR-337–5p, miR-370, miR-455–5p, miR-483–5p, miR-449a, miR-339–3p, miR-493, miR-542–5p, miR-874, miR-887, miR-886–5p, miR-654–3p, miR-503, miR-489, miR-31, miR-134, miR-190b, miR-10b, miR-95, miR-135b, miR-203, miR-21–5p, miR-99b-3p, miR-140–3p, miR-218	WNT MAPK ErbB TGFβ	[54,123]
	Bovine	miR-640, miR-654–5p, miR-873, miR-1272, has-let-7c, miR-21, miR-26b, miR-30b, miR-33a, miR-132, miR-155, miR-191, miR-451, miR-526b, miR-582–5p, miR-573, miR-491–5p, miR-450b-3p, miR-221, miR-373, miR-449b, miR-324–3p, miR-363, miR-199a-5p	ubiquitin-mediated pathway, neurotrophin signaling, MAPK signaling and insulin signaling pathways	[124]
	Horse	miR-24	Decrease the secretion of estradiol	[125]
		miR-132	Increase the secretion of estradiol Regulate the secretion of hCG/LH in periovulatory granulosa cells Show different between small and large follicles	
		miR-222	Increase the secretion of estradiol Express differently in large and small follicles	
		miR-125	Express differently in large and small follicles	
		miR-19b	Mediate follicular–luteal transition	
		miR-199		
		miR-212	Regulate the secretion of hCG/LH in periovulatory granulosa cells	
		miR-181a	Prevent cellular proliferation	
Spermatogenesis	Human	ELSPBP1	Enhance protection against oxidative stress, ROS removal, sperm capacitation	[126]
		CRISPP1	Regulate calcium channels in sperm membranes	
		SPAM1	Regulate the interaction between sperm and oocyte	[127]
		Ubiquitin	Eliminate defective sperm	
		ANXA2	Promote membrane transport and fusion	[128]
		KIF5B	Ensure the release and function of exosomes	
		LDHC, HK1, PNP, APRT, SLC2A14	Promote spermatozoa's energy production	[129]
		HIST1H2B, MSMB, MPO, MIF, KLK2	Promote sperm DNA organization, semen liquefaction, sperm-egg fusion	
Fertilization	Rat	PMCA4a	Prevent premature sperm capacitation	[130]
	Mice and Human	Izumo	Modulate sperm-egg fusion	[131]
Early embryonic development	Mice	miR-21	Promote embryonic development on the 4-cell and 8-cell stages	[132]
		miR-290, miR-291, miR-292, miR-293, miR-294, miR-295	Adjust pluripotency	[133]
	Human	miR-372	Promote embryonic development	[134]
		miR-20a-5p, miR-20a-5p	Affect the development ability of blastula before implantation	[135]
		miR-142–3p	Indicate blastocyst implantation failure	[136]
Embryo implantation	Mice	Let-7a/g	Promote implantation Induce embryonic diapause	[75]
		miR-21	Promote embryonic development	[137]
	Human	miR-31	Promote endometrial receptivity	[138]
		miR-200	Inhibit proliferation and receptive ability	[139]
		HLA-G	Avoid maternal immune rejection of embryos mediate communication with target cells	[140]
	Bovine	Matrix metalloproteinase (MMP)	Affect the invasive ability of trophoblast cells	[141]
Pregnancy	Mice	miR-126	Remodel the uterine vasculature	[142]
	Human	Albumin, Apolipoprotein E, Apolipoprotein M, Eukaryotic translation elongation factor 2, ATPase, class V, type 10A, Group-specific component (vitamin D binding protein),HBD、Myosin heavy chain 9 (MYH9)	Promote the migration of vascular smooth muscle cells	[143]
		miR-520c-3p	Regulate partial steps of spiral artery remodelling	[144]
		B7–H1 (CD274), B7–H3 (CD276), human Leukocyte antigen-G5 molecules (HLA-G5)	Modify the maternal immunological environment	[145]
		miR-517b	Regulate tumor necrosis factor-mediated signaling	[146]
		miR-516b-5p, miR-517–5p, miR-518a-3p	Target the PI3K-Akt and the insulin signaling pathways	[147]
		Syncytin-2	Modulate immune response	[148]
		Heat shock protein family E (HSPE1)	Induce the differentiation of human CD4+T cells	[149]
	Bovine	miR-499	Target the Lin28B/let-7 signaling axis and maintain a slight proinflammatory profile	[117]

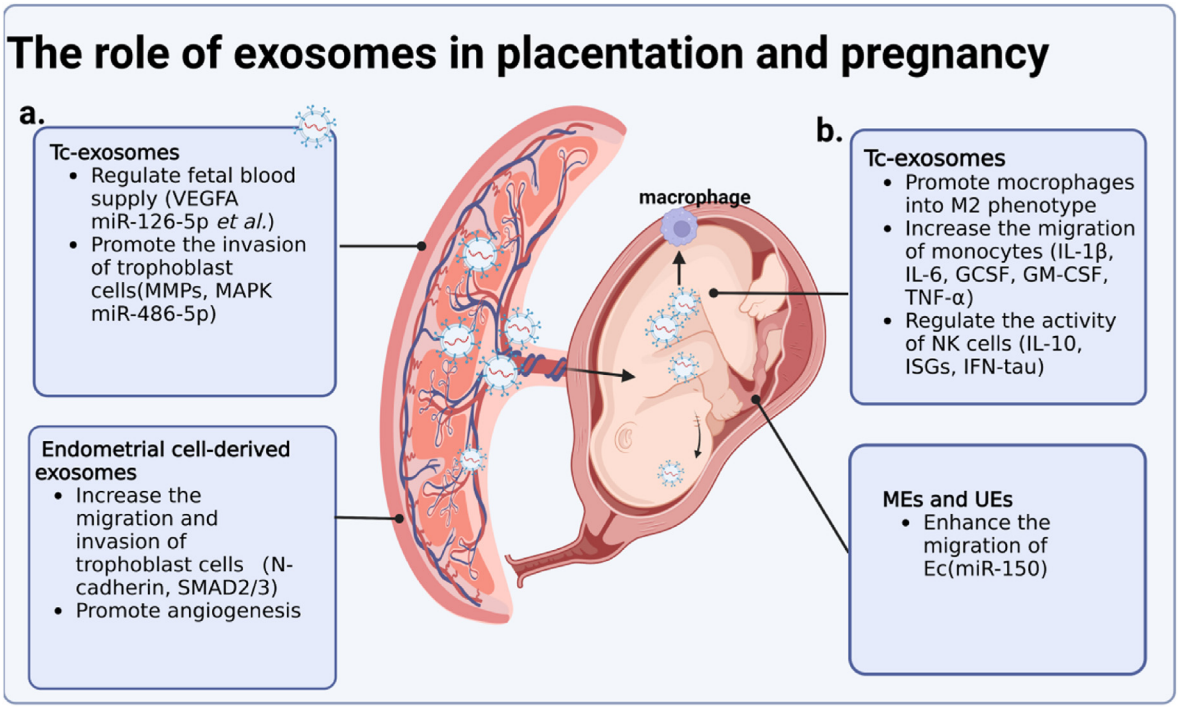

Fig. 7. The role of exosomes in placentation and pregnancy. (A) Trophoblast cells (Tc)-derived exosomes are involved in regulating fetal blood supply (Transporting VEGFA, miR-126–5p et al.) and promoting the invasion of trophoblast cells (MMPs, MAPK and miR-486–5p transportation) in the process of placentation [122]. At the same time, endometrial cell-derived exosomes increase the migration and invasion of trophoblast cells (N-cadherin, SMAD2/3) and promote angiogenesis [103]. (B) During pregnancy, Tc-derived exosomes promote mocrophages into M2 phenotype, increase the migration of monocytes (IL-1β, IL-6, GCSF, GM-CSF and TNF-α transportation) and regulate the activity of NK cells (IL-10, ISGs and IFN-tau transportation) [115].

pregnancy [98]. For example, human placenta derived mesenchymal stem cells (MSCs)-derived exosomes enhance the angiogenesis of human umbilical vein endothelial cells (HUVEC) [99]. Other studies have shown that maternal and umbilical serum-derived exosomes can enhance the proliferation, migration and angiogenesis of endothelial cells by angiogenic related miRNAs transportation, including miR-210–3p, miR-376c-3p, miR-151a-5p, miR-296–5p, miR-122–5p and miR-550a-5p [100]. During the third trimester of pregnancy, p-Exo can regulate fetal blood supply by delivering vascular endothelial growth factor A (VEGFA), angiogenic stimulants and vascular growth factors and miRNAs [101]. Similarly, porcine trophoblast ectoderm cells (PTEs)-derived exosomes also deliver several miRNAs that play major roles in angiogenesis, such as miR-126–5p, miR-296–5p, miR-16 and miR-17–5p [102].

7.2. Role of endometrial cells-derived exosomes in placentation

But beyond all that, the stromal/decidual cells-derived exosomes have also been investigated as important mediators in placentation [103]. Exosomes derived from *in vitro* decidualized endometrial stromal cells increase the migration and invasion of trophoblast cells [104,105]. These exosomes increase the expression of N-cadherin in trophoblast cells and also elevate the phosphorylation of SMAD family member 2 (SMAD2) and SMAD family member 3 (SMAD3). Stromal cells-derived exosomes are internalized into the endothelial cells suggesting their paracrine action in the regulation of angiogenesis [106]. Exosomes derived from stromal cells can induce the tube formation of human umbilical vein endothelial cells in *in vitro* [107]. Beyond epithelial and stromal cells, endometrial mesenchymal stromal cells-derived exosomes trigger the release of proangiogenic molecules in embryos, such as vascular endothelial growth factor (VEGF) and platelet derived growth factor-AA (PDGF-AA) [108].

8. The role of exosomes in the maintenance of pregnancy

Mammalian reproduction has also to face and solve the immunological challenge of accepting a semiallogeneic fetus and supporting its development and growth in the uterine cavity. In almost all species, the placenta and the fetal allograft evade a harmful maternal immune attack and enjoy an immunologic privilege in the uterine cavity. Therefore, the immunomodulation of endometrial bed is crucial for a successful pregnancy. In a murine pregnancy model, the macrophages represent a major leukocyte subset in the decidua that creates an active but tolerant immune microenvironment for the proliferation of trophoblast cells [109,110]. More and more studies have revealed the important roles of exosomes in pregnancy maintenance by regulating the immune tolerance environment of the maternal uterus (Fig. 7b). The Tc-Exo regulates the polarization of decidual macrophages into the M2 phenotype and favours the maternal immune tolerance to the fetus, vascularization and extracellular matrix degradation [111,112]. Monocytes appear to rapidly uptake trophoblast cells-derived exosomes via endocytosis and then promote the migration of monocytes and increases the production of IL-1β, IL-6, granulocyte colony-stimulating factor (GCSF), granulocyte/monocyte colony-stimulating factor (GM-CSF) and tumor necrosis factor α (TNF-α) [113]. Progesterone induced blocking factor (PIBF) has been detected in embryo-derived exosomes and adheres to the surface of $CD4^+$ and $CD8^+$ peripheral T cells and stimulate the production of IL-10 and regulate the activity of natural killer (NK) cells [114]. Another study reported that exosomes derived from the serum of non-pregnant and pregnant women were taken up by NK cells and then enhanced the caspase-3 activity in NK cells. In addition, functional Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL) were also carried by human p-Exo and induced the apoptosis of immune cells, and conferring immune privilege on the fetus [115]. In ruminant pregnancy models, interferon tau can be delivered by p-Exo and promote the

expression of interferon stimulated genes (ISGs) in co-incubated EECs and maintain pregnancy [116].

Exosomal miRNAs have also been investigated as mediators of many functions during pregnancy. In an *in vitro* model, placental-derived exosomal bta-miR-499 inhibits the activation of nuclear factor-κB (NF-κB) by targeting the Lin28B/let-7 axis at the maternal-fetal interface in the early gestation of dairy cows and other mammals [117]. Maternal-derived exosomes (MEs) and umbilical-derived exosomes (UEs) greatly enhance the migration of endothelial cells (ECs), which was mostly attributed to the different expression profiles of exosomal miRNAs [100]. Angiogenesis in pigs with intrauterine growth restriction is associated with umbilical cord blood-derived exosomal miR-150 [118].

In addition to regulating the communication of local cells in the uterus, some studies have shown that exosomal cargos can be transported from the fetus to the maternal uterine tissue through systemic blood circulation during pregnancy [119]. For example, exosomal serum total bilirubin is released into the maternal circulation throughout gestation in normal pregnancy and appears to have an immunoregulatory role in inhibiting the response of T and NK cells [120].

9. Prospects and shortcomings

Among the various classes of EVs, exosomes are of particular interest, because cargo sorting in exosomes is a regulated, nonrandom process and exosomes play essential roles in cell-to-cell communication. However, some microbubbles (100–1000 nm) are as large as exosomes (30–150 nm) in diameter, and there is no definite way to separate them completely. Therefore, EVs are universally used in most literature. There is an urgent need for a technical means to effectively distinguish microvesicles and exosomes, to more accurately distinguish the functions of microvesicles and exosomes.

Exosomes and their inclusions released by reproductive organs under disease conditions are extremely important for the diagnosis of related diseases. As we all know, the reproductive process is a complex regulatory process, from gametogenesis, maturity to fertilization, the establishment, recognition, maintenance of pregnancy and even childbirth and lactation are multiply regulated by nervous, endocrine and immune systems. Endocrine regulation with hormone as the core is a dynamic change of time and space. For example, the four periods of estrus cycle are regulated by different hormones in time and space. Most of the published literature so far has studied the role of exosomes in reproduction in an ideal environment, without much description of the effects of neural, endocrine and immune states on the role of exosomes. We believe that neurologic, endocrine and immune states, which play important roles in regulating the reproductive process, should be fully considered in the research, and exosome marker molecules are really used for reproductive labeling and diagnosis which should be screened with the help of new nucleic acid and protein technologies, such as in-depth omics.

Given that exosomes mediate a variety of physiological and pathological processes, take advantage of exosomes' properties of high biocompatibility and low immunogenicity as well as their ability to cross the placental barrier. Further use of homing molecular surface modification will be able to customize drug delivery systems to specific reproductive organs, which will have a greater role in the field of reproductive drug development and new therapeutic modalities.

Author contributions

Xiangguo Wang: Conceptualization, Writing – review & editing, Funding acquisition, Supervision. Chang Chen: Writing – original draft, Visualization. Zhenghao Zhang: Writing – original draft. Xu Gu: Visualization. Longfei Xiao: Writing – review & editing, Conceptualization. Xihui Sheng: Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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