Oviductal Extracellular Vesicles

Subjects: Obstetrics & Gynaecology
Contributor: Joy Winuthayanon

In this review, we have described characteristics of extracellular vesicles in the oviduct from different species and their role in supporting oocytes, sperm, and embryos.

Keywords: egg ; embryo ; extracellular vesicle ; exosome ; fallopian tube ; microvesicle ; oocyte ; oviductosome ; oviduct ; sperm

1. Introduction

Extracellular vesicles (EVs) participate in intercellular and interorganismal communications (reviewed by [1]). EVs is the collective term used for both exosomes and microvesicles. Exosomes are vesicles with an approximate size of 30–100 nm in diameter. Exosomes are derived from endocytotic origin and are released from cells through plasma membrane fusion of a multi-vesicular body [2]. However, microvesicles (100–1000 nm) readily bud from the cell membrane (reviewed by [3]). EVs communicate their signal to recipient cells by transferring their molecular cargos using endocytosis and cellular fusion [4]. These cargos usually contain DNA, RNA, proteins, and other metabolites [1] In this review, we have described characteristics of EVs in the oviduct from different species and their role in supporting oocytes, sperm, and embryos.

2. Extracellular Vesicles

2.1. General Characteristics of EVs

Exosomes are formed as intraluminal vesicles (ILVs) within multivesicular bodies (MVBs). MVBs then either fuse with cellular lysosomes and degrade, or fuse with the plasma membrane. MVB-fused plasma membranes are released as exosomes into the extracellular space (reviewed by [5]). Specific markers for exosomes used in different studies of oviductal EVs (oEVs) have also been identified. These oviduct exosomal markers include tetraspanin transmembrane superfamily (i.e., CD9, CD63, and CD81), heat shock proteins (HSPs; i.e., HSPA1A, HSP70, and HSPA8), annexin A1 (ANXA1), actin-linking ezrin-radixin-moesin (ERM), and tumor susceptibility gene 101 (TSG101) [6].

In contrast to exosomes, microvesicles are formed by an outward budding from the plasma membrane [7]. Marker proteins for microvesicles include TSG101, arrestin domain containing 1 (ARRDC1), gelatinases, ADP ribosylation factor 6 (ARF6), major histocompatibility complex 1 (MHC-1), β1-integrin, vesicle-associated membrane protein 3 (VAMP3), and membrane type 1-matrix metalloproteinase (MT1MMP) [8]. Apoptotic bodies are also considered a subclass of EVs. These apoptotic bodies are released only during apoptotic cell death and have molecular signals that attract phagocytes and promote apoptotic cell clearance (reviewed by [9]). However, we will focus solely on exosomes and microvesicles in this review.

2.2. EV Biogenesis

Proteins involved in the biogenesis of exosomes include Ras-related proteins (RAB11/RAB35, RAB27A/B, RAB7), diacylglycerol kinase alpha (DGKα), and vesicle associated membrane protein 7 (VAMP7) [8]. *Rab11a*$^{-/-}$, *Rab35*$^{-/-}$, and *Rab7*$^{-/-}$ mice are embryonically lethal in mice [10][11][12]. Rab27a/b double knockout mice have shown deficiency in exosome secretion, leading to a low-grade inflammatory phenotype [13]. However, *Dgkα*$^{-/-}$ and *Vamp7*$^{-/-}$ mice are viable [14][15]. Proteins involved in the biogenesis of microvesicles include ARRDC1, TSG101, vesicle-fusing ATPase (VSP4), RAB22A, hypoxia-inducible factors (HIF), ARF6, phospholipase D (PLD), extracellular-signal-regulated kinase (ERK), and myosin light-chain kinase (MLCK) [8]. However, only TSG101 and ARF6 appear to have indispensable biological functions in mammals as *Tsg101*$^{-/-}$ mice die around the time of implantation [16] whereas *Arf6*$^{-/-}$ mice die during mid-late gestation [17]. These findings indicate that some of the proteins involved in EV biogenesis are crucial for cellular function in mammals.

3. Are oEVs the Missing Key in Assisted Reproductive Technologies?

3.1. Natural Conception vs. In Vitro Fertilization

Assisted reproductive technologies (ARTs) include in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), intrauterine insemination (IUI), and embryo transfer (ET). In the United States, according to the Center for Disease Control and Prevention's report for 2017, approximately 306,197 ART cycles were performed, resulting in 73,831 live births out of 3.79 million [18]. Approximately 1.9% of infants born in the United States are conceived using ARTs. IVF procedures include the development of the embryo to the blastocyst stage in culture media, or for 3–7 days, depending on the protocol, followed by the transfer of embryo(s) into the uterine cavity. With these procedures, the entire Fallopian tube is bypassed. In procedures like ZIFT and GIFT, the zygote or gametes are transferred directly into the Fallopian tube. While there are no differences between implantation rates using ZIFT compared to IVF in healthy women, pregnancy and implantation rates are significantly higher when ZIFT is performed in women with repeated implantation failure using IVF (35.1% success rate with ZIFT vs 11.1% for IVF) [19]. It is obvious that the Fallopian tube is superior for fertilization and embryo development than artificially modified conditions in vitro. However, it is virtually unknown how oEVs from the Fallopian tube provide an optimal microenvironment for gametes and embryos in humans.

3.2. oEVs Could Improve the Quality of ART-Derived Embryos

Within the Fallopian tube, embryos are bathed in fluid containing oEVs, which are missing in culture media. Although the majority of babies born using ARTs are healthy, culture conditions in ARTs have been associated with epigenetic changes in the embryo. Alteration of expression patterns in imprinted genes may indicate imprinting disorders. Out of 10,000 live births following ARTs procedures, 3.9 children are diagnosed with Angelman syndrome, 3.9 with Beckwith-Wiedemann syndrome, 2.2 with Prader–Willi syndrome, and 1.5 with Silver-Russel syndrome [20]. The frequency of these imprinting disorders in the normal population is approximately 2 children out of every 10,000 live births [20].

As mentioned above, co-culture of embryos with oviductal fluid collected at various stages of embryo development differentially altered methylation patterns in bovine embryos [21]. Blastocysts that were cultured in SOF with addition of fetal calf serum exhibited downregulation of the imprinted gene called small nuclear ribonucleoprotein polypeptide N (*SNRPN*) compared to blastocysts cultured in synthetic fluid containing oEVs [22]. Accordingly, decreased *SNRPN* expression has been associated with Prader–Willi syndrome [23]. Therefore, it is possible that in vivo-derived oEVs are directly involved in methylation control in embryos. However, to date, we still cannot pin-point as to which proteins or molecular cargos from oEVs are responsible for normal embryo development. It is likely that the cumulation of distinct proteins present chronologically in the oEVs is correspondingly responsible for proper functions of gametes and embryos at various developmental stages.

References

1. Maas, S.L.N.; Breakefield, X.O.; Weaver, A.M. Extracellular Vesicles: Unique Intercellular Delivery Vehicles. Trends Cel l Biol. 2017, 27, 172–188.
2. Valadi, H.; Ekstrom, K.; Bossios, A.; Sjostrand, M.; Lee, J.J.; Lotvall, J.O. Exosome-mediated transfer of mRNAs and m icroRNAs is a novel mechanism of genetic exchange between cells. Nat. Cell Biol. 2007, 9, 654–659.
3. Colombo, M.; Raposo, G.; Thery, C. Biogenesis, secretion, and intercellular interactions of exosomes and other extrace llular vesicles. Annu. Rev. Cell Dev. Biol. 2014, 30, 255–289.
4. Raposo, G.; Stoorvogel, W. Extracellular vesicles: Exosomes, microvesicles, and friends. J. Cell Biol. 2013, 200, 373–3 83.
5. Thery, C.; Ostrowski, M.; Segura, E. Membrane vesicles as conveyors of immune responses. Nat. Rev. Immunol. 2009, 9, 581–593.
6. Almiñana, C.; Bauersachs, S. Extracellular Vesicles in the Oviduct: Progress, Challenges and Implications for the Repr oductive Success. Bioengineering 2019, 6, 32.
7. Lopera-Vasquez, R.; Hamdi, M.; Maillo, V.; Gutierrez-Adan, A.; Bermejo-Alvarez, P.; Ramirez, M.A.; Yanez-Mo, M.; Rizo s, D. Effect of bovine oviductal extracellular vesicles on embryo development and quality in vitro. Reproduction 2017, 1 53, 461–470.
8. Tesfaye, D.; Hailay, T.; Salilew-Wondim, D.; Hoelker, M.; Bitseha, S.; Gebremedhn, S. Extracellular vesicle mediated m olecular signaling in ovarian follicle: Implication for oocyte developmental competence. Theriogenology 2020, 150, 70–74.

9. Fu, B.; Ma, H.; Liu, D. Extracellular Vesicles Function as Bioactive Molecular Transmitters in the Mammalian Oviduct: A n Inspiration for Optimizing in Vitro Culture Systems and Improving Delivery of Exogenous Nucleic Acids during Preimpl antation Embryonic Development. Int. J. Mol. Sci. 2020, 21, 2189.
10. Sobajima, T.; Yoshimura, S.; Iwano, T.; Kunii, M.; Watanabe, M.; Atik, N.; Mushiake, S.; Morii, E.; Koyama, Y.; Miyoshi, E.; et al. Rab11a is required for apical protein localisation in the intestine. Biol. Open 2014, 4, 86–94.
11. Klinkert, K.; Echard, A. Rab35 GTPase: A Central Regulator of Phosphoinositides and F-actin in Endocytic Recycling a nd Beyond. Traffic 2016, 17, 1063–1077.
12. Kuchitsu, Y.; Fukuda, M. Revisiting Rab7 Functions in Mammalian Autophagy: Rab7 Knockout Studies. Cells 2018, 7, 2 15.
13. Alexander, M.; Ramstead, A.G.; Bauer, K.M.; Lee, S.H.; Runtsch, M.C.; Wallace, J.; Huffaker, T.B.; Larsen, D.K.; Tolma chova, T.; Seabra, M.C.; et al. Rab27-Dependent Exosome Production Inhibits Chronic Inflammation and Enables Acut e Responses to Inflammatory Stimuli. J. Immunol. 2017, 199, 3559–3570.
14. Nascimento, E.B.M.; Manneras-Holm, L.; Chibalin, A.V.; Bjornholm, M.; Zierath, J.R. Diacylglycerol kinase alpha deficie ncy alters inflammation markers in adipose tissue in response to a high-fat diet. J. Lipid Res. 2018, 59, 273–282.
15. Danglot, L.; Zylbersztejn, K.; Petkovic, M.; Gauberti, M.; Meziane, H.; Combe, R.; Champy, M.F.; Birling, M.C.; Pavlovi c, G.; Bizot, J.C.; et al. Absence of TI-VAMP/Vamp7 leads to increased anxiety in mice. J. Neurosci. 2012, 32, 1962–19 68.
16. Wagner, K.U.; Krempler, A.; Qi, Y.; Park, K.; Henry, M.D.; Triplett, A.A.; Riedlinger, G.; Rucker, I.E.; Hennighausen, L. Ts g101 is essential for cell growth, proliferation, and cell survival of embryonic and adult tissues. Mol. Cell Biol. 2003, 23, 150–162.
17. Suzuki, T.; Kanai, Y.; Hara, T.; Sasaki, J.; Sasaki, T.; Kohara, M.; Maehama, T.; Taya, C.; Shitara, H.; Yonekawa, H.; et a l. Crucial role of the small GTPase ARF6 in hepatic cord formation during liver development. Mol. Cell Biol. 2006, 26, 6 149–6156.
18. Centers for Disease Control and Prevention. 2017 Assisted Reproductive Technology Fertility Clinic Success Rates Re port; US Department of Health and Human Services: Atlanta, GA, USA, 2019.
19. Farhi, J.; Weissman, A.; Nahum, H.; Levran, D. Zygote intrafallopian transfer in patients with tubal factor infertility after r epeated failure of implantation with in vitro fertilization-embryo transfer. Fertil. Steril. 2000, 74, 390–393.
20. Cortessis, V.K.; Azadian, M.; Buxbaum, J.; Sanogo, F.; Song, A.Y.; Sriprasert, I.; Wei, P.C.; Yu, J.; Chung, K.; Siegmun d, K.D. Comprehensive meta-analysis reveals association between multiple imprinting disorders and conception by ass isted reproductive technology. J. Assist. Reprod. Genet. 2018, 35, 943–952.
21. Barrera, A.D.; Garcia, E.V.; Hamdi, M.; Sanchez-Calabuig, M.J.; Lopez-Cardona, A.P.; Balvis, N.F.; Rizos, D.; Gutierrez -Adan, A. Embryo culture in presence of oviductal fluid induces DNA methylation changes in bovine blastocysts. Repro duction 2017, 154, 1–12.
22. Suzuki, J., Jr.; Therrien, J.; Filion, F.; Lefebvre, R.; Goff, A.K.; Smith, L.C. In vitro culture and somatic cell nuclear transf er affect imprinting of SNRPN gene in pre- and post-implantation stages of development in cattle. BMC Dev. Biol. 2009, 9, 9.
23. Ozcelik, T.; Leff, S.; Robinson, W.; Donlon, T.; Lalande, M.; Sanjines, E.; Schinzel, A.; Francke, U. Small nuclear ribonu cleoprotein polypeptide N (SNRPN), an expressed gene in the Prader-Willi syndrome critical region. Nat. Genet. 1992, 2, 265–269.
