Exosomes and their Role in Immunity, Metabolic, Cardiovascular, Neurodegeneration, Reproduction and Development

Zainab Abdullah Waheed[1], Nadia Habeeb Sarhan[2]

[1]Ass.lec Department of Medical Laboratories Techniques – AL-Toosi University College of - Iraq/ Naja,
[2]Ass.lec Department of Basic Science - College of Nursing– University of Kufa- Iraq/ Najaf

Abstract

Exosomes are produced by an endocytic cellular route which consists of three steps:first: Cellular membranes invagination forms the endocytic vesicles, then,The inward budding of the endosoma membrane starts at the second level, and multivesicular bodies emerge.. In third and last step the multivascular bodies combine with the cell membrane and Produces the substances of the vesicular**,** exosomes are used to transfer Set cell prostaglandins to specific cells exosomes Represent a new mode of contact between cells, which in many biological processes may play a significant role, for example, immune response,Transduction of signals,antigen presentation- Intercellular communication mediated by exosome Cells usually communicate with surrounding cells by direct cell-cell touch, involving interaction of the gap between the cell's surface proteins and protein c interactions Communicate with regional cells via induction soluble Factors like: hormones as well as cytokines Improve the transmission of the signals, Electrical and chemical signals**.** And also Exosomes may play a role in the process of metabolic conditions and cardiovascular disorders they were found to hold metabolites and allowing intra - cellular communication by exosomal miRNA exchange between skeletal muscles , adipose tissue, pancreatic b-cells, and the mouse liver and the human .

Key words: *Exosomes, APCs, miRNA, EVs, neurodegeneration*

Introduction

Exosomes are membrane vesicles of 30-150 nm size which are produced endogenously by nearly every type of cells. Rose Johnstone had first used the word (exosomes) , who discovered exosomes In Reticulocytes of sheep in1970 (1) These exosomes were known as Cell Homeostasis by-products until 1990 ,When it was discovered the revolution in exosomes Find that the β-cells produce functioning exosomes that transform antigen (2)

- Exosomes formation and its role in immunity

Exosomes are produced by an endocytic cellular route which consists of three steps:first: Cellular membranes invagination forms the endocytic vesicles, then,The inward budding of the endosoma membrane starts at the second level, and multivesicular bodies emerge.. In third and last step the multivascular bodies combine with the cell membrane and Produces the substances of the vesicular (exosome) (3)

Exosomes are special because of their protein and Lipid content, that presents an important hint for Recognizing them. Exosomes usually involve fusion Proteins and transport proteins As in phospholipases and other lipids releated proteins .(4)

The exosomes are also riched in Lipids such as cholesterol, sphingolipids, phosphoglycerides, ceramids and also are enriched With long saturated chains of fatty acid (5)

Study Researchs indicates that exosomes are used to transfer Set cell prostaglandins to specific cells (6) exosomes also have miRNA in large amounts (7) exosomes Represent a new mode of contact between cells, which in many biological processes may play a significant role, for example, immune response (8) Transduction of signals (9)antigen presentation (10) - Intercellular communication mediated by exosome Cells

usually communicate with surrounding cells by direct cell-cell touch, involving interaction of the gap between the cell's surface proteins and protein c interactions Communicate with regional cells via induction soluble Factors like: hormones as well as cytokines Improve the transmission of the signals[11] Electrical and chemical signals (e.g. nuclear elements, fatty acids and other signals) Also interested in communication [12] Exosomes are now accepted with a cell of protein , lipids and nucleic cell-specific cargo Acids can function as a new communication between cells Method. The theory of is based on evidence exosomes from parental cells may communicate directly with target cells , which leads to a future infusion of cell behavior and phenotype characteristics [13] the Exosomal biological applications are very dependent on effective supply of genetic materials, that can be accomplished through interactions between receptors, direct fusion of membranes or integration via endocytosis[14] When the exosomes are internalized fuse with the endosome compact membrane resulting in the transmission of its genetic material horizontally into Accurate cell cytoplasm.

The biologically active Molemolecules that impact were seen in exosomes the following pathways are used to target cells:1- direct attach occurs when surface ligands Stimulate Target cells 2- Move to recipient cells with active receptors;3- Recipient cell epigenetic reprogramming with function proteins , lipids and RNAs.[15] (Fig:1) exosomes play an important role in immunoregulation in the immune system, such as antigen presentation, immune activation, immune suppression and Immune tolerance by intercellular contact exosome-mediated. CD4 + T derivative exosomes Dendritic cells (DCs) can connect cells and cell CD8 + T cells via peptide / major complex histocompatibility Interactions between MHC / TCR and ICAM-1 / LFA-1 Conduct DC apoptosis and thus mediate antigen-specific DCmediated T cell silence[16] The outcomes that Exosomes produced by B-cell lines are co-stimulating MHC class II and Adhesion molecules indicated the stimulation of exosomes which stimulate CD4 T-cells Clones directly[17]

Exosomes produced by antigen presenting cells (APCs) Surface MHC Class-I and MHC Class-II molecules and therefore may be potentially stimulating. CD8 and CD4 T cells, respectively. APC-derived at high levels ,peptide-MHC-bearing exosomes (p-MHC) complexes serve as Ag-presenting vesicles for cells, lines and hybrids, and for ready T cells[18,19,20] The stimulating activity of T-cells by free exosomes appears to be less effective than for the parent APCs.[21,22] It could be. Explain the low ability to activate native T cells in vitro by free APC-derived Exosomes[23]The low stimulating potential of free exosomes on T-cells in Vitro also was likely due to its tiny size and Brownian vesicle diffusion Motion, In fact, when Exosomes derived from APC are coated at high levels of latex or when direct loading increases the amount of p-MHC complexes per exosome it is significantly increase their T-cell inducing capacity in the exosome with peptide in culture [24,25,2

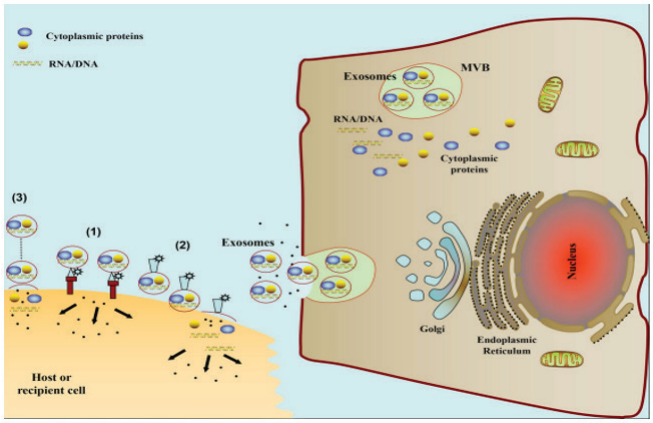


Fig:1: model signaling pathways in exosome mediated cell- (1) Cells receiving signals through direct exosomes to-cell communication Ligands that are surface-bound. (2) Transfer of active receptor exosomes to cells of the recipient. (3) Exosomes can reprogram recipient cells epigenetically by Protein, lipids and RNAs provide functional (13)

Even when it is no serious immune reaction should be observed in Mice had been multiple times administered with with a comparatively tiny(mouse dose or exosomes derived from human cells) for prolonged Time periods[27,28]Transfusions of Blood and /or plasma for decades do not seem to be related with exosomes-mediated immune response, even,no (human leukocyte antigen(HLA) , extracellular uptaking and intracellular exosomes producing In this way ,can induce immune response and this considerd as dose-dependent manner. Latest studies with modified exosomes have however shown a role of exosomes triggered both adaptive and innate Immunity, support their effectiveness for the advancement of treatment and its possible contribution in Organising the immune reactions to Infectious or cancerous agents(fig:2) The Purpose of exosomes in regulation of immunity seem to be probable if antigenic is transferred and presented of Peptides antigens, DNA-inducing cGASSTING distributions (Cyclic GMP-AMP synthase) Receiver signaling by Cells (an immunity process by which it senses Cytosolic DNA induces inflammatory response Genes and IFN reaction type I MiRNA, and specific signaling induction Surface ligand pathways exist on the exosomes.

Exosomes derivative from Antigen-presenting cells (APCs) Bring p-MHC-II [majo histocompatibility complex together with Antigenic peptide II (p)] and costimulative Signals, and display the antigenic peptide directly causes activation of different T cells. moreover, for purposes still to be Illustrated, exosomal T-cell stimulation is Less effective than that resulted by APCs[29,30] Tumor eradication and growth deficiency were measured in mice by Single intradermal infusion reported

of APC-derived exosomes loaded with MHC-II a peptide tumour[31] The strength and the effectiveness Of the CD8 + Cytotoxic T cell -antitumor immunity It also indicated controlled antitumor response

Indirect presentation of antigen due to various transfer of antigenic peptide on exosomes to APCs which really, effect, naïve T and/or Activation of B cells immature dendritic mouse cells triggered by immunogenic derivative of exosome Peptides activate APCs indirectly, and stimulate particular multiplication of the CD4 + T cells , exosomes produced by dendritic cells of humans enhance a T Helper response ,(production of IFNg) in culture[32] exosomes function in antigen presentation is also important in bacterial infections , such as (Mycobacterium tuberculosis and Helicobacter pylori),

In which exosomes may improve antibacterial properties of immune system response ,by inducing antigene presenting of bacteria from exosomed (derived from macrophages) This could have an influence later on Adaptive Immune Response[33] the Production of IFNa and IFNg, tumor necrosis factor

a (TNFa), and exosomal interleukin produced by macrophages which leads to to maturation of dendritic cell and activation of CD4 + and CD8 + T Cells [34]

The exosomal nucleic acid cargo, which is DNA and miRNA, was involved in the regulation of immune response both of innate and adaptive immunity. the Intracellular DNA of bacteria such as: (*listeria, Franciscella tularensis*) are located into exosomes that having the ability to enhance cGAS-STING signalling pathways in neighboring cells inducing innate immune efficiently

Responses. As for *Listeria,* however, which takeplace at the expense repressing of T cells and therefore reduces antibacterial defensive capabilities[35] Where as the significant role of exosomes in Fungal immune response cAnd parasitic infections is obure; afew other researches concerned exosomes derived from parasites have noted such an exosomes could be involved In pathogenesis of disease[36,37] human monocytes which take up exosomes Including parasitic DNA may cause STING-dependent DNA sensing which is considerd a decoy process to improve parasite survival[38]

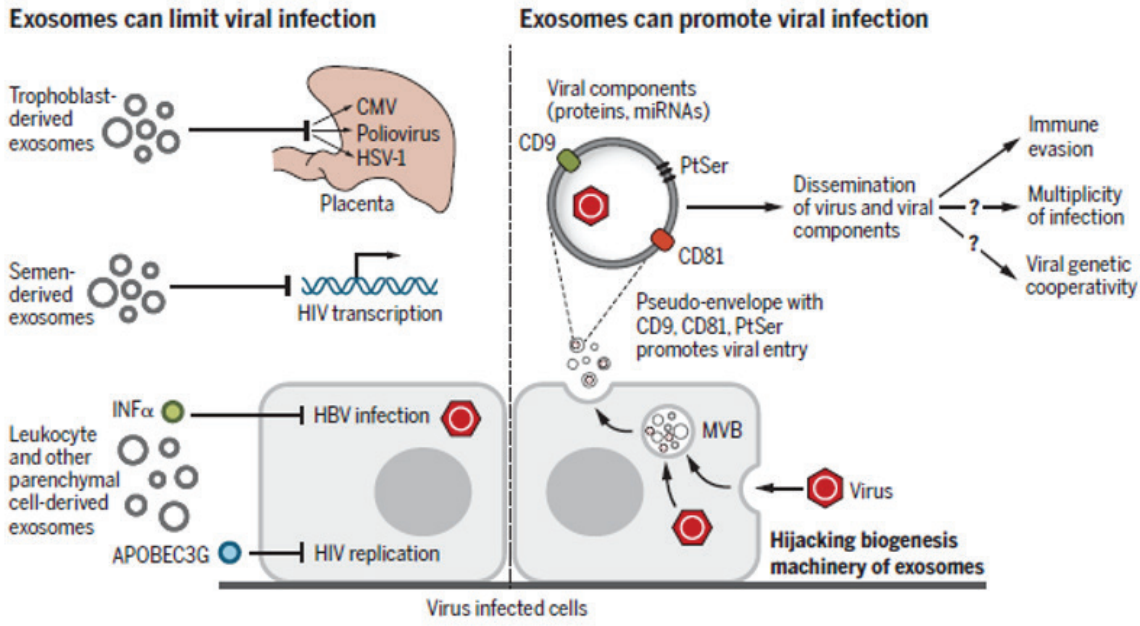


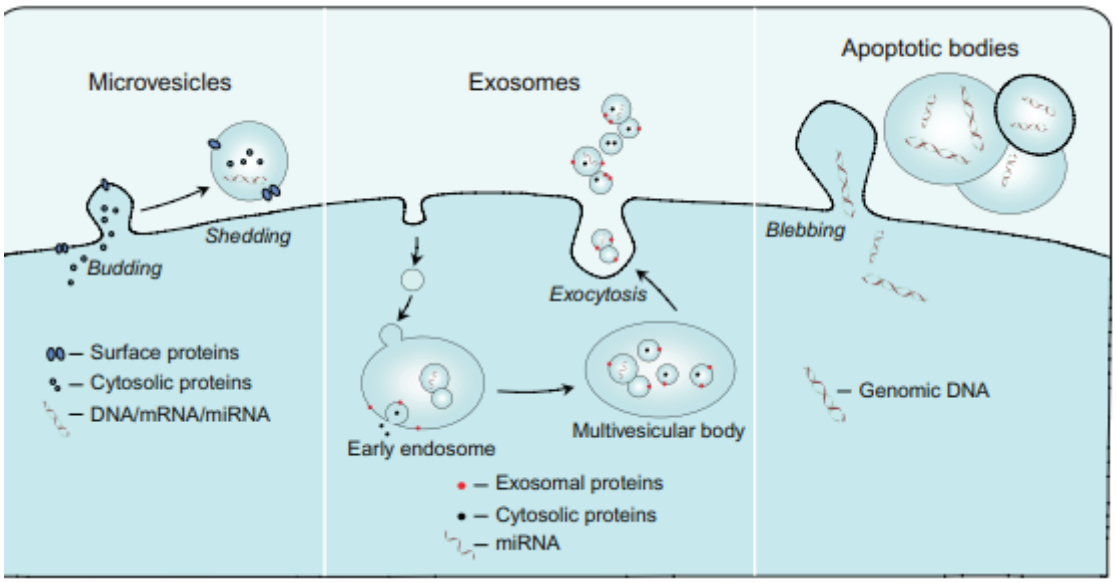
Fig. 2: Role of exosomes in viral infection Virus-infected exosomes could really reduce or enable viral infection

Exosomal cargo, including such cIFNa or APOBEC3 Gan supress infection by reducing or restricting the viral multiplication or improve antiviral immune response. Exosomes can assist as a pseudoenvelope improving Viral entry tetraspanins (CD81, CD9) and PtSer interaction and uptake to the host cell and to enable them evade immune antiviral. Co-transport of aviral Elemes (proteins and miRNA) can also improve pathogenicity exosome-mediated viral transmission could take an active part in genetic cooperative viruses and Infection multiplicity. CMV, and cytomegalovirus (39)

-exosomes role in metabolic / cardiovasicular diseases:

Patients with metabolic diseases have been well known notably resistance to insulin and diabetic mellitus type 2 (T2DM), or over nearly twice probability of developing increased CVD, which include atherosclerosis, stroke and coronary artery disease(40) coronary artery disease is largest cause of death around that leads to T2DM death and excess threat of women's mortality comparison to male(41) Relatively small extra cellular vescles(EVs) about (50 nm to 2 mm) are produced by the membrane of many cell types into different body fluids , including plasma, milk, sweat, saliva, blood, urine, tears, etc. There are many EV categories, exosomes, microvesicles (MVs),and apoptotic bodies formed by various

Processes.-Mechanisms. The most attention is given recenltly to exosomes which are extracted from cells when the plasma membrane fuses within multivesicular bodies (MVB; also known as multivosicular endosomes, MVE). in a carefully controlled mechanism and their contents released(42). One of the features of all EVs is the Phosphatidyl serine (PS) presence on the ground surface; loss of asymmetry of membrane when blebbing (apoptotic bodies) or budding (MV) and internal folding membrane during the formation of vesicles in MVBs exosomes .(fig:3)This could be determined by the label attachment ANNEXIN V, an frequently used flowcytometric reagent of Apoptotic cell examination. More significantly, a variety of groups find MVs without PS on the external membrane that does not seem required for MV preparation(43,44) which are 0.2-2.0 mm microvesicles coming from the cell membrane by budding and thus can contain common cell origin surface markers (45)



(Fig:3): Schematic representation of (microvesicles,exosos,and apoptotic bodies) formation processes

Asignificant percentage of the heart volume is formed by thecardiac muscle, while nonmyocyte is the most prevalent Cardiac fibroblast (CF) containing approximately 90 % of nonmuscular cells Endothelial cells (ECs) with important functions in cardiac homeostasis are in contact with those cells. In addition, several research indicate the presence of cardiac derived- progenitor cells (CPCs) which are involved in the response of post-injury , the existenc of such cells in the heart indicates the significance and the need to find the ways of heterocellular communication such communication occurs in which . EXOs are the primary mediation between the different populations of the cells. (46)

Exosomes may play a role in the process of metabolic conditions and cardiovascular disorders they were found to hold metabolites and allowing intra - cellular communication by exosomal miRNA exchange between skeletal muscles , adipose tissue, pancreatic b-cells, and the mouse liver and the human(47)

Reciprocal adipocyte signaling and macrophages via exosomes in the spontaneous leptin gene-knockout pathway of the RBP4 (retinol binding protein) suggests obesity (protein 4) in macrophage activation and insulin resistance(48) Obesemice had a fat diet show separate exosomal circulating

miRNAs that are sufficient to stimulate insulin lean mice resistance, probably via inhibition of proliferator-activated peroxisome receptor alpha presence in fatty tissues (49) fCachexia, a dangerous disease of lossing weight and muscle mass associated with chronic conditions such as cancer or paraneoplastic metabolisms disorders (such as: new-acquired diabetes in pancreatic cancer) Cancer cell-derived exosomal can be aggravated mouse and human adipocyte and muscle cell (50)

Adrenomenomedulline,a peptide hormone was detected that stimulates lipolysis. in human pancreas produced exosomes mouse and induced cancer cells and adipocytes in humans (51) Such results support for exosomes from cancer cells change non-cancer cell metabolism, including pancreatic islet cells, adipocytes, and thus supporting the production functionally in the paraneoplastic and cachexia syndrome. mouse and human cell culture xosomes Supernatant (, cardiac Fibroblast, cardiomyocytes and cardiac orginator cells seemed to be correlated with metabolic disorders such as atherosclerosis, diabetes-related disorder metabolic and cardiovascular disease (CVD) heart failure(52)

- **Exosomes role in neurodegeneration**

The development of exosomal biogenesis and the control of neuronal secretory vesicles new insights into

the putative were provided by cells communication and pathogenesis between exosomes of diseases that cause neurodegeneration. Exosomes may enable or reduce unfolded accumulation and abnormally folded brain proteins[53,54]

Exosomes may be involved in removing misfolded proteins ,Hence, practicing neuroprotective and detoxifying features,or assist in the proliferation and accumulation in misfolded proteins, supports effectively protein aggregates are "infective" and leading to the spread of diseases. GW4869 Pharmaceutical blockage(Inhibiting the flow of MVBs inward) or improvement of development of exosomes with monensin (with such an intracellular Ca2 + increase). adecrease in or generation of MVB increase of the transmission, respectively

PrPsc's contagious prion protein Creutzfeldt – Jakob disease in combination in vitro , Tau and Ab (generated with b-amyloid) by the amyloid precursor cleavage the Alzheimer's disease, protein [APP], exosomes, including patients, are considered exosomes derived from brain spinal fluid (Tau); supernatantderived mouse cell culture exosomes and supernatant exosomes of the mouse and human cell culture lines (Ab). Tau 's pathological spread in vitro ,exosome accumulation has been reported in vivo and in vtrio [55,56] The exosome biogenesis can be neuroprotective exosomes can trigger neurotoxic impairments the formation of oligomers, or even may move them out of cells, inhibition of exosome secretion in vivo but the suppression of exosome secretion in vivo utilize GW4869 in Transgenic TDP-43A325 T mice were detrimental, so it seemed to reduce pathogenic TDP-43 clearance of neurons the exosomal role in the pathophysiology of neurodegenerative disease and ASD needs more researchs , Such stimulation is empowered in large part by the intrinsic characteristics of exosomes to pass efficiently through blood – brain barrier, a working vascular network as a way to keep toxins , or drug far from brain [57]

-Exosomes role in reproduction and development

since small EVs are identified in the intercellular information exchange, numerous studies have indicated the impact of these vesicles in process of replication , tiny EVs shown in follicular fluid [58] and oviductal fluid [59] secreted by embryos in culture media [60] Furthermore, the information of molecular pathways of EVs promotes new technology progress of bio-roles, diagnostic and treatment potential(61) such significant structure is an ovarian follicle within the ovary, the microenvironment formed by theca cells , granulosa, cumulus and the

Oocyte , in the antral follicles which are formed by folliculogenesis having the follicular fluid , the microenvironment of follicle is managed via endocrine , paracrine and autocrine through its development , hence the contact between the cells is essential for the growth of oocytes and follicles.

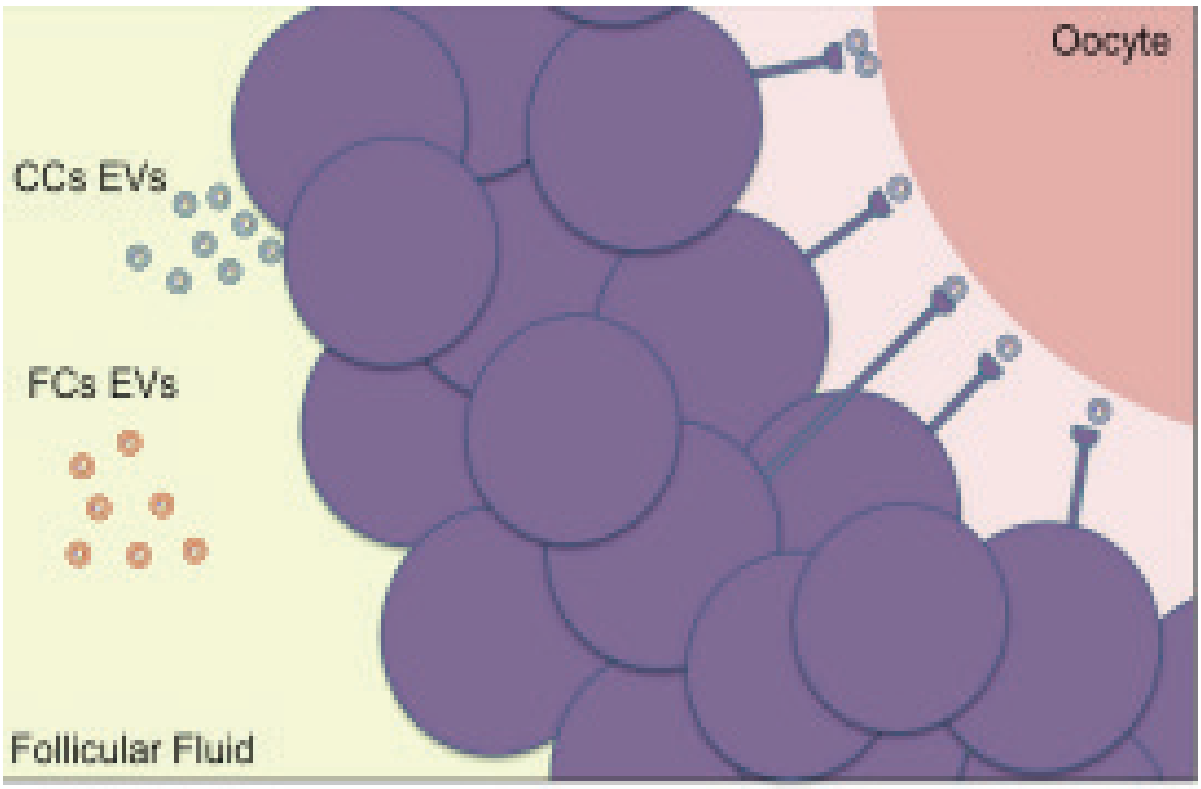
Folicular cells could also secrete EV in follicular fluid,that assist in transmitting of information between cells(fig: 4) [62]

EVs of follicular fluid has important biological content due to the development of follicle and oocytes for example, effects from these EVs can be detected in cumulus and cells of granulosa hormones and development able to effect theollicle environment that lead to alter biogenesis of EVs and contents, therefore, ovarian follicle physiology an essential to increase the application of EVs in the reproductive driven strategies.[63]

Researchers find alternative enhancement strategies for fertility levels and increase the probability of pregnancy in women by reproductive assistance and advanced materials for medication. ,inescapable correlation is between fertility and reproductive functions effective folliculogenesis, Oogensis, implantation, embryo development and pregnancy cell-to - cell contact is affected by exosomes, necessary cross-talk between mother and fetus and gene and protein expression rates during pregnancy from Reproductive system[64,65,66]

It has been shown that exosomes have an important role to play in transporting; the ability to modulate molecular cargos , normal follicular transcription and translations development, proliferation and distinguishing of granulous cells, gametogenesis, oocyte maturation , fertilization rate, embryo development, development of blastocysts, and appears result pregnancy [67,68] Identifying the exosomes in the reproductive system demonstrates their potential roles in pre- and post-conception intercellular communication during maternal aging advanced.

However, the efficiency and abundance of human exosomes is recently used as an indicator for pregnancy and pregnancy related diseases[69,70]



(Fig;4): Extracellular vesicles can hold and move bioactive molecules such as proteins in the follicular fluid RNAs, miRNAs, lipids and metabolites which contribute to oocyte maturation[71]

Ethical Clearance: Nil

Source of Funding- Self

Conflict of Interest :Nil

Refrences

1. Trajkovic K, Hsu C, Chiantia S, Rajendran L, Wenzel D, Wieland F, Schwille P, Brügger B, Simons M. Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science. 2008 Feb 29;319(5867):1244-7..
2. Murtaza G, Ahmad A, WAHEED AA, NAEEM AM. SALBUTAMOL SULPHATE-ETHYLCELLULOSE MICRO PARTICLES: FORMULATION AND IN-VITRO EVALUATION WITH EMPHASIS ON MATHEMATICAL APPROACHES.
3. Batista BS, Eng WS, Pilobello KT, Hendricks-Muñoz KD, Mahal LK. Identification of a conserved glycan signature for microvesicles. Journal of proteome research. 2011 Oct 7;10(10):4624-33.
4. Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. Nature reviews immunology. 2009 Aug;9(8):581-93.
5. Vickers KC, Remaley AT. Lipid-based carriers of microRNAs and intercellular communication. Current opinion in lipidology. 2012 Apr;23(2):91..
6. Théry, C., Ostrowski, M., & Segura, E. (2009). Membrane vesicles as conveyors of immune responses. Nature reviews immunology, 9(8), 581-593
7. Baran J, Baj-Krzyworzeka M, Weglarczyk K, Szatanek R, Zembala M, Barbasz J, Czupryna A, Szczepanik A, Zembala M. Circulating tumour-derived microvesicles in plasma of gastric cancer patients. Cancer Immunology, Immunotherapy. 2010 Jun 1;59(6):841-50.
8. Greening DW, Gopal SK, Xu R, Simpson RJ, Chen W. Exosomes and their roles in immune regulation

and cancer. InSeminars in cell & developmental biology 2015 Apr 1 (Vol. 40, pp. 72-81). Academic Press.

9. Gangoda L, Boukouris S, Liem M, Kalra H, Mathivanan S. Extracellular vesicles including exosomes are mediators of signal transduction: are they protective or pathogenic?. Proteomics. 2015 Jan;15(2-3):260-71..
10. Mittelbrunn M, Gutiérrez-Vázquez C, Villarroya-Beltri C, González S, Sánchez-Cabo F, González MÁ, Bernad A, Sánchez-Madrid F. Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells. Nature communications. 2011 Apr 19;2(1):1-0.
11. Camussi G, Deregibus MC, Bruno S, Cantaluppi V, Biancone L. Exosomes/microvesicles as a mechanism of cell-to-cell communication. Kidney international. 2010 Nov 1;78(9):838-48.
12. Nazimek K, Bryniarski K, Santocki M, Ptak W. Exosomes as mediators of intercellular communication: clinical implications. Pol Arch Med Wewn. 2015 Jan 1;125(5):370-80.
13. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. Cell & bioscience. 2019 Dec 1;9(1):19.
14. Tian, T., Wang, Y., Wang, H., Zhu, Z., & Xiao, Z. (2010). Visualizing of the cellular uptake and intracellular trafficking of exosomes by live-cell microscopy. Journal of cellular biochemistry, 111(2), 488-496.
15. Khalyfa A, Gozal D. Exosomal miRNAs as potential biomarkers of cardiovascular risk in children. Journal of translational medicine. 2014 Dec 1;12(1):162..
16. Zhang H, Xie Y, Li W, Chibbar R, Xiong S, Xiang J. CD4+ T cell-released exosomes inhibit CD8+ cytotoxic T-lymphocyte responses and antitumor immunity. Cellular & molecular immunology. 2011 Jan;8(1):23-30.
17. Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding CV, Melief CJ, Geuze HJ. B lymphocytes secrete antigen-presenting vesicles. Journal of Experimental Medicine. 1996 Mar 1;183(3):1161-72.
18. Buschow SI, Anderton SM, Stoorvogel W, Wauben MH. Activated T cells recruit exosomes secreted by dendritic cells via LFA-1. Blood. 2009 Feb 26;113(9):1977-81..
19. Muntasell A, Berger AC, Roche PA. T cell-induced secretion of MHC class II–peptide complexes on B cell exosomes. The EMBO journal. 2007 Oct 3;26(19):4263-72..
20. Admyre C, Bohle B, Johansson SM, Focke-Tejkl M, Valenta R, Scheynius A, Gabrielsson S. B cell–derived exosomes can present allergen peptides and activate allergen-specific T cells to proliferate and produce TH2-like cytokines. Journal of Allergy and Clinical Immunology. 2007 Dec 1;120(6):1418-24..
21. Vincent-Schneider H, Stumptner-Cuvelette P, Lankar D, Pain S, Raposo G, Benaroch P, Bonnerot C. Exosomes bearing HLA-DR1 molecules need dendritic cells to efficiently stimulate specific T cells. International immunology. 2002 Jul 1;14(7):713-22.
22. Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, Ricciardi-Castagnoli P, Raposo G, Amigorena S. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell derived exosomes. Nature medicine. 1998 May;4(5):594-600.
23. Muntasell A, Berger AC, Roche PA. T cell-induced secretion of MHC class II–peptide complexes on B cell exosomes. The EMBO journal. 2007 Oct 3;26(19):4263-72.
24. Théry C, Duban L, Segura E, Véron P, Lantz O, Amigorena S. Indirect activation of naïve CD4+ T cells by dendritic cell-derived exosomes. Nature immunology. 2002 Dec;3(12):1156-62.
25. Hsu DH, Paz P, Villaflor G, Rivas A, Mehta-Damani A, Angevin E, Zitvogel L, Le Pecq JB. Exosomes as a tumor vaccine: enhancing potency through direct loading of antigenic peptides. Journal of immunotherapy. 2003 Sep 1;26(5):440-50..
26. Qazi KR, Gehrmann U, Domange Jordö E, Karlsson MC, Gabrielsson S. Antigen-loaded exosomes alone induce Th1-type memory through a B cell-dependent mechanism. Blood. 2009 Mar 19;113(12):2673-83..
27. Kamerkar S, LeBleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, Lee JJ, Kalluri R. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. Nature. 2017 Jun;546(7659):498-503.

28. Mendt M, Kamerkar S, Sugimoto H, McAndrews KM, Wu CC, Gagea M, Yang S, Blanko EV, Peng Q, Ma X, Marszalek JR. Generation and testing of clinical-grade exosomes for pancreatic cancer. JCI insight. 2018 Apr 19;3(8).
29. Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding CV, Melief CJ, Geuze HJ. B lymphocytes secrete antigen-presenting vesicles. Journal of Experimental Medicine. 1996 Mar 1;183(3):1161-72.
30. Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, Ricciardi-Castagnoli P, Raposo G, Amigorena S. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell derived exosomes. Nature medicine. 1998 May;4(5):594-600..
31. Montecalvo A, Shufesky WJ, Stolz DB, Sullivan MG, Wang Z, Divito SJ, Papworth GD, Watkins SC, Robbins PD, Larregina AT, Morelli AE. Exosomes as a short-range mechanism to spread alloantigen between dendritic cells during T cell allorecognition. The Journal of Immunology. 2008 Mar 1;180(5):3081-90.
32. Tkach M, Kowal J, Zucchetti AE, Enserink L, Jouve M, Lankar D, Saitakis M, Martin□Jaular L, Théry C. Qualitative differences in T□cell activation by dendritic cell□derived extracellular vesicle subtypes. The EMBO journal. 2017 Oct 16;36(20):3012-28.
33. Cheng Y, Schorey JS. Exosomes carrying mycobacterial antigens can protect mice against M ycobacterium tuberculosis infection. European journal of immunology. 2013 Dec;43(12):3279-90..
34. Giri PK, Schorey JS. Exosomes derived from M. Bovis BCG infected macrophages activate antigen-specific CD4+ and CD8+ T cells in vitro and in vivo. PloS one. 2008 Jun 18;3(6):e2461..
35. Nandakumar R, Tschismarov R, Meissner F, Prabakaran T, Krissanaprasit A, Farahani E, Zhang BC, Assil S, Martin A, Bertrams W, Holm CK. Intracellular bacteria engage a STING–TBK1–MVB12b pathway to enable paracrine cGAS–STING signalling. Nature microbiology. 2019 Apr;4(4):701-13.
36. Wang J, Yao Y, Chen X, Wu J, Gu T, Tang X. Host derived exosomes-pathogens interactions: Potential functions of exosomes in pathogen infection. Biomedicine & Pharmacotherapy. 2018 Dec 1;108:1451-9.
37. Marcilla A, Martin-Jaular L, Trelis M, de Menezes-Neto A, Osuna A, Bernal D, Fernandez-Becerra C, Almeida IC, Del Portillo HA. Extracellular vesicles in parasitic diseases. Journal of extracellular vesicles. 2014 Jan 1;3(1):25040.
38. Sisquella X, Ofir-Birin Y, Pimentel MA, Cheng L, Abou Karam P, Sampaio NG, Penington JS, Connolly D, Giladi T, Scicluna BJ, Sharples RA. Malaria parasite DNA-harbouring vesicles activate cytosolic immune sensors. Nature communications. 2017 Dec 7;8(1):1-5..
39. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020 Feb 7;367(6478).
40. Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, Ricciardi-Castagnoli P, Raposo G, Amigorena S. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell derived exosomes. Nature medicine. 1998 May;4(5):594-600.
41. Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. Cell metabolism. 2013 Jan 8;17(1):20-33.
42. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events..
43. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annual review of cell and developmental biology. 2014 Oct 6;30:255-89..
44. Larson MC, Woodliff JE, Hillery CA, Kearl TJ, Zhao M. Phosphatidylethanolamine is externalized at the surface of microparticles. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2012 Dec 1;1821(12):1501-7.
45. Hou S, Grillo D, Williams CL, Wasserstrom JA, Szleifer I, Zhao M. Membrane phospholipid redistribution in cancer micro-particles and implications in the recruitment of cationic protein factors. Journal of Extracellular Vesicles. 2014 Jan 1;3(1):22653.
46. Lawson C, Vicencio JM, Yellon DM, Davidson SM. Microvesicles and exosomes: new players in

metabolic and cardiovascular disease. Journal of Endocrinology. 2016 Feb 1;228(2):R57-71.

47. , Bellin G, Gardin C, Ferroni L, Chachques JC, Rogante M, Mitrečić D, Ferrari R, Zavan B. Exosome in cardiovascular diseases: a complex world full of hope. Cells. 2019 Feb;8(2):166.
48. Guay C, Regazzi R. Exosomes as new players in metabolic organ cross□talk. Diabetes, Obesity and Metabolism. 2017 Sep;19:137-46..
49. Deng ZB, Poliakov A, Hardy RW, Clements R, Liu C, Liu Y, Wang J, Xiang X, Zhang S, Zhuang X, Shah SV. Adipose tissue exosome-like vesicles mediate activation of macrophage-induced insulin resistance. Diabetes. 2009 Nov 1;58(11):2498-505.
50. Castaño C, Kalko S, Novials A, Párrizas M. Obesity-associated exosomal miRNAs modulate glucose and lipid metabolism in mice. Proceedings of the National Academy of Sciences. 2018 Nov 27;115(48):12158-63.
51. Chitti SV, Fonseka P, Mathivanan S. Emerging role of extracellular vesicles in mediating cancer cachexia. Biochemical Society Transactions. 2018 Oct 19;46(5):1129-36..
52. Sagar G, Sah RP, Javeed N, Dutta SK, Smyrk TC, Lau JS, Giorgadze N, Tchkonia T, Kirkland JL, Chari ST, Mukhopadhyay D. Pathogenesis of pancreatic cancer exosome-induced lipolysis in adipose tissue. Gut. 2016 Jul 1;65(7):1165-74.
53. Zhang Y, Hu YW, Zheng L, Wang Q. Characteristics and roles of exosomes in cardiovascular disease. DNA and cell biology. 2017 Mar 1;36(3):202-11.
54. Budnik V, Ruiz-Cañada C, Wendler F. Extracellular vesicles round off communication in the nervous system. Nature Reviews Neuroscience. 2016 Mar;17(3):160-72..
55. Levy E. Exosomes in the diseased brain: first insights from in vivo studies. Frontiers in neuroscience. 2017 Mar 23;11:142.
56. Guo BB, Bellingham SA, Hill AF. Stimulating the release of exosomes increases the intercellular transfer of prions. Journal of Biological Chemistry. 2016 Mar 4;291(10):5128-37.
57. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020 Feb 7;367(6478).
58. Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, Wolozin B, Butovsky O, Kügler S, Ikezu T. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nature neuroscience. 2015 Nov;18(11):1584.
59. Baker S, Polanco JC, Götz J. Extracellular vesicles containing P301L mutant tau accelerate pathological tau phosphorylation and oligomer formation but do not seed mature neurofibrillary tangles in ALZ17 mice. Journal of Alzheimer's Disease. 2016 Jan 1;54(3):1207-17.
60. da Silveira JC, Veeramachaneni DR, Winger QA, Carnevale EM, Bouma GJ. Cell-secreted vesicles in equine ovarian follicular fluid contain miRNAs and proteins: a possible new form of cell communication within the ovarian follicle. Biology of reproduction. 2012 Mar 1;86(3):71-1.
61. Al-Dossary AA, Strehler EE, Martin-DeLeon PA. Expression and secretion of plasma membrane Ca 2+-ATPase 4a (PMCA4a) during murine estrus: association with oviductal exosomes and uptake in sperm. PloS one. 2013 Nov 14;8(11):e80181.
62. Kropp J, Salih SM, Khatib H. Expression of microRNAs in bovine and human pre-implantation embryo culture media. Frontiers in genetics. 2014 Apr 24;5:91.
63. Saadeldin IM, Oh HJ, Lee BC. Embryonic–maternal cross-talk via exosomes: potential implications. Stem cells and cloning: advances and applications. 2015;8:103.
64. Andrade GM, Bridi A, Gimenes LU, Meirelles FV, Perecin F, da Silveira JC. Extracellular vesicles and its advances in female reproduction. Animal Reproduction (AR). 2019 Mar 8;16(1):31-8.
65. Hung WT, Navakanitworakul R, Khan T, Zhang P, Davis JS, McGinnis LK, Christenson LK. Stage-specific follicular extracellular vesicle uptake and regulation of bovine granulosa cell proliferation. Biology of reproduction. 2017 Oct 1;97(4):644-55.
66. Machtinger R, Laurent LC, Baccarelli AA. Extracellular vesicles: roles in gamete maturation, fertilization and embryo implantation. Human reproduction update. 2016 Mar 1;22(2):182-93.
67. da Silveira JC, Veeramachaneni DR, Winger QA, Carnevale EM, Bouma GJ. Cell-secreted vesicles in equine ovarian follicular fluid contain miRNAs and proteins: a possible new form of cell communication within the ovarian follicle. Biology of reproduction. 2012 Mar 1;86(3):71-1.
68. Ng YH, Rome S, Jalabert A, Forterre A, Singh H,

Hincks CL, Salamonsen LA. Endometrial exosomes/microvesicles in the uterine microenvironment: a new paradigm for embryo-endometrial cross talk at implantation. PloS one. 2013 Mar 13;8(3):e58502..

69. Mobarak H, Rahbarghazi R, Lolicato F, Heidarpour M, Pashazadeh F, Nouri M, Mahdipour M. Evaluation of the association between exosomal levels and female reproductive system and fertility outcome during aging: a systematic review protocol. Systematic reviews. 2019 Dec 1;8(1):293.
70. Tsochandaridis M, Nasca L, Toga C, Levy-Mozziconacci A. Circulating microRNAs as clinical biomarkers in the predictions of pregnancy complications. BioMed research international. 2015 Oct;2015.
71. Andrade GM, Bridi A, Gimenes LU, Meirelles FV, Perecin F, da Silveira JC. Extracellular vesicles and its advances in female reproduction. Animal Reproduction (AR). 2019 Mar 8;16(1):31-8.