EXOSOMES — A NEW WINDOW OF HEALTH FROM DISEASE, TREATMENT, DIAGNOSIS, AESTHETICS, AND LIFESPAN

Migena Gega, Admir Nake, Klerida Shehu, Jonida Stefa, Orgeta Dervishi

Faculty of Medical and Technical Sciences, University of Medicine, Tirana, Albania.

Correspondence E-mail: migenagega@yahoo.com

Abstract

Exosomes are extracellular vesicles (30–200 nm) that come out of every cell. They include micro-vesicles and apoptotic bodies, and they are very important for communication between cells, epigenetic regulation, and sending messages close (paracrine function) or far away (endocrine function). Exosome era targets and promotes therapeutic and research approaches, from early laboratory or imagery biomarkers to monitoring of prognosis, even though they have not received the green light from the FDA (Food and Drug Administration).

Aim. Highlighting the characteristics and the windows that are opened by recent investigations of exosomes in many fields of medicine, diagnosis, laboratory biomarkers, preventive medicine, drug therapies, drug delivery, and cosmetics, including diagnosis and treatment of cancer.

Material and Methods. Recently, articles using words such as exosome, biogenesis, function, and structure, and phrases such as exosome and cancer, exosome and influencing factors", exosome in physiological condition, exosome and diseases, and artificial exosome

Results and Conclusions. Exosomes, as a "mirror of intracellular and membrane life" and "intracellular dynamics," show very early the status of a healthy or disease process happening in the organelles of cells, its "natural and social microenvironment," and are therefore a useful tool" for a new, efficient synergy of evidence-based medicine with personalized medicine, where the focus is not only on the disease but also on improving health status, aesthetics, anti-ageing, and lifespan.

Key words.: exosome, oncosome, nano-therapy, early biomarkers

EKZOZOMET - NJË DRITARE E RE SHËNDETI NGA SËMUNDJET, TRAJTIMI, DIAGNOZA, ESTETIKA DHE JETËGJATËSIA

Abstrakt

Eksozomet janë fshikëza ekstraqelizore, të madhësisë 30-200 nm, që dalin nga çdo qelizë, ku përfshihen gjithashtu mikrofshikëzat dhe trupat apoptotikë, të rëndësishme për komunikimin ndërqelizor, rregullimin epigjenetik dhe përcjelljen afër (funksioni parakrin) dhe në distancë (funksioni endokrin) të mesazheve biologjike, si në kushte normale edhe patologjike. "Era" e

eksozomeve synon dhe promovon shumë terapi dhe qasje hulumtuese nga kapja e hershme laboratorike ose imazherike, deri tek monitorimi prognostik, edhe pse nuk ka ende për to një dritë jeshile miratimi nga FDA.

Qëllimi: Theksimi i karakteristikave të eksozomeve dhe dritareve që hapen nga njohja e thellë dhe e duhur e tyre në fushën mjekësore, diagnostikuese, monitoruese, trajtuese, klinike, laboratorike, eksperimentale, farmaceutike, preventive, referuar studimeve më të fundit të literaturës.

Materiali dhe Metoda: Jane studiuar artikujt më të fundit duke përdorur fjalët "exosome," "biogenesis,"function," "structure" si edhe tog-fjalëshat : "exosome and cancer", "exosome and influencing factors", "exosome in physiological condition", "exosome and diseases", "artificial exosome"

Rezultate dhe Përfundime: Eksozomet "si pasqyrë e jetës qelizore" dhe "dinamizmit ndërqelizor" tregojnë shumë herët statusin e qelizsë së shëndoshë apo të sëmurë, "mikromjedisit nayral dhe social të saj", për rrjedhojë janë instrument i dobishëm për një hop të ri, një ndërthurje sa më efikase të "evidenced based medicine" me mjekësinë e personalizuar, ku fokusi është jo vetëm sëmundja, por edhe përmirësimi i statusit shëndetësor, estetik parandalimi i plakjes dhe jetëgjatësia.

Fjalë kyç. exozome, oncozome, nanoterapi, shenjues të hershëm

Introduction

The term exosome belongs to the beginning of the 1980s, although researched years earlier. Trams in 1981 was the first that used this term for extracellular vesicles, to which he attributed physiological and cellular elimination mechanisms (1). Meanwhile, in 1983, Pan and Johnstone observed the removal of transferrin receptors from reticulocytes, precisely through these extracellular vesicles (2, 3). These extracellular vesicles have a lipid membrane with transmembrane protein structures that, in addition to their structural role, play the role of receptors and messengers (1, 2, 4). Exosomes are formed and placed in homeostatic equilibrium as a result of the synergy between several biochemical pathways, such as the secretory, endocytic, recycling, retrograde, anterograde, and exosome release pathways (2, 5). Exocytosis begins with the activation of the endocytic pathway through two possible ways, well known as the clathrin-dependent pathway or the clathrin-independent pathway (6). Important actors of the exosomal substrate and their fate are also lysosomes, as well as the Golgi apparatus, in concert with the cell membrane that invaginates and ensures the exosomal lipid membrane (7,8).

Rab-5 and GTPases, with a pH presence of 6.5 and phosphatidylinositol, are the key regulators of the formation of what are called early endosomes (3). Rab7 and GTPases contribute to the formation of exosomes in the presence of a pH of 5.5. Also, Rab5-Rab7 actively maintain the biogenesis of endosomes (2,3). As F-actin forms near early endosomes with the help of annexins A2, moesin, and cortactin, the Arp2/3 complex moves on to the next step in making exosomes, which is the formation of mature multivesicular bodies. In this process, lysosomal hydrolases and SNARE proteins also contribute (2, 3). Certainly, this

process cannot be realised without the presence of the ESCRT sorting complex, the elements of which act sequentially. Meanwhile, without the presence of the ESCRT complex, the pathways of their formation, primarily involving ceramides and tetraspanins, also describe themselves (3). On the other hand, membrane fusion enables the formation of endo-lysosomes, which allows functional and structural interaction and the contribution of lysosomes in the further pathway of exosome formation, but also in the formation of what are called endosome-related organelles such as melanosomes into pigmented cells, alpha dense granules into platelets, Prader-Willi bodies into endothelial cells, or the formation of specialised lysosomes like melanocytes (3,4). The endosome-lysosome pathway can be affected by some genetic pathologies such as Chediak-Higashi and Hermansky-Pudlak (3,4). Anterograde and retrograde transport involve dynamic interaction with the Golgi apparatus and late endosomes (multivesicular bodies) (3,4). The aim of our study is highlighting the characteristics and the windows that are open by recent investigation of exosomes in many fields of medicine, diagnosis, laboratory biomarkers, preventive medicine, drug therapies, drug delivery, and cosmetics, including diagnosis and treatment of cancer.

Materials and methods

This is a narrative review, with updating purpose, referred recent literature of international prestigious journals, using title of articles that include words such as exosome, biogenesis, function, and structure, and phrases such as exosome and cancer, exosome and influencing factors", exosome in physiological condition, exosome and diseases, and artificial exosome.

Main including criteria:

1. Article published during two recent years, 2023 and 2024 in prestigious journals and prestigious platforms, such as Frontier Medicine, Elsevier, PubMed 2. Only one reference belongs to 2019 because it is a PhD thesis and include clear surprisingly useful scientific information about exosome.

2. We selected firstly articles that explain terminology of exosome, published in these prestigious journals.

3. Article that realize clarification of relation structure-function and dynamism or "versions of life" of exosome. 4. Article that explain role of exosome in health and disease, and field of dermatology 5. Owing to the aim of this article and title we investigate articles that explain role of exosomes in diagnosis, therapy and lifespan. Asking question if exosome have other attributes we saw their role in contemporary medicine aspects such are attributes of early biomarkers, new drugs or route for therapy. Following this point of view, promptly derive logical questions: Are exosome FDA approved and which is trend of expenses to realize that exosome are really an hot spot and new window of medicine or just only an illusion or just still far from the applied stage?

Excluding criteria:

1. Article before 2023, respecting update purpose

2. At about 100 articles are studied but are excluded because were before 2023, or part of other fields of studies in medicine or our highlighted focus.

Results

Terminology. The size of exosomes, exosome-linked vesicles, and artificial exosomes. Exosomes, from their inception until their incorporation into the target cell, are found with the status of exosomes 30-200 nm, vesicles with sizes of 200-1000, and apoptotic bodies with sizes of 1000-5000 (1- 5). In contrast, ectosomes, unlike exosomes, are vesicles 100-1000 nm in size that exit directly into the extracellular environment, without intracellular interactions, and therefore structurally do not interact and exchange with the Golgi apparatus, lysosomes, or the intracellular environment, having a different structural composition (1-5).

Amphisomes are hybrid organelles resulting from the fusion of autophagosomes with late exosomes at the intracellular level (2, 9-11, 13). Exosomes derived from cancer cells are larger, over 1000-10000 nm, and are called oncosomes (5, 10, 12, 13).

Migrasomes are a variant of exosomes with sizes of 500-3000 nm, with a maximum presence of about 400 min, mainly consisting of structural proteins, RNA, organelles, and a number of smaller vesicles. The formation of migrasomes is influenced by the phosphatidylinositol (3,4) bisphosphate-Rab 35 pathway, as well as by pH and temperature, but also, like exosomes, by some viruses and drugs. The formation, rupture, and release of migrasomes (migracytosis) remain to be studied (10, 11).

Exomers are smaller than 50 nm, and supermers are smaller than 30 nm, and the way they are formed is unknown (10, 11). Artificial exosomes (synthetic nanoparticles) have also become part of the industrial market of exosomes and have seen rapid development in recent decades. These include liposomes, micelles, dendrimers, nanocapsules, nanoemulsions, nanodiamonds, nanosponges, and self-assembled peptides, studied especially for targeted cancer therapy (13- 15).

Actors of exosomes are responsible for completing the structural "puzzle."

Action scenes and the exosomal actors' pathways are the intracellular environment, the extracellular environment, biological fluids (blood, urine, plasma, saliva, cerebrospinal fluid), tumour microenvironment, healthy cells of the body, and cells under pathological conditions, including cancer cells (27, 28, 9, 13-15). So, if we look at exosomes through an electronic microscope, we can see that they are made up of plasma membrane components from the ones that come from inside cells, the Golgi apparatus, and lysosomes, which form vesicles like early and late endosomes (2,3). Also, plasma components anchored to the surface of exosomes are part of their structure and can either speed up or slow down the delivery of their message to the target cell. Therefore, the composition of exosomes depends on the nature of the cell components (membrane, lysosomes, Golgi apparatus) from which they originate, as well as the modulation they undergo during the transition through all stages, from biogenesis to the target cell (host) with extracellular components, as well as plasma components (3, 17, 18). Cells that produce exosomes at the highest rate are cancer cells, called oncosomes (2, 9,18). Among non-cancerous cells are platelets, dendritic cells, T lymphocytes, and B lymphocytes. The rate of exosome production is also studied under

experimental conditions, with cell lines aimed at applying exosome-producing "machines" as therapies, from cancer to cosmetic goals (10, 14).

- Main components of exosomes

RNA, DNA fragments, tetraspanins, annexins, protein biomarkers, transcription factors, metabolites, and different miRNAs make up most of exosomes. Exosomes have heat shock proteins, antigen-presenting proteins, glycoproteins, adhesion molecules, cytoskeletal proteins, ESCRT (endosomal sorting complex required transport), growth factors, and cytokines (2,5). Exosomes also have lipid structures such as cholesterol, phosphatidic acid, ceramide, sphingomyelin, phosphatidylinositol, phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine, and gangliosides. Mitochondria can also be found in exosomes (2, 3).

- Some factors influence the rate of exosome production.

Exosomal and endosomal factors

The promotion of exosome production and their arrival in the target cell is multifactorial. Factors are biological, biochemical, intracellular, or extracellular; natural or unnatural (in experimental artificial conditions) (2,3). A lot of people talk about how important it is for exosome production (initiation) and modulation that contact is blocked, Rab homeostasis, or Ral, especially Rab 27A and Rab 27B, or the dynamic balance between Rab 27 and Rab 7. What makes up exosomes determines whether early endosomes are taken over by lysosomes or move on to become exosomes (2,3). The rate of glycosylation (N-linked glycosylation), the degree of interaction with the Golgi apparatus, and oligomerisation condition the production of exosomes in the respective cell and their transport to the target cells. Therefore, syndecan, heparan sulphates, proteoglycans, and cytoplasmic adaptors such as syntenin play the role of mediators in the biogenesis of exosomes (2,3). Complex lipids such as ceramides, phosphatidylserine, phosphatidylethanolamine, and phosphatidic acid promote exosome production, and through their structural addition or subtraction, exosome homeostasis is also modulated (2,3, 12).

Cholesterol is also an important lipid in the rate of exosome production. Endogenous vesicles play a significant role in the potential exosome production pathway. If they are rich in cholesterol, they enter the exosome production pathway, and if they are poor in cholesterol, they are sequestered by lysosomes (15, 16). Cellular stress, hypoxia, inflammation, and hypoglycemia condition the protein composition and RNA components of exosomes.

Extracellular factors influencing the degree of exosome expression

pH, or Ca++. ionophores, hypoxia, hormonal modulation (it is now accepted that hormones can also be transmitted through exosomes), circadian rhythm hormones, and temperatures are external factors influencing the inhibition or continuation of exosome production (2,3, 17). Important studied hormones that give impact in exosome production are cortisol, while oestradiol stimulates specific miRNA exosomes in breast cancer, and as a synergistic partner, exosomes have circadian rhythm hormones such as melatonin (8, 13).

Discussion

There is still a lot of potential for exosomes and a significant amount of work to be done in order to find as many applications as possible. Nevertheless, it is worth highlighting some modern approaches to them.

- Exosomes, Dermatology, and Longevity

One of the clinical areas that has turned attention to exosomes is dermatology, especially aesthetic dermatology, which is already an important part of it and has developed vigorously, especially during recent years. People now view exosomes as a form of regenerative therapy (8,18,19). For example, various dermatoses can be treated with ointments containing exosomes, which bring re-epithelialization and regulate cutaneous inflammation (20). After clinical cutaneous aspects such as ichthyosis, eruptions, cutis lesions, skin thickening-lipodystrophy, hypopigmentation, hyperpigmentation, and hair loss, the dynamism of exosomes (vesicular trafficking) can be hidden, a consequence of certain genetic alterations (10, 20). Exosomes are seen as very useful for increasing human lifespan; why not for other living beings? For example, various miRNAs, such as miRNA 335 and miRNA-34, modulate the lifespan of mesenchymal cells by inhibiting the action of enzymes such as superoxide dismutase and thioredoxin reductase, enzymes that contribute to oxidative stress, thus the instability of the respective organelles (17, 21, 22) Exosomes are seen as aesthetic dermatological applications; for example, ointments based on exosomes applied with laser therapy are more effective than laser therapy alone, for example, in melanin indexes, skin wrinkles, skin radiance, or photo-ageing (7). Many other diseases in other organs can result precisely from the jeopardized dynamism of exosomes, a consequence of certain genetic alterations (10). Such as hepatosplenomegaly, cardiomyopathies, acute renal failure, tubulopathies, cataracts, retinopathies, and corneal anomalies, may also have genetic alterations as the cause, already studied and confirmed to bring the jeopardizing of exosome dynamics (vesicular trafficking) (10, 13). Studies according to Lang et al. say that SIRT-4 proteins affect mitochondrial homeostasis, and meanwhile miRNA-15b is the one that modulates SIRT-4, influencing lifespan (17, 21, 22).

- Exosomes and the spread of diseases in organisms

Exosomes can influence the inhibiting or promoting development of many diseases. Exosomes influence disease spread; for example, viral diseases are more spectacular, and the spread of the cancer process (1, 2, 4, 9, 13). Exosomes during the cancer process influence invasion, metastasis, neovascularisation, and angiogenesis (13).

- Exosome, early and prognostic laboratory biomarkers"

Since the initial mechanisms of the disease serve to find "early biomarkers," an in-depth study of the mechanism of spread directly contributes to finding new therapies and "prognostic biomarkers" (13). Moreover, the intertwining of bioinformatics and artificial intelligence with the latest advances in exosomes aims at applying biosensors for miRNA exosomes, representative with value for capturing early cancer processes (24- 26).

- Exosome Machinery and the Pharmaceutical Industry

On the other hand, the pharmaceutical industry is increasingly developing an "exosome machinery," an exosome industry with continuous and high production rates. According to economic reports on the exosome research market, the trend of predictions for the money spent in function of this industry until 2028 is exponential, from 148 million in 2022 and 169 million in 2023 to 356 million in 2028. As a matter of fact, research studies conducted over the past decade on exosomes have also seen exponential growth (27-31). The current trend is their use in nanotechnology, molecular diagnostics, cardiovascular diseases, pharmaceutical purposes, neurodegenerative diseases, biotechnology, diagnostics, and cancer research (32, 36). The future trend is their use together with artificial intelligence in drug discovery, "point of care" tests, telemedicine, CAR-T cell therapy, nanorobotics, microfluidics, and 3D bioprinting (37-39). The study of partners of exosomes in therapeutic approaches has resulted in many synergistic tangos, such as the potentiation of melatonin-exosome effects in anticancer and anti-inflammatory processes and the slowing of degenerative processes, embryonic development, renal insufficiency, wound healing, and liver lesions (40).

- Exosomes: A New Way for Drug Administration

Moreover, the use of artificial exosomes (synthetic nanoparticles) as an effective and maximally efficient way of transmitting drugs directly to the center of action or target cell is now seen as an optimal and new way of direct bar passage, minimizing the effect of "drug loss," side effects, or complications, as occurs in classic routes such as oral, muscular, or intravenous (40).

Conclusions

Exosomes, as a "mirror of intracellular and membrane life" and "intracellular dynamics," show very early the status of a healthy or disease process happening in the organelles of cells, its "natural and social microenvironment," and are therefore a useful tool" for a new, efficient synergy of evidence-based medicine with personalized medicine, where the focus is not only on the disease but also on improving health status, aesthetics, anti-ageing, and lifespan.

References

1. MacDonald E, Salem N Jr. Dr. Eberhard Trams-The man who coined the name "exosomes"-A prescient but largely forgotten pioneer. J Extracell Vesicles. 2023;12(10):e12370. doi:10.1002/jev2.12370
2. Wang Y, Xiao T, Zhao C, Li G. The Regulation of Exosome Generation and Function in Physiological and Pathological Processes. Int J Mol Sci. 2023;25(1):255. Published 2023 Dec 23. doi:10.3390/ijms25010255
3. Roberta Palmulli. Role of CD63 in the biogenesis and the function of exosomes. Cellular Biology. Université Paris Cité, 2019. English. ffNNT : 2019UNIP5033ff. fftel-03969520f
4. Koh HB, Kim HJ, Kang SW, Yoo TH. Exosome-Based Drug Delivery: Translation from Bench to Clinic. Pharmaceutics. 2023 Jul 29;15(8):2042. doi: 10.3390/pharmaceutics15082042.
5. Kumar MA, Baba SK, Sadida HQ, et al. Extracellular vesicles as tools and targets in therapy for diseases. Signal Transduct Target Ther. 2024;9(1):27. Published 2024 Feb 5. doi:10.1038/s41392-024-01735-1

6. Gupta D, Wiklander OPB, Wood MJA, El-Andaloussi S. Biodistribution of therapeutic extracellular vesicles. Extracell Vesicles Circ Nucl Acids. 2023;4(2):170-190. Published 2023 Apr 19. doi:10.20517/evcna.2023.12
7. Wang CK, Tsai TH, Lee CH. Regulation of exosomes as biologic medicines: Regulatory challenges faced in exosome development and manufacturing processes. Clin Transl Sci. 2024;17(8):e13904. doi:10.1111/cts.13904
8. Ram Kumar RM, Logesh R, Joghee S. Breast cancer derived exosomes: Theragnostic perspectives and implications. Clin Chim Acta. 2024;557:117875. doi:10.1016/j.cca.2024.117875
9. Wang W, Sun H, Duan H, et al. Isolation and usage of exosomes in central nervous system diseases. CNS Neurosci Ther. 2024;30(3):e14677. doi:10.1111/cns.14677
10. Xie J, Zheng Z, Tuo L, et al. Recent advances in exosome-based immunotherapy applied to cancer. Front Immunol. 2023;14:1296857. Published 2023 Nov 7. doi:10.3389/fimmu.2023.1296857
11. Wang J, Yue BL, Huang YZ, Lan XY, Liu WJ, Chen H. Exosomal RNAs: Novel Potential Biomarkers for Diseases-A Review. Int J Mol Sci. 2022;23(5):2461. Published 2022 Feb 23. doi:10.3390/ijms23052461
12. Wang Y, Jiang M, Zheng X, et al. Application of exosome engineering modification in targeted delivery of therapeutic drugs. Biochem Pharmacol. 2023;215:115691. doi:10.1016/j.bcp.2023.115691
13. Reiss AB, Ahmed S, Johnson M, Saeedullah U, De Leon J. Exosomes in Cardiovascular Disease: From Mechanism to Therapeutic Target. Metabolites. 2023;13(4):479. Published 2023 Mar 27. doi:10.3390/metabo13040479
14. Zanirati G, dos Santos PG, Alcará AM, Bruzzo F, Ghilardi IM, Wietholter V, Xavier FAC, Gonçalves JIB, Marinowic D, Shetty AK, et al. Extracellular Vesicles: The Next Generation of Biomarkers and Treatment for Central Nervous System Diseases. International Journal of Molecular Sciences. 2024; 25(13):7371. https://doi.org/10.3390/ijms25137371.
15. Xie J, Zheng Z, Tuo L, et al. Recent advances in exosome-based immunotherapy applied to cancer. Front Immunol. 2023;14:1296857. Published 2023 Nov 7. doi:10.3389/fimmu.2023.1296857
16. Li, J., Wang, J. & Chen, Z. Emerging role of exosomes in cancer therapy: progress and challenges. Mol Cancer **24**, 13 (2025). https://doi.org/10.1186/s12943-024-02215-4
17. Rodriguez C, Porcello A, Chemali M, Raffoul W, Marques C, Scaletta C, Lourenço K, Abdel-Sayed P, Applegate LA, Pelissier Vatter F, et al. Medicalized Aesthetic Uses of Exosomes and Cell Culture-Conditioned Media: Opening an Advanced Care Era for Biologically Inspired Cutaneous Prejuvenation and Rejuvenation. Cosmetics. 2024; 11(5):154. https://doi.org/10.3390/cosmetics11050154
18. Vyas KS, Kaufman J, Munavalli GS, Robertson K, Behfar A, Wyles SP. Exosomes: the latest in regenerative aesthetics. Regen Med. 2023;18(2):181-194. doi:10.2217/rme-2022-0134
19. Li, J., Wang, J. & Chen, Z. Emerging role of exosomes in cancer therapy: progress and challenges. Mol Cancer **24**, 13 (2025). https://doi.org/10.1186/s12943-024-02215-4
20. Wang M, Shu H, Cheng X, et al. Exosome as a crucial communicator between tumor microenvironment and gastric cancer (Review). Int J Oncol. 2024;64(3):28. doi:10.3892/ijo.2024.5616

21. Reiss AB, Ahmed S, Johnson M, Saeedullah U, De Leon J. Exosomes in Cardiovascular Disease: From Mechanism to Therapeutic Target. Metabolites. 2023;13(4):479. Published 2023 Mar 27. doi:10.3390/metabo13040479
22. Sen S, Xavier J, Kumar N, Ahmad MZ, Ranjan OP. Exosomes as natural nanocarrier-based drug delivery system: recent insights and future perspectives. 3 Biotech. 2023;13(3):101. doi:10.1007/s13205-023-03521-2
23. Kumar, M.A., Baba, S.K., Sadida, H.Q. et al. Extracellular vesicles as tools and targets in therapy for diseases. Sig Transduct Target Ther **9**, 27 (2024). https://doi.org/10.1038/s41392-024-01735-1
24. Drula R, Pardini B, Fu X, et al. 17β-estradiol promotes extracellular vesicle release and selective miRNA loading in ERα-positive breast cancer. Proceedings of the National Academy of Sciences of the United States of America. 2023 Jun;120(23):e2122053120. DOI: 10.1073/pnas.2122053120. PMID: 37252969; PMCID: PMC10266002
25. Chu X, Hou M, Li Y, Zhang Q, Wang S and Ma J (2024) Extracellular vesicles in endometriosis: role and potential. Front. Endocrinol. 15:1365327. doi: 10.3389/fendo.2024.1365327
26. Romero-García N, Mas-Bargues C, Huete-Acevedo J, Borrás C. Extracellular Vesicles and Cellular Ageing. Sub-cellular Biochemistry. 2023 ;102:271-311. DOI: 10.1007/978-3-031-21410-3_11. PMID: 36600137.
27. Perpiñá-Clérigues, C., Mellado, S., Català-Senent, J.F. et al. Lipidomic landscape of circulating extracellular vesicles isolated from adolescents exposed to ethanol intoxication: a sex difference study. Biol Sex Differ **14**, 22 (2023). https://doi.org/10.1186/s13293-023-00502-1
28. Perpiñá-Clérigues C, Mellado S, Galiana-Roselló C, et al. Novel insight into the lipid network of plasma extracellular vesicles reveal sex-based differences in the lipidomic profile of alcohol use disorder patients. Biol Sex Differ. 2024;15(1):10. Published 2024 Jan 25. doi:10.1186/s13293-024-00584-5
29. Zeng K, He H, Lv Z, et al. Profiling of circulating serum exosomal microRNAs in elderly patients with infectious stress hyperglycaemia. Clin Transl Disc. 2023; 3:e205. https://doi.org/10.1002/ctd2.205
30. Rasti M, Parniaei AH, Dehghani L, et al. Enhancing the wound healing process through local injection of exosomes derived from blood serum: An in vitro and in vivo assessment. Regen Ther. 2024;26:281-289. Published 2024 Jun 19. doi:10.1016/j.reth.2024.06.004
31. Qi R, Wang Y, Yan F, Zhong J. Exosomes derived from ITGB1 modified Telocytes alleviates LPS-induced inflammation and oxidative stress through YAP1/ROS axis. Heliyon. 2024;10(5):e27086. Published 2024 Mar 8. doi:10.1016/j.heliyon.2024.e27086
32. Martínez-Espinosa I, Serrato JA, Cabello-Gutiérrez C, Carlos-Reyes Á, Ortiz-Quintero B. Exosome-Derived miRNAs in Liquid Biopsy for Lung Cancer. Life. 2024; 14(12):1608. https://doi.org/10.3390/life14121608
33. Metcalf GAD. MicroRNAs: circulating biomarkers for the early detection of imperceptible cancers via biosensor and machine-learning advances. Oncogene. 2024;43(28):2135-2142. doi:10.1038/s41388-024-03076-3
34. Tang, H., Yu, D., Zhang, J. et al. The new advance of exosome-based liquid biopsy for cancer diagnosis. J Nanobiotechnol **22**, 610 (2024). https://doi.org/10.1186/s12951-024-02863-0

35. Shin H, Choi BH, Shim O, et al. Single test-based diagnosis of multiple cancer types using Exosome-SERS-AI for early stage cancers. Nat Commun. 2023;14(1):1644. Published 2023 Mar 24. doi:10.1038/s41467-023-37403-1
36. Li B, Kugeratski FG, Kalluri R. A novel machine learning algorithm selects proteome signature to specifically identify cancer exosomes. Preprint. bioRxiv. 2023;2023.07.18.549557. Published 2023 Dec 20. doi:10.1101/2023.07.18.549557
37. Baghban N, Kodam SP, Ullah M. Role of CD9 Sensing, AI, and Exosomes in Cellular Communication of Cancer. Int J Stem Cell Res Ther. 2023;10(1):079. doi:10.23937/2469-570X/1410079
38. Sharma P, Roy A, Dhamija RK, et al. A comprehensive proteomic profiling of urinary exosomes and the identification of early non-invasive biomarker in patients with coronary artery disease. J Proteomics. 2024;293:105059. doi:10.1016/j.jprot.2023.105059
39. Banavar, G., Ogundijo, O., Toma, R. et al. The salivary metatranscriptome as an accurate diagnostic indicator of oral cancer. npj Genom. Med. **6**, 105 (2021). https://doi.org/10.1038/s41525-021-00257-x
40. Kim, H.I., Park, J., Zhu, Y. et al. Recent advances in extracellular vesicles for therapeutic cargo delivery. Exp Mol Med **56**, 836–849 (2024). https://doi.org/10.1038/s12276-024-01201-6