REVIEW ARTICLE

Exosomes as mediators of intercellular communication: clinical implications

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KEY WORDS

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ABSTRACT

Cells of multicellular organisms exchange informative signals by diverse mechanisms. Recent findings uncovered the special role of extracellular vesicles, especially exosomes, in intercellular communication. Exosomes, present in all tested human bodily fluids, carry various functional compounds including proteins, lipids, and diverse RNA molecules. The composition of exosome cargo in vivo is likely formed by a regulated selection of specific components and can express the current status of the exosome-secreting cell. Therefore, particular emphasis is now placed on the extremely high potential of exosomes as essentially noninvasive prognostic and diagnostic biomarkers, but also as therapeutic nanocarriers, especially after the discovery that their cargo as well as cell-targeting specificity could be shaped in vitro. In addition, targeting the exosomes mediating pathological intercellular communication may also express high therapeutic potential. Hence, numerous studies are conducted to explore the profile and function of exosomes and their cargo in health and disease and to shape their properties to facilitate their clinical application. The present review summarizes the current knowledge on the role of exosomes in different physiological and pathological mechanisms of intercellular communication with a particular focus on the use of exosomes in the diagnosis and treatment of various inflammatory, cardiovascular, metabolic, and neurodegenerative disorders as well as malignant neoplasms.

Introduction Studies of the last decade uncovered the special role of extracellular vesicles, especially exosomes, in local and systemic cell-to-cell communication. Moreover, exosomes were shown to carry various bioactive compounds including proteins, lipids, and diverse RNA molecules. At present, particular emphasis is placed on the extremely high potential of exosomes as prognostic and diagnostic markers as well as therapeutic nanocarriers, especially after demonstration that their cargo and targeting specificity could be manipulated.

The current review briefly summarizes the role of exosomes in intercellular signaling pathways orchestrating varied biological mechanisms, with a special focus on the use of exosomes in the diagnosis and treatment of various inflammatory, cardiovascular, metabolic, and neurodegenerative disorders as well as cancer.

Modes of cell-to-cell communication Neighboring cells can interact and communicate with one another by the exchange of signaling compounds mainly through: 1) simple membrane-crossing diffusion (eg, transport of steroids); 2) active transport via membrane ion-channels, pumps, or transporting proteins; 3) the formation of synapses including immunological and nerve synapses; and 4) the exchange of cell membrane fragments termed trogocytosis.[1] Furthermore, cells communicate in an auto-, para-, and endocrine manner by sensing circulating endogenous bioactive compounds including: 1) proteins (eg, hormones, cytokines), lipoproteins, lipids, and steroids; 2) simpler compounds such as eicosanoids, monoamines (eg, neurotransmitters), endorphins, or cannabinoids; and, finally, 4) extracellular microRNA (miRNA) molecules associated with protein chaperones. The majority of these signaling compounds were found in the content of extracellular vesicles, mainly exosomes. It should be stressed that the interaction of extracellular vesicles with targeted cells can produce varied biological effects mainly resulting from direct exosome-cell stimulation and action of transferred exosome cargo.[2] Exosomes release their content into an acceptor

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cell cytoplasm after their clathrin-mediated endocytosis, phagocytosis, or micropinocytosis.

Exosomes as potent communicating molecules and biomarkers of organism welfare or disorders Cells of multicellular organisms secrete various types of membrane vesicles to the extracellular milieu, termed extracellular vesicles and including, among others, exosomes, ectosomes, apoptotic bodies, and microvesicles.[3,4] Exosomes, as vesicles that range in the diameter from 50 to 100 μm, originate from intracellular multivesicular bodies and are excreted via exocytosis after the fusion of multivesicular bodies with the cell membrane.[5] Exosomes have been detected in several studied human bodily fluids[6] including plasma, saliva, and breast milk, from which they can be engulfed by macrophages.[7] Usually, exosomes are isolated for further analysis by ultracentrifugation followed by purification, using different techniques including affinity chromatography separation.[8] As mentioned above, exosomes can intercellularly transfer various functional molecules, thus playing an essential role in cell-to-cell communication resulting in altered acceptor cell function.[5] RNA content of exosomes mainly consists of miRNA molecules acting as an RNA interference mediator, ie, double-stranded, small-interfering RNA (siRNA), composed of 19 to 24 base pairs and associated with proteins to form an RNA-induced silencing complex. The sequence of nucleotides of the siRNA leading strand is complementary to that of messenger RNA (mRNA), and thus can block its translation, which results in the reduction or elimination of the corresponding protein product (FIGURE 1). However, each individual siRNA is capable of suppressing multiple mRNA targets, and one mRNA can be targeted by numerous siRNA molecules. It is also probable that delivered siRNA can stimulate Toll-like receptors (TLR), mainly TLR3 and TLR7, leading to proinflammatory activation of TLR-bearing cells. As a caveat, the action of siRNA may result in unexpected side effects, which can be reduced by manipulation of siRNA delivery, mainly by using specific exosomes (as discussed below).

Ontogenesis and reproduction also seem to remain under control of exosomes and their cargo, especially miRNA molecules. Epididymal maturation of sperm requires the transmission of essential functional proteins from the epithelium to sperm surface, and, recently, these proteins were shown to be transported by exosomes.[9] This previously unknown role of exosomes in male gamete maturation through functionally equipping with proteins warrants optimal fertilizing ability. Furthermore, placental exosomes contribute significantly to the development of maternal immune tolerance to fetus antigens in pregnant women.[10] Intriguingly, depending on the cellular origin of placental extracellular vesicles, they can either suppress or activate maternal immune response.[11] In physiological conditions, both processes result in the development of immune privilege of the fetus. Nevertheless, the diminished balance between activating and suppressing signals leads to diverse complications including pregnancy loss. Placental exosomes also mediate cell trafficking and fusion during the formation of syncytiotrophoblast and can confer the resistance to viral infections.[12] Furthermore, an imbalanced profile of placental miRNA molecules, mostly carried by exosomes, corresponding to placental abnormalities, can be easily detected in maternal blood as an early prognostic marker of pregnancy complications.[10] In addition, immune functional exosomes are detected in human breast milk,[12] suggesting their important role in the development of newborn immunity.

As recently reviewed,[13] exosomes originating from various immune and nonimmune cells greatly influence the mechanisms of innate immunity. Evidently, the acquired immune response mechanisms also involve exosome-mediated communication. Extracellular vesicles, including exosomes, originating from both pathogens and host cells of the immune system greatly contribute to intercellular communication during the course of infection. Pathogen-associated molecular patterns enriched in circulating microvesicles were demonstrated to efficiently activate the cells of the immune system further facilitating antimicrobial immune responses. However, exosomes mediating pathogen–host interactions subsequently either support or deteriorate anti-infectious immunity[14] and promote or block the spread or resolution of infection.[15] Marcilla et al.[16] reviewed diverse functions of exosomes and other nanovesicles in parasitic diseases, indicating their possible diagnostic potential. Interestingly, exosomes are likely involved in the regulation of the adaptive immune response directed against microbiota and other antigens in the gut.[17] In brief, they act mainly by the transmission of information about the composition and condition of the intestinal microbiome to the mesenteric lymph nodes to further induce either tolerance or immune response. Intestinal dendritic cell or epithelial cell-derived exosomes can also mediate the induction of tolerance to food allergens and antigens.

The pioneering discoveries concerning extracellular vesicles in the immune response suggested their role in the activation of apoptosis of immune cells and mediation of peripheral immune tolerance.[18] At that time, the proapoptotic signaling mediated by microvesicles was assigned to the process of self-limitation of activated T-cell response to prevent excessive inflammation and tissue damage. Recent findings predominantly confirmed previous suggestions and greatly expanded the general knowledge about the role of extracellular vesicles, mainly exosomes, and their cargo in the immune response. As reviewed previously, exosome-transferred miRNA molecules play an important role in the modulation of immune response.[19] Furthermore,

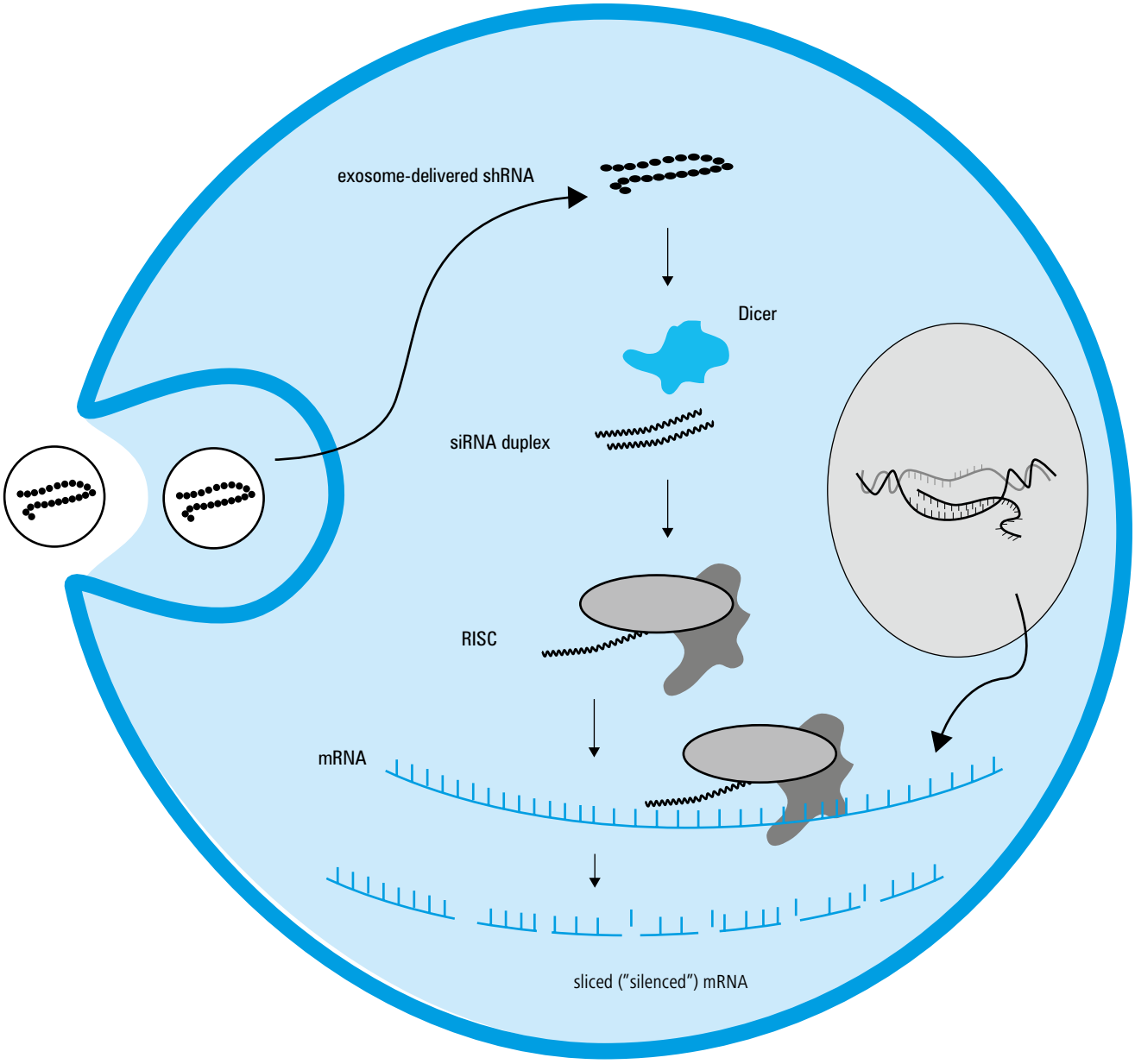

FIGURE 1 Mechanism of intracellular action of exosome-delivered small-interfering RNA (siRNA). Therapeutic RNA interference-mediating molecules delivered to an acceptor cell by exosomes in a form of small hairpin RNA (shRNA) are processed by Dicer enzyme to double-stranded siRNA. The siRNA leading strand, whose sequence is complementary to that of messenger RNA (mRNA), binds to proteins to form an RNA-induced silencing complex (RISC) that binds to mRNA. As a result, mRNA translation is silenced, and the corresponding protein product synthesis is blocked.

antigen-presenting B cell-derived exosomes were shown to induce in vitro T cell-dependent immune response,[20] and T cell-derived miRNA in exosomes were shown to regulate gene expression of antigen-presenting cells in immunological synapses.[21] Moreover, T cell receptor-bearing microvesicles released by a T lymphocyte forming an immunological synapse in turn activate an antigen-presenting B lymphocyte.[22] Intriguingly, immunological facilitation, an immune tolerance mechanism, among other things, could be mediated by circulating soluble human leukocyte antigen G, which has been recently demonstrated to be transmitted by exosomes.[23] Furthermore, the profile of circulating miRNA released mainly in exosomes by immune system cells likely express the parental cell activation status. Thus, the qualitative assessment of serum exosome-carried miRNA profile may serve as a biomarker of T and B lymphocyte activation, especially to determine the efficiency of vaccination in humans, with the current emphasis on exosome-associated miRNA-150.[24]

Various allergic, autoimmune, and inflammatory disorders could likely be monitored by the detection of related exosomes as biomarkers, as it was reviewed for multiple sclerosis.[25] Interestingly, it was proposed that, apart from bronchoalveolar lavage fluid, exhaled breath condensate is a potent and noninvasive source of biomarkers of pulmonary disorders, including extracellular vesicle-derived miRNA molecules appearing to be clinical biomarkers of asthma.[26] Moreover, dendritic cell-derived extracellular vesicles can transmit allergens to further induce allergen-specific T helper 2 lymphocytes,[26] which may exacerbate

the course of asthma. Recently, we have described a novel mechanism of antigen-specific immune suppression mediated by suppressor T CD8+ lymphocyte-derived exosomes carrying miRNA-150 and coated with antigen-specific antibody light chains from B1 cells.[8] These specific exosomes loaded with miRNA-150 suppress effector T lymphocytes of hapten-induced contact sensitivity and protein antigen-induced delayed type hypersensitivity reactions in an antigen-specific manner, as shown in dual reciprocal criss-cross experiments,[8] through the action on antigen-presenting cells (APC), especially macrophages.[27,28] It is suspected that the antigen-specificity of this mechanism is due to the recognition of antigen complexed with major histocompatibility molecules on the surface of APCs by specific antibody light chains on exosomes, followed by engulfment of exosomes by APCs, which then suppress effector T cell response. This study reinvestigated one of the first research papers on immune suppression describing the functional entity of suppressor T lymphocyte origin, termed T suppressor factor (TsF), which was confirmed to act hapten-specifically to suppress contact sensitivity response in mice.[29] Hence, our current research greatly expanded the general knowledge on exosome action and is an important part of the current trend of exosome biology exploration. Since exosomes as physiological nanocarriers have a more prolonged plasma half-life than artificial liposomes, our observations open up new possibilities to transfer functional information in an antigen-specific manner (as discussed below).

Recently, it has been demonstrated that breast cancer cell exosomes contain different enzymes of miRNA biogenesis pathway that could process premature miRNA also present in cancerous exosomes into mature oncogenic miRNA (so called oncomiRs), which then induce, in targeted normal cells, a neoplastic phenotype.[30] Hence, nanovesicles from the cells of cancer patients carry oncomiRs that can initiate tumor formation in normal cells. Exosome-associated oncogenic miRNA molecules play a detrimental role in endometriosis and cancers of a female reproductive tract and are claimed to be emerging clinical markers.[31] Similarly, exosomes may transmit viral oncomiRs affecting the tumor microenvironment.[30] Tumor cell-derived exosomes carry functional molecules responsible for angiogenesis, stromal tissue remodeling, tumor growth, and, finally, resistance to chemotherapy,[32] mainly through the sequestration of chemotherapeutics.[30] Additionally, exosomes loaded with cancer cell content interact locally and at a distance with other cell populations to promote tumor formation and metastasis mainly via modulation of specific gene expression resulting in cell production of various triggering stimuli.[33] Finally, these exosomes can serve as potent biomarkers collected by so called noninvasive tumor biopsies in cancer diagnosis and control of its progression, and as anticancer drug-delivery vehicles.[34] The characteristic contents originating from various cancer cells that were detected in circulating exosomes allowing for their usage as biomarkers were recently briefly summarized[35] and also defined for cancer stem cell exosomes.[36] In addition, blood plasma or serum-derived exosome-associated miRNA molecules characterized as specific for a particular cancer in humans have been recently listed as diagnostic biomarkers.[37] Additionally, a newly described protocol for phenotyping of exosomes from blood plasma of patients with non-small cell lung carcinoma requires as little as a 10-µl sample of plasma,[38] which should greatly facilitate further clinical analysis of exosomes as biomarkers. The clinical application of tumor cell-derived exosomes has been recently summarized in detail.[39] Moreover, the biomarker function of particular exosomal cargo components was discussed on the basis of prostate cancer.[40]

Exosome-dependent communication mechanisms contribute to homeostasis of the hematopoietic system and to erythropoiesis,[41] but also to the pathogenesis of diverse hematological disorders including hemoglobinopathies, leukemias, and lymphomas. Additionally, exosomes transport various molecules (eg, tissue factor activating coagulation cascade) that further mediate the clinical symptoms and complications of hematological diseases such as thrombosis as well as drug resistance of malignant cells.[42] Consequently, these exosomes can likely serve as potent biomarkers of hematological disorders and targets of their complex therapy.

Also, extracellular vesicles, mainly exosomes, found in urine were shown to be interesting biomarkers of various kidney disorders, transplant rejection,[43,44] and diabetic nephropathy.[45] Exosomes were also reported to play a dual, beneficial and adverse, role in various cardiovascular disorders.[46,47] The beneficial function of mesenchymal stem cell-derived exosomes in cardiovascular disorders has been recently reviewed.[48] In brief, analogous to their parental cells, exosomes of mesenchymal stem-cell origin and their cargo have antiapoptotic and anti-inflammatory potential and promote neovascularization as well as regeneration of cardiomyocytes. Therefore, administration of these exosomes should be considered as an interesting alternative for mesenchymal stem cell transplantation as an essentially noninvasive procedure leading to an analogous beneficial therapeutic effect in cardiovascular disorders. Current evidence suggests that exosomes may play a significant role in the mobilization and trafficking of bone marrow and cardiac stem cells into the site of myocardial infarction to mediate regeneration processes.[49] On the other hand, under hypoxic stress, cardiomyocytes were shown to release HSP60-containing exosomes suspected of inducing the apoptosis of neighboring cardiomyocytes.[47] Furthermore, exosomes derived from vascular smooth muscle cells were demonstrated to promote vascular calcification.[50] Nevertheless, exosomes could likely

be used in clinical practice as biomarkers of cardiovascular system function. For instance, exosome-carried miRNA molecules are claimed to be a good prognostic and diagnostic marker for evaluating the risk of cardiovascular disease in children with obesity or sleep-disordered breathing.[51] They may also serve as markers of vasculature dysfunction in patients with metabolic syndrome.[52] Finally, circulating exosomes can be successfully utilized to monitor organ function during the course of drug-induced liver failure,[53] especially since they may carry organ-specific miRNA molecules.[54] Transport of eicosanoids, cholesterol, and other lipids by exosomes impacts the metabolism of these compounds, and thus deleterious exosomes may possibly be involved in the development of lipid metabolic diseases.[55] Furthermore, exosome-carried miRNA molecules have recently been demonstrated to affect chronic inflammation associated with obesity, diabetes, and atherosclerosis.[56]

Recently, Kawikova and Askenase[5] have summarized the role of exosomes in the central nervous system (CNS) and concluded that they may serve as yet unavailable biomarkers of various CNS disorders. While neurons, astrocytes, oligodendrocytes, and microglia can communicate in an exosome-dependent manner to maintain local homeostasis, in the pathogenesis of Alzheimer and Parkinson diseases, multiple sclerosis, glioblastoma, and even schizophrenia, exosomes significantly contribute to the alteration of cellular interactions.[5] Exosomes were also proposed to be potential biomarkers of brain injuries by allowing to monitor neurodegeneration progress.[57] Recently, exosomes have been proved to be involved in the transmission of misfolded prion proteins in Creutzfeldt–Jakob disease and processing of amyloid precursor protein in Alzheimer disease[58] as well as mutation-resulting altered self-proteins that are toxic to neurons and other cells in the CNS.[59] Thus, exosome-dependent transport is responsible for the spread of various pathological processes including neurodegeneration and tumor formation.[60] Furthermore, vesicle-mediated mechanisms can also influence neurotransmission because some neurotransmitters are stored in synaptic vesicles.[61] However, Schwann cell-derived extracellular vesicles were recently shown to stimulate growth as well as postinjury regeneration of axons.[62] In turn, this beneficial property may be applied to the supporting therapy of peripheral nerve damage, which should greatly facilitate the recovery of damaged nervous system.

The extremely high clinical importance of essentially noninvasively collected exosomes as biomarkers expresses significant therapeutic potential[63-67] (FIGURE 2) and highlights the necessity of future studies to explore exosome profile characteristics for successive diseases. Interestingly, attempts to elaborate point-of-care diagnostic tools to detect exosome-associated miRNA in human blood plasma are also currently being made.[68] This should potently simplify the usage of exosomes and miRNA as convenient biomarkers for the fast and accurate diagnosis and monitoring of various diseases. Especially when the time of diagnosis is crucial for patient survival, as in the case of malignant tumors, including pancreatic cancer.[69]

Therapeutic potential of exosomes Naturally occurring exosome-mediated intercellular communication has great therapeutic potential[70] as a system of specific delivery of selected cargo to the acceptor cells (FIGURE 3). In vivo composition of exosomes seems not to be formed in a random process but by a regulated selection of specific components.[71] Several most recent studies on therapeutic potential of extracellular vesicles of various origin were presented by Merino et al.[72] On the other hand, it should be stressed that approaches to target exosomes mediating pathological intercellular communication during the disease course may also show high therapeutic potential[73] (FIGURE 3A).

So far exosome-based therapeutic approaches have been tested in clinical trials for the treatment of cancer (dendritic cell-derived exosomes,[74,75] often termed "dexosomes",[76] tumor cell-derived exosomes,[77] and ascites-derived exosomes combined with granulocyte-macrophage colony-stimulating factor)[78], and in stem cell transplantation, which showed that it could be successfully replaced by administration of stem cell-derived exosomes.[79] Nevertheless, a recent clinical trial using dexosomes in cancer therapy has shown that these dendritic cell-derived nanovesicles were well tolerated by patients, but the efficiency of the induction of the immune response was insufficient.[76] Hence, the immunogenicity and cell targeting of exosomes need to be improved for enhancement of the efficiency of exosome-based therapy (as discussed below).

The clinical applicability of stem cell-derived exosomes prompted researchers to focus on their possible utility in regenerative medicine, which also opened up the possibility to use exosomes in in-situ tissue engineering and remodeling.[80] As mentioned above, mesenchymal stem cell-derived exosomes could likely be applied in the therapy of various cardiovascular disorders.[48] Moreover, the therapeutic potential of mesenchymal stem cell transplantation after stroke depends also on the exosomal miRNA-encoded information exchange between transplanted cells and nervous system cells, which promotes the recovery of injured brain tissue.[81] The clinical trials using mesenchymal stem cell-derived vesicles in the therapy of tumors and injuries of different organs were comprehensively reviewed.[82] Finally, the beneficial therapeutic effect of mesenchymal stem cell-derived exosome administration to patients with rheumatic diseases, including rheumatoid arthritis and osteoarthritis, was implied.[83]

Exosomes play beneficial but also adverse roles in angiogenesis depending on the cell origin of

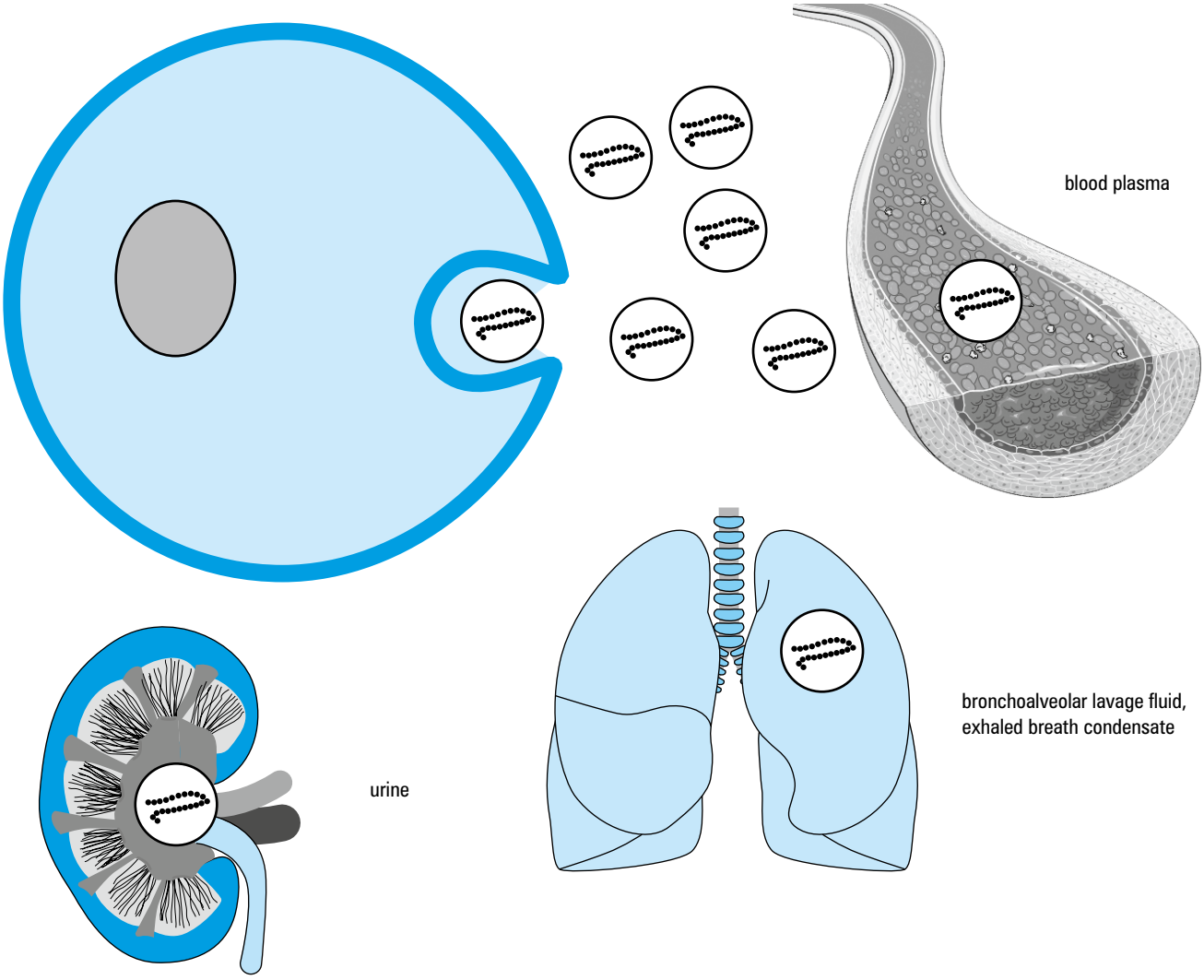

FIGURE 2 Exosomes as biomarkers of the current condition of specific cells. Secreted exosomes together with their profile and content express the current condition of the parental cell, and, after release into various bodily fluids or excretions collected by so called noninvasive biopsies, they could become useful biomarkers of homeostasis or disease.

these vesicles.[84] In brief, tumor cell-derived exosomes carry proangiogenic factors that generally further stimulate endothelial cells to form new blood vessels allowing for the delivery of nutritional compounds to cancer cells and for the formation of distant metastases. On the other hand, platelet-derived exosomes can stimulate either apoptosis or proliferation of endothelial cells, which depends on the conditions that induced their release as well as on their cargo, while high proangiogenic potential is expressed by exosomes derived from bone marrow stem cells and cardiomyocytes. Therefore, properly designed and shaped exosomes can be used as an efficient vehicle for the delivery of pro- or antiangiogenic factors for alleviation of tissue hypoxia complications or prevention of cancer development, respectively.

Lee et al.[85] analyzed exosomes as nanocarriers of genetic information that could be effectively applied in gene therapy. This, in turn, could greatly accelerate the application of gene targeting therapeutic strategies into clinical medicine as well as allow omission of the possible side effects of such therapy. The latter should be achieved through the highly specific delivery of RNA interference-mediating molecules to selected acceptor cells, which may be enabled by proper shaping of exosome specificity (as discussed below).

Research on the clinical applicability of exosomes as therapeutic tools was initiated by a study finding that they can substitute for dendritic cells in their antigen-presenting function leading to induction of specific immune response of T cells.[86] This opened up the possibility to activate antitumor immune response through the administration of exosomes from dendritic cells bearing tumor antigens. As a result, exosomes can serve as noncellular vaccines activating immune response against tumor cells, and also against pathogenic microbes[87] and parasites.[16] Moreover, exosomes with diverse immune-potentiating function can also be used to activate antitumor immunity.[88] On the other hand, exosomes expressing major histocompatibility complex molecules were suggested to be a promising source of alloantigens in therapeutic approaches to induce tolerance to the transplanted organ.[89] Furthermore, the adoptive

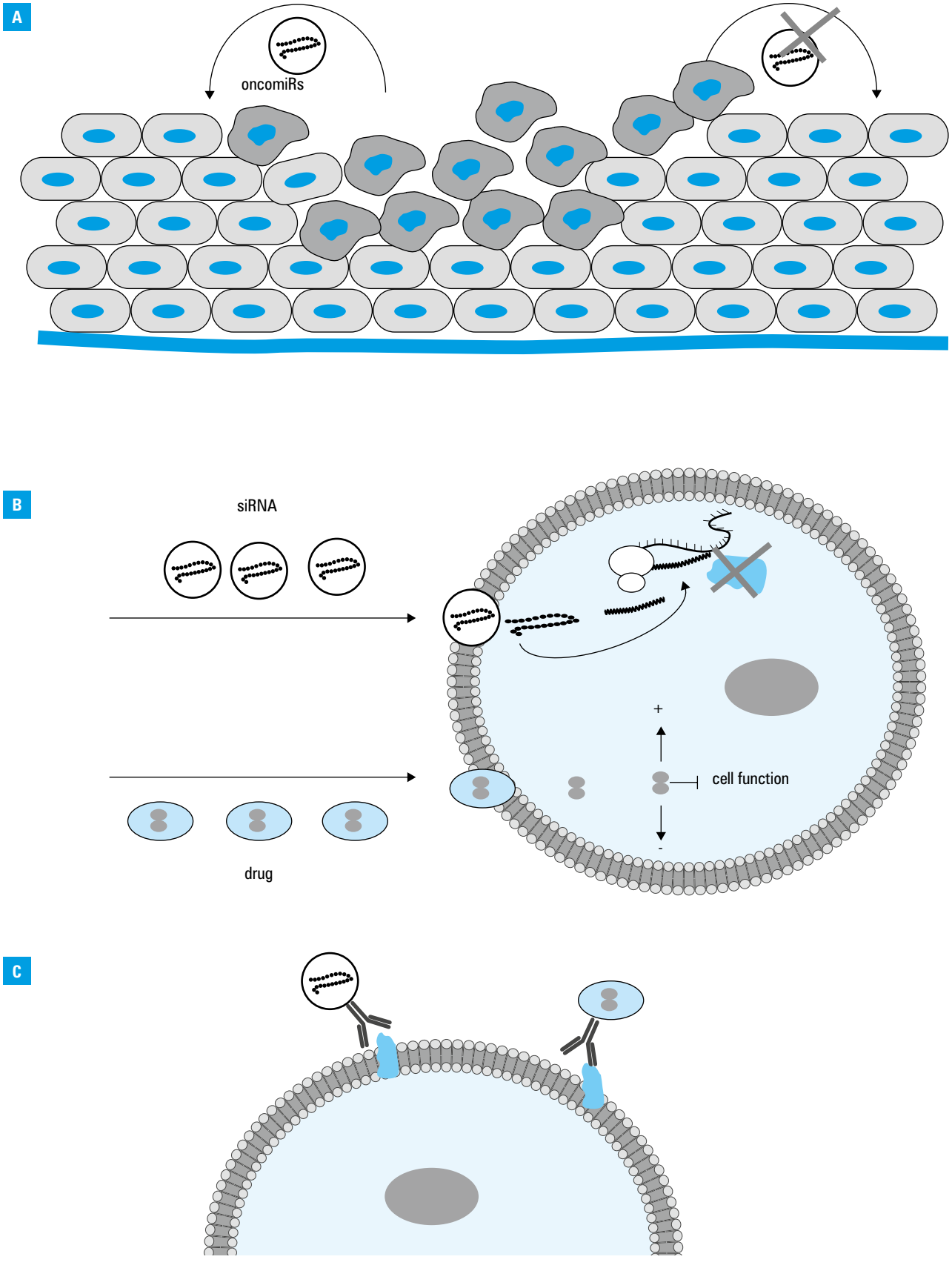

FIGURE 3 Therapeutic application of exosomes. Blocking of pathological intercellular communication mediated by exosomes may show high therapeutic potential, for example, in the prevention of tumor formation induced by exosome-transferred oncogenic microRNAs (oncomiRs) (**A**). On the other hand, exosomes are effective vehicles for the delivery of therapeutic agents, such as small-interfering RNA inhibiting mRNA translation and protein synthesis or various drugs that can facilitate, block, or diminish the specific function of targeted cell (**B**). Finally, the coating of therapeutic exosomes with antibodies of chosen specificity enables selective targeting of cells that express specific surface antigen to enhance the selectivity of exosome-cell interaction and to reduce the possible side effects caused by transferred exosome cargo (**C**).

transfer of human T regulatory lymphocytes seems to be a promising method for inducing effective tolerance after transplantation. However, T regulatory cells were formerly shown to be able to convert their phenotype under particular conditions into a proinflammatory one to then mediate effector immune response; therefore, administration of human T regulatory cell-derived exosomes is suspected to be safer for patients by reduction of the risk associated with cell transfer itself.[37] Interestingly, consumption of cow milk was suggested to have a protective effect against the development of atopy in children. Recently, it has been demonstrated that this effect is mediated by miRNA-155 carried by exosomes present in milk, which activates T regulatory lymphocytes and further prevents allergic response. This has opened up a novel possibility to administer protective antiallergic agents via milk-derived exosomes and, additionally, explained the higher probability of transmission of maternal rather than paternal atopy to the breast milk-nourished newborn.[90] Furthermore, this study has also proved that the mechanism of T lymphocyte maturation in the thymus is controlled by varied exosome-dependent interactions.[90] Altered exosome-mediated intercellular communication is observed in the course of multiple sclerosis, and the influence of several routinely used drugs on these exosomal pathways has been studied before, generally showing the inhibition of exosome generation.[25] Moreover, exosomes were highlighted as novel and promising vehicles for specific and targeted drug delivery in the therapy of multiple sclerosis,[25] other neuropathologies,[91] and even neuroinfections.[92] As reviewed, administration of exosome-encapsulated drugs, and especially flavonoids, shows high therapeutic potential in neurodegenerative and psychiatric disorders.[59] Intriguingly, intranasally derived exosome-encapsulated drugs can act locally in the CNS to suppress experimental autoimmune encephalomyelitis.[93] The latter observation implies that the route of exosome administration also plays a significant role in achieving the highest therapeutic efficiency possible.

Recently, splenic and hepatic macrophages have been shown to be responsible for rapid and effective clearance of intravenously administered exosomes.[94] This suggests that administration of therapeutic exosomes via a different route could allow to avoid clearance. On the other hand, it may be assumed that macrophages can sense the signal carried by circulating exosomes, recognize the crucial information, and properly respond to it, possibly through the generation of a secondary signal acting systemically. This suggests that properly stimulated macrophages may play a key role in exosome-based therapies. Recently, we have presented a similar finding in an antigen-specific immune suppression mechanism, in which the regulatory activity of exosome-delivered miRNA-150 was transmitted from T suppressor to T effector lymphocytes only in the presence of macrophages.[27,28]

As mentioned above, extracellular vesicles express high potential as vehicles delivering RNA-based therapeutics (FIGURE 3B).[87] However, as currently used in clinical trials, a therapeutic RNA interference delivery platform based on artificial nanoparticles, such as liposomes, requires the activation of transient immune suppression due to the aforementioned interaction with the cells of the innate immune system.[95] Thus, a possibility to transmit siRNA in exosomes coated with antigen-specific antibodies directly to targeted cells, which we have presented recently,[8,96] should greatly facilitate the therapeutic delivery system (FIGURE 3C) and reduce the necessity to induce immune suppression. As mentioned above, a direct therapeutic use of siRNA may lead to unexpected side effects resulting from the silencing of other mRNA molecules or activation of TLRs. However, manipulation of siRNA delivery by loading it into exosomes specifically targeting selected cells could limit these adverse effects. Other main issues that need to be addressed before clinical application of exosomes as therapeutic agents include: 1) the selection of particular extracellular vesicles and the method of their isolation and purification; 2) the eventual method of drug loading or association with exosomes; 3) the enhancement of exosome stability; and 4) the increase of the specificity of cell targeting by prepared exosomes.[97] Thus, our research findings described herein should strongly facilitate the clinical application of exosomes.[8,28,96]

Concluding remarks: are we able to shape exosome cargo and specificity of acceptor cell targeting? As mentioned above, exosomes are very promising carriers for drugs and other therapeutic agents, including siRNA (FIGURE 3B).[98] Recently, it has been clearly demonstrated that exosome-encapsulated drugs are more efficiently delivered to targeted cells than those encapsulated into liposomes.[99] This study also compared the efficiency of several active methods of drug encapsulation into exosomes, namely, electroporation, saponin-assisted transport, extrusion, and dialysis, with passive encapsulation through simple incubation for 10 minutes at room temperature, showing, as expected, that assisted methods express higher efficacy.

However, the study of Bryniarski et al.[8] mentioned above showed that mere incubation for 30 minutes at 37°C of inactive exosomes with synthetic miRNA-150 or antigen-specific antibody light chains renders them biologically active. Thus, the efficiency of the encapsulation process seems to depend on experimental conditions. Furthermore, this study also implied that light chains and miRNA can associate with lipids on the surface of exosomes and that miRNA-150 can even enter into exosomes in a SID-1-dependent manner.[96] Thus, it seems very likely that various molecules can easily adhere

to and enter into exosomes, which offers an interesting possibility to shape both, the exosome cargo and the specificity of its delivery to desired acceptor cells (FIGURE 3C). This, in turn, could be applied into therapy based on exosome-mediated delivery, at least partially related to natural cell-to-cell communication and allowing for specific targeting and the limitation of side effects.[100] Furthermore, animal studies[96] suggested the possibility of isolating the exosomes from an individual patient, then loading them in vitro with selected regulatory and/or therapeutic agents (eg, drugs, siRNA, hormones), and subsequently transferring these modified exosomes into the donor patient to induce the expected clinical effects. Exosomes in this model could possibly be transferred in minute doses, similar to those that are efficient in physiological conditions. Hence, this study proves that exosomes may become a powerful tool in new therapeutic maneuvers using cell-targeted delivery of specific miRNA/siRNA cargo.

To summarize, exosomes as physiological mediators of intercellular communication could be isolated and further modified in vitro to become a useful tool for diagnostic and therapeutic approaches, with the limitation of potential side effects, which would be greatly reduced if the delivery specificity of the chosen exosome cargo to desired cells was enhanced.

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REFERENCES

1 Nakayama M. Antigen presentation by MHC-dressed cells. Front Immunol. 2015; 5: 672.

2 Ratajczak J, Wysoczynski M, Hayek F, et al. Membrane-derived microvesicles: important and underappreciated mediators of cell-to-cell communication. Leukemia. 2006; 20: 1487-1495.

3 Gyorgy B, Szabo TG, Pasztoi M, et al. Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles. Cell Mol Life Sci. 2011; 68: 2667-2688.

4 Lötvall J, Hill AF, Hochberg F, et al. Minimal experimental requirements for definition of extracellular vesicles and their functions: a position statement from the International Society for Extracellular Vesicles. J Extracell Vesicles. 2014; 3: 26913.

5 Kawikova I, Askenase PW. Diagnostic and therapeutic potentials of exosomes in CNS diseases. Brain Res. 2014 Oct 7. doi: 10.1016/j.brainres.2014.09.070. [Epub ahead of print].

6 Witwer KW, Buzas EI, Bemis LT, et al. Standarization of sample collection, isolation and analysis methods in extracellular vesicle research. J Extracell Vesicles. 2013; 2: 20360.

7 Lasser C, Alikhani VS, Ekstrom K, et al. Human saliva, plasma and breast milk exosomes contain RNA: uptake by macrophages. J Transl Med. 2011; 9: 9.

8 Bryniarski K, Ptak W, Jayakumar A, et al. Antigen-specific, antibody-coated, exosome-like nanovesicles deliver suppressor T-cell microRNA-150 to effector T cells to inhibit contact sensitivity. J Allergy Clin Immunol. 2013; 132: 170-181.

9 Sullivan R, Saez F, Girouard J, et al. Role of exosomes in sperm maturation during the transit along the male reproductive tract. Blood Cells Mol Dis. 2005; 35: 1-10.

10 Tsochandaridis M, Nasca L, Toga C, et al. Circulating microRNAs as clinical biomarkers in the predictions of pregnancy complications. Biomed Res Int. 2015; 2015: 294954.

11 Mincheva-Nilsson L, Baranov V. Placenta-derived exosomes and syncytiotrophoblast microparticles and their role in human reproduction: immune modulation for pregnancy success. Am J Reprod Immunol. 2014; 72: 440-457.

12 Record M. Intercellular communication by exosomes in placenta: a possible role in cell fusion? Placenta. 2014; 35: 297-302.

13 van der Grein SG, Nolte-t Hoen EN. "Small Talk" in the Innate Immune System via RNA-Containing Extracellular Vesicles. Front Immunol. 2014; 5: 542.

14 Schorey JS, Cheng Y, Singh PP, et al. Exosomes and other extracellular vesicles in host-pathogen interactions. EMBO Rep. 2015; 16: 24-43.

15 Lai FW, Lichty BD, Bowdish DM. Microvesicles: ubiquitous contributors to infection and immunity. J Leukoc Biol. 2015; 97: 237-245.

16 Marcilla A, Martin-Jaular L, Trelis M, et al. Extracellular vesicles in parasitic diseases. J Extracell Vesicles. 2014; 3: 25040.

17 Smythies LE, Smythies JR. Exosomes in the gut. Front Immunol. 2014; 5: 104.

18 Farsad K. Exosomes: novel organelles implicated in immunomodulation and apoptosis. Yale J Biol Med. 2002; 75: 95-101.

19 Fernandez-Messina L, Gutierrez-Vazquez C, Rivas-Garcia E, et al. Immunomodulatory role of microRNAs transferred by extracellular vesicles. Biol Cell. 2015; 107: 61-77.

20 Raposo G, Nijman HW, Stoorvogel W, et al. B lymphocytes secrete antigen-presenting vesicles. J Exp Med. 1996; 183: 1161-1172.

21 Mittelbrunn M, Gutierrez-Vazquez C, Villarroya-Beltri C, et al. Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells. Nat Commun. 2011; 2: 282.

22 Dustin ML. What counts in the immunological synapse? Mol Cell. 2014; 54: 255-262.

23 Alegre E, Rizzo R, Bortolotti D, et al. Some basic aspects of HLA-G biology. J Immunol Res. 2014; 2014: 657625.

24 de Candia P, Torri A, Pagani M, et al. Serum microRNAs as biomarkers of human lymphocyte activation in health and disease. Front Immunol. 2014; 5: 43.

25 Saenz-Cuesta M, Osorio-Querejeta I, Otaegui D. Extracellular vesicles in multiple sclerosis: what are they telling us? Front Cell Neurosci. 2014; 8: 100.

26 Fujita Y, Yoshioka Y, Ito S, et al. Intercellular communication by extracellular vesicles and their microRNAs in asthma. Clin Ther. 2014; 36: 873-881.

27 Nazimek K, Nowak B, Marcinkiewicz J, et al. Enhanced generation of reactive oxygen intermediates by suppressor T cell-derived exosome-treated macrophages. Folia Med Cracov. 2014; 54: 37-52.

28 Nazimek K, Ptak W, Nowak B, et al. Macrophages play an essential role in antigen-specific immune suppression mediated by T CD8+ cell-derived exosomes. Immunology. 2015 Mar 23. doi: 10.1111/imm.12466. [Epub ahead of print].

29 Ptak W, Nazimek K, Askenase PW, et al. From mysterious supernatant entity to miRNA-150 in antigen-specific exosomes: a history of hapten-specific T suppressor factor. Arch Immunol Ther Exp (Warsz). 2015 Feb 18. [Epub ahead of print].

30 Anastasiadou E, Slack FJ. Malicious exosomes. Science. 2014; 346: 1459-1460.

31 Gilabert-Estelles J, Braza-Boils A, Ramon LA, et al. Role of microRNAs in gynecological pathology. Curr Med Chem. 2012; 19: 2406-2413.

32 Taylor DD, Gercel-Taylor C. The origin, function, and diagnostic potential of RNA within extracellular vesicles present in human biological fluids. Front Genet. 2013; 4: 142.

33 Ge R, Tan E, Sharghi-Namini S, et al. Exosomes in cancer microenvironment and beyond: have we overlooked these extracellular messengers? Cancer Microenviron. 2012; 5: 323-332.

34 Zocco D, Ferruzzi P, Cappello F, et al. Extracellular vesicles as shuttles of tumor biomarkers and anti-tumor drugs. Front Oncol. 2014; 4: 267.

35 Carvalho J, Oliveira C. Extracellular vesicles – powerful markers of cancer EVolution. Front Immunol. 2015; 5: 685.

36 Kumar D, Gupta D, Shankar S, et al. Biomolecular characterization of exosomes released from cancer stem cells: possible implications for biomarker and treatment of cancer. Oncotarget. 2015; 6: 3280-3291.

37 Agarwal A, Fanelli G, Letizia M, et al. Regulatory T cell-derived exosomes: possible therapeutic and diagnostic tools in transplantation. Front Immunol. 2014; 5: 555.

38 Jakobsen KR, Paulsen BS, Baek R, et al. Exosomal proteins as potential diagnostic markers in advanced non-small cell lung carcinoma. J Extracell Vesicles 2015; 4: 26659.

39 Sun Y, Liu J. Potential of cancer cell-derived exosomes in clinical application: a review of recent research advances. Clin Ther. 2014; 36: 863-872.

40 Soekmadji C, Russell PJ, Nelson CC. Exosomes in prostate cancer: putting together the pieces of a puzzle. Cancers 2013; 5: 1522-1544.

41 Vidal M. Exosomes in erythropoiesis. Transfus Clin Biol. 2010; 17: 131-137.

42 Aharon A, Rebibo-Sabbah A, Tzoran I, et al. Extracellular vesicles in hematological disorders. Rambam Maimonides Med J. 2014; 5: e0032.

43 Gamez-Valero A, Lozano-Ramos SI, Bancu I, et al. Urinary extracellular vesicles as source of biomarkers in kidney diseases. Front Immunol. 2015; 6: 6.

44 Salih M, Zietse R, Hoorn EJ. Urinary extracellular vesicles and the kidney: biomarkers and beyond. Am J Physiol Renal Physiol. 2014; 306: 1251-1259.

45 Musante L, Tataruch DE, Holthofer H. Use and isolation of urinary exosomes as biomarkers for diabetic nephropathy. Front Endocrinol. 2014; 5: 149.

46 Gonzalez-Calero L, Martin-Lorenzo M, Alvarez-Llamas G. Exosomes: a potential key target in cardio-renal syndrome. Front Immunol. 2014; 5: 465.

47 Zhao W, Zheng XL, Zhao SP. Exosome and its roles in cardiovascular diseases. Heart Fail Rev. 2015; 20: 337-348.

48 Huang L, Ma W, Ma Y, et al. Exosomes in mesenchymal stem cells, a new therapeutic strategy for cardiovascular diseases? Int J Biol Sci. 2015; 11: 238-245.

49 Sahoo S, Losordo DW. Exosomes and cardiac repair after myocardial infarction. Circ Res. 2014; 114: 333-344.

50 Kapustin AN, Chatrou ML, Drozdov I, et al. Vascular smooth muscle cell calcification is mediated by regulated exosome secretion. Circ Res. 2015; 116: 1312-1323.

51 Khalyfa A, Gozal D. Exosomal miRNAs as potential biomarkers of cardiovascular risk in children. J Transl Med. 2014; 12: 162.

52 Agouni A, Andriantsitohaina R, Martinez MC. Microparticles as biomarkers of vascular dysfunction in metabolic syndrome and its individual components. Curr Vasc Pharmacol. 2014; 12: 483-492.

53 Yang X, Weng Z, Mendrick DL, et al. Circulating extracellular vesicles as a potential source of new biomarkers of drug-induced liver injury. Toxicol Lett. 2014; 225: 401-406.

54 Hornby RJ, Starkey Lewis P, Dear J, et al. MicroRNAs as potential circulating biomarkers of drug-induced liver injury: key current and future issues for translation to humans. Expert Rev Clin Pharmacol. 2014; 7: 349-362.

55 Record M, Poirot M, Silvente-Poirot S. Emerging concepts on the role of exosomes in lipid metabolic diseases. Biochimie. 2014; 96: 67-74.

56 Hulsmans M, Holvoet P. MicroRNA-containing microvesicles regulating inflammation in association with atherosclerotic disease. Cardiovasc Res. 2013; 100: 7-18.

57 Taylor DD, Gercel-Taylor C. Exosome platform for diagnosis and monitoring of traumatic brain injury. Philos Trans Roy Soc Lond B Biol Sci. 2014; 369. pii: 20130503. doi: 10.1098/rstb.2013.0503.

58 Coleman BM, Hill AF. Extracellular vesicles – their role in the packaging and spread of misfolded proteins associated with neurodegenerative diseases. Semin Cell Dev Biol. 2015; 40: 89-96.

59 Tsilioni I, Panagiotidou S, Theoharides TC. Exosomes in neurologic and psychiatric disorders. Clin Ther. 2014; 36: 882-888.

60 Candelario KM, Steindler DA. The role of extracellular vesicles in the progression of neurodegenerative disease and cancer. Trends Mol Med. 2014; 20: 368-374.

61 Ferguson SM, Blakely RD. The choline transporter resurfaces: new roles for synaptic vesicles? Mol Interv. 2004; 4: 22-37.

62 Lopez-Verrilli MA, Court FA. Transfer of vesicles from Schwann cells to axons: a novel mechanism of communication in the peripheral nervous system. Front Physiol. 2012; 3: 205.

63 Boukouris S, Mathivanan S. Exosomes in bodily fluids are a highly stable resource of disease biomarkers. Proteomics Clin Appl. 2015; 9: 358-367.

64 Julich H, Willms A, Lukacs-Kornek V, et al. Extracellular vesicle profiling and their use as potential disease specific biomarker. Front Immunol. 2014; 5: 413.

65 Revenfeld AL, Baek R, Nielsen MH, et al. Diagnostic and prognostic potential of extracellular vesicles in peripheral blood. Clin Ther. 2014; 36: 830-846.

66 Sato-Kuwabara Y, Melo SA, Soares FA, et al. The fusion of two worlds: non-coding RNAs and extracellular vesicles - diagnostic and therapeutic implications (Review). Int J Oncol. 2015; 46: 17-27.

67 Zheng X, Chen F, Zhang J, et al. Exosome analysis: a promising biomarker system with special attention to saliva. J Membr Biol. 2014; 247: 1129-1136.

68 Vaca L. Point-of-care diagnostic tools to detect circulating microRNAS as biomarkers of disease. Sensors. 2014; 14: 9117-9131.

69 Zöller M. Pancreatic cancer diagnosis by free and exosomal miRNA. World J Gastrointest Pathophysiol. 2013; 4: 74-90.

70 van der Meel R, Fens MH, Vader P, et al. Extracellular vesicles as drug delivery systems: lessons from the liposome field. J Control Release. 2014; 195: 72-85.

71 Moreno-Gonzalo O, Villarroya-Beltri C, Sanchez-Madrid F. Post-translational modifications of exosomal proteins. Front Immunol. 2014; 5: 383.

72 Merino AM, Hoogduijn MJ, Borras FE, et al. Therapeutic potential of extracellular vesicles. Front Immunol. 2014; 5: 658.

73 Kosaka N, Yoshioka Y, Tominaga N, et al. Dark side of the exosome: the role of the exosome in cancer metastasis and targeting the exosome as a strategy for cancer therapy. Future Oncol. 2014; 10: 671-681.

74 Escudier B, Dorval T, Chaput N, et al. Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: results of the first phase I clinical trial. J Transl Med. 2005; 3: 10.

75 Pitt JM, Charrier M, Viaud S, et al. Dendritic cell-derived exosomes as immunotherapies in the fight against cancer. J Immunol. 2014; 193: 1006-1011.

76 Gehrmann U, Naslund TI, Hiltbrunner S, et al. Harnessing the exosome-induced immune response for cancer immunotherapy. Semin Cancer Biol. 2014; 28: 58-67.

77 Adams M, Navabi H, Croston D, et al. The rationale for combined chemo/immunotherapy using a Toll-like receptor 3 (TLR3) agonist and tumor-derived exosomes in advanced ovarian cancer. Vaccine. 2005; 23: 2374-2378.

78 Dai S, Wei D, Wu Z, et al. Phase I clinical trial of autologous ascites-derived exosomes combined with GM-CSF for colorectal cancer. Mol Ther. 2008; 16: 782-790.

79 Maguire G. Stem cell therapy without the cells. Commun Integr Biol. 2013; 6: e26631.

80 De Jong OG, Van Balkom BW, Schiffelers RM, et al. Extracellular vesicles: potential roles in regenerative medicine. Front Immunol. 2014; 5: 608.

81 Xin H, Li Y, Chopp M. Exosomes/miRNAs as mediating cell-based therapy of stroke. Front Cell Neurosci. 2014; 8: 377.

82 Akyurekli C, Le Y, Richardson RB, et al. A systematic review of preclinical studies on the therapeutic potential of mesenchymal stromal cell-derived microvesicles. Stem Cell Rev. 2015; 11: 150-160.

83 Maumus M, Jorgensen C, Noel D. Mesenchymal stem cells in regenerative medicine applied to rheumatic diseases: role of secretome and exosomes. Biochimie. 2013; 95: 2229-2234.

84 Ribeiro MF, Zhu H, Millard RW, et al. Exosomes Function in Pro- and Anti-Angiogenesis. Curr Angiogenes. 2013; 2: 54-59.

85 Lee Y, El Andaloussi S, Wood MJ. Exosomes and microvesicles: extracellular vesicles for genetic information transfer and gene therapy. Hum Mol Genet. 2012; 21: R125-134.

86 Kovar M, Boyman O, Shen X, et al. Direct stimulation of T cells by membrane vesicles from antigen-presenting cells. Proc Natl Acad Sci USA. 2006; 103: 11671-11676.

87 Lasser C. Exosomes in diagnostic and therapeutic applications: biomarker, vaccine and RNA interference delivery vehicle. Expert Opin Biol Ther. 2015; 15: 103-117.

88 Greening DW, Gopal SK, Xu R, et al. Exosomes and their roles in immune regulation and cancer. Semin Cell Dev Biol. 2015; 40: 89-96.

89 Monguio-Tortajada M, Lauzurica-Valdemoros R, Borras FE. Tolerance in organ transplantation: from conventional immunosuppression to extracellular vesicles. Front Immunol. 2014; 5: 416.

90 Melnik BC, John SM, Schmitz G. Milk: an exosomal microRNA transmitter promoting thymic regulatory T cell maturation preventing the development of atopy? J Transl Med. 2014; 12: 43.

91 Gupta A, Pulliam L. Exosomes as mediators of neuroinflammation. J Neuroinflammation. 2014; 11: 68.

92 Sampey GC, Meyering SS, Asad Zadeh M, et al. Exosomes and their role in CNS viral infections. J Neurovirol. 2014; 20: 199-208.

93 Zhuang X, Xiang X, Grizzle W, et al. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. Mol Ther. 2011; 19: 1769-1779.

94 Imai T, Takahashi Y, Nishikawa M, et al. Macrophage-dependent clearance of systemically administered B16BL6-derived exosomes from the blood circulation in mice. J Extracell Vesicles. 2015; 4: 26238.

95 Haussecker D, Kay MA. RNA interference. Drugging RNAi. Science. 2015; 347: 1069-1070.

96 Bryniarski K, Ptak W, Martin E, et al. Free extracellular miRNA functionally targets cells by transfecting exosomes from their companion cells. PlosONE. 2015; 10: e0122991.

97 Gyoergy B, Hung ME, Breakefield XO, et al. Therapeutic applications of extracellular vesicles: clinical promise and open questions. Annu Rev Pharmacol Toxicol. 2015; 55: 439-464.

98 Johnsen KB, Gudbergsson JM, Skov MN, et al. A comprehensive overview of exosomes as drug delivery vehicles – endogenous nanocarriers for targeted cancer therapy. Biochim Biophys Acta. 2014; 1846: 75-87.

99 Fuhrmann G, Serio A, Mazo M, et al. Active loading into extracellular vesicles significantly improves the cellular uptake and photodynamic effect of porphyrins. J Control Release. 2015; 205: 35-44.

100 Tian Y, Li S, Song J, et al. A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. Biomaterials. 2014; 35: 2383-2390.

ARTYKUŁ POGLĄDOWY

Egzosomy jako nośnik informacji w komunikacji między komórkami – znaczenie kliniczne

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SŁOWA KLUCZOWE

biomarkery,
egzosomy,
mikropęcherzyki,
zastosowanie terapeutyczne

STRESZCZENIE

Komórki organizmu wielokomórkowego wymieniają sygnały informacyjne poprzez różnorodne mechanizmy. Ostatnie badania ujawniły szczególną rolę pozakomórkowych mikropęcherzyków, a zwłaszcza egzosomów, w komunikacji międzykomórkowej. Egzosomy, obecne we wszystkich badanych ludzkich płynach ustrojowych, transportują aktywne biologicznie związki, w tym białka, lipidy oraz różnorodne cząsteczki RNA. *In vivo* wybór składników wydzielanych przez komórkę w egzosomach zdaje się podlegać ścisłej regulacji i może odzwierciedlać jej aktualny stan aktywacji. Dlatego specjalną uwagę zwrócono na niezwykle istotne znaczenie egzosomów jako niemal nieinwazyjnie pobieranych markerów prognostycznych i diagnostycznych, jak również nośników cząsteczek leczniczych, zwłaszcza po odkryciu, iż składniki egzosomów oraz swoistość ich dostarczenia mogą podlegać zmianom *in vitro*. Ponadto hamowanie patologicznej komunikacji międzykomórkowej zależnej od egzosomów może znaleźć zastosowanie w terapii. Stąd liczne prowadzone obecnie badania dążą do dokładnego poznania profilu i funkcji egzosomów oraz ich składników wydzielanych przez komórki w zdrowiu i chorobie, a także podejmują próbę kształtowania właściwości egzosomów w celu znalezienia ich zastosowania klinicznego. Niniejszy artykuł poglądowy przedstawia aktualną wiedzę o roli egzosomów w różnych fizjologicznych i patologicznych mechanizmach komunikacji międzykomórkowej, ze szczególnym uwzględnieniem zastosowania egzosomów w diagnostyce i leczeniu różnorodnych schorzeń zapalnych, sercowo-naczyniowych, metabolicznych, neurodegeneracyjnych oraz nowotworów złośliwych.

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