Chapter

Effectiveness of Exosomes in the Immune Cascade

Gözde Atila Uslu and Hamit Uslu

Abstract

In order to treat and/or control a disease or prevent its occurrence, first of all, physiological pathways must be understood very well. In the previous 10 years, there has been a lot of interest in the function of exosomes in intercellular communication, particularly in studies on cancer and neurodegenerative disorders. This has led to plenty of research in this area. Exosomes are tiny transmembrane vesicles that are produced by endocytosis and are found in a variety of bodily fluids, including blood, saliva, cerebrospinal fluid, and breast milk. They are also released by a variety of tissues. Exosomes have a varied composition depending on where they come from, but they are often rich in cytosolic and cell surface proteins, lipids, DNA, and RNA. In recent years, the interactions between exosomes and the immune system have been frequently studied. However, despite all the researches, the physiological purposes of exosomes are still largely unclear.

Keywords: exosomes, immune system, T cells, NK cells, mast cells

1. Introduction

Exosomes; although it was first defined as microparticles released from neoplastic cell lines, it was later determined that these structures were secreted by almost all cells in the body, and it was concluded that it would be more accurate to call them membrane-bound extracellular vesicles produced with endosomal division [1, 2]. It is stated that these microvesicles have an average diameter range of 40–160 nm and are formed by endocytic cellular pathways consisting of three different stages that have been identified so far. First stage; It is stated that is the invagination of the cell membrane from endocytic vesicles and leads to the formation of an early-shorting endosome (ESE), after which either novo formation occurs or can directly fuse with a pre-existing ESE, moreover golgi apparatus and the endoplasmic reticulum participate in this process. In the second stage, it is stated that ESEs can mature into late-shorting endosomes (LSEs) and multivesicular bodies are formed by accumulation of intraluminal vesicles in these bodies. In the third stage, it has been determined that multivesicular bodies can undergo proteosomal degradation, function as a temporary storage area (for major histocompatibility complex (MHC) class II), or combine with the plasma membrane to release exosomes (**Figure 1**) [3–7]. Exosomes can enter cells directly by different mechanisms or can be produced by cells by the process of endocytosis as mentioned above. It has been determined that exosome production, release,

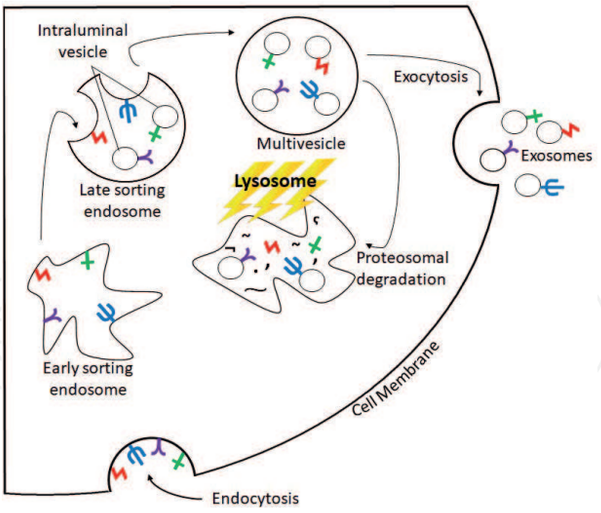

Figure 1.
Exosome biogenesis.

and uptake may change with oxidative stress, radiation, inhibiting a proton pump, altering cellular pH decrease in membrane cholesterol and increase in intracellular calcium level [8–11]. Numerous proteins, including the tetraspanins CD63, CD81, and CD9, TSG101, Alix, and HSP70, have been discovered to be present in exosomes. In addition, cell type-specific proteins may vary due to their endosomal origin, but they also have conserved proteins identified in almost all exosomes (hsc70, tetraspanin, CD63) [3]. It has been reported that exosomes also have lipid bilayer, which is mostly composed of phosphatidylcholine (PC), ganglioside GM3, phosphatidyl ethanolamine (PE), sphingomyelin (SM), and cholesterol [12]. Exosomes contain a wide variety of RNAs; some of these have been shown to be mRNA, miRNA, rRNA, tRNA, lncRNA, piRNA, snRNA, and small nucleolar RNA [13].

Although the functions of exosomes are not entirely understood and are still the subject of debate, they are involved in remodeling the extracellular matrix, homeostasis and adaptation of plasma membranous glycoprotein models, signal transduction between cells, immunity, tissue homeostasis, and many aspects of human health and disease which including cancer and neurodegenerative diseases have stated that have important functions [14–17]. They may have a role in the spread of prions throughout the body and the exchange of membranes between cells in infectious neurodegenerative illnesses, also known as prion diseases [18]. In their study on the synaptic physiology of neurons, Chivet et al. [19] found that the lipids, proteins, and RNAs in the exosomes released by neurons in response to synaptic activity can directly alter signal transmission and protein expression in recipient cells and play a crucial role in information transfer between synapses. It has been emphasized that intercellular communication has a very important role in vascular remodeling, and although direct intercellular contact or paracrine effects are focused on in this process, recently, it may be effective in this process in extracellular vesicles. When the effectiveness of exosomes in the neovascularization process was investigated, it was shown that they can act with the Notch signaling pathway, which is one of the cell interaction mechanisms, and an increase in blood vessel frequency and bifurcation number [20]. In order to treat and/or control a disease or prevent its occurrence, the physiological pathways must first be understood very well. Exosomes can also have an impact on the immune system by directly contacting the cell's plasma membrane during this process

and then inducing intracellular signal cascades. The immune system plays a significant role in the emergence and development of disease pathophysiology as well as the emergence of acute and chronic complications.

2. Exosomes and T cells

In the case of contact with foreign antigens, such as in the case of infection, several days are needed for the formation of the immune responses, which we call cell-mediated or cellular immunity, by the effector T cells. For this reason, this type of immunity is also called delayed-type immune response. Antigen presenting cells (APC) such as macrophages, dendritic cells, and B cells are needed in this process. These constructs process antigenic constructs and antigen processing and presentation is performed with MHC class I or MHC class II. The term human leukocyte antigen (HLA) can also be used instead of MHC proteins in humans. AHS binary signaling is triggered by the binding of the intracellular adhesion molecule (ICAM) on the ASH surface and the lymphocyte function-associated antigen 1 (LFA-1) on T cells. This process can be opened as follows: (1) Recognition of the antigen by the T cell receptor and its co-receptor (CD8 molecules on cytotoxic T cells and CD4 molecules on helper T cells are called co-receptors). (2) The binding of the B7 protein in ASH and the CD28 protein on the T cells leads to rapid proliferation, clonal expansion, and differentiation in T cells [21]. In addition, suppression mediated by regulatory T (Treg) cells had found to be effective in making the immune system tolerant to most autoantigens and preventing host damage [22]. As mentioned above, a large number of extracellular and intracellular signals are needed to initiate the rapid proliferation, differentiation, and migration of T cells to peripheral infection sites (**Figure 2**).

Exosomes, which have been determined to be secreted by almost all cells in the body, are also secreted from various hematopoietic cell types such as reticulocytes, B lymphocytes, platelets, T lymphocytes, and dendritic cells. It is known that exosomes secreted from dendritic cells contain proteins such as MHC class I and II and CD86 (provide necessary signals for T cell activation and survival) and these structures

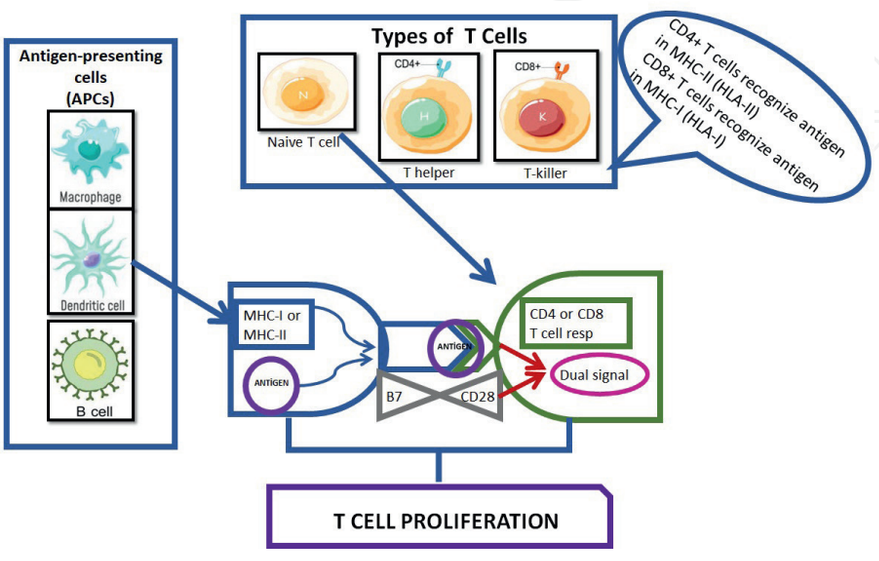

Figure 2.
T cell activation.

are effective in T cell stimulation. Exosome production may occur in peripheral tissues, after dendritic cells have traveled to lymph nodes, or in both cases, according to reports, but there is currently insufficient evidence to make a firm determination [23]. Exosomes that are loaded with specific peptides or antigens serve as vehicles for antigen presentation and can activate T cells (CD4+ and CD8+) also in the lack of dendridic cell. It has been established that exosomes have a positive impact on the immune system through various activities such as antigen presentation, stimulation, suppression, and tolerance of immunity [24]. It is also mentioned that some exosomes can express chemokine sequences like CCL2-5, CCL7, CCL20, CCL28, CXCL1-2, and CXCL16 because they can start other leukocytes like T cells from migrating to the infection sites [25, 26]. It is known that dendritic cell-T cell interactions cause an increase in calcium mobilization and Interleukin-2 and Interferon-gamma levels, resulting in T-cell activation. In addition, it is emphasized that co-stimulatory molecules such as CD86 strengthen intercellular interactions and T-cell functional activation in this process [27]. Zitvogel et al. [28] found that tumor peptide-pulsed dendritic cells-derived exosomes could eradicate or suppress the growth of tumors in a T-cell-dependent manner.

While it has been reported that synoviocyte-produced microparticles in inflammatory conditions like rheumatoid arthritis may exacerbate cartilage damage by increasing the synthesis of inflammatory mediators and cartilage-degrading enzymes [29, 30], other studies have suggested that T cell-stimulated TRAIL- and FasL-containing microvesicules produced in the synovium may also be helpful in preventing autoimmune damage in rheumatoid diseases [31]. In fact, exosomes originating from immunosuppressive dendritic cells have been shown to be more efficient and safe than modified dendritic cells in the therapies of autoimmune disorders like rheumatoid arthritis [32]. However, there are studies showing that exosomes produced from cancer cells could disturb the functions of T and B cells, monocytes/macrophages, NK cells and dendritic cells [33–35]. Exosomes synthesized from other cells could affect T cell functions, and the T-cells themselves too synthesize exosomes. It has been shown that these exosomes have a lipid bilayer and contain structures such as CD2, CD3/TCR, CD4, CD8, CD11c, CD25, CD69, LFA-1, CXCR4, FasL [36]. Tregs are subtypes of T cells, and it has been determined that the expression of CD73 by these cells shows a suppressive effect by converting extracellular adenosine 5-monophosphate to adenosine, in the same way that exosomes secreted from these cells also contain CD73 and exerting a suppressive effect with same pathway [37]. It is stated that exosomes derived from Tregs have a suppressive role in acute rejection and inhibit the proliferation of T cells, therefore exosomes released from Tregs may be a good alternative to prevent transplant rejection [38]. In another study, it is stated that the antigen-specific CD41 T-cell exosome (expressing CD4, TCR, LFA-1, CD25, and Fas ligand) may act as an immunosuppressant in the transplant rejection and treatment of autoimmune diseases [39]. Scientists have demonstrated that exosomes isolated from CD3+ T cells stimulated with IL-2 interact with and promote proliferation in resting autologous T cells [40]. It has been emphasized that high-level regulation of the miR-765/PLP2 axis of CD45RO-CD8+ T cell-derived exosomes can limit the cancer-supporting effects of estrogen on uterine corpus endometrial cancer [41].

3. Exosomes and natural killer (NK) cells

While NK cells were at first idea to be large granular lymphocytes with built-in cytotoxicity against tumor cells, they have since been identified as a distinct class of

lymphocytes with effector capabilities that enable them to produce cytokines in addition to their natural cytotoxicity [42]. Since it was not known at the time what strategies NK cells use to differentiate between normal and abnormal cells and thus participate in the defense mechanism, the missing self hypothesis was suggested. According to this theory, NK cells recognize and eliminate cells that do not express their MHC Class-1 (MHC) molecules [43]. However, it is now known that NK cells have a large number of activating and inhibitory receptors that can combine MHC class-1 molecules, MHC class-1-like molecules and non-MHC related molecules [44]. Although not previously known, it is now well established that NK cells, in addition to their cytotoxic effector functions, can secrete cytokines and serve to control the immune system as regulatory lymphocytes that can interact with both innate and adaptive immune cells such as monocytes and macrophages, dendritic cells and T lymphocytes [45, 46]. Detailed studies have shown that conventional NK cells (cNK) are distributed in circulation in the blood, spleen, and bone marrow [47–49]. However, it has also been shown that NK cells can infiltrate tissues. They also have resident NK cells, defined as resident NK cells (trNK), in the lungs, skin, kidneys, lymph nodes, liver, intestines, and virgin uterus [47, 49, 50]. In addition to the peritoneal region and placenta, NK cells are also present in peripheral circulation, where they account for 10–15% of all lymphocytes [51].

Defined as a subgroup of extracellular vesicles of endocytic origin [52–55], 30–150 nm sized exosomes [53–57] are secreted by various cell types and are involved in complex physiological and pathological processes [58]. Exosomes can move far within the body and have been found in a variety of bodily secretions, including blood, saliva, cerebrospinal fluid, breast milk, urine, gastric juice, and semen [55]. Exosomes are produced by a wide variety of cell types, but it is known that exosomes released by cancer cells are specifically taken up by different immune cells, including Treg, dendritic cells, and NK cells, and are therefore successful in controlling their functions [59, 60]. Exosomes excreted by cancer cells are thought to help tumor cells escape immune surveillance in their microenvironment by stimulating angiogenesis and metastasis, as well as inhibiting the function of immune cells (**Figure 3**) [61]. Despite all this information, how exosomes secreted from tumor cells affect the health of individuals with cancer has not been fully elucidated [60, 61]. Exosomes can carry many different molecules with the ability to stimulate the immune system depending on the cell of origin from which they are secreted.

In particular, exosomes secreted from dendritic cells have been shown to carry ligands that can activate NK cells and can also be loaded with antigen to activate invariant NKT (a subset of T cells with characteristics of NK cells and conventional T cells) cells and induce T and B cell responses that are specific to the antigen [62]. Several studies in the last decade have provided evidence supporting the important role of cancer-originate exosomes in regulating the cancer microenvironment [63, 64]. Exosomes released by human tumors like myeloid leukemia, cervical cancer, breast cancer, hepatoblastoma, T cell cancer, pancreatic cancer, and multiple myeloma that are dyed with PKH67 membrane have been shown to associate with, infiltrate, and be engulfed by NK cells [65–67]. Li et al. [60] showed that exosomes derived from genetically modified K562 cells secreting IL-15, IL-18, and 4-1BBL on their surface carry the proteins of these three molecules similar to the source cell, and that these exosomes can increase the activity of NK cells after 4 h of treatment and even strengthen their cytotoxicity on some tumor types. In contrast, they reported that prolonged treatment (48 h) may suppress the cytotoxicity of NK cells by inhibiting the expression of activated receptors on NK cells. In mouse B16 melanoma, MC38 colon adenocarcinoma, and KLN205 squamous cell carcinoma cell lines, both

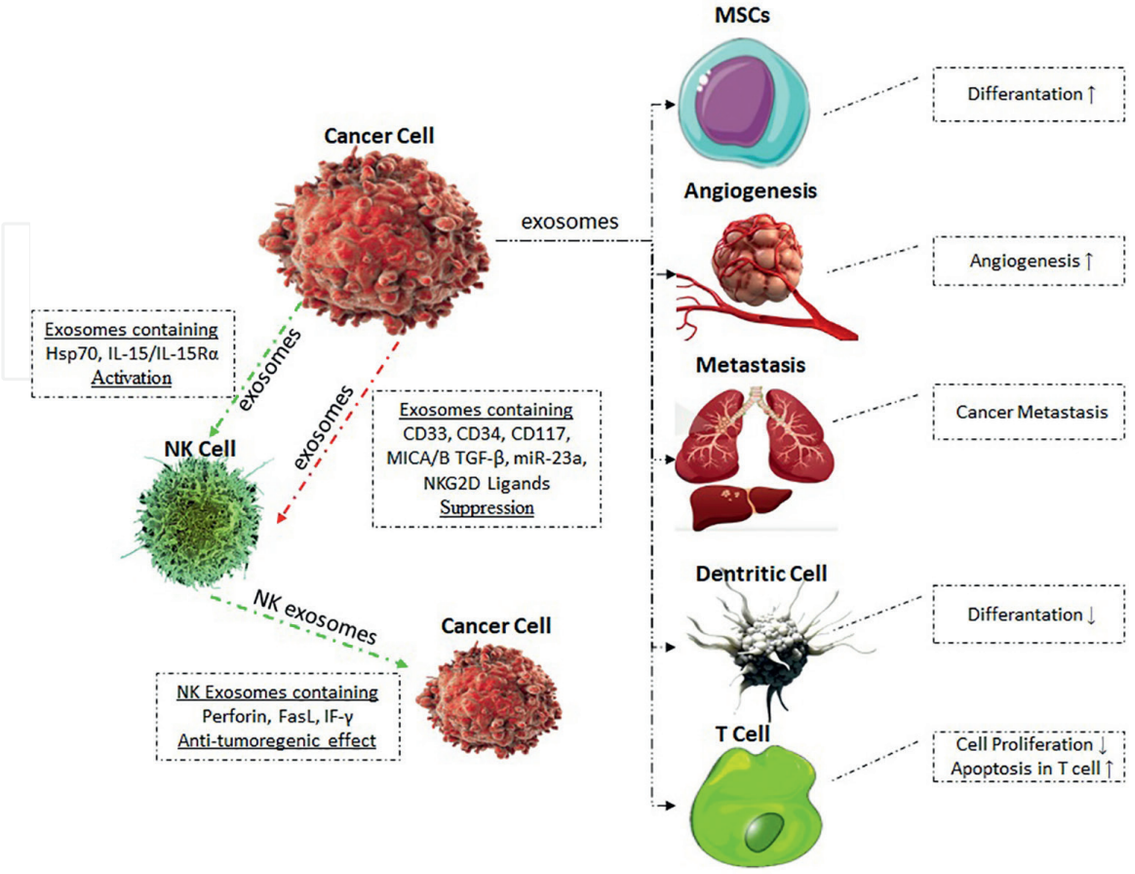

Figure 3.
Some roles of cancer cell-derived exosomes.

dendritic cells and exosomes secreted from dendritic cells can cause caspase activation and apoptosis, and exosomes released from dendritic cells can activate NK cells, according to research by Munich et al. [68]. In addition, TNF generated by exosomes of dendritic cells stimulates interferon gamma secretion by binding with NK cell TNF receptors. Jiang et al. [69] in NK92 and NK92-hIL-15 cell lines exposed to hypoxia for 48 h, they demonstrated that cytotoxicity was significantly increased and that hypoxia increased FasL, perforin, and granzyme B secretion. They revealed that exosomes produced from these NK cell lines under hypoxic conditions were effective in inhibiting both cell proliferation and migration while promoting apoptosis of breast cancer (MCF-7) and ovarian cancer (A2780) cells. However, this strategy, which encourages the overproduction of exosomes from NK cells as a consequence of NK cell hypoxia induction, might be a hopeful one for treating malignancy.

As a result, it is widely believed that exosomes produced by immune cells can strengthen immunity against cancer. In contrast, exosomes derived from cancer cells may decrease immunity and even alter the tumor microenvironment to promote self-enhancement and metastasis [70].

4. Exosomes and mast cells

Paul Ehrlich discovered mast cells 145 years ago and named them "mastzellen," meaning "nourishing cells," because of their appearance [71]. CD34+ progenitor

cells, which are mast cell precursors of hematopoietic stem cells (CD34−), are produced in the bone marrow during hematopoiesis and are introduced into the bloodstream [72]. These hematopoietic progenitor cells are thought to stay undifferentiated in the circulation but mature into mast cells in the presence of different growth factors secreted from the microenvironment of the tissues where they must settle. C-kit ligand and stem cell proteins are a few of these [73]. Mature mast cells are not detected in circulation under normal circumstances. However, under the control of stem cell factor (SCF) and a number of mediators, CD34+ progenitor cells move to regions where they finish differentiating into mast cells [73, 74]. Mast cells are distributed in the skin and mucosal tissues such as the stomach, intestines, and respiratory tract, which are the entry points of antigens, as well as in the peritoneum and chest cavities, smooth muscle tissue, connective tissue surrounding hair follicles, the central nervous system, and all tissues with blood vessels except the retina [73, 75–77]. Mast cells are mainly recognized for their role in allergy. They are also known to mediate vital symptoms such as skin blistering and flare reactions, bronchospasms in asthma, congestion and excessive mucus secretion in allergy-induced rhinitis and even systemic anaphylaxis [77, 78].

On the membrane of every mast cell, there is a high affinity IgE receptor called FcεRI. Due to its high affinity, IgE molecules can no longer detach after binding to the receptor and consequently mast cells are coated with IgE. This stimulation leads to the secretion of exosomes containing a large number of proinflammatory mediators (proteases, chemokines, amines, and cytokines) that are stored and newly synthesized in mast cells [79, 80]. Of course, this extra vesicular composition varies according to the stimulation received by mast cells, but they frequently cause the secretion of numerous cytokines, growth factors, and mitogens such as TNF-α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-11, IL-11, IL-12, IL-13, IL-16, IL-33, EGF, FG2, GM-CSF, IF-γ, NGF, PDGF, SCF, FGF-β1, and VEGF (**Figure 4**) [80].

Mast cells contribute to the promotion of angiogenesis. Mast cells promote angiogenesis, or the bud-like growth of new blood vessels from old ones, by secreting angiogenic factors like bFGF, VEGF, TGF-β, IL-8, and TNF-α. Mast cells also exude proteases that exude pro-angiogenic factors that bind to heparin and promote their release. However, there is also a proof that mast cells promote angiogenesis in the development of cancerous cells [73, 81]. Exosomes released by human mast cells have been shown by Ekström et al. [82] to be capable of RNA cell-to-cell transmission. They also showed that these exosomes have enough mRNA to equal 15% of the content of the source cell. Xiao et al. [83] also reported that exosomes containing KIT (labeled with PKH67), a cytokine receptor expressed mainly on the surface of hematopoietic stem cells, were secreted from a human mast cell line (HMC-1) and that these exosomes could be taken up by the lung epithelial cell line A549, and could also cause increased proliferation in recipient cancer cells by activation of the PI3K signaling pathway. Exosomes from human adipose-derived mesenchymal stem cells have been shown to effectively suppress atopic dermatitis in mice with the condition by lowering blood eosinophil counts, serum IgE levels, and the expression of the cytokines IL-4, IL-23, IL-31, and TNF- at the mRNA level [84]. However, in a model of cerebral malaria in C57BL/6 mice infected with Plasmodium berghei ANKA strain, it has been shown that intravenous administration of exosomes derived from mast cells to infected animals increases the incidence of the disease, exacerbates both liver and brain damage, contributes to disruption of the brain vascular endothelial structure, and increases the corruption of the blood-brain barrier (**Figure 5**) [85].

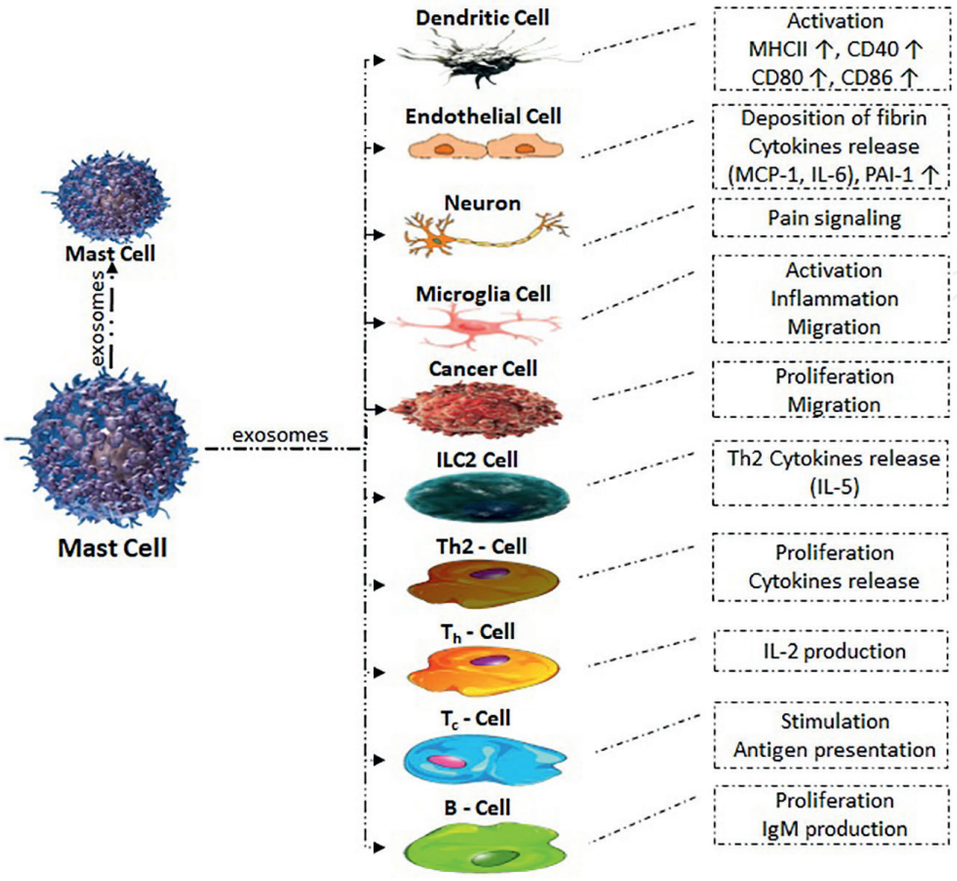

Figure 4.
Interactions of exosomes produced from mast cells with some other cells.

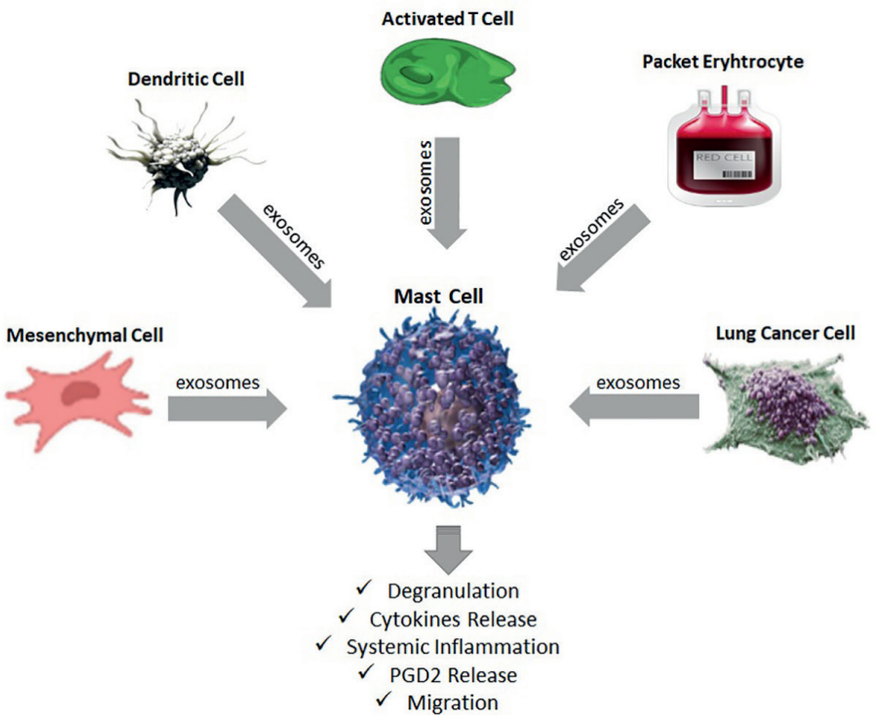

Figure 5.
Various cells' released exosomes' effects on the activation of mast cells.

5. Conclusion

In the literature reviews, it was observed that the activity of exosomes on the immune system has not been fully elucidated. Exosomes formed by other cells under normal physiological conditions and affecting cells in the immune system and exosomes expressed by cells that are effective in the immune system may have different activities. In addition, it has been determined that exosomes secreted under normal physiological conditions and exosomes secreted under pathological conditions have different routes of action (one of the main reasons for this difference is surface proteins), therefore, exosomes can exhibit immunomodulatory effects by showing both immunosuppressive and immunostimulatory effects depending on the current conditions.

Funding

There is no organization that financed this study.

Conflict of interest

The authors declare that there are no conflicts of interest.

Author details

Gözde Atila Uslu* and Hamit Uslu
Faculty of Medicine, Department of Physiology, Erzincan Binali Yıldırım University, Erzincan, Turkey

*Address all correspondence to: gzd.gozde@hotmail.com

References

[1] Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation. Association of plasma-membrane activities with released vesicles (exosomes). The Journal of Biological Chemistry. 1987;**262**:9412-9420

[2] Théry C, Zitvogel L, Amigorena S. Exosomes: Composition, biogenesis and function. Nature Reviews Immunology. 2002;**2**(8):569-579

[3] Mathivanan S, Ji H, Simpson RJ. Exosomes: extracellular organelles important in intercellular communication. Journal of Proteomics. 2010;**73**(10):1907-1920

[4] Batista BS, Eng WS, Pilobello KT, Hendricks-Muñoz KD, Mahal LK. Identification of a conserved glycan signature for microvesicles. Journal of Proteome Research. 2011;**10**(10):4624-4633

[5] Qin J, Xu Q. Functions and application of exosomes. Acta Poloniae Pharmaceutica. 2014;**71**(4):537-543

[6] Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;**367**(6478):eaau6977

[7] Kleijmeer M, Ramm G, Schuurhuis D, Griffith J, Rescigno M, Ricciardi-Castagnoli P, et al. Reorganization of multivesicular bodies regulates MHC class II antigen presentation by dendritic cells. The Journal of Cell Biology. 2001;**155**(1):53-64

[8] Zhang W, Liu R, Chen Y, Wang M, Du J. Crosstalk between oxidative stress and exosomes. Oxidative Medicine and Cellular Longevity. 2022;**2022**:3553617

[9] Hazawa M, Tomiyama K, Saotome-Nakamura A, Obara C, Yasuda T, Gotoh T, et al. Radiation increases the cellular uptake of exosomes through CD29/CD81 complex formation. Biochemical and Biophysical Research Communications. 2014;**446**(4):1165-1171

[10] Pant S, Hilton H, Burczynski ME. The multifaceted exosome: biogenesis, role in normal and aberrant cellular function, and frontiers for pharmacological and biomarker opportunities. Biochemical Pharmacology. 2012;**83**(11):1484-1494

[11] Parolini I, Federici C, Raggi C, Lugini L, Palleschi S, De Milito A, et al. Microenvironmental pH is a key factor for exosome traffic in tumor cells. Journal of Biological Chemistry. 2009;**284**(49):34211-34222

[12] de Gassart A, Géminard C, Février B, Raposo G, Vidal M. Lipid raft-associated protein sorting in exosomes. Blood. 2003;**102**(13):4336-4344

[13] Huang X, Yuan T, Tschannen M, Sun Z, Jacob H, Du M, et al. Characterization of human plasma-derived exosomal RNAs by deep sequencing. BMC Genomics. 2013;**14**:319

[14] Wang L, Hu L, Zhou X, Xiong Z, Zhang C, Shehada HM, et al. Exosomes secreted by human adipose mesenchymal stem cells promote scarless cutaneous repair by regulating extracellular matrix remodelling. Scientific Reports. 2017;**7**(1):13321

[15] Staubach S, Razawi H, Hanisch FG. Proteomics of MUC1-containing lipid

rafts from plasma membranes and exosomes of human breast carcinoma cells MCF-7. Proteomics. 2009;**9**(10):2820-2835

[16] Van Niel G, Mallegol J, Bevilacqua C, Candalh C, Brugiere S, Tomaskovic-Crook E, et al. Intestinal epithelial exosomes carry MHC class II/peptides able to inform the immune system in mice. Gut. 2003;**52**(12):1690-1697

[17] De Toro J, Herschlik L, Waldner C, Mongini C. Emerging roles of exosomes in normal and pathological conditions: new insights for diagnosis and therapeutic applications. Frontiers in Immunology. 2015;**6**:203

[18] Fevrier B, Vilette D, Archer F, Loew D, Faigle W, Vidal M, et al. Cells release prions in association with exosomes. Proceedings of the National Academy of Sciences. 2004;**101**(26):9683-9688

[19] Chivet M, Javalet C, Hemming F, Pernet-Gallay K, Laulagnier K, Fraboulet S, et al. Exosomes as a novel way of interneuronal communication. Biochemical Society Transactions. 2013;**41**(1):241-244

[20] Sheldon H, Heikamp E, Turley H, Dragovic R, Thomas P, Oon CE, et al. New mechanism for Notch signaling to endothelium at a distance by Delta-like 4 incorporation into exosomes. Blood. 2010;**116**:2385-2394

[21] Silbernagl S, Despopoulos A. Color Atlas of Physiology. 6th ed. New York: Thieme; 2009. 978-3-13-545006-3

[22] O'garra A, Vieira P. Regulatory T cells and mechanisms of immune system control. Nature Medicine. 2004;**10**(8):801-805

[23] 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;**3**(12):1156-1162

[24] Admyre C, Johansson SM, Paulie S, Gabrielsson S. Direct exosome stimulation of peripheral humanT cells detected by ELISPOT. European Journal of Immunology. 2006;**36**(7):1772-1781

[25] Chen T, Guo J, Yang M, Zhu X, Cao X. Chemokine-containing exosomes are released from heat-stressed tumor cells via lipid raft-dependent pathway and act as efficient tumor vaccine. Journal of Immunology. 2011;**186**:2219-2228

[26] McKelvey KJ, Powell KL, Ashton AW, Morris JM, McCracken SA. Exosomes: mechanisms of uptake. Journal of Circulating Biomarkers. 2015;**4**:7

[27] Lim TS, Goh JKH, Mortellaro A, Lim CT, Hämmerling GJ, Ricciardi CP. CD80 and CD86 differentially regulate mechanical interactions of T cells with antigen-presenting dendritic cells and B-cells. PLoS One. 2012;**7**(9):e45185

[28] Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, et al. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell derived exosomes. Nature Medicine. 1998;**4**(5):594-600

[29] Berckmans RJ, Nieuwland R, Kraan MC, Schaap MC, Pots D, Smeets TJ, et al. Synovial microparticles from arthritic patients modulate chemokine and cytokine release by synoviocytes. Arthritis Research & Therapy. 2005;**7**:1-9

[30] Cicero AL, Majkowska I, Nagase H, Di Liegro I, Troeberg L. Microvesicles shed by oligodendroglioma cells and

rheumatoid synovial fibroblasts contain aggrecanase activity. Matrix Biology. 2012;**31**(4):229-233

[31] Martínez-Lorenzo MJ, Anel A, Saez-Gutierrez B, Royo-Cañas M, Bosque A, Alava MA, et al. Rheumatoid synovial fluid T cells are sensitive to APO2L/TRAIL. Clinical Immunology. 2007;**122**(1):28-40

[32] Kim SH, Bianco NR, Shufesky WJ, Morelli AE, Robbins PD. Effective treatment of inflammatory disease models with exosomes derived from dendritic cells genetically modified to express IL-4. The Journal of Immunology. 2007;**179**(4):2242-2249

[33] Wen SW, Sceneay J, Lima LG, Wong CS, Becker M, Krumeich S, et al. The biodistribution and immune suppressive effects of breast cancer-derived exosomes. Cancer Research. 2016;**76**(23):6

[34] Schuler PJ, Saze Z, Hong CS, Muller L, Gillespie DG, Cheng D, et al. Human CD4+ CD39+ regulatory T cells produce adenosine upon co-expression of surface CD73 or contact with CD73+ exosomes or CD73+ cells. Clinical and Experimental Immunology. 2014;**177**(2):531-543

[35] Liu Y, Xiang X, Zhuang X, Zhang S, Liu C, Cheng Z, et al. Contribution of MyD88 to the tumor exosome-mediated induction of myeloid derived suppressor cells. The American Journal of Pathology. 2010;**176**(5):2490-2499

[36] Lu J, Wu J, Tian J, Wang S. Role of T cell-derived exosomes in immunoregulation. Immunologic Research. 2018;**66**:313-322

[37] Smyth LA, Ratnasothy K, Tsang JY, Boardman D, Warley A, Lechler R, et al. CD73 expression on extracellular vesicles derived from CD4+ CD25+ Foxp3+ T cells contributes to their regulatory function. European Journal of Immunology. 2013;**43**(9):2430-2440

[38] Yu X, Huang C, Song B, Xiao Y, Fang M, Feng J, et al. CD4+ CD25+ regulatory T cells-derived exosomes prolonged kidney allograft survival in a rat model. Cellular Immunology. 2013;**285**(1-2):62-68

[39] 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;**8**(1):23-30

[40] Wahlgren J, Karlson TDL, Glader P, Telemo E, Valadi H. Activated human T cells secrete exosomes that participate in IL-2 mediated immune response signaling. PLoS One. 2012;**7**(11):e49723

[41] Zhou WJ, Zhang J, Xie F, Wu JN, Ye JF, Wang J, et al. CD45RO-CD8+ T cell-derived exosomes restrict estrogen-driven endometrial cancer development via the ERβ/miR-765/PLP2/Notch axis. Theranostics. 2021;**11**(11):5330

[42] Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. Nature Immunology. 2008;**9**(5):503-510

[43] Ljunggren HG, Kärre K. In search of the 'missing self': MHC molecules and NK cell recognition. Immunology Today. 1990;**11**:237-244

[44] Caligiuri MA. Human natural killer cells. Blood, The Journal of the American Society of Hematology. 2008;**112**(3):461-469

[45] Mattiola I, Pesant M, Tentorio PF, Molgora M, Marcenaro E, Lugli E, et al. Priming of human resting NK cells by

autologous M1 macrophages via the engagement of IL-1β, IFN-β, and IL-15 pathways. Journal of Immunology. 2015;**195**:2818-2828

[46] Di Vito C, Mikulak J, Mavilio D. On the way to become a natural killer cell. Frontiers in Immunology. 2019;**10**:1812

[47] Habif G, Crinier A, André P, Vivier E, Narni-Mancinelli E. Targeting natural killer cells in solid tumors. Cellular & Molecular Immunology. 2019;**16**(5):415-422

[48] Diefenbach A, Colonna M, Koyasu S. Development, differentiation, and diversity of innate lymphoid cells. Immunity. 2014;**41**:354-365

[49] Sojka DK, Yang L, Yokoyama WM. Uterine natural killer cells. Frontiers in Immunology. 2019;**10**:960

[50] Victorino F, Sojka DK, Brodsky KS, McNamee EN, Masterson JC, Homann D, et al. Tissue-resident NK cells mediate ischemic kidney injury and are not depleted by anti-asialo-GM1 antibody. Journal of Immunology. 2015;**195**:4973-4985

[51] Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends in Immunology. 2001;**22**(11):633-640

[52] Guo W, Gao Y, Li N, Shao F, Wang C, Wang P, et al. Exosomes: New players in cancer (Review). Oncology Reports. 2017;**38**:665-675

[53] Zhang X, Yuan X, Shi H, Wu L, Qian H, Xu W. Exosomes in cancer: Small particle, big player. Journal of Hematology & Oncology. 2015;**8**:83

[54] Rajagopal C, Harikumar KB. The origin and functions of exosomes in cancer. Frontiers in Oncology. 2018;**8**:66

[55] Batista IA, Quintas ST, Melo SA. The interplay of exosomes and NK cells in cancer biology. Cancers. 2021;**13**(3):473

[56] Ruivo CF, Adem B, Silva M, Melo SA. The biology of cancer exosomes: Insights and new perspectives. Cancer Research. 2017;**77**:6480-6488

[57] Thakur BK, Zhang H, Becker A, Matei I, Huang Y, Costa-Silva B, et al. Double-stranded DNA in exosomes: A novel biomarker in cancer detection. Cell Research. 2014;**24**:766-769

[58] Yáñez-Mó M, Siljander P, Andreu Z, Zavec A, Borràs F, Buzas E, et al. Biological properties of extracellular vesicles and their physiological functions. Journal of Extracellular Vesicles. 2015;**4**:27066

[59] Whiteside TL. Immune modulation of T-cell and NK (natural killer) cell activities by TEXs (tumour-derived exosomes). Biochemical Society Transactions. 2013;**41**(1):245-251

[60] Li Q, Huang Q, Huyan T, Wang Y, Huang Q, et al. Bifacial effects of engineering tumour cell-derived exosomes on human natural killer cells. Experimental Cell Research. 2018;**363**(2):141-150

[61] Taylor DD, Gercel-Taylor C. Exosomes/microvesicles: Mediators of cancer-associated immunosuppressive microenvironments. Seminars in Immunopathology. 2011;**33**:441-454

[62] Gehrmann U, Näslund TI, Hiltbrunner S, Larssen P, Gabrielsson S. Harnessing the exosome-induced immune response for cancer immunotherapy. Seminars in Cancer Biology. 2014;**28**:58-67

[63] Kahlert C, Kalluri R. Exosomes in tumor microenvironment influence

cancer progression and metastasis. Journal of Molecular Medicine. 2013;**91**:431-437

[64] Wang Z, Chen JQ, Liu J, Tian L. Exosomes in tumor microenvironment: Novel transporters and biomarkers. Journal of Translational Medicine. 2016;**14**:297

[65] Huyan T, DU Y, Huang Q, Huang Q, Li Q. Uptake characterization of tumor cell-derived exosomes by natural killer cells. Iranian Journal of Public Health. 2018;**47**:803-813

[66] Zhao J, Schlößer H, Wang Z, Qin J, Li J, Popp F, et al. Tumor-derived extracellular vesicles inhibit natural killer cell function in pancreatic cancer. Cancers. 2019;**11**:874

[67] Vulpis E, Cecere F, Molfetta R, Soriani A, Fionda C, Peruzzi G, et al. Genotoxic stress modulates the release of exosomes from multiple myeloma cells capable of activating NK cell cytokine production: Role of HSP70/TLR2/NF-kB axis. Oncoimmunology. 2017;**6**:e1279372

[68] Munich S, Sobo-Vujanovic A, Buchser WJ, Beer-Stolz D, Vujanovic NL. Dendritic cell exosomes directly kill tumor cells and activate natural killer cells via TNF superfamily ligands. Oncoimmunology. 2012;**1**(7):1074-1083

[69] Jiang Y, Jiang H, Wang K, Liu C, Man X, Fu Q. Hypoxia enhances the production and antitumor effect of exosomes derived from natural killer cells. Annals of Translational Medicine. 2021;**9**(6):473

[70] Shoae-Hassani A, Hamidieh AA, Behfar M, Mohseni R, Mortazavi-Tabatabaei SA, Asgharzadeh S. NK cell-derived exosomes from NK cells previously exposed to neuroblastoma cells augment the antitumor activity of cytokine-activated NK cells. Journal of Immunotherapy (Hagerstown, Md.: 1997). 2017;**40**(7):265

[71] Ehrlich P. Beiträge zur theorie und praxis der histologischen Färbung. In: The Collected Papers of Paul Ehrlich. Pergamon, Turkey: Elsevier; 2013. pp. 29-64

[72] Shea-Donohue T, Stiltz J, Zhao A, Notari L. Mast cells. Current Gastroenterology Reports. 2010;**12**:349-357

[73] Krystel-Whittemore M, Dileepan KN, Wood JG. Mast cell: A multi-functional master cell. Frontiers in Immunology. 2016;**6**:620

[74] Zhang T, Finn DF, Barlow JW, Walsh JJ. Mast cell stabilisers. European Journal of Pharmacology. 2016;**778**:158-168

[75] da Silva EZ, Jamur MC, Oliver C. Mast cell function: A new vision of an old cell. The Journal of Histochemistry and Cytochemistry. 2014;**62**(10):698-738

[76] Galli SJ, Tsai M. Mast cells in allergy and infection: Versatile effector and regulatory cells in innate and adaptive immunity. European Journal of Immunology. 2010;**40**(7):1843-1851

[77] Weller CL, Collington SJ, Williams T, Lamb JR. Mast cells in health and disease. Clinical Science. 2011;**120**(11):473-484

[78] Collington SJ, Williams TJ, Weller CL. Mechanisms underlying the localisation of mast cells in tissues. Trends in Immunology. 2011;**32**(10):478-485

[79] Lecce M, Molfetta R, Milito ND, Santoni A, Paolini R. FcεRI signaling in the modulation of allergic response:

Role of mast cell-derived exosomes. International Journal of Molecular Sciences. 2020;**21**(15):5464

[80] Mukai K, Tsai M, Saito H, Galli SJ. Mast cells as sources of cytokines, chemokines, and growth factors. Immunological Reviews. 2018;**282**(1):121-150

[81] Norrby K. Mast cells and angiogenesis. APMIS. 2002;**110**(5):355-371

[82] Ekström K, Valadi H, Sjöstrand M, Malmhäll C, Bossios A, Eldh M, et al. Characterization of mRNA and microRNA in human mast cell-derived exosomes and their transfer to other mast cells and blood CD34 progenitor cells. Journal of Extracellular Vesicles. 2012;**1**(1):18389

[83] Xiao H, Lässer C, Shelke GV, Wang J, Rådinger M, Lunavat TR, et al. Mast cell exosomes promote lung adenocarcinoma cell proliferation—role of KIT-stem cell factor signaling. Cell Communication and Signaling. 2014;**12**:1-10

[84] Cho BS, Kim JO, Ha DH, Yi YW. Exosomes derived from human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis. Stem cell Research & Therapy. 2018;**9**(1):1-5

[85] Huang K, Huang L, Zhang X, Zhang M, Wang Q, Lin H, et al. Mast cells-derived exosomes worsen the development of experimental cerebral malaria. Acta Tropica. 2021;**224**:106145