Review Article:
Exosomes: Mediators of Immune Regulation

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ABSTRACT

Extracellular Vesicles, including exosomes, are small membrane fragments released from many cell types, like Mesenchymal Stem Cells (MSCs). They were recognized as a mechanism of intercellular communication. They can transfer proteins, lipids and nucleic acids to other cells. Thus, they have many physiological (angiogenesis, coagulation and tissue repair, etc.) and pathological (e.g. in autoimmune diseases and cancer) effects. The immunomodulatory properties of them have drawn a lot of interest. In particular, MSC-derived exosomes seem to have therapeutic potentials for many diseases. We reviewed the biopathological effects of exosomes and their roles in modulating immune responses.

Introduction

Extracellular Vesicles (EVs) have drawn much interest during the past two decades, because of their role in intercellular communication [1]. EVs are composed of a phospholipid bilayer that contains many transmembrane proteins, adhesion molecules, and lipids. Their diameter ranges from 30 nm to approximately 2000 nm [2]. These vesicles are produced by almost all cells. Thus, they are present in body fluids such as amniotic fluid, breast milk, plasma, serum, urine and even conditioned culture media [3]. The vesicles have many biological functions. For example, most of them play a key role in coagulation, immune surveillance, tissue repair, and many other functions [2, 4].

History

The discovery of EVs dates back to 1946 when Chargaff and West [5] investigated the effects of different centrifugal speeds on the clotting times of plasma. They found that plasma has procoagulant factors that precipitate after prolonged high-speed centrifugation. Then, Wolf [6] identified microvesicles derived from platelets by electron microscopy and termed them "platelet dust".

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Table 1. The characteristics of 3 main types of EVs

Characteristics	Exosomes	Microvesicles	Apoptotic Bodies
Origin [51]	Endosomal network	Plasma membrane	Plasma membrane
Size [1, 2]	50-150 nm	50-1000 nm	500-2000 nm
Markers [2, 21]	Tetraspanins (CD63, CD9), ESCRT components, Alix, TSG101, flotillin, MFGE8	Integrins, selectins, CD40 ligand	Extensive amount of phosphatidylserine
Morphology [21]	Cup-shaped	Irregular	Heterogeneous
Contents [2, 51]	mRNA, miRNA, cytoplasmic and membrane proteins, including receptors and MHC molecules	mRNA, miRNA, cytoplasmic and membrane proteins, including receptors	Histones, DNA, cell organelles

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A few years later, Pan and associates reported the first observations of exosomes [7].

Classification

On the basis of biogenesis, vesicles are classified into 3 major types, including exosomes, microvesicles, and apoptotic bodies [2]. We summarized the main characteristics of these vesicle types in Table 1.

Exosome Biogenesis

The exosomes biogenesis consists of 2 mechanisms as follows: Endosomal Sorting Complex Required for Transport (ESCRT)-dependent, as the main mechanism, and ceramide-dependent that is not well recognized [8]. The main one requires ESCRT components and other molecules such as Alix and Tumor Susceptibility Gene 101 (TSG101) [9]. First, membrane molecules, such as proteins, lipids, etc. are internalized by endocytosis. They are stored by ESCRT components in the endosomal membrane and budding as Intraluminal Vesicles (ILVs) into the Multivesicular Bodies (MVBs). Afterward, they are released by exocytosis when these MVBs fuse with the plasma membrane. After exocytosis, these ILVs are called exosomes [10, 11]. MVBs can also follow the lysosomal pathway instead of the secretory pathway and fuse with lysosomes resulting in the degradation of ILVs [12].

Interaction With Recipient Cells

After exocytosis, exosomes interact with target cells and transfer their contents to them. This procedure may occur in 3 different ways. First, to directly fuse with the membrane of target cells. Second, through phagocytosis, macropinocytosis or endocytosis, by clathrin, caveolae, or lipid rafts. Third, through endocytosis by receptors. This way, some molecules such as Intercellular Adhesion Molecule (ICAM), integrins, Extracellular Matrix (ECM) components, and phosphatidylserines are involved [1, 13].

Table 2. The effects of MSC-derived exosomes on the immune system

Source of Exosome	Target Cells	Exosome Effects	Reference
Human AD-MSCs	T-lymphocytes	Down-regulation of T-cells proliferation	Blazquez et al. [52]
Human BM-MSCs	T-lymphocytes	Immuno-suppression through A2A receptor	Amarnath et al. [53]
Human BM-MSCs	T-lymphocytes	Increasing the release of IL-10 from T regulatory cells	Del Fattore et al. [54]
Human BM-MSCs	MSC, NK, B cells	Inhibition of NKs and B-cell proliferation Increase of MSCs immunosuppressive properties	Di Trapani et al. [55]
Murine BM-MSCs activated with IL-1β	Murine auto-reactive lymphocytes	Apoptosis of activated T cells Secretion of IL-10 and TGF-β Generation of Tregs	A.Mokarizadeh et al. [56]
Human BM-MSCs	PBMCs from patients with type 1 diabetes	In vitro down-regulation of Th1 responses In vitro increase of the proportion of Treg In vitro reduce the percentage of Th17 cells	Favaro et al. [57]

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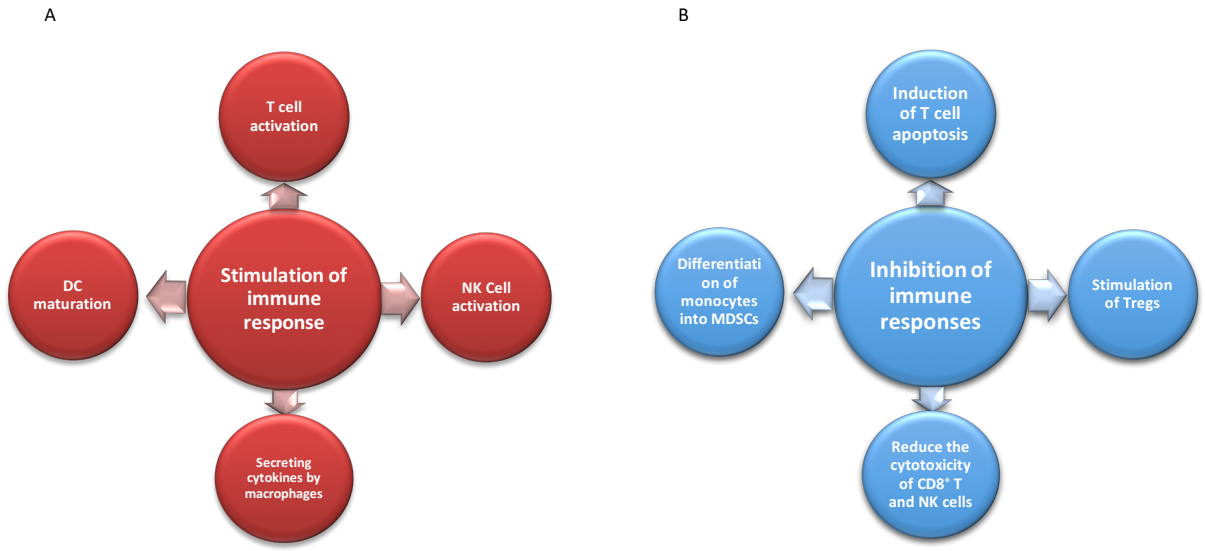

Figure 1. Immunomodulatory effects of exosomes

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Biological and Pathological Roles of Exosomes

Exosomes may be beneficial or detrimental to the host, depending on the cell source and body condition. They have many important functions in physiological conditions, such as immune surveillance and tissue repair. They can also enhance coagulation and participate in hemostasis [14]. In spite of these beneficial characteristics, many studies reported their roles in different pathological processes. For example, in autoimmune diseases [15, 16] and cancer [17], these vesicles may be detrimental through spreading the autoantigens or tumor antigens to other cells, respectively. Furthermore, they can spread neuropathological agents in neurodegenerative diseases, e.g., β-amyloids in Alzheimer disease [18]. Moreover, they can aggravate infectious diseases, e.g. by transferring C-C Chemokine Receptor type 5 (CCR5) to other cells in HIV infection [19].

Exosomes and Immunomodulation

Many studies demonstrated that exosomes have immunomodulatory properties. They could both stimulate and inhibit immune system functions. We will summarize the roles of these vesicles in immune responses [20, 21].

Stimulation of Immune Response

One of the most important mechanisms of exosomes in initiating the immune responses is the presentation of antigenic peptides loaded onto Major Histocompatibility Complex I (MHC I), or MHC II molecules to T $CD8^+$ or T $CD4^+$ cells, directly or indirectly. Exosomes secreted by almost all cells bear MHC I molecules that can induce T $CD8^+$ cell activation. In addition, it is important in cancer and intracellular infections [22]. APC-derived exosomes bear MHC II molecules and can be recognized by $CD4^+$ T cells, resulting in T cell activation [23-25].

Exosomes also have pro-inflammatory activities in innate immune system. For example, the infected macrophages release exosomes that contain the antigenic determinants of the pathogen, uptaken by immature Dendritic Cells (DCs). It could also cause the maturation of them [3, 21], or they may be uptaken by macrophages and stimulate them to secrete pro-inflammatory cytokines [26]. Many studies reported that if tumor cells are exposed to stress conditions like heat shock, they release exosomes that express Heat Shock Protein 70 (HSP70) and can induce Natural Killer (NK) cell activation [27], and pro-inflammatory cytokines secretion by macrophages (Figure 1) [28].

Inhibition of Immune Responses

Despite the stimulating properties of tumor-derived exosomes, many studies reported their immunosuppressive properties [29]. They can induce T cell apoptosis via their surface molecules such as galectin-9 [30] and Fas Ligand (FasL) [31-33]. Furthermore, they can inhibit T cell proliferation [34], induce differentiation into regulatory T cells (Tregs) [35], reduce the cytotoxicity of $CD8^+$ T [36], and NK cells [37-39], and induce monocytes differentiation into Myeloid-Derived Suppressor Cells (MDSCs) [40-43], instead of DCs [44]. Exosomes purified from body fluids like milk seem to

inhibit T cell activation and proliferation. They also can decrease CD3ζ expression by T cells [45]. HIV-infected cells can secrete exosomes that can induce the apoptosis of uninfected T cells [46].

Immunomodulation by MSC-Derived Exosomes

Mesenchymal Stem Cells (MSCs) are multipotent cells that have attracted great interest in regenerative medicine, due to their immunomodulatory properties. They can affect both innate and adaptive immune cells in 3 different methods. They can directly communicate with cells (cell-cell contact), secrete soluble factors, and release exosomes [47]. These exosomes express the surface molecules of cells of origin, such as CD73, CD44, and CD105 [48] as well as some specific exosomal markers, such as CD107, CD9, CD63, and CD81 [49]. Some studies suggest that MSC-derived exosomes have the same immunomodulatory properties as MSCs [50]. Some studies about the immunomodulatory effects of MSC-derived exosomes on the immune system are summarized in Table 2.

Concluding Remarks

The present review demonstrated that intercellular communications through releasing exosomes have key roles in multicellular organisms. We described the available literature, supporting the idea that exosomes have immunomodulatory properties. Sometimes, they activate the immune system and can be useful for anticancer therapy and in eliminating infections. Depending on the cell source and condition, they can also suppress immune responses. Thus, they may be beneficial and considered as therapeutic agents in autoimmune and inflammatory diseases. These points provide an exciting perspective for future investigations.

Ethical Considerations

Compliance with ethical guidelines

There was no ethical principle to be considered in conducting this research.

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Authors contributions

Supervision and validation: Seyed Mahmoud Hashemi; Investigation and resources: Mohammad Mahmoudi, Mahsa Taghavi Farahabadi; Conceptualization, writing original draft, review and editing: All authors.

Conflict of interest

The authors declare no conflict of interest.

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