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Immune System Modulation by Extracellular Vesicles: Implications for Disease Treatment

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ABSTRACT

Extracellular vesicles (EVs), including exosomes and microvesicles, have emerged as crucial mediators of intercellular communication, playing a significant role in immune system modulation. These nanosized vesicles transfer bioactive molecules such as proteins, lipids, and nucleic acids, influencing immune responses and contributing to various disease processes, including cancer, autoimmune disorders, and infections. The dual functionality of EVs capable of either activating or suppressing immune responses depending on their origin and cargo highlights their therapeutic potential. This review explores the mechanisms through which EVs modulate immune functions, their implications in disease pathogenesis, and their innovative applications in therapeutic strategies. In oncology, tumor-derived EVs can promote immune evasion, while engineered EVs show promise as vehicles for targeted drug delivery and cancer immunotherapy. In autoimmune diseases, EVs can either exacerbate inflammation or facilitate tolerance, offering new avenues for treatment. Furthermore, EVs hold potential as biomarkers for disease diagnosis and monitoring due to their stability in bodily fluids and ability to reflect cellular states. However, challenges remain in standardizing EV isolation, characterization, and clinical application. Future advancements in bioengineering, along with improved understanding of EV biology, are crucial for harnessing their therapeutic potential. This review emphasizes the importance of EVs in immune modulation and their promising implications for innovative disease treatment strategies.

Keywords: Extracellular vesicles, immune modulation, cancer therapy, autoimmune diseases, biomarkers

INTRODUCTION

Extracellular vesicles (EVs) are membrane-bound particles released by nearly all cell types and play critical roles in cell-to-cell communication. These vesicles are classified into different subtypes, primarily exosomes and microvesicles, based on their biogenesis, size, and content [1]. EVs carry a diverse range of cargo, including proteins, lipids, mRNA, miRNA, and DNA, which can be transferred to recipient cells, leading to changes in their behavior or function [2]. Over the past decade, EVs have gained attention for their role in immune system modulation, with the potential to either activate or suppress immune responses. In the context of disease, EVs have been implicated in immune regulation in cancer, autoimmune diseases, infections, and tissue injury. Tumor-derived EVs can modulate the tumor microenvironment, promoting immune evasion, while in autoimmune diseases, EVs can contribute to either immune activation or suppression [3]. This dual functionality makes them attractive targets for therapeutic intervention, either by harnessing their natural immune-modulatory properties or engineering them for specific purposes, such as targeted drug delivery or as vehicles for immunotherapy [4]. This review aims to provide a comprehensive overview of the role of EVs in immune system modulation, their implications for disease treatment, and emerging therapeutic applications. We will explore their mechanisms of action, their role in various diseases, and the challenges and opportunities in translating EV-based therapies into clinical practice.

Types of Extracellular Vesicles and Their Cargo

EVs are generally classified into two main types: exosomes and microvesicles. Exosomes are small vesicles (30–150 nm in diameter) that originate from the endosomal system, while microvesicles are larger (100–1000 nm) and bud directly from the plasma membrane [5]. Both types of vesicles carry biologically active cargo that can influence immune responses.

The cargo of EVs is diverse and reflects the cell of origin. This includes:

Proteins: EVs contain a range of proteins, including those involved in antigen presentation (MHC molecules), immune activation (cytokines, chemokines), and immune suppression (e.g., PD-L1, TGF-β) [6].

Lipids: EV membranes are enriched with bioactive lipids, which can modulate immune cell signaling and inflammation [7].

Nucleic acids: EVs carry mRNA, miRNA, and other non-coding RNAs, which can regulate gene expression in recipient cells and influence immune function [8].

The selective packaging of these molecules into EVs is a highly regulated process, allowing cells to modulate immune responses in a targeted and dynamic manner.

MECHANISMS OF IMMUNE MODULATION BY EXTRACELLULAR VESICLES

EVs can influence the immune system in multiple ways, affecting both the innate and adaptive immune responses.

Innate Immunity

EVs play a critical role in modulating the activity of innate immune cells such as macrophages, dendritic cells (DCs), and natural killer (NK) cells. Tumor-derived EVs, for example, can suppress the activation of NK cells and reduce their cytotoxicity, thereby promoting tumor immune evasion [9]. Similarly, EVs from infected cells can transfer viral components to uninfected cells, leading to the spread of infection or altering the immune response to pathogens [10]. On the other hand, EVs from certain immune cells can stimulate innate immune responses. For instance, DC-derived EVs can carry antigens and present them to T cells, thereby promoting immune activation. Moreover, EVs carrying danger-associated molecular patterns (DAMPs) can activate pattern recognition receptors (PRRs) on innate immune cells, triggering inflammatory responses [11].

Adaptive Immunity

EVs also play a crucial role in regulating adaptive immune responses. EVs from antigen-presenting cells (APCs), such as dendritic cells and B cells, can present antigens to T cells and stimulate adaptive immune responses. These vesicles are enriched in MHC molecules, which are essential for antigen presentation to CD4+ and CD8+ T cells [12]. Conversely, EVs can also promote immune tolerance. Regulatory T cell (Treg)-derived EVs can suppress the activation of effector T cells and reduce inflammation in autoimmune diseases [13]. Additionally, tumor-derived EVs that carry immune checkpoint molecules like PD-L1 can inhibit T cell function, promoting tumor progression by allowing cancer cells to escape immune surveillance [14].

Extracellular Vesicles in Disease

EVs are implicated in the pathogenesis of several diseases by modulating immune responses.

Cancer

In cancer, EVs derived from tumor cells can suppress anti-tumor immunity and promote tumor progression. Tumor-derived EVs can carry immunosuppressive molecules such as PD-L1, which inhibits T cell activation [15]. These EVs can also influence the tumor microenvironment by promoting angiogenesis and metastasis, as well as inducing the differentiation of myeloid-derived suppressor cells (MDSCs), which further dampen immune responses [16]. Despite their role in immune suppression, EVs also have therapeutic potential in cancer. For example, DC-derived EVs carrying tumor antigens can be used to stimulate anti-tumor immune responses. These EVs are being explored as cancer vaccines, either alone or in combination with other immunotherapies [17].

Autoimmune Diseases

In autoimmune diseases, EVs can either exacerbate or suppress immune responses. For instance, EVs from inflamed tissues can carry pro-inflammatory cytokines and autoantigens, which can perpetuate immune activation and tissue damage [18]. Conversely, EVs from regulatory cells, such as Tregs, can suppress immune responses and reduce inflammation. In diseases like rheumatoid arthritis and systemic lupus erythematosus, EVs have been shown to contain autoantigens that contribute to the propagation of autoimmune responses [19]. However, EVs derived from mesenchymal stem cells (MSCs) have demonstrated potential in suppressing inflammation and promoting tissue repair, making them attractive candidates for therapeutic intervention in autoimmune diseases [20].

Infectious Diseases

EVs play a dual role in infectious diseases. Pathogen-infected cells release EVs that can contain viral or bacterial components, which can either enhance the immune response or facilitate pathogen spread. For example, HIV-infected cells release EVs containing viral proteins that can manipulate the

immune system, while in viral hepatitis, EVs can carry viral RNA that promotes chronic infection [21,22]. On the positive side, EVs derived from immune cells can promote anti-pathogen responses. For example, macrophage-derived EVs can transfer pathogen-derived antigens to DCs, enhancing antigen presentation and promoting adaptive immune responses [23].

Therapeutic Potential of Extracellular Vesicles

Given their natural role in immune modulation, EVs have great potential as therapeutic agents. Engineered EVs can be designed to carry specific therapeutic cargos, such as anti-inflammatory molecules, immune checkpoint inhibitors, or nucleic acids that can silence disease-related genes [24]. This makes EVs highly attractive for drug delivery, especially in diseases where immune modulation is required. EVs are also being explored as biomarkers for disease diagnosis and monitoring [25]. Due to their stability in bodily fluids and their ability to reflect the state of the cell of origin, EVs can be used to track disease progression or treatment response in real-time.

EV-based Cancer Therapies

In cancer, EVs are being used as vehicles for delivering therapeutic agents directly to the tumor site, thereby reducing off-target effects [26]. EVs can be engineered to carry chemotherapy drugs, siRNA, or immune-modulating agents that boost anti-tumor immunity [24].

EVs in Autoimmune Disease Therapy

For autoimmune diseases, EVs from mesenchymal stem cells (MSCs) are being explored for their ability to suppress inflammation and promote tissue regeneration [27]. These EVs have been shown to modulate immune cell activity, promote Treg function, and reduce the production of pro-inflammatory cytokines, offering promise in conditions like multiple sclerosis and rheumatoid arthritis.

Challenges and Future Directions

While the therapeutic potential of EVs is promising, several challenges remain. Standardization in the isolation and characterization of EVs is crucial for their clinical application [28]. Methods for purifying EVs must be refined to ensure the consistency and purity of EV preparations. Furthermore, the mechanisms underlying EV cargo selection and the specific targeting of recipient cells are not fully understood, limiting the precision of EV-based therapies. Advances in bioengineering and nanotechnology will likely enhance the therapeutic utility of EVs [29]. Future research should focus on improving the scalability of EV production, optimizing EV loading with therapeutic agents, and developing better targeting strategies

CONCLUSION

In conclusion, extracellular vesicles (EVs) represent a dynamic and versatile component of the immune system, with significant implications for disease treatment and management. Their ability to modulate immune responses—either promoting or suppressing activity—offers exciting opportunities for therapeutic interventions in cancer, autoimmune disorders, and infectious diseases. As research continues to unveil the complex mechanisms governing EV function and cargo selection, the potential for engineered EVs as targeted delivery systems and biomarkers for disease monitoring becomes increasingly viable. Overcoming the current challenges in standardization and clinical application will be crucial for fully harnessing the therapeutic promise of EVs in precision medicine.

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