

Dynamic Regulation of Tumor Cell-Immune Cell Exosome Interactions and Therapeutic Applications

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Abstract: The interaction between tumor cells and immune cell-derived exosomes is crucial in tumor initiation, progression, and response to treatment. Exosomes, as key mediators of intercellular communication, transport a range of biomolecules that can modulate immune cell function and impact the formation and evolution of the tumor microenvironment. However, challenges remain in elucidating the precise mechanisms of exosome-mediated tumor-immune interactions, including limitations in isolation techniques, content analysis, and functional validation, which hinder their clinical translation. In this paper, through a systematic review of relevant literature, we investigated the modulatory effects of exosomes derived from tumor cells on immune cells, the impact of exosomes secreted by immune cells on the behavior of tumor cells, as well as the dynamic regulatory mechanism of exosomes in the interaction between tumors and immune cells, and further analyzed the prospects of the application of exosomes in tumor immunotherapy. Studies have shown that exosomes have important roles in tumor immune escape, anti-tumor immunity, and tumor therapy, and they have broad application potential as biomarkers and drug delivery carriers. However, the isolation and identification techniques, content analysis, and mechanism of action of exosomes still need further in-depth study to promote their clinical application in tumor therapy.

Keywords: Exosomes, Tumor-Immune Interaction, Tumor Immunotherapy, Immune Escape

1. Introduction

Tumorigenesis and progression is a complex process involving the interaction of multiple cell types, in which the immune system plays a crucial role. The interaction between tumor cells and immune cells is essential for immune escape and immune surveillance, and ultimately the therapeutic effect of the tumor. The involvement of exosomes in the interactions between tumor cells and immune cells, as important mediators of intercellular communication, is of increasing interest. Exosomes are small nanoscale vesicles secreted by cells, which contain a variety of biomolecules such as proteins, lipids, nucleic acids, etc., and can be taken up by other cells, thus facilitating intercellular communication and regulation. Nevertheless, many challenges remain in the current research on the interaction between tumor cells and exosomes derived from immune cells, such as the immature technology of exosome isolation and identification, the lack of in-depth analysis of the contents, and the incomplete clarity of the mechanism of action, etc. These problems have limited the research on the application of exosomes in the treatment of tumors. Thus, investigating the mechanism underlying exosome-mediated interactions between tumor cells and immune cells, along with its potential

applications in cancer therapy, holds significant theoretical and clinical importance. This review aims to systematically analyze the dual roles of exosomes in tumor-immune crosstalk, evaluate current therapeutic strategies, and propose future directions for overcoming technical and clinical challenges.

2. Literature review

2.1. Regulation of immune cells by tumor cell exosomes

2.1.1. Secretion and composition of exosomes

The amount and composition of exosomes secreted by tumor cells are regulated by a variety of factors, including cell type, growth status, and microenvironmental stimuli [1]. The secretion process of exosomes involves dynamic changes in the intracellular membrane system, such as the participation of the endoplasmic reticulum, Golgi apparatus and endosomes. The membrane structure of exosomes is mainly derived from the cell membrane, its surface is equipped with various specific markers, including CD9, CD63, CD81, among others.[2].The inside of exosomes, on the other hand, contains abundant proteins, lipids and nucleic acids, and these components endow exosomes with powerful biological functions. Studies have shown [3] that tumor cells increase exosome secretion under microenvironmental stimuli such as hypoxia, nutrient deficiency, and cellular stress, thereby regulating immune cell function more effectively.

2.1.2. miRNAs, proteins and metabolites in exosomes secreted by tumor cells

Exosomes derived from tumor cells are abundant in miRNAs, which can be internalized by immune cells, thereby modulating their gene expression and function.[4]. For example, miR-21 in exosomes derived from tumor cells can suppress the PTEN gene expression in T cells, thereby promoting T cell apoptosis. For instance, it has been shown [5] how miRNAs, proteins, and metabolites in tumor cell exosomes affect gene expression, signaling, and metabolic processes in immune cells through different mechanisms, thereby promoting tumor immune escape. In addition, proteins in exosomes have important biological functions, such as PD-L1 in tumor cell exosomes can bind to the PD-1 receptor on the surface of T cells and inhibit T cell activation and proliferation [6]. Metabolites in exosomes, such as lactic acid and amino acids, are also able to affect the metabolism and function of immune cells. Together, these biomolecules make tumor cell exosomes an important tool for regulating immune cell function.

2.1.3. The role of tumor exosomes in immune escape

Tumor exosomes play a key role in immune escape. They are able to carry immunosuppressive molecules, such as PD-L1, TGF- β , and IL-10, which act directly on immune cells to inhibit their activation and function [4, 7]. For example, PD-L1 present in exosomes from tumor cells can bind to the PD-1 receptor on T cell surfaces, thereby inhibiting T cell proliferation and their cytotoxic activity. In addition, exosomes are able to promote immune escape by inducing differentiation and functional enhancement of immunosuppressive cells. For example, TGF- β in exosomes is able to induce the differentiation of CD4⁺ T cells into regulatory T cells (Tregs), a class of T cell subpopulations with immunosuppressive functions that inhibit anti-tumor immune responses.

2.1.4. Molecular mechanisms of exosome-induced tumor-associated immune escape

The molecular mechanisms of exosome-induced tumor-associated immune escape are complex and diverse, involving multiple aspects of signaling, gene regulation, and intercellular communication [7]. For example, miRNAs in exosomes are able to inhibit immune cell activation by regulating gene

expression in target cells and affecting the activation of signaling pathways. Proteins in exosomes are also able to directly bind to receptors on the surface of immune cells, activating or inhibiting the corresponding signaling pathways. In addition, exosomes are also able to regulate the metabolic state of immune cells and influence their function through the metabolites they carry. For example, lactic acid within exosomes can disrupt the glycolytic process in T cells, leading to a reduction in their energy metabolism, thus inhibiting the activation and proliferation of T cells.

2.2. Regulation of tumor cells by immunocyte exosomes

2.2.1. The role of immune cell exosomes in antitumor immunity

Immune cell exosomes have an important role in anti-tumor immunity. They can carry antigens, cytokines, etc [8], which activate and enhance the anti-tumor response of immune cells. For example, dendritic cell exosomes are able to present tumor antigens to T cells and activate specific anti-tumor immune responses. In addition, exosomes from immune cells can influence the tumor microenvironment and enhance anti-tumor immune responses by delivering cytokines. For example, T-cell exosomes are able to secrete a variety of cytokines, such as IFN- γ and TNF- α , to further enhance the anti-tumor immune response [9].

2.2.2. Macrophage and dendritic cell exosomes and antigen presentation

Macrophages and dendritic cells are the main antigen-presenting cells, and the exosomes they secrete play a crucial role in antigen presentation. Macrophage exosomes are capable of carrying tumor antigens, which are taken up by dendritic cells and then further present the antigens to T cells. Dendritic cell exosomes, on the other hand, are able to present tumor antigens directly to T cells and activate the anti-tumor response of T cells [8]. This process is critical for initiating and maintaining specific anti-tumor immune responses.

2.2.3. Killing effects of T cell exosomes with their secreted cytokines

T-cell exosomes have the ability to kill tumor cells by a mechanism that is mainly through the cytotoxic molecules and cytokines they carry. For example, cytotoxic T-cell exosomes are able to carry perforin and granzyme, which directly kill tumor cells. In addition, T-cell exosomes are able to secrete a variety of cytokines [8], such as IFN- γ and TNF- α , which further enhance the anti-tumor immune response. These cytokines stimulate the activation and proliferation of immune cells while suppressing the growth and metastasis of tumor cells.

2.2.4. Inhibition of tumor cell growth and metastasis by immunocyte exosomes

Exosomes derived from immune cells can suppress tumor cell growth and metastasis through multiple mechanisms.[8]. For example, they are able to carry anti-tumor drugs or gene therapy vectors, which directly act on tumor cells to inhibit their growth. In addition, immune cell exosomes are also able to inhibit tumor cell invasion and metastasis by regulating the tumor microenvironment. For example, certain proteins and cytokines present in exosomes can hinder the epithelial-mesenchymal transition (EMT) process in tumor cells, thereby decreasing their invasive potential.

2.3. Dynamic regulation of tumor-immune cell exosome interactions

2.3.1. Bidirectional regulation: how exosomes affect the balance between tumors and the immune system

The interaction between tumor cells and immune cell exosomes is bidirectional, and together they influence the balance between the tumor and the immune system. Tumor cell exosomes can inhibit the activation and function of immune cells and promote immune escape, while immune cell exosomes can activate and enhance the anti-tumor response of immune cells. This bidirectional regulatory mechanism makes the interaction between tumor and immune system more complex and dynamic [10, 11]. For example, the antitumor effects of immune cell exosomes may dominate in the early stage of tumor, while the immunosuppressive effects of tumor cell exosomes gradually increase during tumor progression.

2.3.2. Mechanisms of exosome regulation between tumor progression and immune surveillance

Exosomes play an important regulatory role between tumor progression and immune surveillance. In the early stage of tumor, exosomes are able to carry antigens, activate immune cells, and enhance immune surveillance; however, during tumor progression, the exosomes secreted by tumor cells gradually increase, and their immune-suppressive effects are gradually enhanced, leading to a decrease in immune surveillance [10]. This regulatory mechanism allows the tumor to progress under immune surveillance.

2.3.3. The role of exosomes in different stages of tumor development

Exosomes play different roles in different stages of tumor development. In the early stage of tumor, exosomes mainly play an anti-tumor role by activating immune cells and enhancing immune surveillance; whereas in the middle and late stages of tumor, the immunosuppressive effect of exosomes gradually increases, promoting immune escape and progression of tumors [10]. In addition, exosomes can impact the growth, invasion, and metastasis of tumor cells by modulating the tumor microenvironment.

2.3.4. The potential for real-time regulation of exosomes in tumor therapy

Exosomes have the potential for real-time regulation in tumor therapy. The interaction between tumor cells and immune cells can be influenced in real time by regulating the secretion and content of exosomes [10]. For example, inhibiting the secretion of tumor cell exosomes can reduce the release of immunosuppressive molecules and enhance anti-tumor immune responses, while promoting the secretion of immune cell exosomes can enhance the anti-tumor function of immune cells.

3. Method

In this study, the research progress on the interaction between tumor cell and immune cell exosomes was systematically sorted out and analyzed mainly by reviewing a large number of domestic and international literatures. Firstly, research literature related to tumor cell exosomes and immune cell exosomes were collected through literature search and screening, covering the secretion, composition, function of exosomes and their roles in tumor immune escape, anti-tumor immunity and tumor therapy. Then, the collected literature is classified and organized, and analyzed in detail according to the themes of secretion and composition of exosomes, regulatory impact of exosomes derived from tumor cells on immune cells., regulatory role of immune cell exosomes on tumor cells, dynamic regulation of tumor-immune cell exosome interactions, and prospects for the application of exosomes

in tumor immunotherapy. On this basis, problems and shortcomings in the current research are summarized, and directions and suggestions for future research are put forward.

4. Conclusion

4.1. Findings

Exosomes dynamically regulate the tumor immune microenvironment through a “dual identity”: on the one hand, tumor exosomes act as immunosuppressive vectors to promote immune escape through molecules such as PD-L1 and miRNAs; on the other hand, immune exosomes activate the anti-tumor response through antigen presentation and cytotoxic molecule release. This bidirectional interplay network provides a theoretical basis for the development of timing-dependent therapeutic strategies such as exosome secretion inhibitors coupled with immune checkpoint blockers. The dual identity of exosomes underscores the need for context-specific therapeutic strategies, such as timed blockade of tumor exosome secretion combined with immune-activating exosome infusion.

4.2. Application prospects

The natural targeting and low immunogenicity of exosomes make them superior to synthetic nanocarriers. For example, engineered modified dendritic cell exosomes can efficiently deliver CRISPR-Cas9 to tumor cells for EGFR knockdown (knockdown efficiency >80%). In addition, exosomes carry circulating miRNAs (e.g. miR-21-5p) that can be used as early diagnostic markers (AUC=0.91).

4.3. Future direction

Technological innovation: developing microfluidic chip combined with mass spectrometry to achieve high-throughput isolation of exosome subpopulations and content resolution; Clinical translation: designing multicenter clinical trials (e.g., NCT05231005) to evaluate the safety of exosome drug delivery systems in solid tumors; Interdisciplinary fusion: combining single-cell sequencing and artificial intelligence to construct a predictive model of exosome-immune cell interactions.

4.4. Research significance

This study provides a new perspective for understanding the complex mechanism of exosome interaction between tumor cells and immune cells, and lays a theoretical foundation for the development of novel exosome-based tumor therapeutic strategies. The in-depth study of exosome secretion and composition, regulatory mechanisms and their roles in tumor immune escape, anti-tumor immunity and tumor therapy can provide new ideas and methods for tumor diagnosis, treatment and prognosis assessment. The study of exosomes as a drug delivery system is expected to improve the targeting and effectiveness of anticancer drugs and reduce the toxic side effects of drugs; the study of exosomes as a target of tumor therapy provides a new way to enhance the anti-tumor immune response and inhibit tumor growth and metastasis.

4.5. Research shortcomings and prospects

Despite the results achieved in this study, there are still some shortcomings. First, the isolation and identification techniques of exosomes still need to be further optimized to improve the purity and quality of exosomes to meet the needs of large-scale applications. Second, the analysis of exosome contents is not deep enough, especially the exploration of the complex protein interaction network and lipid metabolic pathways in exosomes needs to be strengthened. In addition, the research on the

application of exosomes in tumor therapy is still in its infancy, and the safety, efficacy and stability of its clinical application still need to be further verified and explored. Future research can be expanded and deepened in the following aspects: first, to develop more efficient and simple exosome isolation and identification techniques, and to improve the reproducibility and comparability of exosome research; second, to strengthen the systematic analysis and functional study of exosome contents, and to deeply excavate the key molecules and signaling pathways of exosomes in the interaction between tumor cells and immune cells; and third, to carry out large-scale clinical trials to Evaluate the practical application effect of exosomes in tumor diagnosis and treatment, and provide more data support for the clinical transformation of exosomes. Through continuous efforts and exploration, we believe that exosomes will show a broader application prospect in the field of tumor research and treatment.

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