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Research Progress of Exosomes in Vaccine Delivery

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Abstract. Exosomes are nanoscale vesicles secreted by cells, with a lipid bilayer structure, and serve as crucial mediators of intercellular communication. Exosomes have core advantages such as good biocompatibility, low immunogenicity, and strong inherent targeting. Currently, exosomes have demonstrated promising application prospects in antiviral, antitumor, and antibacterial vaccines, but still face challenges including non-standardized production, safety and ethical controversies, and the lack of a dedicated regulatory system for medical aesthetic products and biological agents. In the future, optimizing cargo loading and engineering modification techniques, and developing combination therapy and personalized immunization strategies will facilitate the clinical translation of exosome vaccines, providing new directions for the field of vaccinology.

Keywords: Exosomes, Vaccine delivery, Biocompatibility, Engineering transformation

1. Introduction

Traditional vaccine delivery systems play a significant role in the prevention and control of infectious diseases, but they have limitations such as insufficient immunogenicity, poor stability, and low antigen delivery efficiency, making it difficult to meet the precise and efficient immunization requirements for complex diseases [1]. Exosomes can carry bioactive substances to mediate intercellular communication and possess excellent biocompatibility low immunogenicity and natural targeting, which can make up for the shortcomings of traditional delivery systems and provide new ideas for the development of new vaccines [2]. They can achieve targeted delivery through surface-specific molecules, improving vaccine delivery efficiency and immune efficacy [3], and the potential for engineering modification can expand functions to meet the needs of diverse vaccines, becoming an important research direction to break through the bottleneck of traditional vaccine delivery [4].

By reviewing the biological characteristics of exosomes, this paper clarifies the mechanisms and pathways for breaking through the bottleneck of traditional vaccine delivery [5]. First, the basic characteristics of exosomes and their core advantages in vaccine delivery are expounded. Then, the construction strategies and application cases of exosome vaccines are systematically sorted out to answer the core questions of exosomes in making up for the deficiencies of traditional delivery. At the same time, the research progress in this field is reviewed and discussed around advantages, methods, applications and challenges to provide theoretical references for clinical translation [4].

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2. Literature review

2.1. Synthesis and function of exosomes

Exosomes are natural nanovesicles ranging from 30 to 100 nm in size with a lipid bilayer membrane, which highly express signature proteins including CD9, CD63 and CD81 on their surface, and carrying active substances such as proteins and nucleic acids inside [6]. They feature structural stability and favorable biocompatibility, and can mediate intercellular signal transduction and immune regulation, thus providing theoretical support for vaccine delivery research [7].

Exosome synthesis and secretion are precisely regulated through three core stages: cell membrane invagination to form early endosomes, transformation into polyvesicles, and fusion of polyvesicles with cell membranes or lysosomes. The secretion process is regulated by factors such as cell type, microenvironment, inflammation, and viral infection [8, 9], and has the potential for controllable preparation.

2.2. The development of exosomes in vaccine delivery systems

Vaccine delivery systems have undergone iterative upgrades from traditional to novel vectors to meet the demands for enhanced vaccine safety and efficacy [10]. Traditional vaccine delivery methods have drawbacks such as weak immunogenicity, poor stability, and potential side effects. Although new carriers such as liposomes and polymer nanoparticles optimize vaccine performance, they still have shortcomings such as poor biocompatibility and difficulty in large-scale production [11].

Exosomes, with their natural biological advantages, have become ideal delivery carriers and have broad application prospects in antiviral, anti-tumor and bacterial vaccines [12]. They can efficiently deliver antigens and activate the immune response of the body, and have achieved positive results in the development of several vaccines. However, current exosome vaccines still face challenges such as large-scale production, purity control, and clinical safety, and a standardized production and quality control system needs to be established to promote clinical translation [3].

2.3. Core advantages of exosomes as vaccine vectors

Exosomes, as natural extracellular vesicles, are highly advantageous vaccine delivery vectors. Their membrane components possess excellent biocompatibility and low immunogenicity, which can reduce immune rejection responses and improve vaccine safety [13]. At the same time, exosome surface proteins and lipids give them inherent targeting, which can precisely identify target cells, and the targeting varies with the type of mother cells, which can improve vaccine delivery efficiency, reduce non-specific toxicity [14], and further optimize targeting performance [15]. In addition, exosomes have high engineering flexibility and can be modified through gene editing and physicochemical methods to carry multiple vaccine components, enhancing vector function and immune effect, and have broad prospects for vaccine research and development applications [16].

3. Construction of exosome vaccines

3.1. "Unmodified" natural exosomes

Some cell-derived exosomes are naturally enriched in immunomodulatory molecules or antigen presentation-related proteins. For instance, dendritic cell-derived exosomes express MHC molecules

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and co-stimulatory molecules to directly activate T-cell immunity [17]; tumor cell-derived exosomes inherently carry tumor-associated antigens and can serve as unmodified candidates for antitumor vaccines [18]. However, these exosomes have limited carrying capacity, making it difficult to precisely control the types and doses of antigens. Although they are easy to operate and retain their natural properties, their efficacy and specificity still need to be optimized for practical application [19].

3.2. Cell engineering

Genetic engineering or chemical modification of parent cells can remarkably enhance the vaccine delivery function of derived exosomes [20]. This strategy is widely applied in antitumor vaccine research; for example, exosomes secreted by dendritic cells overexpressing tumor-associated antigens can effectively activate $CD8^+$ T cell-mediated antitumor immune responses [21]. However, this method has concerns about the stability and safety of exogenous gene expression, and cell culture conditions need to be optimized for large-scale production, and there are still bottlenecks in the application of the technology [22].

3.3. Exosome loading strategy

The loading methods of exosome vaccines mainly include three types: physical, chemical, and covalent binding [23]. The core characteristics are compared as follows (Table 1), and the method selection should take into account the nature of the cargo, loading efficiency, and the impact on vesicle integrity.

Table 1. Comparison of the core characteristics of different exosome loading methods

Method Type	Represents technology	Advantages	Limitations
Physical method	Electroporation, ultrasound	Easy to operate, universal	Improper parameters may damage the membrane structure and affect stability
Chemical method	Saponin permeation, hydrophobicity	It causes less membrane damage and has good compatibility	Loading efficiency is greatly affected by reagent concentration, and the applicable range is limited
Covalent binding	Amidation reaction	Precise localization, high controllability, and strong immunogenicity	The reaction conditions are harsh and may alter the surface properties of exosomes

4. Research applications of exosomes in different types of vaccines

4.1. Antiviral vaccines

Exosomes have shown good application potential in the development of a variety of antiviral vaccines. In COVID-19 vaccine research, engineered exosomes can efficiently carry S protein or RBD antigens of SARS-CoV-2 [24]. With superior structural stability, they can simultaneously trigger T-cell immunity and neutralizing antibody responses, thereby enhancing immunogenicity and lowering adverse reaction risks [25]. For influenza viruses, exosomes can target and deliver HA and NA antigens to dendritic cells and co-deliver multiple subtype antigens, providing a new direction for universal influenza vaccines [26]. In the field of Ebola virus vaccines, exosomes modified to load glycoproteins (GP) can induce specific immunity. Although there are still challenges in antigen

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loading efficiency and long-term stability, they have important research and development prospects [27].

4.2. Anti-tumor vaccines

Exosomes are widely applied in antitumor vaccine research owing to their diverse cellular sources and modification approaches. Dendritic cell-derived exosomes can efficiently present tumor antigens and activate T cells via surface MHC and co-stimulatory molecules. Meanwhile, they feature simple preparation and convenient storage, compensating for the limitations of conventional DC vaccines [28]. Tumor cell-derived exosomes naturally carry tumor-associated antigens and can further enhance the immune effect after loading adjuvants such as GM-CSF, but attention should be paid to their potential tumor-promoting risks and long-term safety [29]. Engineered exosomes can express molecules such as IL-12 and PD-L1 antibodies through gene editing, or co-load drugs and siRNA for combined therapy to regulate the tumor microenvironment, yet they still face challenges including complicated preparation procedures, high cost and difficulties in scaled-up production [30].

4.3. Bacterial vaccines

4.3.1. Bacterial antigen vaccines

Exosomes can efficiently present bacterial antigens and activate host immunity, providing new avenues for the development of bacterial vaccines [31]. Loading bacterial antigens such as lipopolysaccharides and outer membrane proteins into exosomes can significantly enhance immunogenicity and induce strong humoral and cellular immune responses [32], and their surface molecules can also promote binding to immune cells and improve antigen presentation efficiency. Studies have verified that exosome vaccines loaded with Streptococcus pneumoniae hemolysin can induce high levels of neutralizing antibodies, effectively prevent bacterial infections, exhibit favorable biosafety, and avoid endotoxin contamination [33].

4.3.2. mRNA vaccines

Exosomes protect mRNA from enzymatic hydrolysis and enable efficient delivery through natural intercellular communication, significantly enhancing the immune effect of bacterial mRNA vaccines [34]. These vaccines activate the immune system by expressing bacterial antigens, and the low immunogenicity and high biocompatibility of exosomes make them ideal delivery vectors [35]. However, there are still problems such as insufficient mRNA loading efficiency and short in vivo half-life, which need to be further optimized [36].

5. Challenges and prospects for future development

5.1. Production standardization challenges

Mass production of exosomes is a prerequisite for clinical application, but there are many technical bottlenecks. Cell culture conditions and other factors affect their yield. Optimizing culture parameters can boost exosome secretion efficiency, yet it entails high costs and complicated experimental design, making industrial-scale application difficult [37]. Although advances have been achieved in production platforms such as microfluidic systems and bioreactors, a considerable

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gap still remains before economically viable scaled-up production can be realized [38]. At the same time, there is no unified standard process for the separation and purification of exosomes. Common separation methods such as ultracentrifugation and immunoaffinity capture have their own technical shortcomings and it is difficult to obtain the high-purity exosomes required for clinical application [39]. On the one hand, separation techniques with high automation and good result repeatability need to be developed. On the other hand, it is necessary to establish a standardized and unified separation and purification operation process to comprehensively evaluate the final quality of the product through multiple detection indicators.

5.2. Safety and ethics

Safety and ethics issues in industry regulation are particularly critical in the clinical translation and application of exosome vaccines. Each major source of exosomes has distinct limitations. Rational source selection should be conducted following scientific screening and comprehensive risk assessment in accordance with clinical therapeutic demands [40]. As novel biological products, exosome vaccines cannot be fully accommodated by existing regulatory frameworks. Currently, unified quality control standards are absent, and full-process supervision of production remains challenging. It is necessary for colleges, enterprises and regulatory agencies to collaborate to improve regulatory guidelines, introduce professional quality management systems and full-process traceability technologies, and promote the compliant development of products.

6. Conclusion

Benefiting from their unique biological characteristics, exosomes have achieved remarkable advances in the research and development of antiviral and antitumor vaccines. Nevertheless, their clinical translation is still hindered by inadequate standardization of production and quality control, safety and ethical disputes, and the lack of compatible regulatory systems. In the future, efforts should be focused on technological optimization to enhance the targeting and comprehensive functionality of exosomes through precise loading and gene editing, explore combined treatment regimens to overcome tumor drug resistance, and develop customized vaccines based on personalized medicine. After breaking through the dual bottlenecks of technology and regulation, exosome vaccines are expected to play a core role in disease prevention and control and promote innovative development in the fields of vaccinology and biomedical materials.

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Although this article aims to provide a comprehensive review of the research progress of exosomes in vaccine delivery, due to my limited ability, there may be some shortcomings, and I sincerely ask readers to criticize and correct them. It is hoped that this article will provide valuable references for subsequent research and promote the further development of the exosome vaccine delivery system.

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