

Dendritic Cell Exosome Vaccine's Research Progress in Oncotherapy

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Abstract. Dendritic Cell-derived Exosomes (DEX) are nanoscale (30-140 nm) extracellular vesicles secreted by dendritic cells (DC), carrying key immune-active components such as MHC-I/II class molecules, costimulatory molecules, and tumor antigens. It has the ability to present natural antigens. Its lipid bilayer structure not only protects the stability of the contents but also enhances the efficiency of penetrating biological membranes and promotes the uptake of antigens by dendritic cells or T cells. Traditional anti-tumor vaccines, such as tumor cell lysate vaccines and peptide vaccines, have drawbacks like immunosuppression and targeting a single antigenic epitope. However, DEX vaccines can make up for these deficiencies through engineering modifications and other means. Other new types of vaccines, such as mRNA vaccines, have their delivery efficiency limited by vectors, while DEX vaccines have a natural membrane structure and possess the advantages of both efficient delivery and low toxicity. Compared with DC cell vaccines, DEX has no cellular structure, avoiding the problem of live cell preservation, is not affected by immunosuppression, and can further enhance its immune activation ability through genetic engineering modification.

Keywords: Dendritic cells exosomes, tumor vaccines, immune checkpoint inhibitors, engineering modifications

1. Introduction

Tumor immunotherapy has shown breakthrough potential in clinical applications. Among them, Dendritic Cells (DCs) have become the core carriers in the research and development of tumor vaccines due to their outstanding antigen presentation ability and immune activation function. However, the clinical application of traditional DC vaccines is still limited by problems such as interference from the immunosuppressive microenvironment and difficulties in large-scale preparation. In recent years, exosomes have gradually become a hot topic in the research of new vaccine vectors. Dc-derived exosomes (DEX) not only inherit the immune activation characteristics of DCs, but also possess excellent low immunogenicity and cross-biological barrier ability, providing a brand-new strategy to overcome the limitations of traditional DC vaccines.

This study aims to systematically review the latest research progress of dendritic cell exosome vaccines (DEX vaccines) in tumor treatment, clarify their immune activation mechanisms and therapeutic potential, analyze current technical bottlenecks and clinical transformation challenges,

and explore optimization strategies. This article will conduct a review from aspects such as the biological characteristics and advantages of DEX vaccines, as well as the research progress in clinical applications. The DEX vaccine has unique advantages in tumor immunotherapy. The research results will provide a scientific basis for promoting the transformation of the DEX vaccine from the laboratory to clinical practice and lay the foundation for it to become a candidate for the next generation of personalized tumor vaccines.

2. Biological characteristics of DEX and tumor vaccines

2.1. Structure and function of DEX

DEX is a nanoscale vesicle secreted by dendritic cells, with a diameter of approximately 30-150 nm. It is rich in antigen polypeptide fragments, major histocompatibility complexes (MHC), co-stimulatory molecules, and tumor antigens, etc. DEX plays a significant role in anti-tumor immunity by presenting antigens and activating T cells. The tumor antigens it carries can directly activate cytotoxic T lymphocytes (CTLs) and induce specific anti-tumor immune responses. In addition, DEX can also inhibit the function of immunosuppressive cells and enhance the anti-tumor effect. Studies have shown that DEX has potential application value in the development of tumor vaccines.

2.2. Advantages of DEX vaccines

Compared with traditional tumor vaccines such as DC cell vaccines, DEX vaccines have obvious advantages. Firstly, the DEX vaccine can more effectively activate T cells and NK cells. The pMHC complexes present on the surface of DEX vaccines are 10 to 100 times more than those in DCs, which can bind to T-cell receptors more fully and enhance the activation signals of T cells. Moreover, exosomes are convenient for genetic modification and can easily reach the required locations of secondary lymphoid organs. Their enrichment in these sites enables them to fully contact T cells and NK cells, thereby enhancing the activation efficiency. Secondly, DEX vaccines are easier to store in vitro for a long time. Because of its relatively simple structure and function, lower requirements for the external environment compared to intact cells, and simpler preparation than DC vaccines, it is easier to preserve in vitro. Finally, DEX does not respond to immunosuppressive molecules due to its lack of complete cellular signaling pathways and its rich content of immune-activating components.

3. Methods for the separation and purification of exosomes

In the research and development process of exosome vaccines, the difficulty in extracting exosomes with high purity and efficiency is a limiting factor. At present, there are various methods for the separation and purification of exosomes, including size exclusion chromatography, microfluidics, ultracentrifugation, ultrafiltration, polymer precipitation, and immunoaffinity, etc [1]. This article mainly introduces size exclusion chromatography and microfluidics.

3.1. Size-exclusion chromatography

Size-exclusion chromatography (SEC) is a method of separating substances based on their hydrodynamic radius and is currently the most widely used size-based separation technique. The principle is that gel particles with different pore sizes are used as the stationary phase. When the sample flows through the chromatographic column, the smaller the diameter, the stronger the ability

to penetrate into the gel matrix, the longer the retention time in the chromatographic column, and the longer the elution time. Because the diameter of exosomes is relatively small, the effluent of exosomes can be obtained by controlling the time for collecting the effluent. This method has obvious advantages. Experiments show that it only takes about 20 minutes to complete the separation of exosomes with a recovery rate of 43%. Compared with the super-speed centrifugation method that lasts for dozens of hours, it greatly saves the separation time.

However, the SEC also has limitations. Firstly, due to its narrow application range, it is not suitable for large-volume samples or mass production. Secondly, based on its principle, the effluent inevitably contains contaminant particles of the same size as the target exosomes, which limits the purity and is not conducive to subsequent research. At the same time, the eluent will dilute the sample, resulting in a lower concentration of the final product. Guo et al. designed a binary SEC method. This method uses Sepharose CL-6B packing material to enhance the separation efficiency of SEC columns for exosomes and simplify the separation process. It only takes about 20 minutes to efficiently separate high-purity exosomes from complex body fluids such as serum/plasma.

3.2. Microfluidic method

Microfluidic method is an important technique for capturing exosomes based on their hydrodynamic characteristics, through size screening, binding to specific affinity substances and other means. With continuous development, it is possible to integrate various components onto a single chip. Although the device is more complex and costly, it breaks the limitation of being inseparable from a complete laboratory, which is conducive to the future development of integration and automation.

This technology can be divided into two major categories: microcurrent control methods based on biological characteristics and microcurrent control methods based on physical characteristics. The former mainly relies on immune affinity and the specificity of aptamers; the latter mainly achieves separation and purification through physical properties such as the size, density and charge of exosomes. Wang et al. combined acoustics with microfluidic technology for the separation of saliva exosomes. Experimental data show that this method can stably separate saliva exosomes from samples without being affected by saliva viscosity and other factors, and the average yield is 15 times higher than that of the traditional ultracentrifugation method [2]. Shi et al. developed a novel insulating structure dielectric moving device that can separate exosomes from 200 μL of samples within 20 minutes at a relatively low (10 Vcm^{-1}) direct current [3]. All these demonstrate that the microfluidic method has a promising future.

4. Clinical treatment of DEX vaccine

4.1. Current status of clinical

Treatment DEX has demonstrated good therapeutic effects in current clinical trials, with patients' conditions under control and to a certain extent, it can enhance patients' autoimmune responses. At present, there are three clinical trial reports on the application of DEXs in treatment [4-7]. In the Phase I clinical trial, DEXs obtained from immature monocyte-derived DC(MoDC) were used as the source of cancer vaccines.

In the Phase I clinical trial of advanced non-small cell lung cancer ($n=9$), after patients received this treatment, only grade 1 to 2 toxicity was observed and no autoimmune response was observed. In the peripheral blood of some patients, the activity of NK cells was significantly enhanced. It is

worth noting that 33.3% of the subjects were induced with specific T-cell immune responses. In two patients, the proportion of regulatory T cells (Tregs) in the total CD4⁺T cells increased.

In the clinical trial on malignant melanoma (n=14), the activity of NK cells in the peripheral blood of patients treated with the DEX vaccine was enhanced, and the condition could be stably controlled for up to 24 months. Among them, the tumor volume of one patient was significantly reduced.

To address the issue of weak specific T-cell responses in clinical trials, exosomes derived from mature DCs were adopted as the vaccine source. Therefore, in subsequent clinical trials, interferon- γ was used to stimulate human MoDC to promote DC maturation, thereby enhancing its ability to activate specific T-cell responses.

To investigate the impact of DEXs on progression-free survival, 22 patients with advanced tumors who responded to platinum-based chemotherapy were included in the Phase II clinical trial. The results showed that 32% of the patients had their conditions stably controlled after nine doses of DEXs vaccination, but the primary endpoint of survival (PFS) of this trial did not reach 50%. Fortunately, one patient's tumor showed a long-term stable state, meeting the conditions for surgical resection and receiving local adjuvant radiotherapy in the later stage.

However, clinical trials have also revealed some problems. First, the purity of exosomes is relatively poor, and the number of cells that can produce exosomes in vitro is limited. Therefore, the technology for isolating and purifying exosomes as well as the capacity for in vitro culture should be enhanced. Second, the multiple effects and complex mechanisms of DEX on the immune system are not yet fully understood. Thirdly, standardized guidelines for the production and application of DEX vaccines have not yet been established.

In conclusion, clinical trials of DEXs vaccine treatment have demonstrated its good safety and tolerability, and some patients have achieved stable disease control. However, due to the small number of patients participating in the DEXs vaccine clinical trial, the observed therapeutic effect was limited. However, the DEXs vaccine still has broad prospects for development.

4.2. Engineering modification strategies

Currently, cancer treatment still requires the use of chemical drugs for combined therapy. However, due to poor water solubility, premature degradation or drug resistance, the drug is difficult to exert its expected effect. However, after the engineering modification of exosomes, enabling them to carry chemical drugs into the body can greatly alleviate these problems. On the one hand, it can reduce drug resistance. Xu et al. found that exosomes containing mi RNA-451a significantly reduced drug resistance to paclitaxel and promoted apoptosis of cancer cells by inhibiting epithelial-mesenchymal transition [8]. On the other hand, engineered and modified exosomes can reduce the sensitivity of cancer cells to chemical drugs. Lou et al. studied the construction of exosomes containing mi R-199a modification [9,10]. This engineered exosome was confirmed to improve the sensitivity of liver cancer cells to doxorubicin through the mTOR pathway.

4.3. Combination therapy

Currently, cancer treatment relying solely on a single treatment approach is unlikely to be effective. Combining multiple treatment plans can effectively enhance the therapeutic outcome. In preclinical and clinical studies, it has been demonstrated that the combination of DEXs vaccine and cyclophosphamide treatment can effectively reduce Tregs function and stimulate T cells that produce dual interferon- γ /interleukin-17. In addition, multiple combination treatment regimens are

in the preclinical research stage, including popular treatment options such as immune checkpoint blockade.

5. Conclusion

DEX vaccines, as an emerging strategy in the field of tumor immunotherapy, have demonstrated significant potential for clinical transformation. This study systematically summarizes the research and development progress of DEX vaccines and reveals their core advantages in overcoming the limitations of traditional DC vaccines. On the one hand, the tumor antigens, MHC molecules and immune activation signals naturally carried by exosomes can efficiently initiate antigen-specific T-cell responses. On the other hand, its nanoscale size, low immunogenicity and cross-biological barrier capability provide technical support for targeted delivery and long-term immune memory. However, the wide application of DEX vaccines still faces multiple challenges. First, the complexity of the tumor immunosuppressive microenvironment may weaken the efficacy of monotherapy, and combination treatment strategies (such as immune checkpoint inhibitors, radiotherapy or metabolic intervention) need to be developed. Secondly, the stability and in vivo metabolic kinetics of exosome engineering modification technology still need to be further optimized. In conclusion, with the deep integration of basic research and clinical practice, DEX vaccines are expected to become the core technology of the next generation of tumor vaccines, providing a brand-new solution for improving patient prognosis and achieving long-term immune monitoring.

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