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Recent Advances of Emerging Spleen-Targeting Nanovaccines for Immunotherapy

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Vaccines provide a powerful tool to modulate the immune system for human disease prevention and treatment. Classical vaccines mainly initiate immune responses in the lymph nodes (LNs) after subcutaneous injection. However, some vaccines suffer from inefficient delivery of antigens to LNs, undesired inflammation, and slow immune induction when encountering the rapid proliferation of tumors. Alternatively, the spleen, as the largest secondary lymphoid organ with a high density of antigen-presenting cells (APCs) and lymphocytes, acts as an emerging target organ for vaccinations in the body. Upon intravenous administration, the rationally designed spleen-targeting nanovaccines can be internalized by the APCs in the spleen to induce selective antigen presentation to T and B cells in their specific sub-regions, thereby rapidly boosting durable cellular and humoral immunity. Herein, the recent advances of spleen-targeting nanovaccines for immunotherapy based on the anatomical architectures and functional zones of the spleen, as well as their limitations and perspectives for clinical applications are systematically summarized. The aim is to emphasize the design of innovative nanovaccines for enhanced immunotherapy of intractable diseases in the future.

1. Introduction

In the past few centuries, the discovery of vaccines has provided a powerful solution to modulate the immune system for disease prevention and treatment.[1] The World Health Organization estimates that vaccines save more than 2 million lives around the world every year.[2] Typically, prophylactic vaccines, including live-attenuated or inactivated pathogens, have effectively prevented numerous infectious diseases such as smallpox, diphtheria, poliomyelitis, tetanus, and rabies.[3] Furthermore, therapeutic vaccines have also attracted much attention for treating cancer and other illnesses in recent decades.[4] These vaccines deliver personalized antigens from patients to professional antigen-presenting cells (APCs) such as dendritic cells (DCs) and macrophages (MΦs), thus activating the naïve lymphocytes, including natural killer (NK) and T cells, to initiate the adaptive immune responses for cancer treatment.[5] Despite the great success of vaccines, some of them are less effective for recipients with hypoimmunity or immunodeficiency,[6] and may even cause adverse reactions after vaccination.[7] Some patients may undergo hypersensitivity due to individual vaccine components, while others may encounter antibody-dependent enhancement that increases the severity of infectious diseases after vaccination.[8] Additionally, the development of successful vaccines to provide long-lasting efficacy at the population level against several fatal pathogens, including human immunodeficiency virus, dengue virus, and plasmodium, still remains challenging in clinics owing to the complexity of disease pathogenesis.[9] Therefore, innovative vaccines are highly demanded based on the principles of vaccination to improve the recipients' immunity against multiple diseases and minimize the unwanted side effects.[10]

Secondary lymphoid organs, including lymph nodes (LNs) and spleen, are the most important places for vaccines to initiate adaptive immune responses in vivo.[11] In these organs, foreign or autologous antigens are captured and transported by APCs,[12] following the spatiotemporal activation of T and B cells effectively.[13] The efficacy of vaccines is highly dependent on the routes and sites of administration, where the initial immune response embarks.[14] Conventional vaccination strategies such as intramuscular or subcutaneous (SC) administration generate prolonged adjuvant and antigen depots at the injection site to recruit APCs (e.g., Langerhans cells) in the skin,[15] which may induce local inflammatory nodules or undesired hypersensitivity.[16] Thereafter, antigen-carrying APCs travel to the draining LNs (dLNs) via afferent lymph vessels to evoke naïve T and B cells in their specific sub-regions,[17] which is the main rate-limiting step in the vaccination process.[18] Further studies have confirmed that the targeted delivery of vaccines directly into LNs could enhance cancer immunotherapy.[19] Nevertheless, the insufficient efficiency of antigen delivery to dLNs and slow immune induction have been considered bottlenecks in improving the speed and strength of adaptive immune responses in vaccines against several diseases, especially fast-growing tumors.[20]

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contamination) of the nanovaccines.[121] In addition, the manufacturing procedure of nanovaccines is complicated as it requires several processes involving multiple components (e.g., antigens, delivery nanocarriers, and adjuvants) and variables (e.g., concentration, pH value, and temperature) before being formulated into the final products.[122] Therefore, the scale-up procedures for nanovaccines need to be completely reconstituted in the factories.

So far, spleen-targeting vaccines have not been approved by the Food and Drug Administration in the US. The emerging nanovaccine could precisely deliver antigens to the spleen via IV injection, followed by rapid DCs activation for antigen-specific cellular and humoral immune responses. Comparing with the conventional vaccination process in the LNs, this approach induces faster immune responses and stronger immunotherapy efficacy due to the highest density of APCs and slow blood circulation rates in the spleen for enhanced antigen capture. So the spleen-targeting nanovaccine is ideally suitable for the treatment of emergency pandemics caused by infectious viruses, or tumors with rapid proliferation in clinics. Recently, several innovative spleen-targeting nanovaccines have been demonstrated for enhanced cancer immunotherapy. For instance, Pan et al. designed a novel nanovaccine to deliver OVA mRNA and TLR agonists into the spleen after IV administration, resulting in a sufficient and persistent anti-tumor cellular immune response.[123] Gu et al. developed a spleen-targeted polymersome as nanovaccine to dramatically boost splenic immune responses in both acute myeloid leukemia, melanoma, and lung metastasis mouse models.[124] We expect to see these innovative formulations for both prophylactic and therapeutic vaccines be approved for clinical applications soon.

In conclusion, the spleen-targeting nanovaccines provide an appealing perspective for enhanced immunotherapy as compared to conventional LNs-targeting vaccines in clinics. Benefiting from the high density of APCs and lymphocytes in the spleen, spleen-targeting nanovaccines appear to be a promising approach for rapid and efficient antigen presentation to elicit robust cellular and humoral immunity. The successive progress of spleen-targeting nanovaccines will facilitate the effective protection and treatment of various intractable diseases, especially for rapid tumor proliferation and mutated viruses infection in the future.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

antigen presentation, immunotherapy, nanovaccines, spleen, targeting

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