

Emerging role of vaccines in cancer therapies

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Abstract. A vast array of illnesses, characterized by abnormal cells that proliferate without restraint and can invade and annihilate regular human tissue, is known as cancer. This malady has the capacity to spread throughout the body. Many biological and experiments basis are needed to develop cancer vaccine, research programs and experimental methods may also be indispensable. There is no doubt that many clinical trial protocol (CTP) have no enough immunogenicity, lead to few clinical responses can be found and researched, this has a great negative impact on research, this has a great negative impact on research. However, many breakthrough advances have been achieved, which support the interest in cancer vaccinations. Regrettably, the unpredictable nature of cancer, particularly in those suffering from its late stages, presents numerous constraints and the possibility for tumors to develop resistance. Moreover, cancer vaccines need to be more specificity because the immune system which is different between people. A review of the clinical development of cancer vaccines, with an examination of the successes and failures, and a look at how the past experience and progress in science and technology have influenced attempts to enhance vaccines, is provided here, as well as a clinical outlook on the potential role of vaccine therapies for cancer in the future. Also, this review explores the mechanisms of cancer vaccines, various delivery methods, and the role of adjuvants in improving treatment outcomes.

Keywords: Vaccine; cancer; therapy.

1. Introduction

The dread of cancer, a broad term for a variety of malignant tumours and neoplasms, is pervasive in human life. Its defining characteristic is the swift emergence of abnormal cells that expand beyond their usual limits, and can then invade neighboring organs and metastasize - a process known as metastasis. The primary cause of cancer-related death is widespread metastases. Currently, 30%-50% of cancers can be prevented by taking precautions against risk factors and using existing evidence-based prevention strategies. Furthermore, the burden of cancer can be reduced by early detection and proper treatment and care of cancer patients. If early diagnosis and proper treatment are achieved, many cancers are likely to be cured. The revolutionization of multiple cancer types and the illumination of cancer patients due to the advent of immunotherapy was deemed the 'breakthrough of the year' in 2013 by the successful translation of fundamental research into clinical treatments, as well as its straightforward yet sophisticated approach [1]. The role of cancer immunotherapy was predominantly underrated in the 20th century on account of the lack of a known mechanism in the field, meanwhile, the routes to develop appropriate clinical schemes are full of twists and turns.

William B. Coley, an American surgeon recognized as a pioneer in immunotherapy, ventured first in the late 19th century to manipulate the immune system to treat inoperable cancer patients. Injecting a combination of live and inactivated bacteria, such as *Streptococcus pyogenes* and *Serratia marcescens*, referred to as "Coley toxin," Coli discovered that cancer patients provoked a powerful immune reaction that inhibited tumor growth. The trial is believed to be the first documented anti-cancer immunotherapy intervention in history. However, due to the lack of understanding of the complex humoral immune system at the time and the significant advancement of traditional treatments, the next revolutionary wave of cancer immunotherapy came at the end of the 21st century, until a consensus was reached that it was recognized that enhancing innate defenses to eliminate malignant cells was a milestone in cancer treatment. The amazing progress made in the field of cancer vaccines has caused them to garner much attention in recent years. This review will explore the types and delivery systems of cancer vaccines, as well as the difficulties they confront.

2. Cancer Vaccines

2.1. Peptide- and Protein-Based Vaccines

Peptide-based vaccines are relatively easy to manufacture, but combination with potent immune adjuvants is often needed to boost immunogenicity, and the number of people who may benefit from a given peptide vaccine is restricted by human leukocyte antigen (HLA) haplotype [2]. Several phase 3 studies investigating early peptide-based vaccines have not demonstrated clinical benefit despite demonstrating some induction of immune responses against TAAs or TSA [3]. The properties of the peptides and adjuvants employed could explain why there was no clinical advantage, and early peptide vaccines may have been inadequate in promoting antigen presentation and creating powerful and enduring anti-tumor immunity [1, 2].

2.2. Cellular Vaccines

DC cells, also known as dendritic cells, were first isolated from the spleen by scientists in 1973. With in-depth research on DC biology and its immune response mechanisms, the development of DC vaccines is becoming increasingly rapid.

Studies indicate that antigens produced by tumors, encompassing those unique to cancer cells, may be introduced to dendritic cells (DCs), eliciting immune reactions in a controlled laboratory setting. For the past two decades, dendritic cell-based vaccines have been utilized in a variety of cancer treatments, including breast, multiple myeloma, prostate, renal, malignant melanoma, colorectal, and non-small cell lung cancers. Numerous studies have suggested that a DC vaccine with a component of antigen is a secure and optimistic approach to tumor treatment [4].

2.3. Genetic Vaccines

Lately, the field of vaccine development through genetic manipulation has emerged as a focal point for scientific investigation. The product of cloning a gene fragment encoded by the protective antigen of the pathogen into the expression vector, transfecting cells or eukaryotic and prokaryotic microorganisms, is a genetic engineering vaccine [5, 6]. Or delete the Virulence Related Genes of the pathogen to make it a gene deletion vaccine without virulence related genes. Viral vector and bacterial vector vaccines are the main components; many viruses, such as adenovirus and poxvirus, are utilized as vectors for recombinant vaccines. The bacterial carriers are mainly *Listeria* and *Salmonella*. This vaccine's benefits include its safety and efficacy, the absence of adjuvant requirements, and its emulation of antigen expression post-infection, thereby eliciting B cell and T cell immune reactions; it is also characterized by its specificity, as the immune responses it prompts are uniquely tailored to target a particular antigen; moreover, it triggers a rapid response.

2.4. mRNA Vaccine

As one of the technologies leading the research and development of the new crown vaccine, compared with the traditional vaccine, mRNA vaccine has its own advantages. First, mRNA does not enter the nucleus and will not insert into the genome, avoiding insertion mutations; moreover, the mRNA vaccine actually uses the body cells to produce antigen proteins, skipping the process of cell culture, antigen extraction and purification, greatly reducing the cost and increasing the production capacity. Specifically, one bioreactor can produce nearly 1million doses of mRNA vaccines in a single reaction; In addition, a single mRNA vaccine can encode a variety of antigens, which has a broad application prospect in viruses that are prone to mutation such as influenza and neocoronavirus.

In 1961, scientists first discovered mRNA and knew its role [7]. Out of concerns about its stability and immune stimulation, mRNA was not initially considered as a potential therapeutic means. The covid-19 pandemic saw mRNA technology's brilliance, which had been greatly advanced in the area of disease prevention and treatment, due to the resolution of the issues of delivery and immunogenicity [8].

A bridge of DNA and protein, messenger ribonucleic acid (mRNA) serves as a fleeting copy of genetic information. Consistent with endogenous mRNA, in vitro transcribed mRNA also contains five parts: 5' cap structure, 5' untranslated region (UTR), protein coding open reading frame (ORF), 3' UTR and poly (a) tail. mRNA in vitro transcription (IVT) takes DNA as template (such as linear plasmid), transcribes and synthesizes under the action of RNA polymerase, and adds 5' end cap and poly (a) tail to obtain mRNA (Figure1).

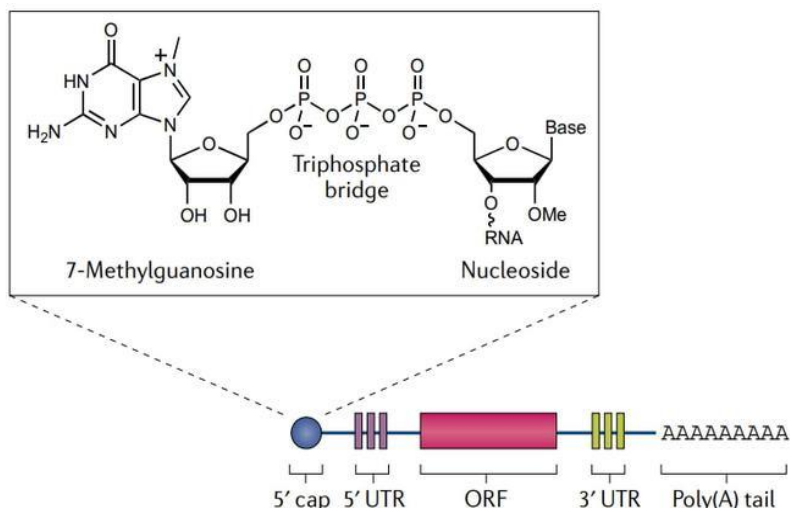


Fig 1. Components of mRNA vaccines [9].

Cap structure is a special structure located at the 5' end produced by eukaryotes in the process of post transcriptional modification. A triphosphate bridge links the 5' end of mRNA to a 7-methylguanosine, which is encapsulated within the 5' end cap. This structure encases the mRNA to protect it from exonucleases' destruction, as well as stimulating MRAN circularization and enlisting ribosomes to initiate translation.

The untranslated region (UTR) includes 5'UTR and 3' UTR, which can regulate the translation and half-life of mRNA. The 5'UTR, situated between the cap structure and the ORF of the coding region, has a considerable impact on the efficacy of translation initiation due to its length and secondary structure. The 3'UTR, situated downstream of the ORF in the coding region, before the stop codon, is a significant functional element of eukaryotic mRNA, playing a critical role in translation regulation and mRNA localization.

Beginning at the start codon and ending at the stop codon, the ORF of the coding region is composed of three bases, each encoding an amino acid. If too many secondary structures and rare codons are present, the translation efficiency will be diminished. To counter this, CureVac, one of the "mRNA big three", substituted the A or u at the third position in the ORF with the more common g or C, and applied this optimization strategy to its covid-19 candidate vaccine concave. But sometimes, rare codons with slow translation are necessary to ensure the accurate folding of proteins, so the use of this replacement method should be cautious.

A poly a sequence, the 3'UTR tail, is analogous to the cap structure. This tail can also guard mRNA from exonucleases' degradation. Furthermore, it is involved in the translation and its regulation, combining with polyadenylate binding protein (PABP) to form a circular complex and initiating translation.

Scientists such as Katalin Karki ó found that adding modified nucleosides (pseudouridine, N6 methyladenosine, and 5-methylcytidine) into mRNA can greatly improve the translation of mRNA. In addition, modified nucleosides also play an important role in inhibiting RNA degradation, improving translation efficiency and regulating half-life. Pattern recognition receptors recognize unaltered mRNAs, like viral RNAs, thus stimulating the immune system.

Pfizer/BioNTech's mRNA vaccine bnt162b2 and Moderna's mrna-1273 both use nucleoside modification technology to replace uridine with pseudo uridine. The mRNA vaccine concave of

CureVac uses unmodified natural mRNA to change the mRNA sequence and optimize codons through its inactive platform to improve the stability and immunogenicity of mRNA [10].

3. Delivery System of Vaccine

The instability of RNA structure and its susceptibility to degradation by enzymes are both inherent. Furthermore, mRNA is a negatively charged long-chain macromolecule, and the cell membrane is also negatively charged, making it difficult for it to enter the cell. Consequently, the same as with other nucleic acid drugs, the delivery issue must be addressed to ensure the widespread use of mRNA. Electroporation, gene gun and other technologies can realize the intercellular delivery of mRNA in culture dishes. To achieve in vivo delivery, it is necessary to use safe, non-toxic and low immunogenicity carriers. At present, LNP is the mRNA delivery carrier with the fastest clinical progress. At this stage, most of the mRNA vaccines approved for marketing and under development are delivered by LNP technology. In addition to mRNA, LNP mainly includes four parts: ionizable lipids, pegylated lipids, neutral auxiliary phospholipids, and cholesterol. These four parts constitute the umbrella of "fragile" mRNA. In addition, cationic nano emulsion, protamine, peptides and dendritic cells have also been developed for in vivo delivery of mRNA.

Currently, there are various other delivery systems in development. Dimensions akin to those of microbial pathogens are exemplified by nanoparticles and microparticles. Such particulate delivery systems can be made from various materials, such as polylactide co-glycolide (PLG), immune stimulating complexes (ISCOMs) (a mixture of cholesterol, phospholipids and Quillaja saponins), chitosan (a chitin-derived polyaminosaccharide), polyanhydrides, hyaluronic acids, starch, proteins or synthetic materials such as polyethylene glycol and polystyrene.

The induction of T helper cell-dependent IgG responses, lasting for a long time, is the foundation of the triumph of the majority, if not all, prophylactic vaccines. Hence, the main focus of classical vaccine development is the optimization of B cell responses. In stark opposition, vaccines for treating chronic illnesses or cancer are based on the activation of strong pro-inflammatory CD4⁺ and CD8⁺ T cell reactions. Hence, for prophylactic and therapeutic vaccines different design strategies are often used.

4. Current Strategies and Scientific Advances Appropriate Antigen

The limited success of therapeutic cancer vaccines despite decades of development by academia and industry raises the questions of why expectations have not been fulfilled and how barriers to successful development can be overcome [3]. Recent advances in understanding antigen immunogenicity, the part played by antigen presentation, and how cancer cells evade and suppress the host's immune response point to the possibility that prior studies may have used inadequate antigen targets, vaccine strategies, and trial methodologies - including the choice of patient groups [4].

In 2015, Melief et al. formulated a list of attributes that cancer vaccines would need to have to be successful. In brief, these attributes stress the importance of broad stimulation of CTLs and T helper cells through two mechanisms: (1) selection of appropriate antigens that induce both T cell populations and (2) rational vaccine designs that achieve concentrated delivery of tumor antigens to activated DCs. Locations where external cancer antigen fragments can be presented via MHC class I molecules by the cross-presentation route and on MHC class II complexes to activate cytotoxic T lymphocytes and T helper lymphocytes accordingly [5]. Over the last decade, therapeutic cancer vaccine strategies have improved, incorporating better immunogenicity, antigen selection, and structural design to meet these criteria.

The development of a therapeutic cancer vaccine is contingent upon the existence of either tumor-associated antigen (TAA) or tumour-specific antigens (TSAs). This vaccine, unlike prophylactic vaccines which are utilized to combat viruses, seeks to activate the immune system to launch an

assault on cancer cells or tissues in the body. Until now, the majority of cancer vaccines have been directed at TAAs, which are self-proteins that are not normally expressed by cancer cells; yet, before creating vaccines against TAAs, there must be a number of challenges surmounted. For example, immune cells may recognize TAAs as self-antigen, remove them from the immune repertoire, leading to failure in immune responses. The specific reaction of TAA antigens to immune cells has caused them to be the focus of much attention, as they are exclusive to tumour cells. However, due to uniqueness of neoantigens to each patient and tumour type, further optimisation needs to be conducted for the sake of reducing the cost and complexity of TAA vaccine.

In spite of the persistent difficulties in terms of effectiveness and security, a variety of therapeutic vaccination techniques have been formulated in the pre-clinical stage or assessed in clinical trials. Based on the platforms used in vaccine development, therapeutic vaccines are classified into various major categories. Promising alternatives to conventional vaccine approaches, mRNA vaccines are among them. Up to now, multiple mRNA cancer vaccines have been employed in various clinical trials, leading to the notion that this strategy can be broadly applicable to cancer vaccines.

Vaccine designs have evolved to elicit effective immune responses characterized by potent and broad stimulation of CTLs and T helper cells as well as enhanced antigen presentation by activated DCs. These optimizations, summarized below for the most encouraging platforms, are currently being used in the next generation of therapeutic cancer vaccines with the hope they will lead to improved immune and clinical responses compared with historical experience. Synthetic long peptide vaccination was employed by the researchers to generate a more resilient and enduring T cell response, and certain experiments were optimized [6-8].

5. Conclusions

The advent of cancer vaccines has ushered in a tremendous revolution in the treatment of cancer. Currently, efforts are still need to enhance the efficiency and safety of cancer vaccines. Critical hurdles to surmount include pinpointing appropriate antigens and vaccine vectors to elicit potent, wide-ranging T cell reactions, customizing vaccine formulations for superior antigen display by specialized antigen-presenting cells, and identifying synergistic collaborators that utilize distinct modes of action to counter the various strategies employed by cancer cells to dodge and weaken immune defenses [9,10]. The field has, in recent years, risen to the occasion, with numerous advances to antigen selection and vaccine designs being made to address this challenge. Exploratory studies, both clinical and preclinical, have examined the use of various agents such as immunotherapies, chemotherapies, and radiation treatments in conjunction with combination approaches.

Therapeutic cancer vaccines may fill a niche not currently met by conventional therapies or other immunotherapies. Evidence from medical practice indicates that immunizations are secure and capable of inducing lasting immunological recall crucial for sustained management of diseases [3]. The presence of multiple mechanisms of immunosuppression in advanced disease, combined with this experience, implies that vaccines may be especially beneficial in the early stages of the illness or in a minimal residual condition. Certainly, the observed advantages of cancer vaccines have manifested in situations involving minimal remaining disease.

References

- [1] Morse, M. A., Gwin, W. R., 3rd, & Mitchell, D. A. (2021). Vaccine Therapies for Cancer: Then and Now. *Targeted oncology*, 16(2), 121–152. <https://doi.org/10.1007/s11523-020-00788-w>
- [2] DeMaria, P. J., & Bilusic, M. (2019). Cancer Vaccines. *Hematology/oncology clinics of North America*, 33(2), 199–214. <https://doi.org/10.1016/j.hoc.2018.12.001>
- [3] Hollingsworth, R. E., & Jansen, K. (2019). Turning the corner on therapeutic cancer vaccines. *NPJ vaccines*, 4, 7. <https://doi.org/10.1038/s41541-019-0103-y>

- [4] Cheever MA, Allison JP, Ferris AS, Finn OJ, Hastings BM, Hecht TT, et al. The prioritization of cancer antigens: a National Cancer Institute pilot project for the acceleration of translational research. *Clin Cancer Res.* 2009;15(17):5323–5337.
- [5] Bijker MS, van den Eeden SJ, Franken KL, Melief CJ, van der Burg SH, Offringa R. Superior induction of anti-tumor CTL immunity by extended peptide vaccines involves prolonged, DC-focused antigen presentation. *Eur J Immunol.* 2008;38(4):1033–1042.
- [6] Melief CJM, van Hall T, Arens R, Ossendorp F, van der Burg SH. Therapeutic cancer vaccines. *J Clin Investig.* 2015;125(9):3401–3412.
- [7] Zwaveling S, Ferreira Mota SC, Nouta J, Johnson M, Lipford GB, Offringa R, et al. Established human papillomavirus type 16-expressing tumors are effectively eradicated following vaccination with long peptides. *J Immunol.* 2002;169(1):350–358.
- [8] Bijker MS, van den Eeden SJ, Franken KL, Melief CJ, Offringa R, van der Burg SH. CD8⁺ CTL priming by exact peptide epitopes in incomplete Freund's adjuvant induces a vanishing CTL response, whereas long peptides induce sustained CTL reactivity. *J Immunol.* 2007;179(8):5033–5040.
- [9] Garg AD, Coulie PG, Van den Eynde BJ, Agostinis P. Integrating next-generation dendritic cell vaccines into the current cancer immunotherapy landscape. *Trends Immunol.* 2017;38(8):577–593.
- [10] Li, Y., Wang, M., Peng, X., Yang, Y., Chen, Q., Liu, J., She, Q., Tan, J., Lou, C., Liao, Z., & Li, X. (2023). mRNA vaccine in cancer therapy: Current advance and future outlook. *Clinical and translational medicine*, 13(8), e1384. <https://doi.org/10.1002/ctm2.1384>