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Review Article

Therapeutic Vaccination and Cancer Immunotherapy

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Abstract

Vaccine development has come center stage in the public domain given the extensive exposure it received during the COVID-19 pandemic. Although messenger RNA (mRNA) technology has been the focus of research and development efforts, particularly for oncology, for over three decades, its recent impact has enhanced the trajectory of vaccine development. mRNA technology is now at the forefront of enormous efforts focused on developing new vaccines against infectious diseases and cancer. This review outlines the current status of cancer vaccination and discusses its potential as a therapeutic modality.

Introduction

In terms of mortality, cancer ranks second among diseases. Conventional cancer treatment approaches include radiotherapy, chemotherapy, surgery, and hormone therapy, in addition to targeted drugs that reduce viability or inhibit tumor cell growth. Tumorigenesis is a complex process that depends on the supportive conditions within the tumor microenvironment (TME) as well as both genetic and epigenetic changes within the tumor cell. The TME is intrinsically involved in tumorigenesis, as it possesses tumor cells that interact with surrounding cells through the circulatory and lymphatic systems, which ultimately impact cancer development and progression. This microenvironment comprises three components: the noncellular extracellular matrix (ECM), the cellular component (both hematopoietic and non-hematopoietic), and the liquid milieu composed of hormones, growth factors, and cytokines.[1] Cancer immunotherapy works by promoting the body's antitumor immune response to remove tumor cells. By amplifying the cytotoxic activity of immune cells that target tumor cells, immunosuppression of cancer cells increases within the TME, allowing the host immune system to combat disease.[2]

Cancer immunotherapy

Cancer immunotherapy has demonstrated clinical effectiveness against multiple cancer types. Immune checkpoint inhibitors (ICIs) are main examples of this therapeutic modality. ICIs are therapeutic monoclonal antibodies that target immune checkpoint molecules, including programmed cell death protein-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 (CTLA-4). Inhibiting these key immunosuppressing molecules has substantial clinical effects on several cancer types.[3] Since many tumor types, such as pancreatic cancer, are considered "cold tumors" due to an immunosuppressive TME, these tumors can prevent immune effector cells, such as natural killer (NK) and T cells, from killing the tumor, precluding ICIs from becoming effective.[4] Using a personalized vaccine approach to turn the "cold" tumor into a "hot" tumor essentially lights up the TME, rendering it conducive for subsequent immune checkpoint inhibition.

Adoptive cell transfer (ACT) therapy is another approach to inhibit tumor growth. In ACT, functional autogenous immune cells that target human leukocyte antigen (HLA)-antigen complexes are isolated from the patient's tumor tissue. These isolated tumor-infiltrating lymphocytes (TILs) are engineered or amplified *ex vivo* and then re-administered to the patient leading to specific cytotoxicity of tumor cells expressing the targeted antigens. ACT therapy is divided into three subtypes: unmodified TILs, chimeric antibody receptor-engineered T cells (CAR-Ts), and T cells with engineered T cell receptor (TCR) fragments (TCR-Ts).[5] CAR T-cell research is advancing at a rapid speed that includes hundreds of clinical trials. To date, the Food and Drug Administration (FDA) has approved six CAR T-cell therapies for treating various blood cancers. Moreover, results from two large clinical trials have shown that CAR T-cell therapy was more effective than the standard treatment for patients with non-Hodgkin lymphoma whose cancer returned post chemotherapy.[6]

NK cells are also the focus of intense investigation as a treatment modality. The correlation between their presence within the tumor and a positive clinical benefit for patients with cancer, has been reported, along with the potential to kill tumor portions resistant to other therapies.[7] NK cells can rapidly attack

Keywords: Cancer; Immunotherapy; Vaccine; Messenger RNA; Tumor microenvironment.

Abbreviations: ACT, adoptive cell transfer; CAR-T, chimeric antibody receptor-engineered T cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; ICIs, immune checkpoint inhibitors; mRNA, messenger RNA; NK, natural killer; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; samRNA, self-amplifying mRNA; TAAs, tumor-associated antigens; TME, tumor microenvironment; TSAs, tumor-specific antigens.

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multiple adjacent cells expressing surface markers associated with oncogenic transformation. Moreover, some *ex vivo* activation and expansion methods have been translated into clinical-grade platforms, with clinical trials of NK cell administration so far yielding promising results. The expression of tumor-derived antigens, termed neo-antigens, that underpin tumor cell killing by T lymphocytes are pivotal to both ACT and ICI treatment outcomes.[8]

Neoantigens

The underpinning foundation for developing anticancer immunotherapies utilizes new proteins expressed on the cancer cell surface as a result of DNA mutations that are referred to as neo-antigens.[9] There are three categories of tumor antigens originating from different sources:

- Oncogenic virus-derived antigens;
- Tumor-associated antigens (TAAs);
- Tumor-specific antigens (TSAs, neo-antigens).

These neo-antigens can be specific for certain tumors that act as targets of spontaneous adaptive immunity and serve as precise targets. They can be harvested and isolated from a patient's tumor following tumor biopsy, and the sequence is determined using standard and sophisticated laboratory-based techniques. The identification of specific tumor antigens, in addition to T cells that recognize them, is paramount for designing appropriate vaccines and ACT-based immunotherapies. Validation using functional assays is also crucial to ensure that T cell activation occurs when it encounters a specific antigenic epitope relative to control, as binding alone may not be sufficient.[10] Several methods are utilized, including the following described below.

cDNA expression library screening

Total RNA is isolated from tumor cells, transfected into recipient cells, such as COS-7 cells, co-cultured with T cells, and assayed for cDNA recognition. Although the screen can identify most tumor antigen types, it is labor intensive and not amenable to high-throughput screening.

Next-generation sequencing (NGS)

T cells are screened using peptides derived from different cellular proteins that include those from tumor-specific mutations and screened using NGS methods, including prediction algorithm and unbiased tumor antigen screening methods.[11]

Immunopeptidomics

Peptides are eluted from MHC complexes following their extraction from tumor cells and subjected to liquid chromatography along with tandem mass spectrometry (LC-MS/MS). MS spectra are then compared with custom databases generated after combining NGS data from tumors from patients with reference protein sequences. Although capable of uncovering multiple tumor antigen classes, immunopeptidomics can be limited by overall sensitivity. Some of the better known TAAs/TSAs have been identified and targeted resulting in marketed drugs that have been proven to be clinically very effective. For example, Rituximab targets antigen CD20 on B cells and is used in the treatment of non-Hodgkin's lymphoma. Trastuzumab targets HER2 and is used to treat HER2 positive breast cancers. P2X7R promotes cancer cell growth and is a potent stimulant of inflammation and immunity, rendering it an attractive target.[12]

Developing agents targeting TAAs/TSAs is currently a very active research area, with scores of agents against many different tumor types currently being tested in preclinical and clinical settings. Neoantigens are an ideal target for cancer immunotherapy, as their recognition by T cells elicits a protective immune response, but they are not affected by central T cell tolerance. Antibodies against TAAs/TSAs can also be used as diagnostic markers in addition to their ability to kill tumor cells primarily mediated through their ADCC effects (e.g. rituximab and trastuzumab). A recent study on breast cancer highlighted the predictive value of neo-antigen load for overall survival and emphasized the importance of accurate and comprehensive neo-antigen profiling and quality control.[13]

Anti-cancer vaccines

Vaccines are biological preparations that elicit an immune response and provide active acquired immunity against a particular infectious or malignant disease. Therapeutic vaccines are different from preventative or prophylactic vaccines that are used for measles, influenza, and tuberculosis. Therapeutic vaccines are distinct as they utilize a patient's own immune system to combat an existing disease, in contrast to prophylactic vaccines that prime the immune system to protect against future disease. As an example, the prophylactic vaccine targeted against human papillomavirus (HPV) is intended to thwart the virus' ability to cause six types of cancer in both men and women. There are several other therapeutic vaccines in development, such as Canvaxin (allogeneic), GVAX (whole-tumor cell), and TroVax (antigen), that are designed to treat invasive bladder cancer, pancreatic ductal adenocarcinoma, and renal cell carcinoma, respectively.

Developing cancer vaccines is currently a major focus of cancer research. BioNTech, who developed the anti-COVID vaccine with Pfizer, were originally working on mRNA vaccines as an anti-cancer strategy. Central to this development is identifying TAAs, which are the ultimate target for designing anti-cancer vaccines. Moreover, knowledge of the TME, which allows the tumor to progress and escape the host's immune system, is paramount for designing cancer vaccines.[14]

Cancer vaccines are specific, tolerable, and safe and therefore are an attractive alternative immunotherapeutic option.[15] There are several antigen-based cancer vaccine types that employ tumor-associated proteins utilizing different delivery systems (Table 1).[16] Cancer vaccines are divided into four discrete categories based on these delivery systems: cell, peptide, viral, and nucleic acid-based vaccines.[16]

Cell-based vaccines

Cell-based cancer vaccines are often prepared from whole cells or cell fragments, resulting in a broad array of tumor antigens that induce a broad immune response. Dendritic-cell (DC) vaccines are an important arm of this vaccine category, as they have shown promising effects in the clinic. However, this approach is limited because the development process is cumbersome and expensive.

Viral-based vaccines

As viruses are naturally immunogenic, their genetic material can be altered to include sequences that encode tumor antigens. Engineered viral-based vaccines, such as an oncolytic virus, act as vectors that can present large quantities of tumor antigens to the immune system resulting in antitumor immunity. It can also lead to long-term immune memory, but the vaccine production process involved in this approach is complex.

Table 1. Vaccine types

Vaccine	Description
Live, attenuated	A weakened form of the disease-causing pathogen creates a strong and long-standing immune response. 1–2 doses can give lifetime protection against diseases such as measles, mumps, rubella (MMP), smallpox. Not ideal for people with weakened immune system, requires refrigeration.
Inactivated	A dead version of the disease-causing pathogen that can lead to elevated level of protection. Not as strong as live that may require several booster shots.
Toxoid	Utilize the toxin created by the pathogen as opposed to the actual pathogen. Used to protect against diphtheria and tetanus. May require booster shots for ongoing protection.
Viral vector	Utilize a modified version of a different pathogen (virus) as a vector to deliver protection, for example, spike protein of COVID-19 DNA inserted into a modified virus. Well established technology that leads to strong immune response involving both B and T cells. Complex to manufacture, previous exposure can reduce effectiveness.
Recombinant, subunit, polysaccharide, and conjugate vaccines	Utilize specific portions of the pathogen such as protein, sugar, or capsid (casing that surrounds the pathogen). Used to protect against hepatitis B and shingles. Strong immune response with widespread usage including people with weakened immune systems. May require booster shots for ongoing protection.
Nucleic acid-based (DNA)	Include both DNA and RNA based that can deliver multiple antigens that can induce humoral and cellular immunity. Safe, stable, and cost-efficient but may have low immunogenicity.
Messenger RNA (mRNA)	Utilizes mRNA corresponding to protein enveloped in a lipid (fat) sphere (nanoparticle). Short manufacturing time, no risk of causing disease, may require boosters.
Self-amplifying mRNA (samRNA)	Leads to enhanced antigen expression at lower doses compared to mRNA. Requires further research and clinical data for optimization.

Peptide-based vaccines

Peptide-based vaccines that include both biosynthetic and chemical preparations of known or predicted specific tumor antigen epitopes can elicit a strong immune response against the particular tumor antigen site. When combined with appropriate adjuvants, these subunits can induce a humoral immune response. They typically require both $CD4^+$ and $CD8^+$ T cell epitopes and have formed the basis of hepatitis B and HPV vaccines for liver and cervical cancers, respectively. However, the immunogenicity of peptide-based vaccines can be weak due to the small size of the antigen epitopes and MHC polymorphisms.

Nucleic acid-based vaccines

Nucleic acid-based vaccines, including either DNA or RNA, can induce strong MHC I mediated $CD8^+$ T cell responses and deliver several antigens that elicit both humoral and cellular immunity. Moreover, their ability to encode full-length tumor antigens allows APCs to cross-present various epitopes or numerous antigens simultaneously.[17,18] DNA vaccines must penetrate the cell nucleus to initiate transcription, whereas mRNA vaccines only need to enter the cytoplasm to be translated and directly express antigens. DNA vaccines also have a potential risk of inserting mutations into the genome, a risk not associated with mRNA. Finally, mRNA antigen production is immediate and efficient, and the vaccine preparation is straightforward and rapid. Thus, mRNA vaccines allow for the development of personalized neo-antigen cancer vaccines, which has gained prominence in vaccine development.[14]

mRNA technology in cancer vaccine development

The development and approval of mRNA vaccines against COVID-19 was a watershed that offers alternative methods for combating diverse health problems. The mechanism of action and vaccine entry into the cell have been previously described and discussed in detail.[19–21] Briefly, mRNA is the DNA material that instructs cells how to manufacture protein. Once sequenced, the mRNA that codes for neo-antigens can be synthesized, inserted into a nanoparticle, and injected into the patient, driving an immune response. The immune system is thus programmed to seek out and destroy cells within the body expressing these proteins, without affecting normal non-malignant cells. Specifically, this personalized medicine approach instructs the immune system to launch a response against the disease by producing highly specific antibodies directed against the aberrant cellular antigens.

To enter the cell, an mRNA vaccine needs to be lyophilized, such as in a nanoparticle. These lyophilized vaccines can then be taken up by specialized immune cells called DCs. Once inside the cell, the mRNA remains in the cell cytoplasm, where it is recognized by ribosomes. The ribosomes read the vaccine mRNA and synthesize proteins corresponding to the encoding mRNA. These proteins are then displayed on the cell surface to be presented to immune cells within the lymph nodes. For example, T helper cells train B cells to generate antibodies directed specifically against the manufactured protein, and cytotoxic T cells can directly kill cells displaying the specific protein or antigen. Use of this system has broad applications. In addition to infectious diseases, mRNA technology has been extensively tested in cancer prevention and treating inherited conditions.

The relatively short time frame required to generate mRNA vaccines that produce specific antigens in an autologous fashion is a major advantage of this vaccine approach. The potential for fast, scalable, and low-cost manufacturing is possible because of the simplicity of mRNA *in vitro* transcription.[22] Moreover, since protein is translated in the cytoplasm, averting any potential interference in the human genome, it is a feasible and safe strategy. Thus, mRNA vaccine development is a highly personalized medicine approach that is currently the focus of intense investigation. However, the technology requires a carrier system to ensure its

stability and the ability to deliver it to specific target areas. Delivery approaches include viruses and lipid nanoparticles and extracellular vesicles (EVs). EVs are naturally produced particles that aid in transporting molecules including nucleic acids and mRNA that do not generate a strong inflammatory response. To date, applications have been limited by the technical complexity of their production, but they have the potential to be used for a number of mRNA therapies.[23]

Clinical trials

A recent report outlined the first clinical trial outcome for Moderna's mRNA vaccine for treating skin cancer.[24] The clinical trial evaluated 107 melanoma patients treated with the combination approach. It took about eight weeks to design a personalized mRNA vaccine for each patient. The vaccine itself, mRNA-4157 (V940), is a novel individualized neo-antigen therapy that consists of a single synthetic mRNA coding up to 34 neo-antigens. The specific "mutational signature" is unique, as it is derived from the DNA sequence of the patient's tumor. Once administered into the body, the vaccine is endogenously translated and undergoes normal cellular antigen processing and presentation. As an example, Moderna's vaccine (4157/V940) is customized for the patient based on the genetic analysis of the patient's tumors after surgical removal and utilizes the algorithmically derived RNA-encoded neo-antigen sequences. Results from this phase IIb clinical trial revealed that the vaccine, in combination with Merck's checkpoint inhibitor, Keytruda, reduced the risk of death or recurrence by 44%, compared to Keytruda alone.

Pancreatic cancer is one of the most lethal forms of cancer, with a mortality rate of 88% and very few effective treatments. Although surgery is the main form of treatment, there is a 90% recurrence rate within seven to nine months. Chemotherapy is only partially effective at delaying recurrence, while immunotherapy is mainly ineffective. Moreover, pancreatic cancers normally do not respond to ICI therapy, as they are thought to express low levels of neo-antigens compared to other tumors and therefore less likely to mount a strong T cell immune response. In a recent phase I clinical trial carried out at Memorial Sloane Kettering Cancer Center, scientists used mRNA vaccines, developed by BioNTech and Genentech, that target the patient's own tumor neo-antigens.[25] After surgically removing the tumors, the authors designed and produced a personalized vaccine containing mRNA corresponding to the chosen neo-antigens. Nine weeks later, 16 patients were treated with mRNA vaccines that were tailored specifically to each individual's specific cancer. They were sequentially administered with anti-PD-L1 atezolizumab, autogenous cerumen, and a modified version of mFOLFIRINOX. Following vaccination, the trial reported that eight of the patients generated a strong T cell response to the vaccines. These individuals also had longer survival, with no reported cancer recurrence 18 months post-treatment, which was the reported median follow-up time. Although the study was small it is nonetheless promising and supports an approach for treating a disease with a poor prognosis, paving the way for further larger studies that will ultimately determine its effectiveness.

Self-amplifying mRNA (samRNA)

In addition to the mRNA technology outlined above, samRNA-based vaccines are believed to display distinct advantages. samRNA is superior to the conventional mRNA technique because of its relatively fewer side effects, lower dosage requirements, and long-lasting effects.[26] Although it shares many structural similarities, samRNA is a much larger molecule that encodes four additional proteins in addition to the vaccine antigen. Non-viral delivery was shown to be capable of producing robust and potent responses from both the innate and adaptive immune responses in preclinical testing of small animals and non-human primates.[27] It has also been reported that 64-fold less material is required for samRNA vaccine development compared to conventional mRNA vaccines, and it can yield a similar result for influenza virus antigen production, rendering it less costly.[28]

Although samRNA technology has not yet received FDA approval, promising results with superior characteristics compared to the conventional mRNA approach have been reported from clinical trials.[29] Currently, Moderna has several mRNA vaccines in different phases of clinical development (mRNA-4157, mRNA-5671, and mRNA-4359).[30] Given the superiority of samRNA, it may theoretically be employed for numerous cancer vaccine development where the conventional mRNA approach is currently applied, leading to a versatile new tool for human immunization.

Future direction

Recent reports from Gritstone, a clinical-stage biotechnology company working to develop potent vaccines, highlighted data from the GRANITE Phase 1/2 study of their personalized neo-antigen vaccine program. This is now in a randomized Phase 2/3 study for first-line microsatellite-stable colorectal cancer. Their antigen prediction platform, EDGE™, focused on neo-antigen prediction within their SLATE program. Advances in EDGE™ models, Gritstone's artificial intelligence-driven neo-antigen prediction platform, enable best-in-class prediction of class II HLA-presented neo-antigens that could drive $CD4^+$ T cell responses.[31] The ongoing survival benefit seen in GRANITE to date correlates with the augmentation of T cells in the periphery and tumor. Biopsy analyses of both paired pre- and post-vaccine studies showed upregulation of gene signatures affiliated with immune infiltration, supporting expansion of T cells and induction of dynamic TCR repertoire changes in the tumor and periphery. The majority of neo-antigens remain in the tumor even after the patient receives treatment prior to GRANITE administration. Immunotherapy focused on neo-antigens results in a durable immune response in patients with advanced tumors where checkpoint inhibitors alone are not effective.

The rapid progress in mRNA vaccine development has been largely attributed to recent developments of innate RNA immune sensing and *in vivo* delivery methods, which have been the result of extensive basic research into RNA, lipid, and polymer biochemistry.[32] The future of mRNA vaccines looks very positive, and the clinical data coupled with resources provided by both industry and institutions will likely substantially energize basic research in the field.

Conclusions

Recent advances in cancer immunotherapy have demonstrated that personalized cancer vaccines remain a promising research area. However, there are still challenges associated with this technology that need to be circumvented to obtain better clinical responses. For example, even though the patient's immune system is stimulated in response to the vaccine, the tumor is not always impacted. Neo-antigen identification and manufacturing can take at least 6–8 weeks, which can negatively impact patients with a short treatment window. Moreover, some of the current neo-antigen prediction algorithms can be inaccurate, so neo-antigen prediction

accuracy requires further optimization of machine-learning platforms. Nonetheless, we have learned how to improve and increase vaccine manufacturing and are continuously learning how mRNA vaccines respond in a larger cohort of patients. This information, coupled with the response of the regulators to this technology, will likely support the acceleration of mRNA-based cancer vaccine development. As such, therapeutic vaccination is a growing research sector that promises to be a new therapeutic modality for cancer immunotherapy.

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Conflict of interest

JFM is the Founder and President of ImmunePCS LLC.

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