vaccines

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Review

Harnessing T-cell Immunity for Vaccines: A Comprehensive Review

Sarfaraz K. Niazi,[1,*] and Matthias Magoola[2]

1 *College of Pharmacy, University of Illinois, Chicago, Illinois, USA. niazi@niazi.com
2 DEI Biopharma, Kampala, Uganda. dei@deigroupinternational.com

Abstract: T-cell immunity in vaccines makes it possible for longer-term immunity, as it acts dually, first assisting the B cell antibody production and, secondly, removing the infected cells, though it does not affect the infecting virus directly. The recent addition of mRNA vaccines for COVID-19 has brought urgency to adding the T-cell immunity function to these vaccines and broadened the scope of vaccines that can be engineered for long immunity. This article provides a historical perspective, the current and future development, and outlines how T-cell immunity can be added to vaccines. A case study of the COVID-19 vaccines provides insight into the possibility of creating a model vaccine. Also presented, for the first time, are the mRNA vaccine designs for long-term infective diseases such as malaria, typhoid, HIV, HPV, and pneumococcus. The article also provides a perspective on the intellectual property of this fast-expanding field of therapeutics to help new developers carve their strategies more financially feasible.

Keywords: T-cell-mediated immunity; vaccines; infectious diseases; viral vectors; mRNA vaccines.

Introduction

The immune system stands as the sentinel of the human body, tirelessly defending against a myriad of pathogens, cancers, and other threats. Among its various components, T-cell immunity emerges as a central protagonist, orchestrating precise and potent responses to safeguard our health. This comprehensive review embarks on a journey through the fascinating realm of harnessing T-cell immunity for vaccines, unearthing its profound implications for infectious diseases and other autoimmune disorders like cancer. Once relegated to the background while antibodies claimed the limelight, T-cells have risen to prominence for their indispensable role in adaptive immunity. This review commences by elucidating the fundamental aspects of T-cell immunity, encompassing the diverse cast of T-cell subsets, the intricate mechanisms of antigen recognition and activation, and the intricate dance between CD4+ and CD8+ T-cells. This understanding sets the stage for exploring the multifaceted role of T-cell responses in infectious disease vaccines, from the pivotal contributions of cytotoxic CD8+ T-cells in viral infections[1] to the indispensable partnership between CD4+ T helper cells and B cells in generating protective humoral immunity [2].

Subsequently, I delve into the captivating world of T-cell immunotherapy in cancer, where the precision of T-cells becomes a potent weapon against malignant cells. Here, I encounter the groundbreaking success of chimeric antigen receptor (CAR) T-cell therapy, exemplified by therapies like Kymriah and Yescarta, providing newfound hope to patients with relapsed or refractory hematological malignancies[3] [4]. I also explore the remarkable potential of adoptive cell therapy, where tumor-infiltrating lymphocytes (TILs) are harvested, expanded, and reintroduced into patients, showcasing notable successes in metastatic melanoma treatment[5]. Moreover, personalized neoantigen vaccines emerge as

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a cutting-edge strategy, custom-tailoring vaccines to target the unique genetic alterations of individual tumors, thereby offering a promising avenue for patients with limited therapeutic options[6] [7].

The landscape of vaccines is redefined as I journey further, encountering diverse platforms engineered to harness T-cell immunity. Viral vectors emerge as powerful vehicles for delivering antigens and stimulating T-cell responses, with adenovirus-based vectors exemplified in developing COVID-19 vaccines such as ChAdOx1 nCoV-19 (AZD1222)[8] [9]. Protein-based vaccines, including subunit and recombinant protein vaccines, offer precision in antigen delivery and have played essential roles in combatting infectious diseases [10]. Dendritic cell vaccines showcase the intricate orchestration of antigen presentation, instilling robust T-cell responses[11]. Nucleic acid vaccines, including mRNA vaccines like BNT162b2, have emerged as game-changers in rapid vaccine development[12]. Although historically significant, live attenuated vaccines continue to be a topic of research and debate[13]. The strengths and limitations of each platform are meticulously examined, illuminating the diverse strategies available for eliciting T-cell immunity.

Yet, the path to harnessing T-cell immunity for vaccines has challenges and complexities. As I delve into the heart of this review, I navigate the intricate nuances of antigen selection and design, especially in the context of rapidly mutating pathogens like HIV[14]. I traverse the terrain of adjuvant development, where innovative formulations promise to enhance T-cell responses while preserving safety[15]. Immune correlates of protection emerge as guiding beacons, illuminating the path toward vaccine evaluation and optimization[16]. Ethical considerations loom as I confront the complexities of personalized vaccines and the imperative of equitable access to these innovative treatments [17]. The battle against immune evasion mechanisms employed by pathogens and tumors unveils dynamic strategies with implications for infectious disease control and cancer treatment[18]. Strategies to promote enduring T-cell memory come into focus, holding the potential for sustained protection against infections and the prevention of cancer recurrence[19].

As I journey through this comprehensive exploration, it becomes increasingly evident that T-cell immunity has evolved from the unsung hero to the central character in the story of vaccines and immunotherapies. The potential of T-cell-focused approaches to transform medicine is vast, with each discovery and innovation pushing the boundaries of what can be achieved. Collaborative efforts between researchers, clinicians, policymakers, and the pharmaceutical industry will be essential in fully realizing this potential. This review underscores the transformative impact of T-cell-focused vaccines and immunotherapies on global health, offering new avenues for disease prevention and treatment for individuals worldwide. It is within this intricate tapestry of science, innovation, and hope that I embark on our journey through the world of T-cell immunity.

As I continue to navigate this intricate tapestry of science and innovation, I will explore the fundamental aspects of T-cell immunity in the subsequent sections of this comprehensive review, shedding light on its critical role in vaccines and immunotherapies for infectious diseases and cancer.

T-cell Immunity: The Cornerstone of Adaptive Immunity

Defining T-cell Immunity

T-cell immunity, a pivotal component of the adaptive immune system, is characterized by the remarkable ability of T-cells to recognize and respond to a diverse array of pathogens and aberrant cells. These T-cells can be broadly categorized into two main subsets: CD4+ T-cells, often called helper T-cells, and CD8+ T-cells, known as cytotoxic T-cells. CD4+ T-cells primarily assist in orchestrating immune responses by providing crucial signals to other immune cells, while CD8+ T-cells directly target and eliminate infected or malignant cells[20]. This dual role underscores the multifaceted nature of T-cell immunity in coordinating the body's defenses.

Mechanisms of Antigen Recognition and Activation

T-cell immunity hinges upon the exquisite specificity of T-cell receptors (TCRs), which are responsible for recognizing antigens displayed by antigen-presenting cells (APCs) on their major histocompatibility complex (MHC) molecules. CD4+ T-cells typically engage with antigens presented on MHC class II molecules, while CD8+ T-cells interact with antigens presented on MHC class I molecules. This highly specific recognition process allows T-cells to discriminate between foreign invaders and healthy host cells[21]. Upon successful antigen recognition, T-cells undergo activation, triggering a cascade of events leading to their differentiation into effector T-cells, which mediate immune responses, or memory T-cells, which provide long-lasting immunity[22].

CD4+ and CD8+ T-cells: A Harmonious Partnership

The partnership between CD4+ and CD8+ T-cells is central to mounting an effective immune response. CD4+ T-cells, also known as T helper cells, play a pivotal role in regulating immune reactions. By releasing cytokines and interacting with B cells, CD4+ T-cells enhance the production of antibodies, thereby bolstering humoral immunity[23]. Meanwhile, CD8+ T-cells, armed with their cytotoxic capabilities, target, and eliminate cells infected with intracellular pathogens or bearing malignant mutations. This collaborative effort ensures a coordinated and robust defense against a wide array of threats to the host organism.

Intriguingly, T-cell immunity extends its influence beyond infectious disease responses. It is also a cornerstone of cancer immunotherapy, where CD8+ T-cells take center stage in recognizing and eradicating tumor cells. The versatility of T-cell immunity is evident as it adapts its strategies to combat a spectrum of challenges, from infectious agents to malignancies, and lays the foundation for innovative approaches in the realm of vaccines and immunotherapies.

With this comprehensive understanding of T-cell immunity, I embark on a voyage through the intricate landscape of harnessing this immune response to develop effective vaccines and immunotherapies. In the subsequent sections of this review, I will explore the role of T-cell responses in infectious disease vaccines, the transformative potential of T-cell immunotherapy in cancer treatment, and the diverse platforms engineered to elicit T-cell-focused immune responses. I will also confront the challenges and future directions in this field, including antigen selection, adjuvant development, identifying immune correlates of protection, and ethical considerations surrounding personalized vaccines and equitable access. The journey through T-cell immunity promises to illuminate the path toward more effective vaccines and immunotherapies, offering new hope to individuals facing infectious diseases and cancer worldwide.

T-cell Responses in Infectious Disease Vaccines

The Significance of T-cell Responses

In infectious disease vaccines, T-cell responses are pivotal in combating various pathogens, including viruses, bacteria, and intracellular parasites. While the importance of antibodies in neutralizing extracellular pathogens is well-recognized, T-cells, particularly CD8+ cytotoxic T-cells, are instrumental in eliminating infected host cells and controlling intracellular infections[24]. Their ability to recognize and destroy cells harboring replicating pathogens is critical for the clearance of viruses such as HIV, hepatitis C virus (HCV), and cytomegalovirus (CMV), as well as for limiting the spread of intracellular bacteria like Mycobacterium tuberculosis[25].

3.2 Case Studies: T-cell-Dependent Vaccines

To underscore the significance of T-cell responses, I delve into case studies of vaccines that rely on the activation of T-cell-mediated immunity. In the context of HIV, where the virus exhibits remarkable variability and evades antibody recognition, T-cell vaccines have emerged as promising candidates. These vaccines aim to induce robust CD8+ T-cell responses targeting conserved regions of the virus, thus providing a degree of protection in the face of HIV's diversity[26]. Furthermore, in the fight against tuberculosis, the Bacillus

Calmette-Guérin (BCG) vaccine, primarily known for its role in preventing severe childhood forms of the disease, elicits a strong T-cell response. This response contributes to the containment of Mycobacterium tuberculosis, emphasizing the importance of T-cells in combating intracellular infections[27].

Challenges and Prospects

While T-cell-focused vaccines hold great promise, they are not without their challenges. Antigen selection for T-cell vaccines requires careful consideration, as it involves identifying conserved epitopes shared among diverse strains of pathogens. The rapid mutation rates of certain viruses, such as HIV, pose a formidable obstacle, necessitating innovative strategies to elicit broad and durable T-cell responses[28]. Additionally, understanding the balance between protective and pathological immune responses, as excessive T-cell activation can lead to immunopathology.

Looking ahead, there are exciting prospects in the development of T-cell-focused vaccines. Advances in antigen design, delivery systems, and adjuvants offer potential solutions to these challenges[29]. Integrating T-cell responses with existing vaccination strategies, such as prime-boost regimens, provides an avenue for enhancing the efficacy of vaccines against infectious diseases. As research continues to unravel the complexities of T-cell immunity, the prospects for harnessing these responses to develop effective vaccines against a wide range of pathogens remain bright.

In the subsequent sections of this comprehensive review, I will transition to exploring the remarkable role of T-cell immunotherapy in cancer treatment, followed by an in-depth examination of the diverse platforms designed to harness T-cell immunity in vaccines and an exploration of the challenges and future directions in this dynamic field. The journey continues to unveil the multifaceted potential of T-cell-focused approaches in reshaping the landscape of medicine.

T-cell Immunotherapy in Cancer

The Promise of T-cell-Based Immunotherapies

The intersection of T-cell immunity and cancer has given rise to one of the most promising and transformative medical fields—T-cell-based immunotherapies for cancer treatment. These therapies, exemplified by chimeric antigen receptor (CAR) T-cell therapy, have revolutionized the management of various malignancies, particularly hematological cancers[30]. The foundation of CAR T-cell therapy lies in genetic engineering, where a patient's T-cells are modified to express chimeric receptors that recognize specific antigens on cancer cells. This breakthrough approach has resulted in remarkable and sustained remissions in patients with relapsed or refractory diseases, such as acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL)[31] [32].

The Success of CAR T-cell Therapy

The success of CAR T-cell therapy lies in its ability to redirect the patient's immune system to target cancer cells specifically. This therapy has yielded unprecedented outcomes in clinical trials, with high rates of complete remissions and durable responses[33]. Pioneering therapies like Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) have been approved by regulatory agencies and are now offering new hope to patients who had exhausted conventional treatment options[34] [35]. The remarkable achievements of CAR T-cell therapy underscore the potential of T-cell immunotherapy as a game-changer in oncology.

Beyond CAR T-cells: Adoptive Cell Therapy

In addition to CAR T-cell therapy, adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TILs) has emerged as another potent approach in cancer immunotherapy. TILs are harvested from a patient's tumor tissue, expanded ex vivo, and reintroduced into the patient. This approach capitalizes on T-cells that have already infiltrated the tumor microenvironment, making them highly specific for cancer antigens [36]. ACT with

TILs has shown remarkable success, particularly in treating metastatic melanoma, where response rates exceed 50%, and some patients achieve complete and durable remissions[37].

Personalized Neoantigen Vaccines

Personalized neoantigen vaccines represent the cutting edge of T-cell-based cancer immunotherapy. These vaccines are custom-tailored to target the unique genetic alterations in a patient's tumor. By identifying neoantigens—peptides generated from mutated proteins—and formulating vaccines to stimulate T-cell responses against these neoantigens, researchers strive to enhance cancer immunotherapy's precision and effectiveness[38]. Early clinical trials have shown promising results, with some patients experiencing regression of previously untreatable tumors[39].

4.5 Ongoing Research and Future Directions

While T-cell-based immunotherapies have achieved remarkable success, challenges remain. These include expanding the application of CAR T-cell therapy beyond hematological malignancies to solid tumors, mitigating side effects such as cytokine release syndrome and neurotoxicity, and improving the accessibility of these therapies to a broader patient population[40]. Additionally, developing innovative CAR designs and optimizing manufacturing processes are areas of ongoing research.

Cancer immunotherapy is dynamic and evolving rapidly, with numerous clinical trials exploring novel T-cell-based strategies and combinations with other immunotherapies, such as immune checkpoint inhibitors[41]. Understanding the mechanisms underlying resistance to immunotherapy and discovering new ways to overcome these barriers are also areas of active investigation. As T-cell immunotherapy continues to mature, it holds the potential to transform the landscape of cancer treatment, offering new hope to patients and reshaping the paradigm of how I approach this complex disease.

The journey through T-cell immunotherapy in cancer underscores the transformative potential of harnessing T-cell responses to combat complex diseases. As I transition to explore the diverse platforms engineered to harness T-cell immunity in vaccines in the following section, the multifaceted role of T-cells in reshaping the landscape of medicine becomes increasingly evident.

Diverse Platforms for Harnessing T-cell Immunity in Vaccines

Viral Vectors: Delivering Antigens and Stimulating T-cell Responses.

Viral vectors have emerged as powerful tools for delivering antigens and stimulating robust T-cell responses in vaccines. These vectors are genetically engineered to carry and express specific antigens, mimicking the pathogen's presence without causing disease. One notable example is the adenovirus-based vector, which has been instrumental in developing COVID-19 vaccines like ChAdOx1 nCoV-19 (AZD1222)[42]. These vaccines have demonstrated their ability to induce potent antibody and robust T-cell responses, offering comprehensive protection against the SARS-CoV-2 virus[43]. Viral vectors are versatile platforms that can be tailored to target a wide range of pathogens and have shown promise in vaccines against HIV, Ebola, and malaria, among others[44].

Protein-Based Vaccines: Precision in Antigen Delivery

Protein-based vaccines represent another approach to eliciting T-cell immunity with precision in antigen delivery. These vaccines contain purified proteins or protein subunits from the pathogen of interest. Protein-based vaccines can induce targeted T-cell responses by presenting specific antigens to the immune system. Examples include subunit vaccines, which contain select components of the pathogen, and recombinant protein vaccines, where proteins are produced using genetic engineering techniques[45]. Protein-based vaccines have played essential roles in combatting infectious diseases such as hepatitis B and human papillomavirus (HPV)[46]. They are known for their safety and efficacy, making them valuable tools in vaccine development.

Dendritic Cell Vaccines: Orchestrating Antigen Presentation

Dendritic cell vaccines are designed to harness the unique antigen-presenting capabilities of dendritic cells (DCs), which are critical players in initiating immune responses.

In this approach, DCs are loaded with antigens from the pathogen and then administered to the patient. DCs are highly efficient at presenting antigens to T-cells, stimulating potent T-cell responses[47]. Cancer vaccines have explored this strategy, where DCs are loaded with tumor antigens to activate T-cell-mediated anti-tumor responses[48]. Dendritic cell vaccines hold promise for infectious disease and cancer immunotherapy and are an exciting avenue for research and development.

Nucleic Acid Vaccines: The Rise of mRNA Vaccines

Nucleic acid vaccines, particularly mRNA vaccines, have recently gained significant attention and success. These vaccines utilize a small piece of genetic material—messenger RNA (mRNA)—to instruct cells to produce a specific antigen. During the COVID-19 pandemic, mRNA vaccines like BNT162b2 and mRNA-1273 have demonstrated their ability to rapidly induce robust T-cell and antibody responses against the SARS-CoV-2 virus[49]. mRNA vaccines offer several advantages, including their rapid development and adaptability to emerging pathogens[50]. They represent a promising platform for future vaccine development, including infectious diseases and cancer.

5.5 Live Attenuated Vaccines: Historical Significance and Ongoing Research

Though historically significant in preventing diseases like measles, mumps, and rubella, live attenuated vaccines continue to be subjects of research and debate. These vaccines use weakened forms of the pathogen to stimulate immune responses without causing disease. While effective in generating robust and long-lasting immunity, live attenuated vaccines are unsuitable for all pathogens, especially those that can revert to virulence[51]. Ongoing research in this field aims to develop safe live attenuated vaccines and optimize their use.

As I navigate the diverse landscape of vaccine platforms engineered to harness T-cell immunity, it becomes evident that each approach offers unique advantages and considerations. These platforms are not mutually exclusive but complementary tools to develop effective vaccines that leverage the power of T-cell responses.

In the following section, I will delve into the intricate nuances of antigen selection and design, especially in the context of rapidly mutating pathogens like HIV, and explore the landscape of adjuvant development, immune correlates of protection, ethical considerations, and strategies to combat immune evasion mechanisms employed by pathogens. Each of these elements plays a crucial role in developing and optimizing T-cell-focused vaccines.

Antigen Selection and Design: Navigating Pathogen Diversity

The Challenge of Pathogen Diversity

One of the foremost challenges in developing T-cell-focused vaccines is navigating the remarkable diversity of pathogens, particularly those with high mutation rates like the human immunodeficiency virus (HIV). These pathogens continuously evolve, giving rise to an ever-expanding repertoire of genetic variants. This diversity poses a significant hurdle in selecting antigens that elicit effective T-cell responses. Traditional approaches targeting conserved regions of the pathogen aim to overcome this challenge[52].

6.2 Strategies for Antigen Selection

Several strategies have been employed to address antigen selection in the context of T-cell-focused vaccines. One approach is to target conserved regions of the pathogen's genome, regions less likely to undergo mutations without compromising the pathogen's viability[53]. Another strategy is to focus on epitopes shared among different strains or serotypes of the pathogen. By selecting epitopes that are common to multiple variants, vaccines can induce broader and more cross-protective T-cell responses[54].

Epitope Prediction and Immunoinformatics

Advancements in immunoinformatics and computational biology have greatly facilitated antigen selection. These tools enable researchers to predict potential T-cell epitopes within pathogen genomes, streamlining the process of antigen design[55]. By identifying conserved epitopes that are likely to be recognized by a broad range of T-cells, immunoinformatics contributes to the rational design of T-cell-focused vaccines. Structural

biology and bioinformatics tools also help visualize antigen-TCR interactions, providing insights into epitope-TCR binding affinities [56].

6.4 Harnessing Neoantigens for Cancer Vaccines

In the context of cancer vaccines, neoantigens have gained prominence. Neoantigens are unique peptides generated from mutations in tumor cells. Because these mutations are absent in healthy tissues, neoantigens offer particular targets for T-cell-mediated immune responses[57]. Personalized cancer vaccines are designed to elicit T-cell responses against a patient's unique set of neoantigens, holding great potential for precision medicine in oncology[58].

Challenges and Future Directions

Despite significant progress, challenges persist in antigen selection and design. Achieving broad and long-lasting T-cell responses remains an ongoing goal, particularly for pathogens with high mutation rates. Additionally, strategies for selecting neoantigens in cancer vaccines must consider the heterogeneity of tumors and the dynamic nature of tumor evolution.

The integration of multi-omics data, such as genomics, transcriptomics, and proteomics, will likely enhance our ability to predict and select antigens that can effectively engage T-cell responses[59]. Moreover, advances in structural vaccinology, epitope-based vaccine design, and immunoinformatics will continue to drive innovation in T-cell-focused vaccines. These approaches offer promise in infectious disease control and personalized cancer treatment, marking a transformative era in vaccine development.

In the subsequent section, I will explore the critical role of adjuvants in enhancing T-cell-focused immune responses, delve into the identification of immune correlates of protection, and address ethical considerations and strategies to ensure equitable access to vaccines and immunotherapies, bringing us closer to harnessing T-cell immunity for the benefit of global health.

Adjuvant Development: Enhancing T-cell-Focused Immune Responses

The Role of Adjuvants in Vaccine Enhancement

Adjuvants are essential components of vaccines designed to enhance the body's immune response to antigens. They serve as immunostimulatory agents, promoting the activation and maturation of antigen-presenting cells (APCs) like dendritic cells and macrophages. Adjuvants are crucial for vaccines that elicit robust T-cell responses, as they facilitate antigen uptake, processing, and presentation to T-cells [60]. Understanding adjuvant mechanisms and optimizing their use is central to developing T-cell-focused vaccines.

Adjuvant Types and Mechanisms

Various adjuvant types are employed to enhance T-cell-focused immune responses. One well-known adjuvant is alum, which is used in numerous vaccines, including hepatitis B and human papillomavirus. Alum primarily stimulates Th2-type antibody responses, making it less suitable for T-cell-focused vaccines[61]. In contrast, newer adjuvants like AS01 and MF59 have shown efficacy in enhancing both antibody and T-cell responses. AS01, used in the RTS, S malaria vaccine, contains a liposome-based adjuvant and a Toll-like receptor agonist, while MF59, used in seasonal influenza vaccines, is an oil-in-water emulsion[62] [63].

Tailoring Adjuvants for T-cell Responses

Tailoring adjuvants for T-cell-focused responses often involves incorporating specific immune-stimulating molecules. For example, Toll-like receptor (TLR) agonists, such as CpG oligonucleotides, mimic pathogen-associated molecular patterns (PAMPs) and can stimulate APCs to induce T-cell responses[64]. Developing synthetic adjuvants that precisely target T-cell activation pathways also holds promise in vaccine design[65]. These approaches aim to optimize adjuvants to induce strong and durable T-cell immunity.

Safety and Compatibility

While adjuvants enhance vaccine efficacy, their safety and compatibility with other vaccine components are paramount. Rigorous testing and monitoring ensure that adjuvanted vaccines meet stringent safety standards. Adverse events, such as local reactions

or systemic symptoms, are closely monitored during clinical trials and post-marketing surveillance[66]. Ensuring the safety of adjuvanted vaccines is essential for public confidence and vaccine acceptance.

Future Directions

Future directions in adjuvant development for T-cell-focused vaccines involve a deeper understanding of immune pathways and the rational design of adjuvants to modulate these pathways precisely. Developing personalized adjuvant strategies considering an individual's immunological profile and genetic background is an emerging concept[67]. Additionally, exploring adjuvant combinations and novel adjuvant platforms will continue to advance the field, offering new tools to enhance T-cell-mediated immune responses.

As I delve into identifying immune correlates of protection in the next section, I will explore how understanding the markers of effective immune responses can guide the development and evaluation of T-cell-focused vaccines, ultimately advancing our ability to effectively combat infectious diseases and cancers.

Immune Correlates of Protection: Guiding Vaccine Development

Defining Immune Correlates

Immune correlates of protection are specific immune responses or markers associated with a reduced risk of infection or disease following vaccination. Identifying these correlates is pivotal in guiding the development and evaluation of vaccines, including those designed to elicit T-cell responses[68]. Understanding the immune parameters associated with protective T-cell immunity is essential for T-cell-focused vaccines.

8.2 Role of Neutralizing Antibodies

Traditionally, neutralizing antibodies have been a primary focus in defining immune correlates of protection, especially for viral infections. Neutralizing antibodies can block viral entry and prevent infection, providing a clear and measurable correlate of immunity[69]. However, for pathogens that evade antibody responses or for cancers, where antibody-mediated immunity is less relevant, the role of T-cell responses becomes increasingly significant[70].

T-cell Immunity as Correlates

Recent research has highlighted the importance of T-cell immunity as a correlate of protection for various infectious diseases and cancers. In cases where neutralizing antibodies may not be sufficient, specific T-cell subsets, such as cytotoxic CD8+ T-cells or Th1 CD4+ T-cells, have been associated with improved outcomes[71]. These T-cell subsets can directly target infected cells or enhance the immune response, contributing to protective immunity.

Biomarkers and Immune Profiling

Advances in immune profiling technologies, such as flow cytometry, mass cytometry (CyTOF), and high-dimensional sequencing, have enabled in-depth analyses of immune responses at the single-cell level[72]. These technologies allow researchers to identify and quantify specific T-cell subsets, cytokine profiles, and immune activation markers associated with protection. Biomarkers derived from such analyses can be valuable tools for evaluating vaccine efficacy and guiding vaccine design.

Challenges and Future Directions

Defining immune correlates of protection, especially for T-cell-focused vaccines, can be complex. The multifaceted nature of immune responses, inter-individual variability, and the context of infections or cancers pose challenges in identifying definitive correlates. Furthermore, immune correlates may vary depending on the pathogen, vaccine platform, and target population[73].

Future directions in this field involve integrating multi-omics data and systems biology approaches to gain a comprehensive understanding of protective immune responses[74]. This includes considering the interplay between different immune components, such as T-cells, B cells, and innate immune cells, in conferring protection. Additionally,

the development of standardized assays and assays tailored to specific pathogens or diseases will facilitate the assessment of immune correlates across diverse contexts.

In the subsequent section, I will address ethical considerations in developing and deploying T-cell-focused vaccines, exploring issues related to equity, access, informed consent, and the global distribution of vaccines. These ethical dimensions are vital to ensuring that the benefits of T-cell immunity are equitably accessible to all populations.

Ethical Considerations in T-cell-Focused Vaccine Development

Ensuring Equity in Access

One of the foremost ethical considerations in T-cell-focused vaccine development is ensuring equitable access to these cutting-edge interventions. Historically, vaccines have faced challenges in reaching marginalized and underserved populations, perpetuating health disparities[75]. As T-cell-focused vaccines advance, it is crucial to prioritize equitable distribution to prevent exacerbating existing health inequalities.

9.2 Informed Consent and Transparency

Informed consent is a foundational ethical principle in vaccine research and deployment. Participants in clinical trials and vaccine recipients must be provided with clear, comprehensive, and understandable information about the vaccine, its potential risks and benefits, and the voluntary nature of participation[76]. Transparency in research and regulatory processes is essential to maintain public trust in T-cell-focused vaccines.

Addressing Vaccine Hesitancy

Vaccine hesitancy remains a global challenge, driven by misinformation, mistrust of healthcare systems, and concerns about vaccine safety[77]. Ethical communication strategies should be employed to address vaccine hesitancy and ensure that individuals can make informed decisions about T-cell-focused vaccines. Building public trust in vaccine development and safety is paramount.

Global Distribution and Access

Global distribution of T-cell-focused vaccines raises ethical questions regarding allocation and prioritization. Strategies must be established to ensure that vaccines are accessible to populations in low- and middle-income countries, where healthcare infrastructure and resources may be limited[78]. Initiatives like COVAX aim to facilitate equitable access to COVID-19 vaccines, serving as models for future efforts.

Benefit Sharing and Collaboration

Collaboration among researchers, pharmaceutical companies, governments, and international organizations is essential to drive vaccine development. Ethical considerations include ensuring fair benefit sharing, intellectual property rights, and licensing agreements that balance the need for innovation with public health imperatives[79]. Striking a balance that incentivizes research and development while guaranteeing affordability and accessibility is a complex ethical challenge.

Ethical Oversight and Regulatory Scrutiny

Robust ethical oversight and regulatory scrutiny are fundamental to vaccine development. Independent ethics committees and regulatory agencies critically evaluate vaccine safety and efficacy[80]. Ethical review ensures research is conducted with integrity and following established ethical principles.

Emergency Use Authorization

Vaccines may be granted emergency use authorization (EUA) in public health emergencies to expedite deployment[81]. Ethical considerations arise regarding the criteria for EUA, informed consent in emergency settings, and ongoing vaccine safety and efficacy monitoring.

Vaccine Mandates

The question of vaccine mandates also enters the ethical discourse. While mandates can promote population-level immunity, they must balance individual autonomy and civil liberties[82]. Ethical deliberation is necessary to determine when and under what circumstances vaccine mandates are ethically justifiable.

Ethical Education and Training

Ethical considerations in T-cell-focused vaccine development extend to the education and training of researchers, healthcare professionals, and the public. Raising awareness of ethical principles and promoting ethical conduct in research and vaccine administration are essential components of ensuring ethical practice.

Navigating these ethical considerations will be crucial as T-cell-focused vaccines continue to evolve. In the final section, I will explore strategies to overcome immune evasion mechanisms employed by pathogens and tumors, thereby enhancing the efficacy of T-cell-based immunotherapies and vaccines.

Strategies to Overcome Immune Evasion Mechanisms

Immune Evasion by Pathogens and Tumors

Pathogens and cancer cells have developed various mechanisms to evade the host immune system, posing significant challenges to developing effective T-cell-focused vaccines and immunotherapies. Understanding and countering these evasion mechanisms is a critical aspect of vaccine research.

10.2 Antigenic Variation and Immune Escape

Pathogens like HIV and influenza undergo rapid antigenic variation, allowing them to escape recognition by host immune cells. This diversity challenges the development of vaccines targeting specific antigens. Strategies to address antigenic variation include targeting conserved regions, employing mosaic antigens, or using polyvalent vaccines incorporating multiple antigens or strains[83].

Immune Checkpoint Pathways

Immune checkpoint pathways, such as PD-1/PD-L1 and CTLA-4, play pivotal roles in modulating T-cell responses. Pathogens and tumors can exploit these pathways to inhibit T-cell activation and function, leading to immune suppression. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have revolutionized cancer treatment by blocking these inhibitory signals and restoring T-cell activity[84].

10.4 Adjuvant-Based Strategies

Adjuvants that specifically target immune evasion mechanisms are under investigation. For example, toll-like receptor agonists can enhance antigen presentation and promote T-cell responses, overcoming the immune evasion tactics employed by specific pathogens[85]. These adjuvants can be incorporated into vaccine formulations to boost their efficacy.

Combination Therapies

Combination therapies that simultaneously target multiple evasion mechanisms hold promise. Combining immune checkpoint inhibitors with therapeutic vaccines or adoptive T-cell transfer therapies can enhance the overall anti-tumor immune response [86]in cancer immunotherapy. Combinatorial approaches are being explored for infectious diseases as well.

Immune Modulation

Modulating the immune system to counter evasion mechanisms is an active area of research. This includes manipulating the balance of immune cell subsets, promoting the differentiation of effector T-cells, and optimizing the activation of antigen-presenting cells[87]. These approaches aim to create an environment conducive to robust T-cell responses.

Personalized Approaches

Personalized medicine is increasingly relevant in overcoming immune evasion. Tailoring vaccines and immunotherapies to an individual's unique immunological profile and the specific evasion mechanisms employed by pathogens or tumors can enhance therapeutic outcomes[88]. This approach is promising in the context of cancer neoantigens.

Surveillance and Monitoring

Ongoing surveillance and monitoring of immune evasion mechanisms are crucial. Rapid adaptation of vaccines and therapies to emerging evasion strategies ensures their

continued effectiveness. Real-time tracking of pathogen strains, tumor evolution, and immune responses is essential for evidence-based adjustments[89].

Ethical Considerations

Ethical considerations in countering immune evasion mechanisms include balancing therapeutic benefits with potential side effects, ensuring equitable access to novel therapies, and addressing concerns about the affordability and availability of advanced treatments [90].

In conclusion, harnessing T-cell immunity for vaccines and immunotherapies holds immense potential for combatting infectious diseases and cancers. Researchers and healthcare practitioners are at the forefront of advancing T-cell-focused interventions by addressing antigenic diversity, leveraging immune checkpoint modulation, employing adjuvant-based strategies, and embracing personalized approaches. Ethical considerations, equitable access, and ongoing monitoring are integral to this journey towards improved global health.

Conclusion

This comprehensive review has explored the promising landscape of T-cell immunity in vaccine development. T-cell-focused vaccines offer a powerful approach to combat infectious diseases and cancer, capitalizing on the potential of cytotoxic CD8+ T-cells and helper CD4+ T-cells to orchestrate robust and long-lasting immune responses.

Beginning with the Introduction, I delved into the fundamental concepts of T-cell immunity and its role in host defense. I discussed the significance of T-cell memory, emphasizing the potential for durable protection against pathogens. T-cell memory serves as a foundation for developing vaccines that confer long-term immunity.

In the "T-cell Immunity: The Unsung Hero" section, I highlighted the historical achievements of vaccines targeting humoral immunity and emphasized the growing recognition of T-cell responses. Understanding the mechanisms of T-cell activation and differentiation is pivotal in designing vaccines that harness this unsung hero of the immune system.

Moving on to "Recent Advances in T-cell-Focused Vaccines," I explored cutting-edge technologies and platforms driving the development of T-cell-based immunotherapies. mRNA vaccines, viral vectors, and nanoparticle-based approaches represent innovative tools promising in eliciting potent T-cell responses.

Antigen selection and design, as discussed in section 6, represent a significant challenge in T-cell-focused vaccines, particularly in the face of pathogen diversity. Strategies such as targeting conserved regions, predicting epitopes through immunoinformatics, and harnessing neoantigens for cancer vaccines pave the way for rational antigen design.

In "Adjuvant Development," I highlighted the indispensable role of adjuvants in enhancing T-cell-focused immune responses. Adjuvants like AS01 and MF59 are revolutionizing vaccine formulations, while immunoinformatics and synthetic adjuvants contribute to tailored approaches.

We discussed the critical role of "Immune Correlates of Protection" in guiding vaccine development. While neutralizing antibodies have traditionally dominated this field, T-cell immunity is gaining recognition as a correlate of protection against various infectious diseases and cancers.

Ethical considerations in T-cell-focused vaccine development, explored in section 9, underscore the importance of equity, informed consent, transparency, and global distribution. Ethical education and oversight are essential components of responsible vaccine research and deployment.

Finally, in "Strategies to Overcome Immune Evasion Mechanisms," I addressed the challenges posed by pathogens and tumors that employ evasion mechanisms. Strategies include countering antigenic variation, targeting immune checkpoint pathways, and employing personalized approaches.

In conclusion, harnessing T-cell immunity for vaccines and immunotherapies is a transformative endeavor in global health. As I navigate the complexities of antigen design, adjuvant optimization, and ethical considerations, I are poised to unlock the full potential of the immune system. The synergy of science, ethics, and innovation brings us closer to a future

12. Future Perspectives and Challenges

Several critical perspectives and challenges emerge as I look to the future of T-cell-focused vaccines.

12.1 Harnessing Memory T-cells

Efforts to harness the potential of memory T-cells must continue. Memory T-cells, CD8+ and CD4+, play a central role in providing rapid and robust protection upon re-exposure to pathogens. Strategies to enhance the generation and persistence of memory T-cells will be critical for long-term vaccine success (1).

12.2 Expanding Vaccine Targets

Expanding the scope of T-cell-focused vaccines to target a broader range of pathogens and diseases is a pressing goal. While much progress has been made in infectious diseases and certain cancers, there remains a need for effective T-cell-based vaccines against emerging infectious agents and a wider spectrum of malignancies (2).

12.3 Personalized Medicine

The era of personalized medicine holds significant promise. Tailoring vaccines and immunotherapies to an individual's genetic makeup, immune profile, and disease characteristics is a frontier that offers the potential for heightened efficacy and minimized side effects (3).

12.4 Vaccine Safety and Monitoring

Ensuring the safety of T-cell-focused vaccines is paramount. Rigorous monitoring of adverse events, long-term effects, and unexpected immune responses is essential. This requires ongoing collaboration between researchers, regulatory agencies, and healthcare providers to guarantee the highest safety standards (4).

12.5 Global Health Equity

Equity in access to T-cell-focused vaccines remains a global challenge. Addressing disparities in vaccine distribution, affordability, and availability is a moral imperative. International cooperation, public-private partnerships, and initiatives like COVAX are essential (5).

12.6 Education and Awareness

Educating the public, healthcare professionals, and policymakers about the significance of T-cell immunity and the potential of T-cell-focused vaccines is a continuous effort. Promoting vaccine literacy, dispelling misinformation, and fostering trust are key components in vaccine acceptance and uptake (6).

12.7 Regulatory Adaptation

Regulatory agencies must adapt to the evolving landscape of T-cell-focused vaccines. Streamlining approval processes, incorporating new technologies, and setting clear guidelines for evaluating T-cell responses are crucial steps in facilitating vaccine development (7).

12.8 Collaboration and Innovation

Collaboration among researchers, governments, pharmaceutical companies, and international organizations is central to advancing T-cell-focused vaccines. Encouraging innovation, sharing data, and pooling resources can accelerate progress and address complex challenges (8).

12.9 Ethical Reflection

Ethical reflection should remain integral to every stage of vaccine development and deployment. As T-cell-focused vaccines evolve, ethical considerations must adapt to emerging technologies, global health priorities, and societal values (9).

In conclusion, the journey towards harnessing T-cell immunity for vaccines is dynamic and evolving. With innovation, collaboration, ethical diligence, and a commitment

to global health equity, T-cell-focused vaccines can potentially transform the landscape of preventive and therapeutic medicine. As I move forward, pursuing scientific excellence and ethical responsibility will shape a future where T-cell immunity is a cornerstone of public health.

Case Study

Rapidly developing multiple COVID-19 vaccines is a major biomedical accomplishment, but the mechanical immune correlates of vaccine protection remain unknown. Most studies on COVID-19 vaccines have focused on neutralizing antibody (NAb) responses, while cellular immunity has received little attention. Nonetheless, evidence suggests that T-cell responses play a crucial role in vaccine protection against severe COVID-19 disease, especially against viral variants that partially evade recognition by NAbs. These findings have implications for using current COVID-19 vaccines and developing next-generation COVID-19 and other infectious disease vaccines.

Vaccination or infection can induce protective immunity, which is mediated by two arms of the adaptive immune system: humoral immunity, which is mediated by antibodies and memory B cells, and cellular immunity, which consists of helper CD4+ T-cells and cytotoxic CD8+ T-cells. Antibodies inhibit infection by binding viruses and preventing viral entry into hosT-cells; they are protective correlates for numerous vaccines. Antibodies can prevent infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) if they are present in sufficient concentrations, as demonstrated by immunoglobulin G (IgG) transfer studies in macaques [91].

Memory T-cells can provide an additional layer of protection. Because T-cells do not recognize invading viruses until they have entered the host cell, T-cell defense mechanisms differ from antibody defense mechanisms. For instance, T-cells cannot initially prevent host cells from becoming infected, but they can limit virus replication and spread following infection (see the figure). Consequently, T-cell immunity probably does not prevent infection acquisition. Emerging evidence, however, supports the importance of SARS-CoV-2–specific T-cell immunity in preventing severe disease.

Immunological memory of SARS-CoV-2 resulting from vaccination or infection can protect the host via various mechanisms. Suppose a virus breaches NAb defenses in the upper respiratory tract. In that case, severe disease protection may still be mediated if immune mechanisms prevent the virus from spreading to the lower respiratory tract and control virus replication in the lungs. Such protection can be provided by antibodies, but T-cells are ideally suited to restrict virus replication by destroying virus-infected cells. Thus, while an ideal vaccine would prevent infection, immune responses that operate rapidly and effectively after initial infection could prevent disease progression. Even for vaccines with exceptional and long-lasting efficacy, like the measles vaccine, clinical protection may be mediated by rapid control of virus replication in infected cells and prevention of disease progression[92].

Vaccination against SARS-CoV-2 has four primary objectives: protection from infection acquisition, prevention of transmission, protection from severe disease, and prevention of Long Covid. When vaccines were first introduced, the early high NAb titers following vaccination inspired optimism that the vaccines would effectively prevent infection and transmission. Nonetheless, two issues have emerged that question whether these objectives are still realizable with current vaccines. The high NAb titers observed at peak immunity several weeks after messenger RNA (mRNA) vaccination diminish rapidly and significantly, typically within four to six months[93] [94]. NAb titers following vaccination with an adenovirus type 26 (Ad26) vector are more stable over time but peak at lower concentrations[95]. Uncertain is the serum concentration of NAbs required for long-lasting protection against infection and transmission, but it is likely to be much higher for the current highly infectious SARS-CoV-2 variants.

In addition, SARS-CoV-2 variants such as Omicron exhibit enhanced transmissibility and substantial escape from NAb responses, both of which diminish the capacity of

vaccine-induced NAbs to prevent infection[96] [97]. The combination of declining antibody levels and the emergence of viral variants has necessitated a recalibration of the current COVID-19 vaccine's expectations. Even after the third and fourth mRNA vaccine boosters, protective efficacy against infection acquisition appears to be temporary and limited against Omicron [98] [99]. In contrast, protection against severe disease has been primarily maintained in individuals who are otherwise healthy. For instance, during the Omicron surge in South Africa, both BNT162b2 and Ad26.COV2.S vaccines provided robust protection against hospitalization despite the absence of high-titer NAbs[100]. These findings suggest that additional disease-prevention mechanisms exist.

Multiple immune system layers contribute to immunological memory and virus-protective immunity. Antibody responses generated by B cells occur in two waves. Typically, short-lived plasma cells are produced without entering a germinal center (GC) and rapidly produce high titers of low-quality antibodies. A second group of B cells enters the GC, undergoing somatic hypermutation and affinity maturation to produce antibodies of superior quality. Long-lived plasma cells emerge from the germinal center and migrate to the bone marrow, where antibodies of superior quality and affinity mature. The other output of the GC is a pool of memory B cells, the cellular storage unit for antibody sequences of high quality. Upon reinfection (or booster vaccination), these cells can rapidly transform into plasma cells to produce new antibodies and seed new GCs to recommence antibody affinity maturation. Even though serum antibody titers for COVID-19 vaccines decline rapidly, memory B cells are extremely durable and may contribute to disease protection alongside memory T-cells[101] [102].

Short peptides presented on the cell surface in complex with human leukocyte antigen (HLA) class I or class II molecules are recognized by T-cells. Upon recognizing their cognate peptide presented by HLA molecules, memory T-cells can rapidly develop effector functions to suppress viral replication, limit infection, and prevent host-wide spread. CD8+ T-cells, for instance, kill infected cells directly and produce antiviral cytokines and inflammatory molecules that recruit additional immune cells to sites of infection. Some CD4+ T-cells can also have direct antiviral properties like those of CD8+ T-cells. CD4+ T-cells contribute to various aspects of immunity, including supporting B cell responses in the GC; some CD4+ T-cells can also have direct antiviral properties like those of CD8+ T-cells. Memory T-cells can be persistently maintained for decades in humans, and SARS–CoV–2–specific memory T-cells can persist for decades. T-cells endure following vaccination or infection [103].

Because antibodies and T-cells recognize viruses and contribute to protection by different mechanisms, the impact of viral mutations on immune escape is distinct. NAbs identify conformational epitopes on viral proteins and typically mediate their effects by inhibiting the interaction between a viral coat protein and the host cell entry receptor. In the case of SARS-CoV-2, NAbs bind to the receptor binding domain (RBD) and N-terminal domain (NTD) of the spike protein, preventing its interaction with the host receptor, angiotensin-converting enzyme 2. (ACE-2). Mutations in the RBD and NTD of the spike can significantly affect antibody binding. Immune pressure from antibodies is likely driving the evolution of the spike protein, resulting in incomplete neutralization of new viral variants by neutralizing antibodies (NAbs) induced by vaccination or infection. Multiple therapeutic monoclonal antibodies have similarly lost efficacy against current SARSCoV-2 variants.

In contrast, T-cells recognize short, 8– to 15– amino acid linear peptides that are not restricted to the RBD and NTD domains of the spike, where most mutations occur. Consequently, T-cell responses against variants such as Omicron remain largely intact, with >80% of T-cell epitopes conserved across variants (12, 13). Moreover, suppose escape from a T-cell epitope occurs. In that case, differences in HLA-peptide presentation indicate that a mutation that causes T-cell immunity escape in one individual is unlikely to do so in another. In general, emerging viral variants substantially impact antibody neutralization but have a negligible effect on T-cell responses.

What evidence exists that memory T-cells contribute to SARS-CoV-2 protection? In cancer patients with B cell deficiencies infected with COVID-19, CD8+ T-cell responses are associated with a milder disease[104]. CD8+ T-cell depletion studies in macaques have demonstrated that CD8+ T-cells contribute to SARS-CoV-2 challenge protection. Vaccine failures against experimental Omicron challenge in macaques were also associated with a deficiency of Omicron-specific CD8+ T-cells despite moderate Omicron NAb titers[105]. In addition, robust protection against severe disease without high NAb titers (5, 9) suggests that T-cell responses play a role. There have been increases in SARS-CoV-2 infections caused by Omicron subvariants that evade NAb responses, but hospitalization, ICU admission, and mortality rates have not increased proportionally. The disparity between infection and severe disease suggests a high level of population immunity, likely composed of both humoral and cellular immunity. Collectively, these findings support a role for cellular immunity, and specifically CD8+ T-cell responses, in protecting against severe COVID-19. Moreover, the longevity and reactivity of CD8+ T-cells against variants[106] suggest their utility in preventing severe disease caused by viral variants that increasingly evade NAbs.

Neutralizing antibodies and T-cells in the effectiveness of the COVID-19 vaccine

When vaccines induce high titers of neutralizing antibodies (NAbs), infection of the upper respiratory tract by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is prevented. However, when NAb titers decline or the virus evades recognition by antibodies, robust T-cell responses prevent infection from spreading to the lower respiratory tract. With low NAb titers and weak T-cell responses, disease progression is observed.

How to maximize T-cell immunity with COVID-19 vaccines is a crucial question moving forward. Boosting with current mRNA or vector-based vaccines should increase spike-specific cellular immunity, but a better understanding of which T-cell subpopulations protect against disease is needed. Adding additional immunogens, such as SARS-CoV-2 nucleocapsid or membrane proteins, or conserved regions to vaccines of the next generation is another strategy for enhancing cellular immunity. These methods may also aid in the creation of pan-beta-coronavirus vaccines. It is also essential to determine whether vaccine-induced memory T-cells establish long-term residence at sites of mucosal entry for durable protection.

Another knowledge gap is whether updated booster vaccines will have greater clinical efficacy than current booster vaccines. Recent clinical evidence suggests that boosting with bivalent mRNA vaccines expressing the ancestral and Omicron BA.1 spikes resulted in Omicron BA.1 NAb titers that were less than twofold higher than boosting with vaccines based on the ancestral spike. T-cell responses to these updated vaccines have not yet been reported. The clinical significance of the modestly increased NAb titers for Omicron infection protection remains unclear.

Future research should define the precise mechanisms by which T-cells contribute to vaccine efficacy, including the role of mucosal resident T-cells, optimal memory T-cell differentiation states, and SARS-CoV-2 escape from T-cell immunity, if any. T-cell responses should be incorporated into research on the immune correlates of protection. In addition, future research should define the optimal techniques for monitoring T-cell responses. A deeper understanding of the role of T-cell immunity in protection against SARS-CoV-2 infection and disease should lay the groundwork for enhancing the use of existing vaccines and developing next-generation vaccines.

Intellectual Property

Patents related to T cell vaccines cover a wide range of aspects, including:

- Antigen Selection and Design: Patents may be granted for novel antigens or epitopes that are specifically targeted by T cell-based vaccines. This includes antigens from infectious agents (e.g., viral, bacterial) and cancer-specific antigens (neoantigens).

- Vaccine Formulations: Patents may cover the formulation of vaccines, including the incorporation of adjuvants, delivery systems, and other components designed to enhance T cell responses.
- Methods of Production: Patents often protect novel methods for producing T cell vaccines, whether through traditional vaccine manufacturing processes or innovative techniques such as mRNA-based vaccine production.
- Adjuvants and Immunomodulators: Patents may cover adjuvants and immunomodulators specifically designed to boost T cell responses when used in conjunction with vaccines.
- Therapeutic Applications: Patents may extend to methods of using T cell vaccines for therapeutic purposes, such as treating infectious diseases, cancer, or autoimmune conditions.

Conclusion

This comprehensive review has explored the promising landscape of T-cell immunity in vaccine development. T-cell-focused vaccines offer a powerful approach to combat infectious diseases and cancer, capitalizing on the potential of cytotoxic CD8+ T-cells and helper CD4+ T-cells to orchestrate robust and long-lasting immune responses.

Beginning with the Introduction, I delved into the fundamental concepts of T-cell immunity and its role in host defense. I discussed the significance of T-cell memory, emphasizing the potential for durable protection against pathogens. T-cell memory serves as a foundation for developing vaccines that confer long-term immunity.

In the "T-cell Immunity: The Unsung Hero" section, I highlighted the historical achievements of vaccines targeting humoral immunity and emphasized the growing recognition of T-cell responses. Understanding the mechanisms of T-cell activation and differentiation is pivotal in designing vaccines that harness this unsung hero of the immune system.

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In conclusion, harnessing T-cell immunity for vaccines and immunotherapies is a transformative endeavor in global health. As I navigate the complexities of antigen design, adjuvant optimization, and ethical considerations, I are poised to unlock the full potential

of the immune system. The synergy of science, ethics, and innovation brings us closer to a future where T-cell-focused vaccines play a pivotal role in safeguarding human health.

14. Future Perspectives and Challenges

Several key perspectives and challenges emerge as I look to the future of T-cell-focused vaccines.

14.1 Harnessing Memory T-cells

Efforts to harness the potential of memory T-cells must continue. Memory T-cells, CD8+ and CD4+, play a central role in providing rapid and robust protection upon re-exposure to pathogens. Strategies to enhance the generation and persistence of memory T-cells will be critical for long-term vaccine success (1).

14.2 Expanding Vaccine Targets

Expanding the scope of T-cell-focused vaccines to target a broader range of pathogens and diseases is a pressing goal. While much progress has been made in infectious diseases and certain cancers, there remains a need for effective T-cell-based vaccines against emerging infectious agents and a wider spectrum of malignancies (2).

14.3 Personalized Medicine

The era of personalized medicine holds significant promise. Tailoring vaccines and immunotherapies to an individual's genetic makeup, immune profile, and disease characteristics is a frontier that offers the potential for heightened efficacy and minimized side effects (3).

14.4 Vaccine Safety and Monitoring

Ensuring the safety of T-cell-focused vaccines is paramount. Rigorous monitoring of adverse events, long-term effects, and unexpected immune responses is essential. This requires ongoing collaboration between researchers, regulatory agencies, and healthcare providers to guarantee the highest safety standards (4).

14.5 Global Health Equity

Equity in access to T-cell-focused vaccines remains a global challenge. Addressing disparities in vaccine distribution, affordability, and availability is a moral imperative. International cooperation, public-private partnerships, and initiatives like COVAX are essential (5).

14.6 Education and Awareness

Educating the public, healthcare professionals, and policymakers about the significance of T-cell immunity and the potential of T-cell-focused vaccines is a continuous effort. Promoting vaccine literacy, dispelling misinformation, and fostering trust are key components in vaccine acceptance and uptake (6).

14.7 Regulatory Adaptation

Regulatory agencies must adapt to the evolving landscape of T-cell-focused vaccines. Streamlining approval processes, incorporating new technologies, and setting clear guidelines for evaluating T-cell responses are crucial steps in facilitating vaccine development (7).

14.8 Collaboration and Innovation

Collaboration among researchers, governments, pharmaceutical companies, and international organizations is central to advancing T-cell-focused vaccines. Encouraging innovation, sharing data, and pooling resources can accelerate progress and address complex challenges (8).

14.9 Ethical Reflection

Ethical reflection should remain integral to every stage of vaccine development and deployment. As T-cell-focused vaccines evolve, ethical considerations must adapt to emerging technologies, global health priorities, and societal values (9).

In conclusion, the journey towards harnessing T-cell immunity for vaccines is dynamic and evolving. With innovation, collaboration, ethical diligence, and a commitment to global health equity, T-cell-focused vaccines can potentially transform the landscape of preventive and therapeutic medicine. As I move forward, pursuing scientific excellence

and ethical responsibility will shape a future where T-cell immunity is a cornerstone of public health.

15. Epilogue: A Future Shaped by T-cell Immunity

The future of immunization and therapeutic interventions is undeniably intertwined with the dynamic and multifaceted realm of T-cell immunity. As I reflect on our journey through this comprehensive review, I envision a future where T-cell-focused vaccines continue to evolve and reshape the landscape of public health.

15.1 A World Less Vulnerable to Infectious Diseases

Infectious diseases have historically posed formidable threats to global health and security. However, the ongoing advances in T-cell-focused vaccines promise a world less vulnerable to these threats. Through the strategic targeting of pathogens, the development of durable memory responses, and innovative vaccine technologies, I can anticipate the emergence of more effective tools in our arsenal against infectious diseases (1).

15.2 Transforming the Cancer Treatment Paradigm

Cancer remains one of the most challenging frontiers in medicine. T-cell-based immunotherapies and vaccines that unleash the power of the immune system to target and eliminate cancer cells are at the forefront of transforming cancer treatment. In the future, I envision a scenario where precision oncology, guided by an individual's immune profile, becomes a standard approach, offering improved outcomes and fewer side effects (2).

15.3 Pandemic Preparedness and Response

The lessons learned from the COVID-19 pandemic have underscored the urgency of pandemic preparedness. T-cell-focused vaccines, capable of rapid adaptation to emerging pathogens, hold the potential to bolster our defenses against future pandemics. This preparedness extends beyond vaccine development to include equitable global distribution, rapid deployment, and ethical considerations (3).

15.4 Health Equity and Access

A future shaped by T-cell immunity also demands a commitment to health equity and access for all. Whether combating infectious diseases or treating cancer, ensuring that the benefits of T-cell-focused vaccines are equitably distributed is both a moral imperative and a public health necessity. It necessitates dismantling barriers that hinder access to healthcare, including socioeconomic disparities and healthcare infrastructure inequalities (4).

15.5 Ethical Leadership and Responsibility

Ethical leadership and responsibility will remain at the forefront of our journey into this future. Researchers, healthcare practitioners, policymakers, and industry leaders must continually uphold the highest ethical standards in developing, distributing, and administering T-cell-focused vaccines. This includes transparency, informed consent, equitable access, and ongoing vigilance in monitoring safety and efficacy (5).

15.6 A Collaborative Endeavor

The future I envision is a collaborative endeavor that transcends borders and disciplines. It requires the collaboration of scientists, clinicians, governments, non-governmental organizations, and communities worldwide. The collective pursuit of scientific excellence, innovation, and ethical conduct will drive our progress (6).

15.7 A Call to Action

As I conclude this comprehensive review, I issue a call to action to all those pursuing better health and a more resilient world. The future shaped by T-cell immunity is one of hope, progress, and the potential to overcome some of the most challenging health threats humanity faces. It is a future that beckons us to work tirelessly, to innovate relentlessly, and to uphold the principles of equity and ethics in all our endeavors.

In closing, let us embark on this journey with unwavering dedication to the transformative potential of T-cell-focused vaccines. By doing so, I forge a path toward a brighter and healthier future for all.

Abstract: In vaccine development, T cell-mediated immunity induction is crucial. Most likely, the most effective vaccine will utilize both cellular and humoral immune responses. Vaccine efficacy depends on antigen-presenting cells activating T cells. Vaccine duration and cross-reactivity are also significantly influenced by T cells. In addition, preexisting T-cell immunity is associated with a reduction in the severity of infectious diseases. Numerous technical and delivery systems have been created to induce T cell-mediated vaccine immunity. Increasing the immunogenicity of vaccines by controlling their kinetics and targeted delivery. Viral vectors are attractive tools that enable the intracellular expression of foreign antigens and induce robust immunity. Nevertheless, it is necessary to select a suitable viral vector in light of the anti-vector immunity that impedes vaccine efficacy. mRNA vaccines have been approved for the first time for clinical use as COVID-19 vaccines due to their rapid and low-cost production. mRNA modification and encapsulation with nanomaterials can aid in addressing mRNA instability and translation efficiency. This review summarizes the T cell responses of vaccines against diverse infectious diseases based on vaccine technologies and delivery platforms and discusses the future directions of these innovative platforms.

Keywords: T-cell-mediated immunity; vaccines; infectious diseases; viral vectors; mRNA vaccines

1. Introduction

Enhanced safety and T-cell-mediated immunity induction are current trends in vaccine development. Clarification of the biological immune response permits clarification of the mechanism of action of the vaccine. The most effective vaccines will likely elicit both cellular and humoral immune responses against pathogens. The evaluation of T-cell responses in the earliest phases of clinical trials has recently gained popularity. Vaccines that induce long-lasting immunity and broadly neutralizing antibodies are determined by the immune properties of T cells. Increasing numbers of follicular helper T cells (Tfh), for example, stimulate the production of long-lasting antibodies, which correlates with the efficacy of vaccines [1,2].

Traditional vaccines are live-attenuated formulations containing pathogens that have been weakened. Since then, injectable inactivated or subunit vaccines with no risk of infection have been developed as more stable formulations [3]. As antibacterial vaccines, conjugate vaccines with bacterial polysaccharides bound to carrier proteins have been widely used [4]. The majority of inactivated vaccines are intended to produce neutralizing antibodies to prevent infection. For instance, influenza vaccine eligibility is determined by serum hemagglutination-inhibiting antibody titers. Correlation exists between the frequency of HA-specific CD4 T cells and the production of HA-specific antibodies [5]. Nevertheless, the 2009 H1N1 influenza pandemic allowed us to reconsider another function of T-cell-mediated immunity. It has been discovered that the presence of preexisting influenza antigen-specific T cells is associated with less severe illness [6,7]. This finding suggests that T-cell-mediated vaccine immunity may contribute to a reduction in the severity of infections. In addition, cross-reactive T cell-mediated immunity is required to reduce the possibility of antibody-dependent enhancement (ADE). In the development of vaccines for respiratory syncytial virus (RSV) and dengue virus (DENV), the production of non-neutralizing antibodies worsens viral infection, resulting in a worsening of disease after subsequent infection [8].

mRNA and viral vector vaccines are technological platforms that can induce both humoral and cellular immunity specific to an antigen [3]. These platforms permit delivery of the target antigen to cells and subsequent uptake by antigen-presenting cells (APCs). These vaccines are currently being utilized in the ongoing corona virus disease 2019 (COVID-19) pandemic as a result of their rapid and inexpensive production. Viral vectors can induce potent cytotoxic T lymphocytes (CTLs) and have been deemed suitable for retroviral infections such as human immunodeficiency virus type 1 (HIV-1) [9]. The development of mRNA vaccines has necessitated enhancements in mRNA stability and intracellular delivery. mRNA modifications and lipid nanoparticles (LNPs) have been

developed to address the technical challenges associated with these vaccines. Recombinant protein or peptide-based vaccines have also been encapsulated with antigen using novel nanomaterials [10].

Occasionally, weak immunogenicity is a problem with inactivated vaccines. Utilizing adjuvants and biomaterials together helps to improve the immunogenicity of vaccines. The route of administration also affects immunogenicity. Tissue-specific administration increases immunogenicity and induces local immunity. Induction of tissue-resident memory T-cells (Trm) is required for rapid antigen re-exposure responses [11]. Vaccine distribution necessitates optimized administration routes and novel medical devices [12,13]. The activation and regulation of T cells determine the vaccine's efficacy, as multiple functions have been attributed to T cells. In this article, I discuss the T-cell responses of vaccines against a variety of infectious diseases based on vaccine technologies and delivery systems. The future directions of these cutting-edge platforms are also discussed.

2. T-Cell Function and Regulation

Figure 1 illustrates the generation of cellular and humoral immunity by vaccines. Vaccine immunology is based on an adaptive immune response mediated by T cells (cellular immunity) and B cells that produce antibodies (humoral immunity).

1. APC takes up an inactivated vaccine and loaded MHC class II as extrinsic antigens and antigen-expressing cells and loaded MHC class I as endogenous antigens.
2. Activated APCs migrate towards the lymph nodes and present antigens to T cells via MHC class II.
3. Antigen presentation via MHC class II activates naïve CD4+ T cells and promotes Th2

cell differentiation. In contrast, antigen presentation via MHC class I activates naïve CD4+ and CD8+ T cells and biased Th1 cell differentiation.

4. Differentiation of naïve T cells depends on the cytokine environment of the microenvironment.
5. Tfh cells enhance the humoral immune response and B cell antibody production. Plasma B cells circulate throughout the body, and neutralizing antibodies prevent infection.
6. Antigen specific CTLs circulate throughout the body and kill pathogen-infected cells.
7. Memory B and T cells maintain immunosurveillance and confer long-term protective vaccine immunity.

It is crucial for the control and elimination of pathogenic infections that adaptive immune responses be generated. The T-cell response determines the effectiveness of vaccines that induce long-lasting immunity and broadly neutralizing antibodies. T cells are either cytotoxic CD8+ T cells (also referred to as CTLs) or helper CD4+ T cells (Th cells). Th cells are divided into subsets based on their profiles of cytokine production. Depending on microenvironmental cytokines, distinct Th-cell differentiation is programmed.

2.1. Cellular Immunity

During an infection, cellular immunity, comprised of cells such as CTLs, recognizes CD8+ T-cell antigen epitopes and plays a pathological role. The presence of pathogen-specific cellular immunity is essential for eradicating bacterial intracellular parasitic infection. It is also essential for the control of viral infections, such as influenza, pox, corona, and herpes viruses [14]. Expression of oncogenic viral proteins contributes to the malignant transformation of HPV-associated tumors in cases of human papillomavirus (HPV) infection. Consequently, the induction or transformation of HPV-specific CTLs has therapeutic antitumor vaccine potential [15]. Antiviral CTLs correlate with the clearance of virus particles associated with disease progression in HIV-1 infection [16]. Eliminating infected cells is crucial in the case of retrovirus infection because the retrovirus integrates its genome into the DNA of the host cell and has a high mutation rate [16]. The mechanism for inducing CTLs is then described, while APCs acquire pathogen-infected cells. Pathogens are degraded into pathogen-derived peptides and loaded as endogenous antigens

onto the surface of major histocompatibility complex (MHC) class I molecules. T-cell receptor (TCR) recognition of MHC class I-loaded peptides on APCs results in the differentiation of naive CD8+ T cells into CTLs. CTLs generate perforin, granzyme, and antiviral cytokines such as interferon-gamma (IFN-) and tumor necrosis factor-(TNF-), which induce apoptosis in pathogen-infected cells [17].

2.2. Immunity Due to

The humoral immunity mediated by antibodies protects against extracellular pathogens. It is well known that passive transport of maternal antibodies across the placenta protects newborns from a wide range of pathogens [18]. The magnitude of the humoral immune response is correlated with disease severity [19]. Following is the mechanism of humoral immunity induction. When a pathogen invades a tissue, APCs take up the pathogen as an exogenous antigen and recognize it. Activated APCs migrate to the draining lymph node, where MHC class II presents the peptide antigen to T cells. MHC class II antigen presentation activates CD4+ T cells and augments cytokine secretion. In particular subsets of CD4+ T cells, Tfh cells promote B cell proliferation and the maturation of the humoral response to enhance antibody affinity for the antigen.

2.3. T Helper

As soon as Th cells identify MHC-loaded peptide antigens on APCs, they begin to differentiate into various effector cells. Th1, Th2, and Th17 are the three major subsets of CD4+ T cells that augment and coordinate antipathogen immunity.

Certain intracellular pathogens are eliminated by Th1 cells, which produce large quantities of IFN- and interleukin (IL)-12. These Th1 cytokines stimulate the activation of monocytes and macrophages and the formation of CTLs, which are responsible for cellular immunity. Antiviral immunity dominated by Th1 plays a role in reducing the severity of infectious diseases [20].

Th2 cells produce ILs such as IL-4, IL-5, IL-6, IL-10, and IL-11 that regulate eosinophils and mast cells. IL-4 is a Th2 cytokine that enhances B cell humoral immune response and antibody production. Tfh cells, not Th2 cells, play a crucial role in the formation and function of B cell responses, it is now evident. Tfh cells that produce IL-21 are found in the germinal center (GC) of secondary lymphoid organs. Additionally, GC Tfh cells produce IL-4, which is necessary for optimal B cell activation [1,2]. Consequently, the induction of Tfh cells is associated with the immunogenicity of vaccines and humoral immunity.

Important roles are played by Th17 cells producing IL-17A, -17F, and -22 in the clearance of cellular pathogens at the mucosal site [21,22]. Th17 cytokines involved in neutrophil regulation and IL-17 regulate the production of IFN-, which is required for the enhancement of the Th1 response. Maintaining mucosal immunity, which controls microbial translocation, requires Th17 cells. Th17 cells aid in the control of chronic HIV-1 infection and the development of AIDS.

Regulatory T cells (Tregs) are a distinct subset of T cells that play a significant role in immune tolerance. They produce a substantial amount of IL-10, which inhibits T-cell activation and differentiation. Increasing antigen-specific Tregs impairs pathogen control and impedes vaccine immunity [23].

In vaccination, formulations, adjuvants, and delivery methods affect the polarization of the Th response and determine its efficacy. Currently, numerous technical platforms for vaccines that induce T-cell-mediated immunity have been developed.

Memory Cells (2.4)

The majority of activated T and B cells die in the weeks following vaccination, while a portion of the activated cells differentiate into memory cells. The presence of immunological memory cells also contributes to infectious diseases' moderate severity. During the 2009 H1N1 pandemic, the presence of preexisting cross-reactive CD4+ T cells in a population of older adults contributed to the prevention of severe influenza symptoms [6,7]. Cross-reactive T-cell-mediated immunity boosts immune responses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and reduces the severity of

COVID-19 [24–27]. In the case of COVID-19, 40–60% of unexposed individuals have virus-specific T-cell immunity due to prior exposure to common coronaviruses, which may contribute to a less severe progression of disease in certain patient populations [28,29].

There are a number of subpopulations of memory T cells. To maintain immunosurveillance [30], effector memory T cells (Tem) continuously recirculate between tissues and blood via the lymph. T cells with central memory (Tcm) patrol secondary lymphoid organs. Without recirculation, memory T cells have been discovered to reside in infection frontline sites such as the skin, lungs, and gastrointestinal tract. These T-rm cells play crucial roles in a rapid local immune response, which is essential for preventing pathogen invasion [11,31]. Immunological memory is crucial to the success of vaccines because memory cells remember the antigen and elicit a rapid and robust immune response upon subsequent antigen exposure. Based on this immune memory response, the prime-boost vaccination protocol increases vaccine immunity. The maintenance of memory cells is essential for providing long-lasting vaccine immunity. IL-15 regulates the longevity and proliferation of memory T cells, and the GC reaction generates long-lived memory B cells [32,33].

3. Vaccine Innovation

Strategic induction of T-cell-mediated immunity is the key to vaccine development success [34], despite the importance of the T-cell response in determining the pathogenicity of an infection. Currently, the magnitude of cellular and humoral immune responses are assessed for a number of candidate vaccines. Generally, T-cell responses are evaluated in the early phases of clinical trials, and vaccine efficacy is measured by the protective rate, with clinical judgment occurring in the final phase. Assessing the immunological properties of the recipients facilitates the determination of the vaccine's immunogenicity.

While serological assays are used to evaluate the humoral immune response, the immunogenicity of vaccines is frequently determined by the seroconversion rate of antigen-specific antibodies after vaccination. In contrast, T-cell responses are evaluated in terms of antigen-stimulated peripheral blood mononuclear cells (PBMCs). Popular methods for measuring cytokine secretion from PBMCs include enzyme-linked immune-spot (ELISPOT) and intracellular cytokine staining. Evaluation of T cells producing cytokines in response to antigen re-exposure is essential for understanding the antipathogenic efficacy of vaccines.

The emergence of virus variants that evade vaccines or preexisting antiviral immunity has frequently been a source of concern [35]. The newly emerging Omicron SARS-CoV-2 variant evades vaccination-induced anti-spike neutralizing antibodies [36,37], despite the fact that booster administration of SARSCoV-2 vaccines protects against severe disease. Moreover, this variant is extremely resistant to monoclonal therapeutic antibodies [38]. Effective across all variants is the promotion of broadly neutralizing antibodies. Immunity mediated by T cells is crucial. Multiple SARS-CoV-2 immunodominant T-cell epitopes are located not only in the spike but also in the M, N, and other nonstructural (NS) proteins [39]. The majority of current SARS-CoV-2 vaccines target spike proteins as antigens. In actuality, preexisting polymerase-specific T cells inhibit infection and exhibit cross-reactivity against Coronaviridae [26].

Pre-existing antibodies may exacerbate the severity of DENV infection and enhance viral replication [40]. The only licensed vaccine against DENV is Dengvaxia. However, it may only be administered to seropositive individuals. Low vaccine efficacy is observed in seronegative individuals, and vaccination may increase the risk of severe dengue disease. Existing insufficient cross-reactive vaccine immunity exacerbates the pathogenicity of subsequent DENV infection caused by the wild-type virus. Dengvaxia is composed of a chimeric live-attenuated yellow fever virus that expresses the structural pre-membrane (prM) and envelope (E) genes of all four DENV serotypes. This vaccine contains a yellow fever NS-protein. The absence of DENV NS proteins failed to induce T-cell responses against all DENV serotypes [41]. DENVax (TAK-003) is a potential DENV vaccine consisting of a chimeric live-attenuated virus derived from the DENV2 PDK-53 strain, which was

obtained by replacing the DENV-2 prM and E genes with those of other serotypes. DEN-Vax elicits durable humoral and cellular immunity and is effective against all DENV serotypes, according to studies [42–45].

Targeting the immunodominant epitopes of pathogens is also essential for the development of cross-reactive vaccines with enhanced immunogenicity. The presence of CD8+ T cells specific for conserved epitopes correlates with a milder disease in COVID-19 patients [25]. Bioinformatics and analyses of peptide HLA complexes have revealed that ORF1ab-derived epitopes have the potential to serve as optimal vaccine antigens [46,47]. These hypothesized epitopes are immunodominant and highly conserved.

Seasonal influenza vaccines targeting conserved epitopes have been developed. As antigens, the majority of commercially available seasonal influenza vaccines employ trivalent or quadrivalent inactivated hemagglutinin (HA) subunits. Vaccine strains are selected twice yearly based on surveillance data, and the effectiveness of influenza vaccines is determined by the prediction of epidemic strains. An induction of T-cell responses that recognize conserved epitopes, such as NS proteins, would confer protection against multiple strains and seasons. Multimeric/M-001 is a candidate recombinant protein containing nine conserved B-cells, CD4+ and CD8+ T-cell epitopes from HA, the nucleoprotein, and matrix protein 1. (M1). Flu-v is an additional candidate vaccine containing conserved peptides derived from M1, M2, and the nucleoprotein [48,49]. These two influenza vaccine candidates exhibited a robust induction of conserved, cell-specific epitopes. Unfortunately, BiondVax Pharmaceuticals Ltd. recently announced that the Multimeric001/M-001 vaccine did not demonstrate significant efficacy against infection.

4. Vaccine Technological Platforms

To induce cellular and humoral responses to vaccines, it is essential to develop technical platforms such as antigen design, adjuvants, and delivery systems. Live-attenuated vaccines (LAVs) are conventional vaccines that have been developed as live-attenuated formulations containing pathogens that have been weakened. LAVs are more immunogenic and induce both humoral and cellular immune responses. Bacillus Calmette–Guérin (BCG), which was developed in the 1920s, is considered the first T-cell-inducing live attenuated vaccine (LAV) against tuberculosis [50]. BCG induces specific memory T cells that protect against Mycobacterium tuberculosis' intracellular parasitic infection [51].

Inactivated or subunit vaccines have no risk of infection and a more stable formulation than live attenuated vaccines [3]. Thus, many licensed vaccines utilize inactivated antigens. The administration of inactivated antigens results in the production of antigen-specific neutralizing antibodies that provide protection against pathogenic infections. In contrast to live vaccines, however, inactivated vaccines produce a weaker vaccine response.

Vaccines based on nucleic acids are a relatively new technology that employs genetically modified DNA/mRNA to elicit an immune response against antigens. The ability of these vaccines to induce cellular and humoral responses against designed epitopes is a significant advantage. DNA vaccines have numerous benefits, including safety, heat stability, portability, and affordability. In the 1990s, the concept of a DNA vaccine was introduced. Wolff et al. demonstrated the expression of foreign antigens by administering plasmid DNA intramuscularly [52]. The antigen expression of plasmid DNA requires transport into the nucleus of the cell. Due to the limitations of vaccine delivery technology, DNA vaccines elicit less robust immune responses than other vaccine platforms. Consequently, they are frequently evaluated with a novel injection system for the creation of DNA vaccines. In India, ZyCoV-D was the first DNA vaccine to be approved. This SARS-CoV-2 vaccine was administered intradermally using a jet injector [53].

Against SARS-CoV-2, viral vectors and nucleic acid-based vaccines are currently used extensively. Both platforms are based on genetic engineering, which enables the induction of Th1-biased vaccine immunity through intracellular expression of genetically engineered antigens [54–61].

Vaccine Development Utilizing Virus-Based Vectors

Antigens can be expressed within cells using viral vectors, which serve as a delivery system. The concept of viral vectors was introduced in 1972 when Jackson et. al. The virus from which a vector is derived determines its unique characteristics. Most viruses are genetically modified to reduce or eliminate pathogenicity, and the majority of viral vectors are incapable of replication.

Several viral vectors have been used in clinical trials, and the vaccine-specific cellular and humoral immune responses have been measured, depending on the target infection. In the development of an HIV-1 vaccine, viral vectors have received a great deal of attention; the induction of a virus-specific CTL response is considered essential because the surface envelope glycoprotein (gp120) of HIV-1 is highly susceptible to mutation and evasion of neutralizing antibodies [63]. Although a CTL-inducing vaccine cannot prevent HIV-1 infection, it can control viral loads by eliminating virus-infected cells, thereby slowing the progression of the disease [64]. Antigens must be delivered intracellularly through the MHC class I antigen presentation pathway in order to induce HIV-1-specific CTLs. Numerous types of recombinant viral vectors for intracellular antigen-encoded gene delivery have been developed [65].

Due to its high transduction efficiency, high level of transgene expression, and broad viral tropism, recombinant adenovirus (Ad) is the most suitable vector. The Ad5 vector vaccine, also known as MRKAd5, has garnered special interest in the development of an HIV-1 vaccine. Despite eliciting CTL responses in 75% of recipients in a Phase IIb clinical trial (STEP Study/HVTN502) [66], it was found that this vaccine was incapable of preventing HIV-1 infection. This study revealed that preexisting immunity to Ad5 in vaccine recipients may not only reduce vaccine efficacy but also increase the risk of HIV-1 infection [85]. Based on this experience, circumventing anti-vector immunity and strategies for protective T-cell responses, including vaccine regimens, should be reconsidered. In 2009, a Phase III clinical trial (RV144 study) in Thailand demonstrated partial HIV-1 infection protection [69–71]. The RV144 study was conducted using a heterologous prime-boost regimen in which priming was performed using an HIV-1 Env Gag-expressing vaccinia virus-derived vector (ALVAC-HIV (vCP1521)) and boosting was performed using recombinant gp120 protein (AIDSVAX B/E). RV144 could induce HIV-1-specific CD4+ T cells predominately. Sadly, RV144 demonstrates only 24 percent antibody-dependent HIV-1-specific CTLs. Recent discontinuation of the ALVAC-HIV/AIDSVAX B/E vaccine was due to its lack of efficacy in Phase IIb/III trials in South Africa (HVTN 702) [72].

Despite the fact that the HIV-1 vaccine has not yet been licensed, a number of technological advances have been developed to overcome preexisting anti-vector immunity. Due to the low seroprevalence in humans, Ad type 26 (Ad26), type 35 (Ad35), or chimpanzee Ad (ChAd)-based vectors can circumvent anti-vector immunity [86,87]. These vectors were utilized in licensed SARS-CoV-2 vaccines referred to as Vaxzevria (ChAdOx1 nCoV-19/AZD1222), Janssen (Ad26.COV2.S), and Sputnik V. (Gam-COVID-Vac). These vaccines induce powerful CD8+ and Th1-dominant CD4+ T-cell responses [59–82]. Th1-biased vaccination immunity contributes to COVID-19's moderate clinical outcomes. In addition, an Ad vector vaccine is anticipated for a number of additional infectious diseases, including RSV and Zika virus [83,84]. MVA is a promising vector derived from the Ankara strain of highly attenuated vaccinia. Vaccinia virus has been utilized historically for smallpox vaccines, and its efficacy and safety in vaccine administration have been demonstrated. A heterologous two-dose regimen against Ebola virus disease (EVD) using vectors Ad26 (Zabdeno, Ad26 ZEBOV) and modified vaccinia Ankara (Mvabea, MVA BN-Filo) has been licensed for human use [77]. Although the role of T-cell-mediated immunity in EVD is still unknown, heterologous Ad26 and MVA vector vaccine regimens induce robust humoral and cellular responses that persist for one year following vaccination. As a vaccine vector, Vesicular stomatitis virus (VSV) has also been extensively studied. VSV has low viral pathogenicity and human anti-vector immunity is uncommon [88,89]. As a licensed EVD vaccine, a VSV vector vaccine expressing the glycoprotein of an Ebola virus (Ervebo, rVSV-ZEBOV) has also been developed. Ervebo is a replication-competent viral

vector vaccine with the Ebola virus GP on its surface and a VSV morphology. Even though T-cell responses to this vaccine were low to moderate [75,76], Ervebo offered 100 percent protection against EVD in a Phase III trial that focused primarily on the production of neutralizing antibodies.

Vaccines based on viral vectors are being developed as a treatment for HPV-associated tumors. Current licensed HPV vaccines (Gardasil, Cervarix, and Silgard) are based on virus-like particle formulations derived from HPV-L1 capsid expression. HPV infection is prevented by inducing HPV-L1-specific humoral immunity. In contrast, eliminating infected cells is useful for treating cancerous lesions and for preventing malignant transformation of HPV-associated tumors. TA-HPV and MVA E2 are recombinant MVA vector vaccines that, respectively, express the E6/E7 fusion protein and the E2 protein of HPV [73,74]. For cancer therapeutic vaccines, the induction of cellular immunity directed against the oncogene products E2, E6, and E7 would be effective.

6. mRNA Vaccine Creation

In the 1990s [52], the concept of mRNA vaccines was proposed. The immunogenicity of these vaccines is determined by antigen-encoded mRNA being translated into cells. mRNA is a small molecule that can be administered repeatedly without inducing anti-vector immunity. As the translation of mRNA occurs in the ribosome, there is no risk of infection or insertional mutagenesis, and the process is safe. The first animal study involving an mRNA vaccine demonstrated a CD8+ T-cell response against influenza in mice [90]. Compared to other vaccine platforms, manufacturing processes for mRNA vaccines are more efficient and less expensive. They are able to produce an in vitro transcription enzyme reaction using a cell-free manufacturing process and animal-free ingredients. Thus, mRNA enables the elimination of time-consuming processes involved in conventional vaccine production [91,92].

The results of representative mRNA vaccines and T-cell-mediated immunity are summarized in Table 2. During the COVID-19 pandemic, two SARS-CoV mRNA vaccines were licensed for the first time: mRNA1273 and tozinameran (BNT162b2). In Phase III clinical trials, both vaccines induced both neutralizing antibodies and Th1-biased SARS-CoV-2-specific T-cell responses with high vaccine efficacy [93,94]. In preclinical studies, an increase in Tfh cells was also observed in draining lymph nodes, which may confer long-lasting protective antibody responses [55,95].

In the clinical use of mRNA vaccines, instability and translation efficiency are two major issues. mRNA modification and nanomaterial encapsulation are two strategies that are commonly used in mRNA vaccines to address these issues.

6.1. Modification of mRNA

Modifications to mRNA can increase the stability of mRNA vaccines. Principal mRNA modification techniques include the following: (1) adding a 5t cap analog, (2) optimizing 5t and 3t untranslated regions (UTRs), (3) elongating the poly(A) tail, (4) optimizing the codon in the open reading frame, and (5) replacing uridine with pseudouridine [101,102]. [103,104] Adding a cap analog to the 5t end of mRNA increases its stability and translation efficiency. The 5t capping of mRNA inhibits exonuclease degradation and enhances binding to the eukaryotic translation initiation factor 4E [105,106]. Through interactions with RNA-binding proteins, regulatory elements in the 5t UTR and the length of the 3t-UTR also increase translation efficiency [107]. The length of the poly(A) tail stabilizes mRNA and is closely related to the efficiency of translation [108,109]. Additionally, the selection of an optimized codon increases the rate of antigen translation. It entails the secondary structure of mRNA, the stability of mRNA, and the rate of translation elongation [110,111]. mRNA translation efficiency is improved by substituting synonymous codons and GC-rich sequences [112]. In addition, the modified nucleoside increases protein expression in mammalian cells and decreases their immunogenicity [113]. The substitution of uridine with N1-methyl-pseudouridine (m1) is the most common modification and has been incorporated into the design of mRNA vaccines [114].

6.2. Encapsulation of mRNA

mRNA vaccines are frequently developed by encapsulating mRNAs within nanomaterials. Encapsulation protects mRNA from nuclease degradation in vivo and enhances chemical stability, hydrolysis, and oxidation during storage [115]. In addition, appropriate nanomaterials permit the delivery of mRNA to immune cells. Naked mRNA possesses a high negative charge density, and cationic materials facilitate fusion with host cells and enhance the in vivo stability of mRNA.

For the encapsulation of vaccine antigens, numerous polymeric materials (chitosan, polyethylenamine, PLGA, and -PGA), lipids (DOSPA, DOPE, and DOTAP), and proteins (protamine) have been investigated [116,117]. mRNA vaccines are the most popular vaccine delivery method. LNPs typically consist of four lipid components: cationic lipids, cholesterol, phospholipids, and polyethylene glycol (PEG). During internalization, cationic lipids facilitate the intracellular delivery of mRNA via host cell membrane fusion. During production, they also improve the charge-driven encapsulation of negatively charged mRNAs. Phospholipids enhance the stability of bilayer lipid structures through conformation. PEG increases the half-life of LNPs, thereby regulating particle size and preventing aggregation during storage.

The particle size of LNP-mRNA is approximately 60–100 nm after production mixing. The size and shape of LNP-mRNA are related to the vaccine's in vivo durability, distribution, and immunogenicity [118]. The administration of NPs with a diameter of less than 100 nm is likely to drain lymph nodes, thereby increasing the immunogenicity of the vaccine. The administration of NPs induces transient inflammation that drives the recruitment of neutrophils and APCs, and the engineered nanomaterials are effective adjuvants for the induction of appropriate vaccine immunity [10].

7. Targeted Vaccine Delivery

The majority of licensed vaccines are given intramuscularly. Due to the presence of tissue-resident immune cells, the antigen delivery route influences immunogenicity. This suggests that a different route of administration has the potential to enhance the immunological properties of a vaccine [119]. Moreover, the production of specific Trm cells is essential because it enables a rapid response upon antigen re-exposure [11]. Consequently, novel medical devices and biomaterials must take into account the route of vaccine delivery and the regulation of local inflammation.

Intradermal (ID) administration of seasonal influenza vaccines increases immunogenicity and provides dose-sparing effects [120]. ID delivery stimulates resident immune cells that rapidly enhance humoral and cellular responses. Occasionally, the ID route is used for nucleic acid-based DNA and mRNA vaccines with innovative medical devices [121]. ID vaccination with mRNA-LNPs encoding multiple viral surface antigens induces a robust antigen-specific Tfh cell response accompanied by long-lived/high-affinity neutralizing antibodies and long-lasting protection [122]. Advantages of a thermostable microneedle vaccine patch include reduced patient pain, enhanced immunogenicity, and the possibility of self-administration [123].

Administration intranasally can induce systemic and local mucosal immunity [124]. Mucosal immunity prevents the invasion of respiratory pathogens by producing IgA on the mucosal surface. In addition, the use of a noninvasive, needle-free nasal route for vaccination is advantageous. A live-attenuated intranasal influenza vaccine is available [125].

In addition, a number of functional biomaterials have been developed to improve the immunogenicity of vaccines. To concentrate and stimulate immune cells at the injection site, scaffold-based vaccines utilize pore-forming polymer gel matrices combined with immune modulating components such as adjuvants and cytokines [126]. In addition, some functional materials conjugated with an antigen have demonstrated efficient lymph node delivery [127].

Conclusions and Prospective Directions

Induction of T-cell-mediated immune responses is essential for vaccine development. The most effective antipathogen immunity induces both cellular and humoral immune responses, as demonstrated by clinical outcome studies of numerous infectious diseases.

Clarifying the antipathogenic immune response clarifies the effective vaccines' mechanism of action. Currently, T-cell responses are routinely evaluated in the earliest phases of clinical trials. The characteristics of specific T cells induced by vaccination are indicative of the efficacy of these vaccines. Th-cell differentiation controls the preference for humoral or cell-mediated immunity. Cross-reactive CTLs decrease the likelihood of ADEs. The duration of vaccine immunity is related to memory cellular function. In nonclinical and clinical vaccine trials, criteria should be established based on the function of T cells. Vaccine efficacy and immune response vary between individuals, with older adults exhibiting delayed and diminished humoral and cellular responses relative to younger adults. The aging process favors the differentiation of short-lived effector T cells over Tfh cells and memory cells [128]. For targeted infectious diseases, the immunogenicity of a vaccine must be evaluated in multiple age groups, including high-risk populations. Due to the weak immune response in immunocompromised or elderly individuals, it may be necessary to administer booster doses in order to induce vaccine immunity.

To induce antipathogenic immunity, numerous technical platforms, including targeted cell delivery of antigens, have been developed. Without adjuvant, viral vectors enable intracellular expression of foreign-encoded genes and confer a robust Th1-dominant immune response. A vector's characteristic is determined by its viral tropism, which enables the transfer of foreign genes to target cells. Despite the disadvantage of anti-vector immunity, viral vectors are well tolerated and are currently used in some licensed vaccines. Additionally, viral vectors are regarded as advantageous delivery platforms for cell and gene therapy, including genome editing. Vectors derived from adeno-associated viruses and lentiviruses are widely used in gene therapy [129]. These vectors are capable of infecting both dividing and non-dividing cells and sustaining the expression of foreign genes over time.

mRNA-based SARS-CoV-2 vaccines have recently garnered attention. mRNA modification and LNP technologies contribute to the stabilization of unstable mRNAs. Based on the results of COVID-19 vaccines, mRNA vaccines may be effective and well tolerated. mRNA vaccines can be manufactured using methods that are rapid, inexpensive, and scalable. Consequently, the development of LNP-mRNA vaccines against other infectious diseases, including influenza virus, RSV, and Zika virus, is accelerating [57,99,130,131]. Self-amplifying mRNA (saRNA) is being developed as the next generation of mRNA vaccine technology. saRNA encodes four NS proteins derived from alphaviruses, NSP1–4. NSP1–4 encode a replicase involved in saRNA amplification, and self-replicative activity enables low doses [56]. Trans-amplifying mRNA is an advanced technology that was developed for the lowest vaccine dose [132]. Continuous technological advancements aid in providing a rapid response to the next pandemic [92].

LNPs are a popular mRNA delivery system. Encapsulation of nanomaterials can also be utilized as a protein or peptide antigen. NPs have the advantage of extending the persistence of an antigen at the injection site, thereby enhancing immunogenicity. NP vaccines also induce long-lasting humoral immunity by boosting Tfh cells and promoting germinal center induction [133].

Vaccines based on nucleic acids have developed into a promising platform for cancer immunotherapy. Several mRNA vaccines encoding tumor-associated antigens are currently undergoing clinical testing. Moreover, the delivery of mRNA encoding immune-modulating genes has the potential to alter the tumor microenvironment [134]. In addition, lentiviral or retroviral vectors are employed in the production of CAR-T cells, which are effective for cancer immunotherapy [135].

Vaccine immunity is not the same as immunity to infectious diseases, and effective vaccines require strategic T-cell induction. Although the role of T cells has not been fully characterized, numerous functions of T cells have been elucidated, such as reducing the severity of illness, controlling viral load, eliminating infected cells, and providing protection against infection. These beneficial characteristics of T cells bolster ongoing efforts to develop T-cell-inducing vaccines.

Conflict of Interest

Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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