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CAR T cells and dendritic cells: vaccinomics perspectives

Abstract

Immunotherapy has revolutionized cancer treatment with Chimeric Antigen Receptor (CAR) T cells and dendritic cell-based vaccines showing remarkable efficacy in certain malignancies. This review provides an integrative overview of recent advances and future directions in vaccinomics. A critical aspect of improving efficacy is the integration of CAR T cells and dendritic cell-based therapies to leverage synergistic effects. Personalization of cancer treatment, facilitated by strategies such as HLA typing and antigen selection, is essential for targeting specific tumor antigens and evading immune resistance. The tumor microenvironment plays a crucial role in modulating immune responses and can be targeted to enhance therapy efficacy. Novel adjuvants and immune modulators, such as Toll-like receptor agonists and checkpoint inhibitors, can further improve efficacy and safety. Predictive biomarkers and patient stratification strategies are essential for optimizing candidate selection. Future research should focus on optimizing CAR T cell and dendritic cell-based therapies, developing novel combinational strategies, and advancing gene editing and manufacturing techniques. Expansion to non-cancerous diseases could greatly broaden the impact on public health. Addressing challenges and limitations associated with these therapies can unlock their full potential and revolutionize the treatment of various malignancies and other medical conditions.

Keywords: immunotherapy, CAR T cells, dendritic cell-based vaccines, vaccinomics, personalized cancer treatment

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Introduction

Immunotherapy has emerged as a powerful and promising approach to treat various malignancies, with Chimeric Antigen Receptor (CAR) T cells and dendritic cell-based vaccines at the forefront of this revolution.[1] These innovative strategies have shown remarkable efficacy in certain cancers; however, there remain significant limitations and challenges that need to be addressed to fully exploit their potential. This review aims to provide an integrative overview of the recent advances in CAR T cells and dendritic cell-based therapies, as well as exploring future directions in the field of vaccinomics.

A. Integrating CAR T cells and dendritic cell-based vaccines

Cancer immunotherapy has gained momentum in recent years, with the development of novel strategies targeting various aspects of the immune system.[2] Among these approaches, CAR T cell therapy and dendritic cell (DC)-based vaccines have shown significant potential in preclinical and clinical studies. CAR T cell therapy involves the genetic engineering of T cells to express CARs, enabling the recognition and killing of cancer cells expressing specific antigens.[3] On the other hand, DC-based vaccines utilize the antigen-presenting capacity of DCs to elicit a robust and specific immune response against tumor cells.[4] Combining these two therapies could potentially enhance their therapeutic efficacy by exploiting the synergistic effects and overcoming individual limitations.

Synergistic effects

The integration of CAR T cell therapy and DC-based vaccines may lead to synergistic effects that enhance the overall therapeutic efficacy.[5] DC-based vaccines can prime the immune system by presenting tumor antigens to T cells, thereby activating the antigen-specific immune response.[6] Simultaneously, CAR T cells can recognize and directly target cancer cells expressing the specific antigens.[7] The combined approach could therefore result in a more robust and sustained anti-tumor immune response. Moreover, the activation of CAR T cells by DCs could potentially increase the expansion and persistence of CAR T cells in vivo. This enhanced expansion may result in a more potent and durable anti-tumor effect. Additionally, the activated CAR T cells could also stimulate the maturation of DCs, leading to an amplified antigen presentation capacity and a more effective immune response against cancer cells.[8–11]

Overcoming limitations of individual therapies

Each immunotherapeutic strategy comes with its own set of limitations, which can be addressed by integrating CAR T cell therapy and DC-based vaccines. One limitation of CAR T cell therapy is the potential development of antigen escape variants, where cancer cells downregulate or lose the target antigen expression, thus evading CAR T cell recognition.[12] By incorporating DC-based vaccines, the immune response can be broadened to target multiple tumor antigens, reducing the likelihood of antigen escape.[13] DC-based vaccines, on the other hand, often face challenges in generating a sufficiently robust and sustained immune response against cancer cells. By combining these vaccines with CAR T cell therapy, the immune response can be amplified, potentially overcoming this limitation. Moreover, CAR T cells can potentially provide additional co-stimulatory signals to enhance the function and survival of antigen-specific T cells, further boosting the overall immune response.[14]

The integration of CAR T cell therapy and DC-based vaccines offers a promising vaccinomics approach to enhance the efficacy of cancer immunotherapy.[15] By harnessing the synergistic effects and overcoming individual limitations, this combined strategy has the potential to revolutionize the treatment of various malignancies.[16] Future research should focus on optimizing the combination of these therapies, including the selection of target antigens, CAR design, and

the delivery and scheduling of DC-based vaccines. Additionally, a deeper understanding of the underlying mechanisms and interactions between CAR T cells and DCs will be crucial in translating these advancements into clinical practice.[17–19]

B. Personalized cancer treatment

Cancer immunotherapy has made significant strides in recent years, with the development of novel strategies such as CAR T cell therapy and DC-based vaccines. CAR T cell therapy involves the genetic engineering of T cells to express CARs that recognize and target cancer cells expressing specific antigens.[20] In contrast, DC-based vaccines utilize the antigen-presenting capacity of DCs to elicit a robust and specific immune response against tumor cells.[4] By integrating these two approaches, we can potentially harness their synergistic effects and overcome the limitations of individual therapies. Personalizing cancer treatment through HLA typing, antigen selection, and targeting the tumor microenvironment could further enhance the overall therapeutic efficacy.[21]

HLA typing and antigen selection

The efficacy of cancer immunotherapy can be enhanced by personalizing treatment based on the patient's unique genetic makeup and tumor characteristics. Human leukocyte antigen (HLA) typing plays a crucial role in this process, as HLA molecules are responsible for presenting tumor antigens to T cells. By analyzing the patient's HLA type, researchers can identify the most immunogenic tumor antigens for each individual, leading to a more effective immune response.[22] The selection of tumor antigens is another critical aspect of personalized cancer treatment. Ideally, antigens should be highly expressed in tumor cells and minimally expressed in healthy cells to reduce the risk of off-target effects.[23] In the context of CAR T cell therapy and DC-based vaccines, selecting tumor-specific antigens can improve the specificity and efficacy of the immune response, while minimizing potential side effects.

Tumor microenvironment targeting

The tumor microenvironment (TME) plays a significant role in shaping the anti-tumor immune response.[24] It is composed of various cellular and non-cellular components, such as immune cells, stromal cells, and extracellular matrix proteins. TME can promote tumor growth, invasion, and immune evasion by creating an immunosuppressive milieu.[25] Therefore, targeting the TME is an essential aspect of personalized cancer treatment.[26] By integrating CAR T cell therapy and DC-based vaccines, researchers can potentially target multiple components of the TME. CAR T cells can directly kill tumor cells and release pro-inflammatory cytokines, which can help modulate the immunosuppressive TME.[27] In parallel, DC-based vaccines can enhance the recruitment and activation of immune cells, such as T cells and natural killer (NK) cells, further contributing to the disruption of the immunosuppressive TME.[28]

The combination of CAR T cell therapy and DC-based vaccines offers a promising vaccinomics approach to personalized cancer treatment. By focusing on HLA typing, antigen selection, and targeting the tumor microenvironment, this strategy has the potential to greatly enhance the efficacy of cancer immunotherapy. Future research should focus on optimizing the integration of these therapies, exploring novel tumor antigens, and developing strategies to modulate the TME effectively. A deeper understanding of the interplay between CAR T cells, DCs, and the TME will be crucial for translating these advancements into clinical practice and ultimately improving patient outcomes.

C. Novel adjuvants and immune modulators

Cancer immunotherapy has undergone rapid advancements in recent years, with the development of CAR T cell therapy and DC-based vaccines. Integrating these approaches offers the potential for a more effective cancer treatment by exploiting the synergistic effects of both therapies. Novel adjuvants and immune modulators, such as TLR agonists and checkpoint inhibitors, may enhance this combination therapy by promoting a more robust anti-tumor immune response.[29] The roles of TLR agonists and checkpoint inhibitors in CAR T cell therapy and DC-based vaccines are explored herein, focusing on their potential to improve personalized cancer treatment.

TLR agonists

Toll-like receptors (TLRs) are a family of pattern recognition receptors that play a critical role in innate immune responses.[30] Activation of TLRs by their agonists can lead to the production of pro-inflammatory cytokines and chemokines, resulting in the recruitment and activation of immune cells.[31] TLR agonists have been widely investigated as adjuvants for cancer immunotherapy, as they can enhance the immunogenicity of vaccines and stimulate anti-tumor immunity.[32] In the context of CAR T cell therapy and DC-based vaccines, TLR agonists can potentially improve treatment efficacy by promoting a more robust immune response.[33] For example, the activation of TLRs on DCs can enhance antigen presentation and stimulate the expansion and activation of CAR T cells, resulting in a stronger anti-tumor response. Moreover, TLR agonists can modulate the tumor microenvironment, promoting the infiltration of immune cells and disrupting the immunosuppressive milieu.[34] Therefore, incorporating TLR agonists into CAR T cell therapy and DC-based vaccines may offer a promising strategy to improve cancer immunotherapy outcomes.

Checkpoint inhibitors

Immune checkpoint inhibitors are a class of drugs that target immune checkpoint proteins, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[35] These proteins function as immune system "brakes," preventing overactivation of immune responses and maintaining self-tolerance. However, tumor cells can exploit these checkpoints to evade immune surveillance and promote immune tolerance.[36] Checkpoint inhibitors block these inhibitory signals, allowing the immune system to mount a more effective anti-tumor response.[37] The combination of CAR T cell therapy and DC-based vaccines with immune checkpoint inhibitors has the potential to enhance cancer treatment efficacy. Checkpoint inhibitors can improve the activation and expansion of CAR T cells, enabling a more potent anti-tumor response.[38] In addition, the combination of checkpoint inhibitors with DC-based vaccines can further stimulate the recruitment and activation of immune cells, promoting a robust and sustained immune response against tumor cells.

The integration of CAR T cell therapy and DC-based vaccines with novel adjuvants and immune modulators, such as TLR agonists and checkpoint inhibitors, offers a promising vaccinomics approach to personalized cancer treatment.[15] By harnessing the synergistic effects of these therapies, researchers can potentially develop more effective and tailored cancer immunotherapies. Future research should focus on optimizing the combination of these approaches, understanding the mechanisms underlying their synergy, and exploring additional adjuvants and immune modulators to further enhance treatment efficacy. Clinical trials are needed to evaluate the safety and effectiveness of these combination therapies in diverse

patient populations and various cancer types.[39] Additionally, the development of predictive biomarkers and patient stratification strategies will be critical for identifying those individuals most likely to benefit from these integrated immunotherapies. As the field of cancer immunotherapy continues to evolve, the incorporation of novel adjuvants and immune modulators into CAR T cell therapy and DC-based vaccines may ultimately lead to more durable and effective treatments for patients. Understanding the complex interplay between the immune system and tumor microenvironment is crucial to harnessing the full potential of these therapies.[40] The exploration of new adjuvants and immune modulators, as well as the optimization of existing approaches, will be pivotal in driving forward the vaccinomics field and improving cancer patient outcomes.

D. Predictive biomarkers and patient stratification

Cancer immunotherapies, such as chimeric antigen receptor (CAR) T cells and dendritic cell (DC)-based vaccines, have revolutionized the treatment landscape for many malignancies.[41] However, response rates to these therapies can be variable, and not all patients derive clinical benefit. To maximize the therapeutic potential of these approaches, it is crucial to develop predictive biomarkers and patient stratification strategies that can help identify individuals most likely to benefit from immunotherapies.[42] In this context, T cell repertoire analysis and tumor mutation burden (TMB) have emerged as promising tools for informing patient selection and treatment decisions.[43]

T cell repertoire analysis

The T cell repertoire represents the diversity of T cell receptors (TCRs) expressed by an individual's T cells, which are essential for recognizing and eliminating cancer cells. Recent advances in high-throughput sequencing technologies have enabled the comprehensive analysis of TCR repertoires.[44] in patients undergoing immunotherapies, such as CAR T cells and DC-based vaccines. This information can provide valuable insights into the immunogenicity of tumor antigens and the dynamics of T cell responses following treatment. Several studies have demonstrated that a diverse T cell repertoire is associated with better clinical outcomes in cancer patients treated with immunotherapies.45 In particular, the presence of tumor-specific T cell clones and the expansion of these clones following treatment have been correlated with improved survival and reduced risk of relapse.[46] Additionally, the persistence of CAR T cells in the peripheral blood has been shown to be a critical factor for maintaining durable responses. By analyzing the T cell repertoire in patients treated with CAR T cells or DC-based vaccines, researchers can identify potential biomarkers for treatment response and resistance, guiding the selection of personalized immunotherapy strategies that are tailored to an individual's immune landscape.

Tumor mutation burden

Tumor mutation burden (TMB) refers to the total number of somatic mutations present within a tumor's genome.[47] High TMB has been associated with increased neoantigen expression, which can render cancer cells more susceptible to immune recognition and elimination.[48] Consequently, TMB has emerged as a promising biomarker for predicting response to immunotherapies, including CAR T cells and DC-based vaccines. Several studies have reported a positive correlation between high TMB and improved clinical outcomes in patients treated with immune checkpoint inhibitors,[49] suggesting that TMB may also have predictive value for CAR T cell therapy and DC-based vaccines. By identifying patients with high TMB, clinicians can potentially select those who are more likely to respond to immunotherapies and tailor treatment strategies accordingly. Moreover, the integration of TMB analysis with other biomarkers, such as T cell repertoire analysis and immune checkpoint expression, could provide a more comprehensive picture of a patient's immune landscape, facilitating the development of personalized immunotherapy approaches that maximize clinical benefit.[50] The identification and validation of predictive biomarkers, such as T cell repertoire analysis and tumor mutation burden,[51] are crucial for optimizing the use of CAR T cells and dendritic cell-based vaccines in cancer patients. By leveraging these tools to inform patient stratification and treatment selection, we can advance the field of vaccinomics and improve patient outcomes in the era of precision oncology.

Future directions

Cancer immunotherapies, such as chimeric antigen receptor (CAR) T cells and dendritic cell (DC)-based vaccines, have shown remarkable success in the treatment of various malignancies. However, there is still significant room for improvement in terms of response rates, duration of response, and minimizing treatment-related toxicities. To further advance the field of vaccinomics and enhance the therapeutic potential of these strategies, future research should focus on optimizing CAR T cell and dendritic cell-based therapies and developing novel combinational strategies.[52] CAR T cells and dendritic cell (DC)-based vaccines have revolutionized cancer immunotherapy, providing remarkable clinical benefits to patients with hematologic malignancies and certain solid tumors. As the field of vaccinomics continues to evolve, future research should focus on advances in gene editing and manufacturing techniques, as well as exploring the potential of these therapies in non-cancerous diseases.[53]

Optimization of CAR T cell and dendritic cell-based therapies

To maximize the clinical benefit of CAR T cells and DC-based vaccines, several aspects of these therapies need to be optimized, including:

I. Antigen selection: Identifying and targeting tumor-specific antigens with minimal expression on healthy tissues will reduce the risk of off-target toxicities and improve the specificity of CAR T cells and DC-based vaccines.

II. T cell engineering: Enhancing the persistence, functionality, and trafficking of CAR T cells by incorporating additional signaling domains or optimizing their costimulatory molecules can potentially improve their anti-tumor efficacy.

III. DC maturation and activation: Improving the activation and maturation of DCs in vaccine formulations may enhance their ability to present tumor antigens and stimulate potent T cell responses, leading to better clinical outcomes.

IV. Delivery systems: Developing novel delivery systems for CAR T cells and DC-based vaccines, such as nanoparticle-based platforms, could improve the bioavailability, targeting, and stability of these therapies, potentially enhancing their therapeutic potential.

Development of novel combinational strategies

Combining CAR T cell therapy or DC-based vaccines with other immunotherapies, targeted therapies, or conventional cancer treatments can potentially overcome the limitations of each individual approach and enhance their overall efficacy.[54] Some promising combinational strategies include:

I. Immune checkpoint inhibitors: Combining CAR T cells or DC-based vaccines with immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4 antibodies, can potentially enhance T cell activation and overcome immune resistance mechanisms within the tumor microenvironment.[55–57]

II. Oncolytic viruses: Oncolytic viruses can selectively infect and kill cancer cells while stimulating anti-tumor immune responses.[58] Combining oncolytic viruses with CAR T cells or DC-based vaccines may lead to synergistic anti-tumor effects and improved clinical outcomes.[59]

III. Targeted therapies: Combining CAR T cells or DC-based vaccines with targeted therapies, such as tyrosine kinase inhibitors or proteasome inhibitors, can potentially enhance the specificity and efficacy of these treatments by modulating the tumor microenvironment or targeting specific signaling pathways involved in cancer progression.[60]

IV. Conventional cancer treatments: Combining CAR T cells or DC-based vaccines with chemotherapy or radiotherapy may enhance their therapeutic potential by inducing immunogenic cell death, increasing tumor antigen release, and promoting T cell infiltration into the tumor microenvironment.[15,54,61]

V. Therefore, optimizing CAR T cell and dendritic cell-based therapies and developing novel combinational strategies have the potential to significantly advance the field of vaccinomics and improve cancer treatment outcomes. By integrating cutting-edge research and technologies from various disciplines, we can pave the way for more effective, personalized, and safer immunotherapies for cancer patients in the future.

Advances in gene editing and manufacturing techniques

Improvements in gene editing and manufacturing techniques are essential for the development of more efficient, safe, and accessible CAR T cell and DC-based therapies. These advancements can potentially enhance the efficacy, safety, and scalability of these treatments, contributing to their broader clinical application.

Gene editing technologies: The emergence of novel gene editing techniques, such as CRISPR/Cas9, TALENs, and ZFNs, can facilitate the engineering of CAR T cells and DCs with enhanced specificity, potency, and safety profiles.[62] For example, gene editing can be employed to knockout immune checkpoint molecules, optimize costimulatory domains, or insert suicide genes for increased control over CAR T cell activity.[63]

Allogeneic CAR T cells: Developing "off-the-shelf" allogeneic CAR T cells from healthy donors can potentially overcome the limitations associated with autologous CAR T cell manufacturing, such as prolonged manufacturing times, patient-specific variability, and high production costs.[64] Gene editing techniques can be used to minimize graft-versus-host disease risks and enhance the compatibility of allogeneic CAR T cells with diverse patient populations.[65]

DC manufacturing: Advancements in the generation, maturation, and antigen loading of DCs can improve the efficacy and consistency of DC-based vaccines.[66] For instance, optimizing the ex vivo culture conditions, incorporating novel maturation stimuli, and utilizing more efficient antigen loading strategies can enhance the immunogenicity and potency of DC-based vaccines.[67]

Dendritic cell vaccines: emerging therapeutic strategies in hematologic malignancies

Several clinical trials evaluating dendritic cell (DC) vaccines in hematologic malignancies have demonstrated potential for improved patient outcomes. Studies have focused on pulsing DCs with tumor-derived proteins or idiotype immunoglobulins, notably in follicular lymphoma and multiple myeloma, to elicit T-cell anti-idiotype responses or provoke reductions in M protein. Trials have yielded varying responses, including delayed time to relapse and improved overall survival in some cases, despite mixed results regarding progression-free survival. Attention has been given to cancer-associated proteins like NY-ESO-1, with ongoing trials exploring peptide vaccines post-autologous transplantation.[68] Trials in chronic myeloid leukemia (CML) have employed ex-vivo generated DC infusions, leading to improved cytogenetic/molecular responses and T-cell proliferative capacity. Despite the limited cytogenetic response observed in a trial using a bcr/abl derived fusion peptide, DC vaccination demonstrates potential in CML treatment. Alternate strategies are under investigation, such as native DC-stimulating protein or peptide vaccinations.[69] Preliminary studies using leukemia-associated antigen WT1 peptides show encouraging results, with observed immunological response and clinical improvements in acute myeloid leukemia patients. Collectively, these findings highlight the promising role of DC vaccines in the treatment of hematologic malignancies.[70]

Advancements and challenges in mRNA-based CAR-T immunotherapy for cancer

The emergence of mRNA vaccines, such as those deployed against COVID-19, has also catalyzed progress in oncology. mRNA vaccines are produced by artificially synthesizing messenger RNA molecules that can be transcribed into functional proteins, thus triggering the immune system's antitumor activity. A promising new approach from BioNTech integrates these mRNA vaccines into adoptive T cell therapy (ACT) to enhance the antitumor activity of CAR-T cell therapy.[71] Using their proprietary RNA-lipoplex (RNA-LPX) delivery system, this approach administers the vaccine to dendritic cells (DCs), stimulating the expansion and persistence of transferred CAR-T cells in cancer patients.[72] Targeting Claudin 6 (CLDN6) and Claudin 18 isoform 2 (CLDN18.2), the vaccine prompts CAR-T cells to proliferate and attack cancer cells, achieving complete tumor regression in a preclinical in vivo study.[73] Early clinical trials have also shown promising results, indicating high response rates in patients with ovarian and testicular cancer. Despite these advancements, challenges still remain in CAR-T immunotherapy, notably in dealing with relapses that occur due to poor persistence of CAR-T cells or loss of tumor antigen.[12] Therefore, novel strategies such as the development of bivalent vaccine boosters targeting multiple tumor antigens and ex vivo DC therapy may help to further improve outcomes. Moreover, the engineering of bispecific CAR-T cell engagers retargeted to DCs could potentially enhance the interaction of CAR-T cells with DCs, thereby stimulating a more potent immune response against cancer cells.[74]

Expansion to non-cancerous diseases

Although CAR T cells and DC-based vaccines have primarily been developed for cancer treatment, their potential therapeutic applications extend beyond oncology. These immunotherapies can potentially be harnessed for the treatment of various non-cancerous

diseases, such as infectious diseases, autoimmune disorders, and transplantation-related complications.

Infectious diseases: CAR T cells and DC-based vaccines can be engineered to target specific pathogens or pathogen-derived antigens, offering a potential therapeutic strategy for combating chronic infections, such as HIV or hepatitis B.[75–77] Moreover, these therapies can be employed as prophylactic interventions to prevent infection or reduce disease severity in high-risk populations.

Autoimmune disorders: Modulating the immune response through CAR T cells or DC-based vaccines may provide a novel approach for treating autoimmune diseases, such as multiple sclerosis or type 1 diabetes. For example, the development of regulatory CAR T cells or tolerogenic DCs can potentially suppress autoreactive immune responses and restore immune tolerance in these conditions.[78]

Transplantation-related complications: CAR T cells and DC-based vaccines can be harnessed to modulate immune responses in the context of transplantation, addressing complications such as graft-versus-host disease, organ rejection, or viral infections post-transplant. For instance, CAR T cells or DC-based vaccines can be tailored to selectively target alloreactive T cells or stimulate tolerance-inducing pathways to improve transplant outcomes.[79–82] The future of vaccinomics lies in advances in gene editing and manufacturing techniques, as well as expanding the application of CAR T cells and dendritic cell-based therapies to non-cancerous diseases. By embracing these innovative approaches, we can unlock the full potential of these immunotherapies, paving the way for more effective, personalized, and versatile treatment options across a wide range of medical conditions. This will ultimately lead to improved patient outcomes and an overall enhancement of public health. Continued research and development efforts in the field of vaccinomics should focus on optimizing the design and delivery of CAR T cells and dendritic cell-based therapies, investigating potential synergistic effects with other immune modulators, and exploring the most effective strategies for patient stratification and personalized treatment plans. Additionally, fostering international collaborations, sharing research findings, and streamlining regulatory processes can expedite the translation of these therapies from the bench to the bedside. Furthermore, an emphasis on the development of cost-effective and scalable manufacturing processes will be crucial in ensuring that these cutting-edge therapies become accessible to a broader patient population.

This can be achieved through innovation in bioprocessing, automation, and quality control, as well as fostering partnerships between academia, industry, and regulatory bodies to facilitate knowledge exchange and resource sharing. To maximize the impact of CAR T cells and dendritic cell-based therapies in the field of vaccinomics, it is essential to educate healthcare professionals, patients, and the general public on the potential benefits and risks associated with these treatment options. This can be accomplished through targeted educational initiatives, such as conferences, workshops, and online resources, as well as engaging with patient advocacy groups and community organizations to disseminate accurate and up-to-date information. Lastly, recognizing and addressing the ethical, legal, and social implications of these advanced therapies is crucial for their successful integration into clinical practice. This includes navigating issues related to patient consent, data privacy, intellectual property, and equitable access to treatment. By fostering open and inclusive dialogue among stakeholders, we can collectively develop responsible policies and guidelines that promote the safe and ethical application of CAR T cells and dendritic cell-based therapies in vaccinomics.

Challenges and limitations

CAR T-cell and dendritic cell-based therapies are promising approaches in the fight against cancer. However, there are significant challenges and limitations associated with their application. For CAR T-cell therapy, off-tumor or off-target toxicity presents a major hurdle. It arises when CAR T cells recognize antigens that are not exclusive to tumor cells, leading to damage to normal tissues.[83] The immunosuppressive tumor microenvironment (TME) also poses a challenge, where inhibitory signals such as PD-1/PD-L1 interaction limit CAR T-cell efficacy.[84] Additionally, antigen loss or mutation may result in the escape of tumor cells from CAR T-cell recognition.[85] Addressing these challenges requires novel strategies. For off-target toxicity, dual CAR T cells that require the recognition of two tumor antigens before activation have been proposed to enhance selectivity.[86] Alternatively, integrating "suicide genes" into CAR T cells provides an off switch to destroy these cells in the event of severe toxicity.[87] For the suppressive TME, combinational therapies with immune checkpoint inhibitors could alleviate the inhibitory signals and restore CAR T-cell functionality.[88]

Dendritic cell (DC)-based therapies are not exempt from challenges either. DCs are pivotal in driving the immune response against tumors, but several factors limit their efficacy. Firstly, the immune response is often insufficient, with inadequate number and persistence of activated T cells.[89] Secondly, the immunosuppressive TME can inhibit DC functionality, resulting in impaired antigen presentation and T-cell activation.[90] Lastly, the production and delivery of DC vaccines remain challenging, with the necessity for individualized treatments and the risks of infection and autoimmunity.[91] To overcome these limitations, advancements are being made in DC vaccine production techniques, including methods to enhance DC longevity and functionality. Co-stimulation of DCs using agonists of Toll-like receptors (TLRs) or CD40 can enhance DC activation and T-cell priming.[92] Similarly, modifying the TME to favor anti-tumor immunity, such as combining DC-based therapy with immune checkpoint inhibitors, is another promising strategy.[93–95]

Current advances in molecular biology and genetic engineering techniques are also offering significant hope to overcome these challenges. The field of synthetic biology might provide an invaluable toolset to engineer more precise, controllable, and effective CAR T cells and dendritic cells. The design of synthetic Notch (synNotch) receptor systems, where the recognition of one antigen can induce the expression of a CAR for a different antigen, might prevent antigen escape by creating a more adaptable and flexible T cell response.[96] In the case of dendritic cell-based therapies, genetic modification of DCs to express specific co-stimulatory molecules, cytokines, or chemokines might augment their immunogenicity and migration ability.[97] Furthermore, nanotechnology could also aid in enhancing DC vaccines by delivering tumor antigens and adjuvants directly to DCs in the body, which could simplify the vaccination procedure and improve patient compliance.[98-100] While CAR T-cell and dendritic cell-based therapies manifest extraordinary potential for revolutionizing cancer immunotherapy, their fruition is impeded by certain limitations. To address these, upcoming studies ought to refine the specificity and efficiency of these therapies, integrate them into combination treatments, and enhance the optimization of production methodologies. Concurrently, the current challenges with these therapies call for multifaceted, inventive solutions that span a gamut of scientific disciplines. Future advancements in the realm of genetic engineering, synthetic biology, and nanotechnology, interwoven with an enriched comprehension of tumor immunology, are poised to steer

the formulation of a novel generation of immunotherapies. Thus, in tandem, these strategies, coupled with meticulous research, are pivotal for harnessing the full potential of CAR T-cell and dendritic cell-based therapies in the field of oncology.

Conclusion

The future of vaccinomics is bright, as advances in gene editing and manufacturing techniques pave the way for the development of more effective, personalized, and versatile immunotherapies. By embracing these innovative approaches and addressing the associated challenges, we can unlock the full potential of CAR T cells and dendritic cell-based therapies, ultimately improving patient care and transforming the landscape of medicine across a wide range of medical conditions.

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Conflicts of interest

The author declares that there is no conflict of interest.

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