

Review

Bidirectional Interplay Between Tumor Vaccines and the Tumor Microenvironment: Mechanisms, Cold-to-Hot Conversion, and Combination Strategies

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Abstract

Therapeutic cancer vaccines are designed to initiate tumor-specific immunity, yet their clinical success depends not only on antigen selection but also on the capacity to overcome the profoundly suppressive tumor microenvironment. Within tumors, abnormal vasculature, hypoxia, nutrient competition, acidic pH, and suppressive myeloid and stromal cells collectively constrain antigen presentation, T-cell priming, trafficking, and effector function, often converting otherwise immunogenic vaccination into an ineffective immune stimulus. Recent advances in neoantigen discovery, dendritic cell engineering, and nucleic acid-based vaccine platforms have improved the precision of antigen delivery, but these gains remain insufficient unless vaccine-induced responses can be sustained and executed within the hostile metabolic and immunologic landscape of the tumor niche. In this context, the tumor microenvironment is not merely a barrier to be overcome, but an active determinant of vaccine outcome that shapes immune editing, promotes exhaustion, and limits intratumoral expansion of cytotoxic lymphocytes. Accordingly, the most promising therapeutic strategies now combine vaccination with checkpoint blockade, radiotherapy, stromal remodeling, or metabolic reprogramming to recondition the tumor ecosystem and permit productive antitumor immunity. Here, we discuss how tumor microenvironmental constraints govern vaccine performance, review emerging platform technologies, and outline combinatorial strategies aimed at converting immune priming into durable tumor control.

Keywords: cancer vaccine; tumor microenvironment; cold-to-hot conversion; immune checkpoint inhibitor; neoantigen; combination immunotherapy; biomarker

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1. Introduction

1.1. Therapeutic Cancer Vaccines: Concepts, Platforms, and Challenges

What they are. Therapeutic cancer vaccines are designed to stimulate the immune system to recognize and attack established tumors, rather than prevent cancer in the first

place. They remain a rapidly evolving immunotherapy platform, with renewed momentum from neoantigen discovery, dendritic-cell approaches, and nucleic-acid vaccine technologies.

What they do. These vaccines target tumor-associated antigens (TAAs), tumor-specific antigens (TSAs), and personalized neoantigens to activate adaptive immunity through exogenous antigen presentation, enabling specific recognition and elimination of tumor cells [1–4]. In recent years, the maturation of whole-exome sequencing (WES), RNA-seq, and HLA-binding prediction algorithms has made it possible to screen immunogenic neoantigens even in tumors with low mutational burden [5–11].

Main platforms. Multiple vaccine platforms are currently under active development, each with distinct advantages and limitations. mRNA vaccines offer rapid production and strong immunogenicity but require lipid nanoparticle delivery systems [12–18]. Peptide vaccines are safe and easy to synthesize but often require potent adjuvants [19]. Dendritic cell vaccines can present multiple antigens but are costly and time-consuming to manufacture [20,21]. Viral-vectored vaccines possess intrinsic adjuvant activity but may be limited by pre-existing immunity [22–25]. DNA vaccines and universal mRNA platforms are also rapidly evolving [26–29].

Approved examples. In melanoma, mRNA-4157 combined with pembrolizumab significantly prolonged recurrence-free survival in adjuvant treatment [12,15]. The individualized mRNA vaccine autogene cevumeran, in a phase I trial (NCT03289962) combined with atezolizumab for solid tumors, induced multi-epitope CD4⁺/CD8⁺ T-cell responses lasting over 23 months, although three grade 4/5 serious adverse events occurred [16,17]. The heterologous prime-boost vaccine GRANITE (ChAd68 + samRNA) plus nivolumab and ipilimumab, in a phase I/II trial (NCT03639714), elicited neoantigen-specific CD8⁺ T-cell responses in 100% of evaluable patients (lasting >52 weeks) [12,18]. In a phase I trial of the long-peptide vaccine NEO-PV-01 combined with pembrolizumab and chemotherapy as first-line treatment for NSCLC, the objective response rate (ORR) among successfully vaccinated patients was 69%; however, 45% of enrolled patients could not receive the vaccine due to disease progression or manufacturing failure [12,19].

Why efficacy is limited. Despite these encouraging results, the overall response rate of single-agent vaccines remains low, particularly in patients with advanced disease, and long-term relapse control remains insufficient [3,30]. The primary reason lies in the immunosuppressive tumor microenvironment (TME), which creates physical, cellular, and metabolic barriers that block vaccine-induced immunity—a challenge that will be discussed in detail in Section 2.

Current directions. To overcome these limitations, current research is focusing on rational combination strategies—integrating vaccines with immune checkpoint inhibitors, TME modulators, chemoradiotherapy, oncolytic viruses, and advanced delivery systems—as well as biomarker-driven patient stratification and personalized neoantigen design. This review systematically examines these approaches and outlines future directions for the field.

1.2. The Tumor Microenvironment (TME) as a Key Barrier to Vaccine Efficacy

The TME is a dynamic and complex regulatory network composed of tumor parenchymal cells, infiltrating immune cells, stromal fibroblasts, extracellular matrix, and multiple soluble factors and metabolites [31–34]. Based on the abundance, activation status, and spatial distribution of immune cells, tumors are classified into immunologically “hot” (inflamed), “cold” (immune-desert), and immune-excluded phenotypes [35–38]. Most clinical solid tumors are of the immune-desert or immune-excluded types, which not only show a lack or spatial segregation of immune cells but also exhibit inflammatory dysregulation, metabolic reprogramming, and aberrant expression of immune-escape molecules,

thereby hindering cancer vaccines at every step—antigen presentation, immune activation, cell infiltration, and effector killing [35,36].

1.3. The Immunosuppressive Tumor Microenvironment: A Multilayered Barrier to Vaccine Efficacy

The immunosuppressive environment in cancer is a coordinated, adaptive ecosystem that actively prevents effective antitumor immunity rather than simply reflecting passive immune failure. It is built from malignant cells, stromal cells, endothelial cells, fibroblasts, extracellular matrix, and infiltrating immune populations that together create a niche that excludes, exhausts, or reprograms effector lymphocytes.

Cellular architecture. At the center of the tumor microenvironment are cancer cells that shape immunity through antigen loss, altered cytokine secretion, immune checkpoint ligand expression, and metabolic rewiring [30,32,39]. Surrounding them, cancer-associated fibroblasts, abnormal vasculature, and dense extracellular matrix can physically restrict T-cell infiltration and create spatial barriers to immune cell access [32,39–42]. Myeloid populations, especially tumor-associated macrophages and myeloid-derived suppressor cells, are major suppressive drivers because they secrete inhibitory mediators and limit antigen presentation [43–48]. Regulatory T cells further reinforce tolerance by suppressing dendritic-cell function and effector T-cell activation [49–51].

Soluble suppressive signals. The tumor milieu is rich in inhibitory cytokines and growth factors, especially TGF- β , IL-10, VEGF, and related mediators that dampen T-cell priming and cytotoxic function [43,52]. These signals also promote immune exclusion, angiogenesis, matrix remodeling, and polarization of myeloid cells toward suppressive phenotypes [53–56]. At the same time, checkpoint pathways such as PD-1/PD-L1 and CTLA-4 impose brakes on T-cell activation and sustain functional exhaustion within the tumor [57]. Together, these pathways convert what should be an inflamed tissue response into a state of chronic immune paralysis.

Metabolic suppression. A defining feature of the immunosuppressive tumor microenvironment is metabolic competition. Tumors consume large amounts of glucose and amino acids, especially tryptophan, while generating lactate, carbon dioxide, and protons that acidify the local milieu. This deprives T cells of essential nutrients and impairs proliferation, cytokine production, and cytotoxicity [43,53–56]. Acidic pH, hypoxia, and low nutrient availability also favor suppressive myeloid cells and reduce the efficacy of dendritic-cell priming. Thus, the tumor microenvironment suppresses immunity not only through receptor-mediated inhibition but also by imposing a hostile metabolic landscape [57].

Immune exclusion and exhaustion. Many tumors are not immunologically “cold” because they lack immune cells entirely, but because infiltrating lymphocytes are rendered dysfunctional. T cells that enter the tumor often become exhausted, with reduced proliferative capacity, diminished cytokine secretion, and sustained expression of inhibitory receptors [35–38]. In parallel, poor antigen presentation and defective dendritic-cell maturation prevent the efficient initiation of new antitumor responses [58–61]. This means the tumor can both block new immune recruitment and neutralize the immune cells already present [62,63].

Stromal and vascular barriers. The physical organization of the tumor also contributes strongly to immune suppression. Abnormal vasculature limits lymphocyte trafficking, and stromal remodeling creates a dense, often collagen-rich matrix that traps immune cells in peritumoral regions rather than allowing them to penetrate the malignant core [40,64,65]. Cancer-associated fibroblasts can reinforce this exclusion through secretion of

chemokines, matrix components, and suppressive factors [36,38,61]. These structural features matter because even a vaccine-primed T-cell response can fail if the effector cells cannot reach the tumor parenchyma.

Relevance for therapy. This immunosuppressive environment explains why many immunotherapies work only in selected patients or in combination regimens. Checkpoint blockade, vaccines, oncolytic viruses, and adoptive cell therapies all face the same barrier: the tumor microenvironment can neutralize immune activation at multiple levels simultaneously [37,66–68]. For therapeutic cancer vaccines specifically, the major challenge is not simply generating tumor-specific T cells, but ensuring those T cells can survive, traffic, and function within a metabolically deprived and suppressive tumor niche [69]. That is why modern strategies increasingly aim to combine immune activation with microenvironmental reprogramming [27,70–76].

In short, the immunosuppressive environment in cancer is a multilayered system of cellular, molecular, metabolic, and structural barriers that collectively prevent productive antitumor immunity. It is not a side effect of cancer biology; it is one of the central mechanisms by which tumors persist and progress. On this basis, this review systematically discusses cold-to-hot conversion strategies, combination regimens, biomarker-guided patient stratification, and current translational challenges, with the goal of providing a framework for advancing precision cancer vaccine therapy.

2. Inhibition of Cancer Vaccine Efficacy by the Tumor Microenvironment

The immunosuppressive TME dampens the priming and amplification of vaccine-induced immunity through multiple layers: physical barriers [64], immunosuppressive cell networks [77], an imbalance of soluble factors [78,79], metabolic dysregulation [80], and defective dendritic cell antigen presentation [81]. Moreover, the immune-desert and immune-excluded TMEs differ significantly in their inhibitory patterns and key targets [35,37,82].

2.1. Physical Barriers: Impeding Immune Cell Infiltration and Vaccine Delivery

Many of the mechanistic insights into tumor physical barriers have been derived from studies of pancreatic ductal adenocarcinoma (PDAC), a malignancy characterized by an exceptionally dense desmoplastic stroma rich in extracellular matrix components. PDAC is often considered an extreme but highly instructive model for studying physical immune exclusion. However, it must be emphasized that PDAC represents a unique tumor entity, and while similar physical barriers exist in other solid tumors—such as breast, lung, and colorectal carcinomas—their extent and composition vary considerably. Therefore, findings from PDAC should be applied to other cancer types with caution.

Excessive cross-linking and deposition of extracellular matrix (ECM), along with malformed tumor vasculature and disturbed blood perfusion, collectively create rigid physical barriers within the tumor lesion [64]. Cancer-associated fibroblasts (CAFs) secrete large amounts of collagen, proteoglycans, and hyaluronic acid, which increase tissue stiffness and interstitial pressure, thereby hindering the penetration of nanoparticles, lipid carriers, and viral vectors [32,39–41]. Abnormal tumor vessels exhibit features such as defective walls, aberrant permeability, and heterogeneous, sparse distribution, further reducing the delivery efficiency of vaccine antigens and circulating immune cells to the tumor site [30,39,42].

In the immune-excluded TME, the number of immune cells is not significantly reduced, but they are confined to the peritumoral stromal area by dense matrix and cannot enter the tumor core to exert their killing function. CAFs specifically interfere with T-cell

chemotactic signals by overexpressing CXCL12, thereby further consolidating the immune-excluded phenotype [36,38,43].

2.2. Inhibiting Vaccine-Induced Immune Activation

Within the TME, regulatory T cells (Tregs), M2-polarized tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and CAFs form an interactive immunosuppressive network [43–48]. Tregs suppress effector T-cell proliferation, activation, and cytotoxicity through direct cell–cell contact or secretion of inhibitory factors such as TGF- β and IL-10 [49–51]. M2-type TAMs, which dominate the macrophage population in the TME, not only secrete abundant immunosuppressive factors that block dendritic cell maturation and antigen presentation but also release matrix-remodeling enzymes that promote ECM deposition and angiogenesis [83]. MDSCs, through the production of reactive oxygen species, nitric oxide, and arginase, deplete essential metabolites required for local immune responses, thereby broadly inhibiting the functions of T cells and dendritic cells; they are key mediators of vaccine resistance in the cold tumor microenvironment [16,43]. Moreover, cancer stem cells can modulate the phenotype of stromal and immune cells via paracrine signals, further amplifying local immunosuppression [48]. In glioblastoma, TAMs are predominant and exhibit an M2 phenotype, with tumor-associated macrophages and MDSCs being the major immunosuppressive populations [41,84]. Similar enrichment of immunosuppressive cells has been observed in various other solid tumors, including head and neck cancer, ovarian cancer, sarcoma, hepatocellular carcinoma, and pediatric rhabdomyosarcoma [85–90].

2.3. Soluble Suppressive Factors and Metabolic Dysregulation: Impairing Immune Cell Function

Tumor cells and stromal cells continuously secrete inhibitory cytokines such as TGF- β , IL-10, and IL-6, which block the maturation and differentiation of dendritic cells and downregulate the expression of co-stimulatory and MHC molecules [43,52]. The Warburg effect-driven metabolic reprogramming of tumor cells, combined with a hypoxic tumor microenvironment, results in multiple metabolic-immune suppressive mechanisms: hypoxia activates the HIF-1 α pathway, upregulating the transcription of immunosuppressive and angiogenic factors; massive lactate accumulation lowers local pH, directly inhibiting effector T-cell proliferation and cytotoxic activity [43,53–56]. The adenosine pathway becomes a metabolic immune checkpoint in hypoxic tumors, where limited oxygen and high extracellular ATP turnover drive accumulation of extracellular adenosine. This adenosine is generated largely through hypoxia-responsive nucleotide catabolism, especially via ectonucleotidase activity, and it rises to levels that are sufficient to reshape local immune behavior rather than merely reflect tissue stress. Once present in the tumor microenvironment, adenosine transmits inhibitory signals mainly through A2A and A2B receptors on immune cells. These receptors couple to cAMP-elevating pathways that suppress T-cell receptor signaling, reduce cytokine production, impair cytotoxic function, and blunt antigen-presenting cell activity. As a result, the earliest phases of antitumor immunity are weakened: dendritic-cell priming becomes less effective, effector T cells are harder to activate, and NK-cell responses are dampened before a productive immune attack can be established [57].

2.4. Defective Antigen Presentation: Compromising Vaccine-Induced Immune Activation

Dendritic cells are the central professional antigen-presenting cells for initiating systemic anti-tumor immunity in response to cancer vaccines, but the immunosuppressive TME can induce DC maturation defects, functional impairment, and increased apoptosis. High levels of TGF- β , VEGF, and other inflammatory inhibitory factors expressed in the TME significantly downregulate the expression of MHC-I/II, CD80, and CD86 on the DC

surface, thereby impairing antigen uptake, processing, and cross-presentation [84–87]. Furthermore, tumor cells reduce overall immunogenicity by downregulating their own antigen expression, losing HLA molecules, and secreting immune-escape-related molecules, which further weakens the recognition and clearance efficiency of vaccine-induced immune cells [62,63].

2.5. Distinct Inhibitory Mechanisms of Immune-Desert and Immune-Excluded Tumor Microenvironments

The immune-desert TME is characterized by a pronounced lack of effector T cells and mature dendritic cells within the tumor parenchyma, accompanied by silenced local chemokine expression, blocked lymphatic homing pathways, and deficient co-stimulatory signals, making it difficult for vaccines to prime effective immune responses [35–38]. In contrast, the immune-excluded TME does not show an obvious paucity of immune cells, but dense extracellular matrix and abnormal blood vessels form physical barriers that prevent vaccine-activated effector T cells from penetrating into the tumor parenchyma, leaving them trapped in the peritumoral area [40,65]. The differences in cellular composition, molecular pathways, and inhibitory characteristics between these two phenotypes provide an important basis for the precision design and individualized adaptation of vaccine combination regimens [37,38] (Figure 1).

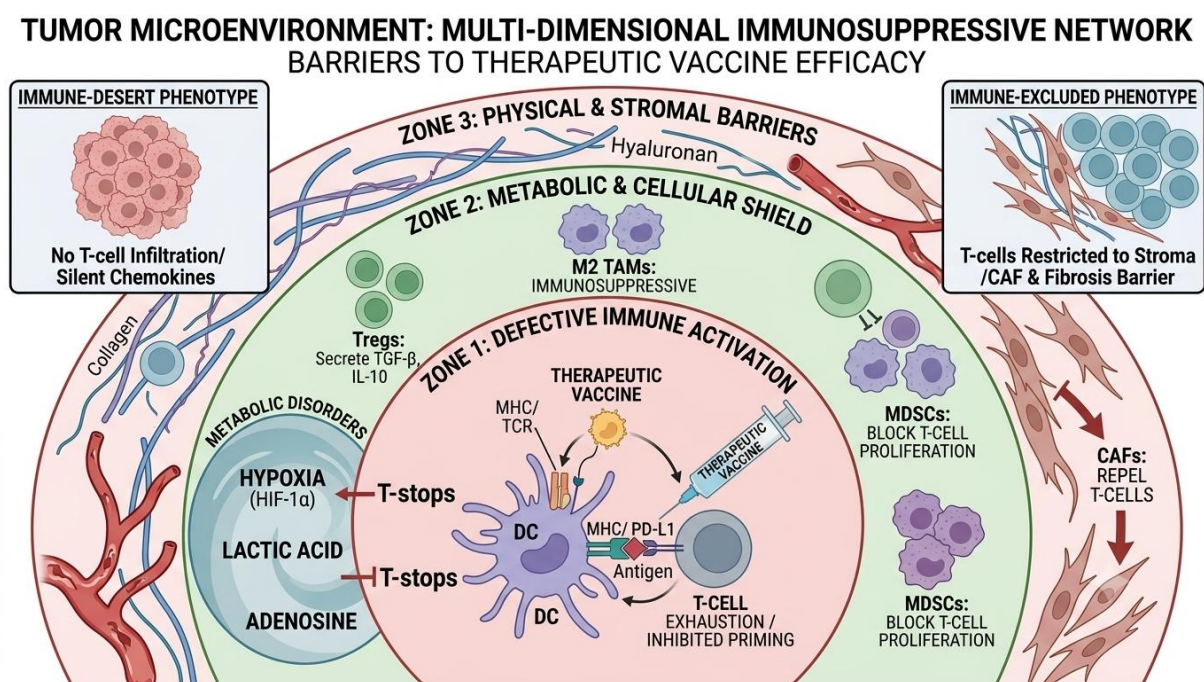


Figure 1. Tumor microenvironment as a multidimensional immunosuppressive network that limits therapeutic vaccine efficacy. The tumor microenvironment is composed of malignant cells, stromal elements, suppressive immune populations, abnormal vasculature, and soluble mediators that together create a barrier to effective anti-tumor immunity. These components restrict antigen presentation, impair dendritic cell function, inhibit effector T-cell priming and infiltration, and promote T-cell exhaustion, thereby blunting vaccine-induced immune responses. In parallel, immunosuppressive cytokines, metabolic competition, hypoxia, and extracellular matrix remodeling further reinforce local immune evasion. Collectively, these mechanisms form a coordinated suppressive niche that surrounds the tumor and prevents therapeutic vaccines from generating durable anti-tumor immunity.

3. Remodeling of the Tumor Microenvironment Driven by Cancer Vaccines

Rather than passively succumbing to TME immunosuppression, different types of cancer vaccines can actively reverse the suppressive microenvironment and promote the transition from cold to immunologically inflamed tumors by activating innate immune signals, regulating the secretion of inflammatory factors, reshaping the polarization balance of myeloid cells, restoring chemokine gradients, and improving vascular and stromal structures [91,92].

3.1. Activating and Recruiting Effector Immune Cells into Tumors

Cancer vaccines efficiently deliver tumor antigens to dendritic cells in the lymph nodes and within the TME, promoting DC maturation and activation, initiating CD4⁺ helper T-cell and CD8⁺ cytotoxic T-cell responses, and establishing long-term immunological memory [93–96]. In the study by Wang et al., an ultrasound-driven nanovaccine (G5-CHC-R) increased CD8⁺ T-cell infiltration to 15.5% in a pancreatic cancer model, accompanied by enhanced IFN- γ secretion [91]. Activated effector T cells secrete chemokines such as CXCL9, CXCL10, and CXCL11, thereby re-establishing chemokine gradients within the TME that guide the directional infiltration of peripheral effector T cells into the tumor lesion [97,98]. Photodynamic therapy combined with nanoparticles can also induce immunogenic cell death (ICD), converting the tumor into an in situ vaccine [99].

3.2. Promoting DC Maturation and Antigen Cross-Presentation

Adjuvant-formulated cancer vaccines are cancer vaccines that include an immune-stimulating adjuvant to make the body mount a stronger, broader, and more durable anti-tumor response. In cancer patients, vaccines often need adjuvants because tumors create an immunosuppressive environment that weakens antigen presentation and T-cell activation. An adjuvant helps the vaccine do more than just deliver antigen. It activates innate immune sensors, promotes dendritic cell maturation, improves antigen processing and presentation, and increases the activation and expansion of tumor-specific T cells. Adjuvant-formulated cancer vaccines comprehensively promote dendritic cell maturation and upregulate the expression of MHC molecules and co-stimulatory molecules by activating pattern recognition receptor signaling pathways such as TLR, STING, and NF- κ B [100,101]. Mature DCs efficiently cross-present exogenous vaccine antigens and activate polyclonal CD8⁺ T-cell responses. In multiple models, the nanovaccine G5-CHC-R combined with whole-body ultrasound promoted DC maturation: in an orthotopic pancreatic cancer model, the proportion of mature DCs (CD11c⁺CD80⁺CD86⁺) within tumors reached 40.3%, and that in lymph nodes reached 17.9%; in a spontaneous breast cancer (4T1) lung metastasis model, the proportion of mature DCs within tumors increased approximately 2.6-fold, lymph node mature DCs also increased, and CD8⁺ T-cell infiltration increased approximately 2.9-fold [91]. A STING agonist is a molecule that activates the STING (Stimulator of Interferon Genes) pathway, a key component of the innate immune system that detects cytosolic DNA and triggers strong antiviral and anti-tumor immune responses. STING (also known as TMEM173 or MITA) is a protein in the endoplasmic reticulum of many cell types, including immune cells, stromal cells, and some tumor cells. It acts as a sensor for foreign or misplaced DNA in the cell's cytoplasm (e.g., from viruses, bacteria, or damaged/dying tumor cells). When cytosolic DNA is detected, the enzyme cGAS produces the natural second messenger 2'3'-cGAMP (a cyclic dinucleotide, or CDN). cGAMP binds to and activates STING, which then triggers a signaling cascade involving TBK1 and IRF3. This leads to the production of type I interferons (e.g., IFN- β), other pro-inflammatory cytokines, and chemokines that recruit and activate T cells, natural killer cells, and

other immune effectors. The pathway bridges innate and adaptive immunity and helps “alert” the immune system to threats like infections or cancer. STING agonists are synthetic or modified compounds designed to mimic natural ligands like cGAMP and directly or indirectly activate STING. They amplify immune responses, particularly useful in cancer immunotherapy: they can turn “cold” tumors (with low immune infiltration) into “hot” ones by promoting inflammation, antigen presentation, and T-cell priming within the tumor microenvironment. They are often studied in combination with checkpoint inhibitors (e.g., anti-PD-1/PD-L1). Types of STING agonists include: (1) Cyclic Dinucleotide (CDN) analogs—direct mimics of cGAMP or bacterial CDNs (e.g., c-di-GMP), such as ADU-S100 (MIW815), MK-1454, and BMS-986301, which are potent but face challenges like poor stability, rapid degradation, or limited systemic delivery; (2) Non-CDN small molecules—more drug-like compounds with better stability and pharmacokinetics, such as diABZI and MSA-2; and (3) Advanced delivery formats—antibody-drug conjugates (ADCs) linking STING agonists to tumor-targeting antibodies, as well as exosomes, nanoparticles, or engineered bacteria (e.g., SYNBI891) for targeted or sustained release. Many STING agonists have shown promising preclinical anti-tumor activity and are in clinical trials (mostly Phase 1/2), often given intratumorally initially to limit systemic toxicity (e.g., cytokine release). Challenges include optimizing delivery, reducing side effects, and identifying responsive patients. Co-administration of a STING agonist can further amplify DC cross-presentation and repair the antigen-presentation defects of the immune-desert TME [102].

3.3. Reshaping the Myeloid Cell Landscape in the Tumor Microenvironment

Cancer vaccines can reshape the polarization and differentiation patterns of myeloid cells in the TME by balancing local pro-inflammatory and anti-inflammatory factor secretion. Pro-inflammatory cytokines such as IFN- γ and TNF- α induced by vaccination drive M2-type macrophages to polarize toward the anti-tumor M1 phenotype, while simultaneously inhibiting the local recruitment and expansion of MDSCs [103]. In a study by Zhang et al., a *Listeria*-vectored cervical cancer vaccine reduced the expression of MDSC-inducing factors through inhibition of the JAK1-STAT1 and JAK2-STAT3 pathways, thereby decreasing MDSC formation and impairing their immunosuppressive function [104]. After inoculation of advanced tumors with the PC7A nanovaccine, infiltration of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) increased, and their immunosuppressive activity was enhanced; CD300ld is a cell-surface immune receptor in the CD300 family, also known as CD300D or CMRF35A4. It is a single-pass type I membrane protein with an Ig-like domain, and in mice, it is strongly associated with neutrophils, especially polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) in tumors. Functionally, recent studies link CD300ld to immune regulation in two different contexts: in cancer, it supports tumor-promoting neutrophil/PMN-MDSC activity and helps create an immunosuppressive microenvironment, while in infection it appears to promote neutrophil bacterial phagocytosis. In the tumor setting, blocking CD300ld reduced tumor growth and improved response to anti-PD-1 therapy in mouse models.

In short, CD300ld is best thought of as a neutrophil-associated immunoregulatory receptor with emerging relevance in both cancer immunology and innate defense. Accordingly, knockout of CD300ld abrogated PMN-MDSC recruitment and T-cell suppressive function, restoring vaccine efficacy [105].

3.4. Improving Vascular Normalization and Reducing Extracellular Matrix Deposition

Personalized neoantigen vaccines and peptide vaccines can inhibit aberrant angiogenesis and promote the normalization of tumor vascular structure and function by modulating the TME cytokine network [106,107]. In a pancreatic cancer model treated with the

anti-gastrin vaccine PAS combined with anti-PD-1, Masson's trichrome staining showed a significant reduction in the fibrosis score in the combination group ($p = 0.0009$), indicating that the vaccine reduced ECM deposition [108]. Cancer vaccines can also inhibit excessive proliferation and activation of CAFs, reduce tumor tissue stiffness and interstitial pressure, break physical barriers, and thereby create favorable conditions for extensive infiltration of effector immune cells [109,110].

4. Strategies for Cold-to-Hot Tumor Conversion Based on Bidirectional Crosstalk

Leveraging the bidirectional regulatory relationship between cancer vaccines and the TME, multidimensional interventions—targeting immunosuppressive cells, correcting metabolic disorders, breaking physical barriers, and optimizing vaccine design with adjuvants and carriers—can precisely reverse the immunosuppressive landscape and efficiently achieve the phenotypic conversion from cold to hot tumors [36,37,65,111].

4.1. Targeting Immunosuppressive Cells in the Tumor Microenvironment

Specific targeted drugs that deplete or functionally inhibit Tregs, M2-type macrophages, and MDSCs can effectively relieve the immunosuppressive constraints of the TME [112–114]. CTLA-4 antibody (ipilimumab) depletes local Tregs in an Fc-dependent manner. However, high expression of the inhibitory Fc receptor Fc γ RIIB on tumor-infiltrating myeloid cells (e.g., tumor-associated macrophages and dendritic cells) in the TME limits antibody-dependent cellular cytotoxicity/phagocytosis (ADCC/ADCP), thereby reducing Treg depletion efficacy; Fc engineering can enhance Treg depletion [115]. Anti-CD25 antibody (Fc-optimized, IL-2-retaining) combined with PD-1 blockade increases the CD8⁺/Treg ratio [116]. Targeting the IL-8/CXCR2 axis with AZD5069 eliminates MDSC activity and sensitizes tumors to anti-PD-L1 [117]. In pancreatic cancer, CXCR2-targeted nanoparticle delivery of JAK2/STAT3 inhibitors suppresses arginase activity and reduces tumor burden, representing a novel strategy to specifically disrupt MDSC-mediated immunosuppression [118]. A *Listeria*-vectored cervical cancer vaccine reduces MDSC formation via inhibition of the JAK-STAT signaling pathway, significantly lowering MDSC levels and function in vivo, which is a key step in dismantling TME immunosuppression [104]. CSF-1R inhibitors (e.g., PLX3397) block M2-type macrophage polarization [119,120]. In the LLC1 lung cancer “cold” tumor model, a neoantigen DC vaccine combined with CpG and anti-CD38 antibody significantly reduced intratumoral Tregs and inhibited tumor growth [26]. A sequential combination of immunosuppressive cell targeting with tumor vaccines can produce strong synergistic effects [121,122].

4.2. Modulating Tumor Microenvironment Metabolism and Breaking Physical Barriers

Targeting features such as TME hypoxia, lactate accumulation, and aberrant adenosine enrichment, agents such as adenosine receptor antagonists (e.g., AZD4635) and lactate metabolism modulators—including LDH or MCT inhibitors, which can starve tumor cells of metabolic flexibility, reduce acid-driven invasion, and weaken lactate-mediated immune suppression in the tumor microenvironment—can reverse metabolic-mediated immunosuppression. Some strategies combine lactate blockade with other metabolic stressors, such as intracellular acidification or oxygen modulation, to amplify antitumor effects [57,123,124]. Using PEGPH20 to degrade hyaluronic acid or FAK inhibitors to reduce matrix stiffness breaks physical barrier constraints from the stromal architecture [125–128]. For the immune-excluded TME, it is necessary to first relieve physical barriers through matrix degradation and anti-angiogenic interventions, followed by sequential administration of cancer vaccines. For the immune-desert TME, antigen presentation and

chemokine signals must first be restored (e.g., using FLT3L or CD40 agonists) before initiating vaccination [129–133].

4.3. Optimizing Vaccine Design to Enhance Tumor Microenvironment Remodeling Capacity

Screening high-affinity neoantigens based on tumor mutational burden, HLA typing, and TME immunophenotype improves vaccine specificity and immune activation strength [134,135]. Optimizing lipid nanoparticles, cell-membrane biomimetic carriers, and exosome delivery systems enables lymph node-targeted and TME-targeted enrichment of antigens [136–138]. Combining multifunctional adjuvants such as TLR (CpG, R848) and STING (ADU-S100) agonists simultaneously activates innate and adaptive immunity, releasing the local immunosuppressive brakes of the TME [139–142]. In glioblastoma patients, the neoantigen vaccine (GAPVAC) induced robust neoantigen-specific T-cell responses in those not receiving dexamethasone, whereas those on dexamethasone showed no response, indicating that immune status is critical for vaccine-driven TME remodeling [143] (Figure 2).

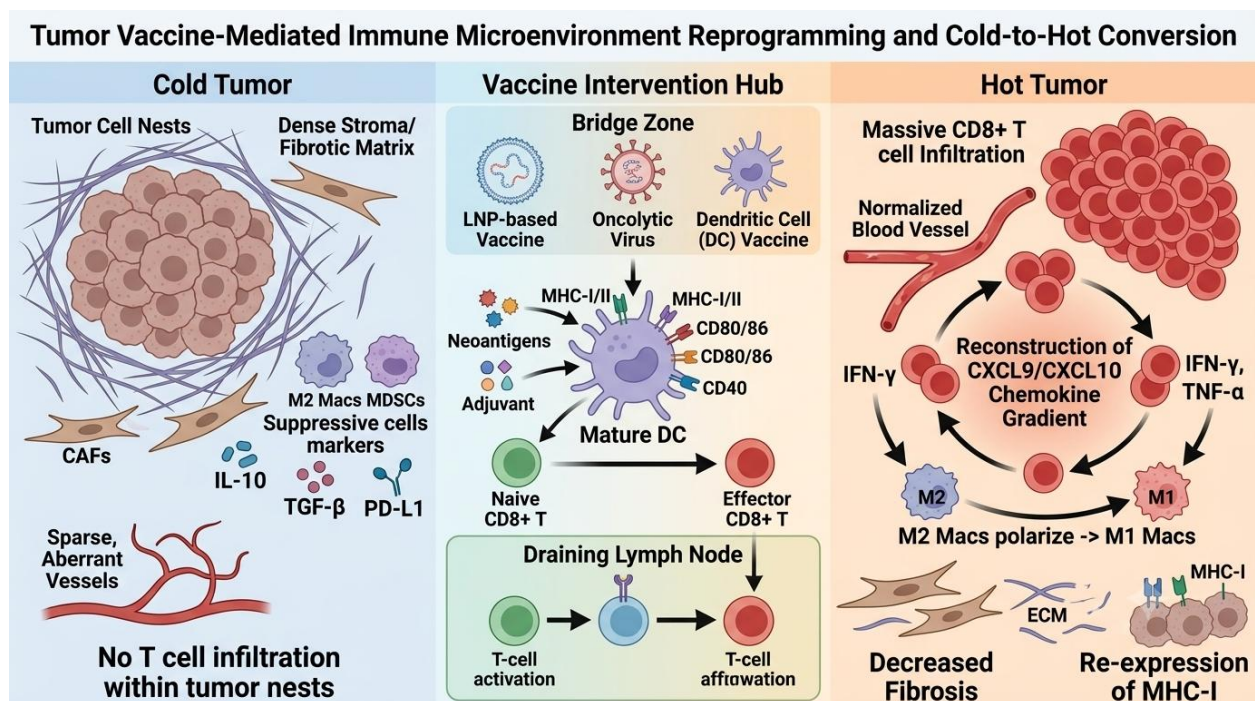


Figure 2. Tumor vaccine-mediated immune microenvironment reprogramming and cold-to-hot conversion.

5. Combination Strategies to Enhance Vaccine Efficacy

Single-agent cancer vaccines are limited by TME heterogeneity, multiple immunosuppressive mechanisms, physical barriers in solid tumors, and insufficient antigen presentation, making it difficult to achieve ideal clinical efficacy. Sequential or simultaneous combination of cancer vaccines with immune checkpoint inhibitors, TME modulators, chemoradiotherapy, oncolytic viruses, and novel delivery systems enables multi-target, multi-timing synergistic regulation of the TME [144–148].

5.1. Cancer Vaccines Combined with Immune Checkpoint Inhibitors

Cancer vaccines prime and expand antigen-specific effector T cells, while PD-1/PD-L1 and CTLA-4 inhibitors relieve T-cell exhaustion and immunosuppressive brakes [146,149–151]. In a phase Ib trial of the GVAX pancreatic cancer vaccine combined with

ipilimumab, more patients in the combination arm showed expansion of mesothelin-specific CD8⁺ T cells, with a trend toward prolonged median overall survival [16]. In melanoma, the oncolytic virus vaccine T-VEC plus ipilimumab achieved an objective response rate (ORR) of 39% (vs. 18% for ipilimumab alone) [152]. In non-small cell lung cancer, durvalumab maintenance therapy after chemoradiotherapy (PACIFIC trial) significantly improved progression-free survival (16.8 vs. 5.6 months) [153]. In hepatocellular carcinoma, atezolizumab plus bevacizumab (IMbrave150) has become a first-line standard [154,155]; the dual immune checkpoint inhibitor combination durvalumab plus tremelimumab was also approved based on the HIMALAYA trial [156,157]. Vaccine-mediated TME remodeling can upregulate PD-L1 expression in the tumor lesion, thereby increasing sensitivity to immune checkpoint inhibitors, while immune checkpoint blockade further promotes deep infiltration of effector T cells into the tumor [158]. Clinical studies have confirmed that this combination approach improves ORR and progression-free survival in various solid tumors [159,160]; however, immune-related adverse events (irAEs) show dose- and timing-dependency, requiring individualized regimen optimization [161,162].

5.2. Cancer Vaccines Combined with TME Modulators

Anti-angiogenic agents (e.g., bevacizumab, cabozantinib) promote tumor vascular normalization, improving tissue perfusion and deep delivery of vaccines and immune cells [163,164]. In the COSMIC-021 trial, cabozantinib plus atezolizumab achieved an ORR of 32% in metastatic castration-resistant prostate cancer [165]. TME modulators such as metabolic regulators, immunosuppressive cell-targeting drugs, and inflammatory pathway modulators can relieve local immunosuppression through metabolic reprogramming, cell phenotype regulation, and inflammatory balance modulation [166,167]. In a pancreatic cancer model, the anti-gastrin vaccine PAS, combined with anti-PD-1, significantly reduced fibrosis and M2-type tumor-associated macrophages [108,168]. The CD40 agonist sotigalimab, combined with chemotherapy and nivolumab, achieved a 1-year overall survival rate of nearly 60% in pancreatic cancer [169]. HDAC3 inhibitors can enhance immunotherapy through the cGAS-STING and ferroptosis pathways [170]. Vagus nerve stimulation, as a non-pharmacological physical intervention, has the potential to convert cold glioblastoma into hot glioblastoma by inhibiting IL-6 [130].

5.3. Cancer Vaccines Combined with Radiotherapy/Chemotherapy

Radiotherapy and chemotherapy directly kill tumor cells, induce immunogenic cell death (ICD), release large amounts of tumor antigens and damage-associated molecular patterns (DAMPs), and thereby create an in situ vaccine effect [171,172]. Radiotherapy combined with a CTLA-4 inhibitor induced an abscopal effect in lung cancer, with shrinkage of non-irradiated lesions by $\geq 30\%$ [173]. In KRAS-mutant pancreatic cancer, the ELI-002 vaccine (amphiphile-modified G12D/G12R long peptides plus CpG) combined with chemotherapy induced T-cell responses and biomarker clearance in a phase I trial [174,175]. Different radiotherapy fractionation regimens, chemotherapy drug types, and administration timing significantly affect the response and safety of combination therapy [97,176,177]. Type I T cells sensitize refractory tumors to chemotherapy by secreting IFN- γ to induce SOCS1, which inhibits oncogenic signaling pathways [97].

5.4. Cancer Vaccines Combined with Oncolytic Viruses

Oncolytic viruses specifically lyse tumor cells, release tumor antigens, and secrete pro-inflammatory factors, actively remodeling the local immunosuppressive microenvironment [22,178,179]. T-VEC (HSV-1 expressing GM-CSF) is the first FDA-approved oncolytic virus vaccine; in melanoma, it significantly increased ORR when combined with

ipilimumab [152,178]. In pancreatic cancer, LOAd703 (an oncolytic adenovirus expressing 4-1BBL and CD40L) combined with chemotherapy and atezolizumab achieved an ORR of 44% and a disease control rate of 94% in 10 patients [180]. The combination of oncolytic viruses and cancer vaccines can doubly enhance antigen presentation and immune cell activation, restore chemokine gradients, and break the intrinsic immune escape pattern of tumors, making it particularly suitable for “cold” tumors [181,182]. In addition to engineered oncolytic viruses, an emerging strategy involves the repurposing of licensed viral vaccines—originally developed for infectious disease prevention—as off-the-shelf anti-tumor immunotherapies. Preclinical studies have demonstrated that vaccines such as measles, mumps, rubella (MMR), yellow fever, Japanese encephalitis, Zika, rabies, influenza, rotavirus, modified vaccinia Ankara (MVA), and dengue vaccines all exhibit oncolytic or immunomodulatory activity against various human cancer cell lines. Similar to oncolytic viruses, these licensed vaccines can reshape the immunosuppressive tumor microenvironment—driving “cold” tumors toward an immune-active (“hot”) state—and synergize with immune checkpoint inhibitors. Mechanistically, live-attenuated vaccines can exert direct oncolytic effects through viral replication, while both live and inactivated vaccines contribute to TME remodeling via type I interferon signaling, upregulation of PD-L1, and recruitment of dendritic cells and CD8⁺ T cells. Importantly, pre-existing immunity to these widely used vaccines does not necessarily impair their antitumor efficacy and may, in some cases (e.g., yellow fever vaccine), even enhance tumor clearance. Clinically, intratumoral injection of the attenuated measles vaccine strain (MV-EZ) has been shown to induce tumor infection and oncolysis in patients with cutaneous T-cell lymphoma and recurrent breast cancer. Given their well-established safety profiles, global availability, and cost-effectiveness, repurposed licensed viral vaccines represent a readily accessible and promising addition to the cancer immunotherapy arsenal, although further randomized controlled trials are warranted to optimize delivery routes and combination regimens [183].

5.5. Cancer Vaccines Combined with Novel Delivery Systems

Novel delivery systems such as lipid nanoparticles [184], cell-membrane biomimetic carriers [185], exosomes [186], and peptide-based composite carriers [187] improve the *in vivo* stability of tumor antigens, their ability to target lymph nodes, and the efficiency of dendritic cell uptake [188,189]. In the study by Wang et al., the G5-CHC-R nanovaccine (constructed based on G5 PAMAM, particle size ~12 nm) exhibited excellent deep penetration ability in a 3D pancreatic cancer tumor spheroid model, delivering sonosensitizers and immune modulators to the tumor core [91]. Integrated design of the delivery system with vaccine antigens and adjuvants enables targeted presentation and controlled release [92,99,111,190]. For example, FeAu-MB complexes self-assemble in the tumor microenvironment and induce ICD when combined with photothermal therapy, converting “cold” tumors into “hot” tumors [191]. Bioorthogonally activated sonodynamic therapy can induce tumor-specific pyroptosis and enhance the *in situ* vaccine effect [92].

6. Biomarkers for Predicting Vaccine Response and Patient Stratification

The efficacy of cancer vaccines shows substantial individual variability, which is closely related to TME immunophenotype, tumor mutational burden, HLA typing, and baseline host immune status [16,88,192–195].

6.1. Tumor Microenvironment-Related Biomarkers

The infiltration density and spatial distribution of CD8⁺ effector T cells and mature dendritic cells within tumor tissues are positively correlated with the response to cancer vaccine therapy; conversely, high infiltration of Tregs, M2-type macrophages, and MDSCs, together with a disordered chemokine profile, indicate a significantly elevated risk of vaccine resistance [34,132,196]. In a glioblastoma neoantigen vaccine trial, patients who did not receive dexamethasone showed an average increase of 71 CD8⁺ T cells/mm² in recurrent tumors [143]. The TME classification system based on immune-desert, immune-excluded, and inflamed (hot) phenotypes can directly guide patient selection for therapeutic regimens and predict long-term prognosis [37,66,197,198].

6.2. Tumor Immunogenicity-Related Biomarkers

Tumor mutational burden (TMB), neoantigen quantity, and HLA typing compatibility are core indicators of intrinsic tumor immunogenicity. dMMR/MSI-H colorectal cancer is highly sensitive to pembrolizumab, with an ORR of 40% [192,199]. In pancreatic cancer, the KRAS G12D mutation can serve as a neoantigen target, and TCR-T cells achieved a 72% partial response in one patient [16,200]. Baseline expression levels of tumor-associated antigens and tumor-specific antigens, combined with mutational spectrum characteristics, enable the precise selection of patient populations that are most likely to benefit from cancer vaccines [135,201].

6.3. Host Immune Status-Related Biomarkers

The distribution of peripheral blood immune cell subsets, the functional homeostasis of dendritic cells, baseline expression of immune checkpoint molecules, and cytokine profiles all directly influence the immune-activation efficacy of cancer vaccines [202–204]. Gut microbiota composition regulates systemic immune homeostasis; *Akkermansia muciniphila* and *Bifidobacterium adolescentis* are positively associated with response to immune checkpoint inhibitors [193,205,206]. The use of glucocorticoids such as dexamethasone severely impairs vaccine-induced T-cell responses [207]. Fecal microbiota transplantation (FMT) can improve responses in PD-1-resistant melanoma [204,208,209]. Molecules related to trained immunity (e.g., BCG- or β -glucan-induced epigenetic reprogramming) may also serve as emerging biomarkers for predicting vaccine responsiveness [195,210,211].

6.4. Clinical Application of Biomarkers

The predictive power of a single biomarker is limited; combining multiple indicators such as TME immunophenotype, TMB, HLA typing, and host immune status significantly improves the accuracy of patient stratification [16,212]. With the widespread adoption of single-cell RNA sequencing, spatial transcriptomics, and multi-omics integration technologies, more novel molecular and cellular biomarkers will be discovered, further supporting the individualized clinical application of cancer vaccines [193,213,214] (Figure 3).

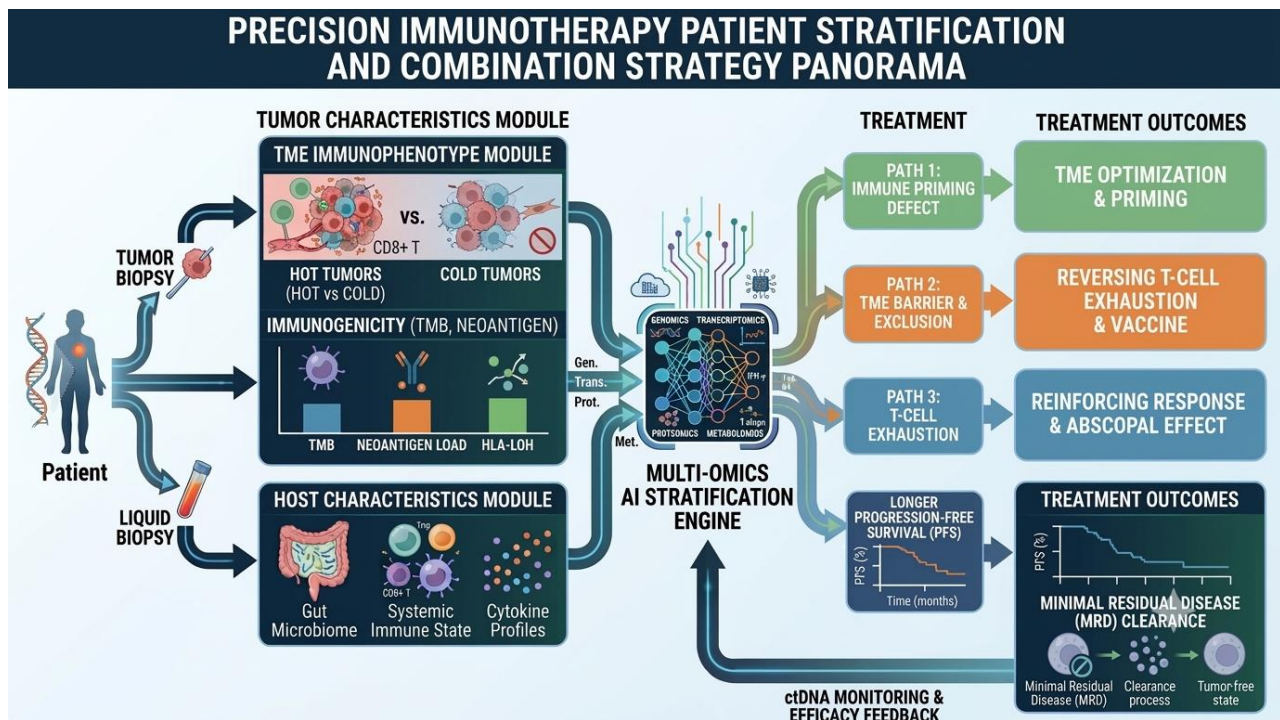


Figure 3. Precision immunotherapy patient stratification and combination strategy panorama.

7. Clinical Trials and Translational Challenges

7.1. Overview of Clinical Trials

In recent years, the number of clinical trials of cancer vaccines as single agents or in multimodal combination therapies has continued to increase. Neoantigen mRNA vaccines (autogene cevumeran, mRNA-4157) combined with PD-1 inhibitors have been shown to prolong progression-free survival in solid tumors such as pancreatic cancer and melanoma [15,215]. The CLDN18.2-targeted CAR-T cell therapy (CT041) enrolled 37 patients with advanced CLDN18.2-positive gastric or pancreatic cancer in a phase I trial. In the pancreatic cancer subgroup ($n = 12$), one partial response (PR) and one complete response (CR) were observed, with an objective response rate (ORR) of 16.7% [16,216]. In hepatocellular carcinoma, atezolizumab plus bevacizumab and durvalumab plus tremelimumab have been approved as first-line treatments [154,155]. In gastric cancer, nivolumab plus chemotherapy (CheckMate 649) has become a first-line standard [217]. In microsatellite-stable (MSS) colorectal cancer, the combination of immune checkpoint inhibitors with chemotherapy plus anti-VEGF (AtezoTRIBE) improved overall survival [218]. Currently, most vaccine combination regimens are still in phase I/II exploratory stages, lacking large-scale, multicenter, phase III evidence-based data, and issues such as administration timing, dose ratio, and applicable indications require further standardization [16,174,219,220].

7.2. Translational Challenges

The clinical translation of cancer vaccines faces multiple practical bottlenecks: (i) pronounced spatiotemporal heterogeneity of the TME, leading to large differences in efficacy of the same vaccine regimen across different pathological types and immune phenotypes of tumors [221–223]; (ii) the lack of a standardized, generalizable multi-omics biomarker system [224,225]; (iii) insufficient deep penetration and targeted delivery capacity of vaccines in solid tumors [226,227]; (iv) the propensity of multimodal combination therapy to induce immune-related adverse events (e.g., CRS, colitis, myocarditis), with grade ≥ 3 irAEs for dual immune checkpoint inhibitor combinations reaching 42–53% [228–230]; (v)

the complexity of mutation screening, carrier preparation, and quality control for individualized neoantigen vaccines, with a production lead time of about 3–4 months, which limits its widespread clinical application [225,231,232]; and (vi) limitations of animal models, as existing models cannot fully recapitulate the human TME [233,234].

7.3. Strategies to Overcome Translational Challenges

In the future, it will be necessary to build standardized biomarker evaluation systems using multi-omics technologies [235,236]; to continuously optimize vaccine antigen screening algorithms (e.g., HLAthena), multifunctional adjuvants, and intelligent nano-delivery carriers [188]; to conduct large-scale, multicenter clinical trials that optimize the timing of combination therapy (e.g., vaccine first, then immune checkpoint inhibitor) [237]; to simplify individualized vaccine preparation and quality control processes (e.g., shortening the production time of mRNA platforms to around 6–8 weeks) [238,239]; to establish comprehensive monitoring and management systems for immune-related adverse events [240]; and to use artificial intelligence to assist neoantigen prediction and digital twin models for vaccine design [5,241,242], thereby pushing cancer vaccines from basic research toward routine clinical application from all directions.

8. Conclusions and Future Perspectives

8.1. Conclusions

There is a close and highly dynamic bidirectional crosstalk between cancer vaccines and the tumor microenvironment (TME), in which each continuously influences the effectiveness of the other. Therapeutic cancer vaccines are intended to induce tumor-specific immunity by enhancing antigen presentation, priming cytotoxic T lymphocytes, and promoting durable immune memory. However, the success of this process depends not only on the quality of the vaccine platform and antigen selection, but also on the local immune context in which the response develops. The TME often functions as a complex suppressive ecosystem that limits vaccine efficacy through multiple, overlapping mechanisms, including defective dendritic cell maturation, poor antigen processing, impaired T-cell trafficking, exclusion of effector lymphocytes, and induction of T-cell exhaustion [16].

At the same time, a successful vaccine response can actively reshape the TME. By increasing the frequency and activity of tumor-reactive T cells, enhancing interferon signaling, and stimulating innate and adaptive immune pathways, vaccines can convert a suppressive niche into a more inflamed and immunologically permissive environment [39,91]. This remodeling may improve immune cell infiltration, increase antigen visibility, and weaken the dominance of suppressive populations such as regulatory T cells, tumor-associated macrophages, myeloid-derived suppressor cells, and tolerogenic dendritic cells. In this sense, cancer vaccines should not be viewed as isolated immune stimulants, but rather as interventions capable of reprogramming the tumor ecosystem when the surrounding barriers can be sufficiently overcome.

Nevertheless, the TME remains a major obstacle to durable clinical efficacy. Hypoxia, nutrient depletion, acidic metabolites, aberrant vasculature, extracellular matrix stiffness, and immunosuppressive cytokines all contribute to immune escape and can severely attenuate vaccine-driven responses. These features may prevent effector cells from reaching the tumor, reduce their viability and function once they arrive, and promote adaptive resistance after initial immune activation. Therefore, the limited success of many cancer vaccines in advanced disease likely reflects not only a lack of immunogenicity but also the inability of vaccine-induced immunity to overcome the multilayered suppressive architecture of the TME.

Taken together, the therapeutic potential of cancer vaccines will depend on strategies that integrate antigen-specific immune activation with deliberate modulation of the TME. Future success is likely to come from combination approaches that pair vaccines with checkpoint inhibitors, myeloid-targeting agents, metabolic modulators, stromal reprogramming strategies, and agents that improve vascular normalization or dendritic cell function [111,121]. Such integrated approaches may shift the balance from immune suppression toward immune activation, thereby enabling more effective, sustained, and clinically meaningful anti-tumor responses. In this framework, understanding and targeting the crosstalk between cancer vaccines and the TME is essential for advancing the next generation of rational cancer immunotherapy [193].

8.2. Future Perspectives

With the rapid development of high-throughput multi-omics, single-cell spatial transcriptomics, artificial intelligence-based antigen screening, and intelligent nano-delivery technologies, personalized neoantigen vaccines will become a core direction for cancer immunotherapy [5,241,243,244]. Precision timing-control strategies based on TME immunophenotyping will enable one-patient-one-regimen individualized customization of vaccine combination therapies [37,38,245,246]. Continuous iterations of novel delivery technologies such as intelligent biomimetic nanocarriers and in situ injectable delivery systems will effectively address the challenges of insufficient tissue penetration, poor targeting, and weak in vivo stability of vaccines in solid tumors [14,99,111,136,190,247]. The cross-disciplinary combination of cancer vaccines with cellular immunotherapies such as CAR-T and CAR-NK [48,211], as well as the combined use of trained immunity inducers (e.g., BCG, β -glucan) with vaccines [242,248], will build a multi-dimensional, three-dimensional anti-tumor immune network. In-depth elucidation of the molecular mechanisms governing the bidirectional crosstalk between cancer vaccines and the TME, together with continuous breakthroughs in key technologies, including antigen screening, adjuvant development, delivery carriers, and optimization of combination regimens, will open up new horizons for precision cancer immunotherapy [16,69,231,249].

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