Molecular Cancer

REVIEW

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Advances in cancer immunotherapy: historical perspectives, current developments, and future directions

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Abstract

Cancer immunotherapy, encompassing both experimental and standard-of-care therapies, has emerged as a promising approach to harnessing the immune system for tumor suppression. Experimental strategies, including novel immunotherapies and preclinical models, are actively being explored, while established treatments, such as immune checkpoint inhibitors (ICIs), are widely implemented in clinical settings. This comprehensive review examines the historical evolution, underlying mechanisms, and diverse strategies of cancer immunotherapy, highlighting both its clinical applications and ongoing preclinical advancements. The review delves into the essential components of anticancer immunity, including dendritic cell activation, T cell priming, and immune surveillance, while addressing the challenges posed by immune evasion mechanisms. Key immunotherapeutic strategies, such as cancer vaccines, oncolytic viruses, adoptive cell transfer, and ICIs, are discussed in detail. Additionally, the role of nanotechnology, cytokines, chemokines, and adjuvants in enhancing the precision and efficacy of immunotherapies were explored. Combination therapies, particularly those integrating immunotherapy with radiotherapy or chemotherapy, exhibit synergistic potential but necessitate careful management to reduce side effects. Emerging factors influencing immunotherapy outcomes, including tumor heterogeneity, gut microbiota composition, and genomic and epigenetic modifications, are also examined. Furthermore, the molecular mechanisms underlying immune evasion and therapeutic resistance are analyzed, with a focus on the contributions of noncoding RNAs and epigenetic alterations, along with innovative intervention strategies. This review emphasizes recent preclinical and clinical advancements, with particular attention to biomarker-driven approaches aimed at optimizing patient prognosis. Challenges such as immunotherapy-related toxicity, limited efficacy in solid tumors, and production constraints are highlighted as critical areas for future research. Advancements in personalized therapies and novel delivery systems are proposed as avenues to enhance treatment effectiveness and accessibility. By incorporating insights from multiple disciplines, this review aims to deepen the understanding and application of cancer immunotherapy, ultimately fostering more effective and widely accessible therapeutic solutions.

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Highlights

- Various aspects of immunotherapy, from its historical evolution to modern strategies and clinical applications, are explored.
- Immunotherapeutic approaches, including cancer vaccines and oncolytic virus therapy, are discussed.
- The efficacy and mechanisms of immune checkpoint inhibitors and adoptive cell therapies are evaluated.
- The complexities of the tumor microenvironment and mechanisms of immune evasion are highlighted.
- Advances in cytokines, chemokines, nanotechnology, and combination therapies that enhance immunotherapy effectiveness are outlined.

Questions

- What are the primary strategies and modalities employed in cancer immunotherapy?
- How does the tumor microenvironment influence the efficacy of cancer immunotherapy?
- What are the key challenges in developing effective cancer vaccines and adoptive cell therapies?
- How do molecular and genetic factors, including noncoding RNAs and epigenetic modifications, contribute to immunotherapy resistance?
- What are the future directions for enhancing the efficacy and accessibility of cancer immunotherapy?

Keywords Cancer immunotherapy, Tumor microenvironment remodeling, Immune evasion, Clinical and pre-clinical, Biomarker

Introduction

General background of cancer

By 2025, approximately 2,041,910 new cancer cases and 618,120 cancer deaths are estimated to occur in the United States alone. Lung cancer is expected to have the highest mortality rate, causing approximately 2.5 times more deaths than colorectal cancer (CRC), which has the second highest mortality rate. Prostate cancer is projected to have the highest incidence in males, whereas breast cancer is anticipated to be the most frequently diagnosed cancer in females [1]. Cancer is a complex disease characterized by abnormal changes in regulatory factors that control cell growth and balance. Neoplastic cells exhibit several distinct characteristics compared to healthy cells, including autonomy in growth signals, insensitivity to inhibitory factors, evasion of cell death, irregular replication, induction of angiogenesis, and heightened metastasis [2–4]. One of the most effective strategies for combating cancer is harnessing the immune system, a method known as cancer immunotherapy. This approach involves modulating the immune system or utilizing immune cells to suppress tumor development [5].

The foundation of cancer immunotherapy can be traced back to the discovery of the anticancer properties of a bacterial blend called Coley's toxins [6, 7] and the subsequent discovery of antibodies [8]. During this period, the immune system was considered a potential factor responsible for tumor regression [9, 10]. Advances in immunology, tumor biology, and molecular biology have significantly improved cancer immunotherapy [11–22]. To date, various structures, materials, and products, such as bacterial lipopolysaccharides (LPSs), tumor-associated antigens (TAAs), cytokines, and antibodies, have been used to enhance immune system activity [5].

Immune surveillance in cancer

Cancer cells employ several mechanisms to evade immune surveillance. They may reduce the expression of surface antigens to lower immunogenicity, increase the expression of immune checkpoints to inhibit T cell function, recruit immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) to establish an immunosuppressive tumor microenvironment (TME), and produce acidic and toxic metabolites that impair immune cell functionality within the TME [23, 24]. When cancer cells successfully escape immune detection, different strategies are employed to enhance the immune system's capacity to recognize and eliminate tumors [25]. Immunotherapeutic approaches, including cancer vaccines, immune checkpoint inhibitors (ICIs), and adoptive T cell transfer, have been developed to strengthen the host's immune response against tumors. Unlike chemotherapy and radiotherapy, which indiscriminately target both healthy and malignant cells, immunotherapy offers unique advantages, including greater specificity, improved biocompatibility, and the potential for long-term anticancer immunity [25].

Despite these advantages, the effectiveness of cancer immunotherapy could be further improved. Current

immunomodulators often demonstrate limited accumulation at tumor sites, leading to suboptimal therapeutic efficacy. Additionally, tumor cells can develop resistance to immunotherapy through various molecular mechanisms, enabling immune evasion and continued proliferation. Given the importance of immunotherapy in cancer treatment, this review aims to evaluate immune system responses in cancer therapy and provide fundamental principles for effective cancer immunotherapy. This review introduces key factors involved in cancer immunotherapy, including cancer vaccines, modified immune cells, and cytokines, while also exploring the combination of immunotherapy with radiotherapy and chemotherapy. The role of peptides, small molecules, phytochemicals, and nanoparticles in enhancing immunotherapy is also discussed. Furthermore, the clinical applications of immunotherapy and associated side effects are summarized. In the final sections, the molecular pathways and interactions governing immune system regulation are examined, spanning from genomic factors to epigenetic modifications.

History of immunotherapy

Immunotherapy, a cancer treatment approach, relies on the immune system's ability to recognize tumor antigens and influence cancer progression within the TME [26]. Understanding the historical development of cancer immunotherapy is crucial before delving into its mechanisms, modern applications, and treatment strategies [27]. The concept of cancer immunotherapy emerged from observations of an increased cancer risk in immunocompromised individuals. As early as the 1700 s, tumor regression and growth suppression were documented, with histopathological analyses providing scientific clarification in the late 18th century.

More than 140 years ago, German researchers Busch [28] and Fehleisen [29] independently observed tumor suppression in patients with erysipelas infections. Busch's 1868 study on erysipelas documented cases of tumor reduction and regression, while Fehleisen identified *Streptococcus pyogenes* as a key factor in these cases. Coley subsequently developed Coley's toxins, an inactivated heat treatment, which initially gained support but later fell out of favor due to inconsistent clinical outcomes [30].

Concurrent with these early efforts, Edward Jenner laid the foundation for immunotherapy in 1796 with the development of the smallpox vaccine [31, 32]. In the 1960s and 1970s, cancer immunotherapy advanced through the use of bacterial extracts, including *Bacillus Calmette-Guérin* (BCG) and *Candida parvum*, to enhance immune responses [33]. Further progress in cancer immunotherapy was driven by discoveries related to tumor antigens, T-cell recognition, dendritic cell (DC) function, and immune response mechanisms. In the 1970s and 1980s, researchers explored the role of immune cells and cytokines, while recombinant DNA technology enabled the large-scale production of cytokines for cancer therapy. Notably, a clinical study was performed in 1983 regarding the immunological functions of IFN-α [34].

IFNα− 2b was introduced as a prominent factor in improving the survival rate of melanoma patients [35], leading to their approval by the FDA as immunotherapeutic agents. In 1987, Fefer, Cheever, and Greenberg [36] demonstrated the therapeutic potential of T cells in a lymphoma model. With further advancements, 157 patients with melanoma received adoptive transfer of lymphokine-activated killer cells in combination with IL-2 [33].

Robert Schreiber, a prominent figure in cancer immunology, introduced the concept of cancer immunoediting, emphasizing the dual role of the immune system in both eliminating cancer cells and shaping their evolution. His research demonstrated that immunocompetent hosts develop fewer immunogenic tumors, highlighting the critical functions of interferons (IFNs) and immune checkpoint pathways in cancer immunity. Additional insights into "cancer immunoediting" can be found in related studies [37–42].

Furthermore, genetic and cellular alterations in immune cells were shown to induce T-cell responses, leading to the identification of the "cancer-immunity cycle." This cycle describes the immune system's balance between recognizing tumor cells as foreign and preventing autoimmunity. The concept was introduced by Chen and Ira Mellman [43]. Figure 1 summarizes the historical evolution and applications of cancer immunotherapy.

Key steps in immunity

To achieve effective cancer immunotherapy, multiple steps must be employed, either naturally or through treatment, to enhance immunosurveillance. DCs play a crucial role in initiating cancer immunotherapy by processing tumor antigens. These tumor antigens may originate locally or be introduced via vaccines and represent protein alterations typically associated with tumors or non-mutated genes expressed by cancer cells. For DCs to effectively capture and present antigens, their engagement with tumor antigens must be sufficiently robust. This process relies on activation signals, which are classified into two categories: exogenous and endogenous. Exogenous signals include Toll-like receptor (TLR) ligands or antibodies targeting CD40, while endogenous signals consist of dying or necrotic cancer cells that promote DC maturation. Tumor cells are particularly

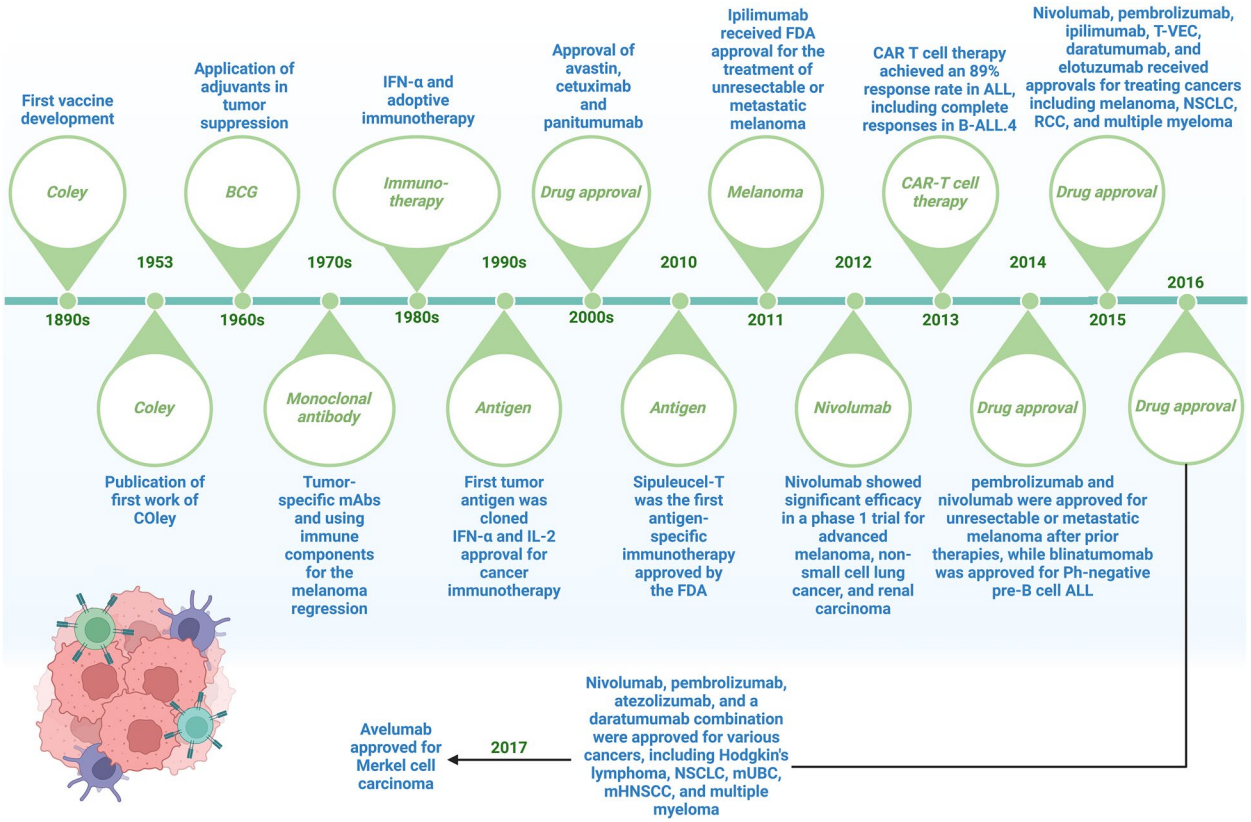

Fig. 1 The progress and use of cancer immunotherapy [44, 45]. Coley's creation of vaccines established the groundwork for cancer immunotherapy. Since that time, notable progress has occurred, featuring the application of BCG as an adjuvant in immunotherapy and the emergence of monoclonal antibodies. Subsequently, cancer immunotherapy strategies integrated IFN-α, IL- 2, and tumor antigens. Since the 2000 s, significant attention has been directed toward the creation of drugs for cancer immunotherapy. The majority of these medications have received approval since 2010 and are currently utilized for treating both hematological and solid tumors. Alongside drug development, there has been a growing focus on the use of CAR-T cells in cancer immunotherapy. *(Created with Biorender.com)*

susceptible to phagocytosis due to the presence of endoplasmic reticulum proteins, such as calreticulin, on their plasma membranes. This enhances the presentation of tumor antigens to MHC-I and MHC-II molecules, thereby stimulating immune responses [46].

Once DCs mature, subsequent processes take place in secondary lymphoid organs, such as lymph nodes. In these sites, DCs present tumor antigens to naïve T cells via MHC molecules. This interaction, which is essential for T cell activation, occurs when the peptide-MHC complex binds to the T cell receptor (TCR) and is accompanied by costimulatory signals, such as CD80/CD86 engaging with CD28 on T cells. Following activation, T cells differentiate into effector cells, including cytotoxic T lymphocytes (CTLs) and Tregs, which are influenced by the TME and cytokine signals. Activated T cells undergo clonal expansion and differentiation, which are critical for targeting and destroying cancer cells. Helper T cells (CD^{4+} T cells) further support immune responses by secreting cytokines such as IL- 2, IFN-γ, and TNF-α, enhancing the function of CTLs (CD^{8+} T cells) and other immune cells. Once primed and expanded, functional T cells leave the lymph nodes and circulate through the bloodstream to reach tumor sites. This migration is guided by chemokines and adhesion molecules, such as CXCL- 9, CXCL- 10, and ICAM- 1. The ability of T cells to infiltrate tumors is influenced by the density of the TME and the presence of physical barriers, such as the extracellular matrix (ECM). CTLs recognize cancer cells by binding to TAA peptides presented on MHC-I molecules through their TCRs, initiating an immune response. CTLs release cytotoxic granules containing perforin and granzymes, which induce apoptosis. Other mechanisms of tumor cell elimination involve the interaction of Fas ligand on CTLs with death receptors such as Fas (CD95) on tumor cells, as well as the secretion of cytokines such as IFN-γ, which exert anti-proliferative effects. The destruction of tumor cells releases additional antigens, further amplifying the immune response by recruiting and activating immune cells, thereby strengthening

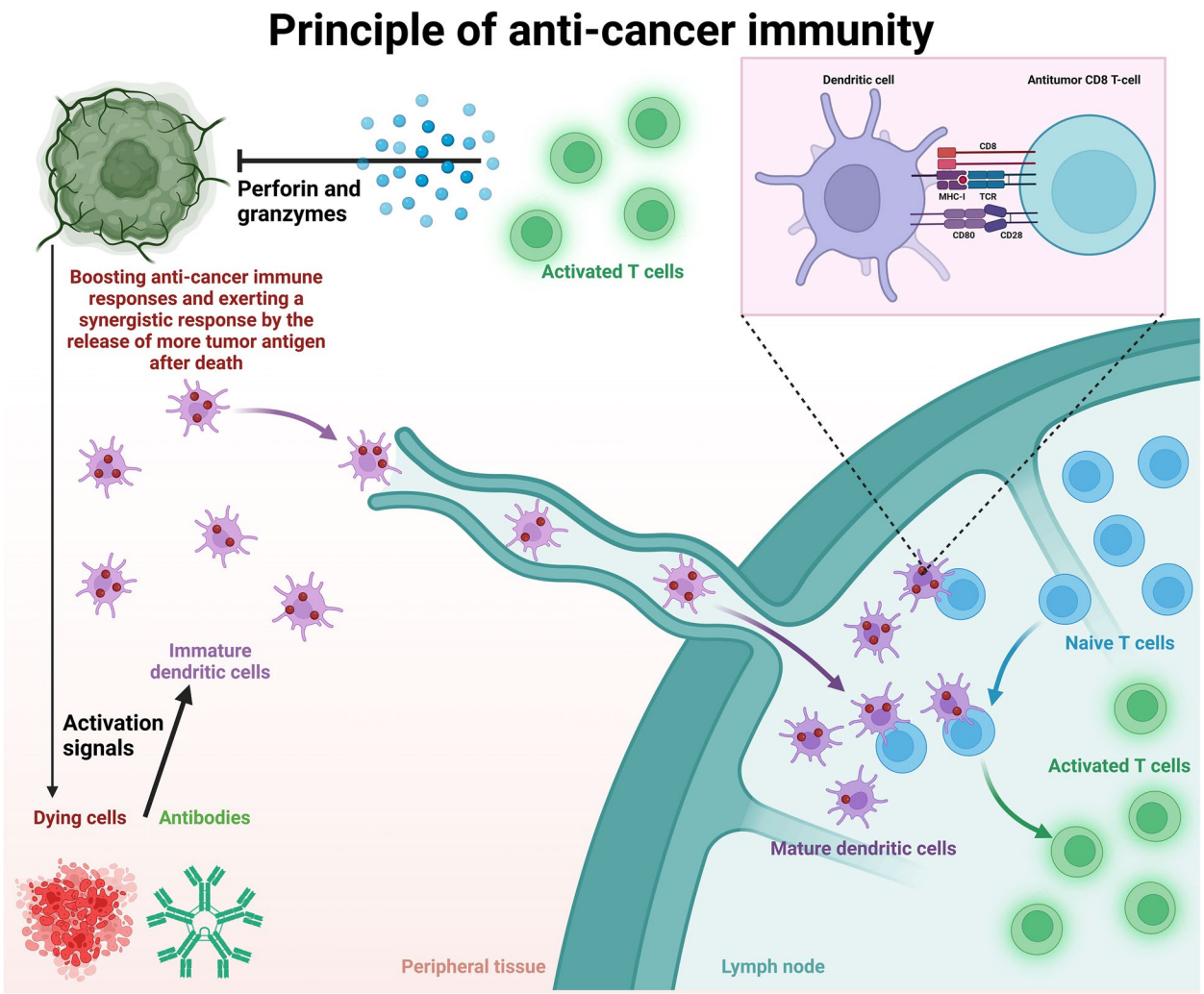

Fig. 2 A depiction showing the development of mature DCs via internal and external signals, their movement to lymph nodes, activation of T cells through targeted interactions, and the resulting inhibition of tumor cells. Cancer immunotherapy boosts immunosurveillance by activating DCs to obtain TAAs from tumors or vaccines. TAAs start the process of antigen processing and showcasing to naïve T cells in LNs via external cues, including TLR ligands or antibodies aimed at CD40, or internal signals from dying tumor cells. Based on TME and cytokines, DCs display TAAs on MHC molecules to T cells in LNs, which activates them and promotes their differentiation into CTLs or Tregs. Activated T cells experience clonal expansion and move toward tumor locations, directed by chemokines such as CXCL- 9 and CXCL- 10, along with adhesion molecules such as ICAM- 1. CTLs identify tumor cells via MHC-I molecules that display TAAs and release cytotoxic granules with perforin and granzymes to trigger the death of tumor cells. Moreover, cytokines such as IFN-γ and Fas-FasL interactions enhance the anti-tumor responses even more. The obliteration of tumor cells releases novel antigens, which boost immune responses and draw in more immune cells, thereby maintaining the therapeutic effect. *(Created with Biorender.com)*

overall immunity. For a more comprehensive understanding of the roles of T cells, DCs, and cancer immunotherapy, relevant studies [47–52] and Fig. 2 provide further insights.

Although the immune system is designed to effectively combat cancer, tumor cells employ multiple strategies to evade immune detection. These include the expression of immune checkpoint molecules such as programmed death-ligand 1 (PD-L1) and CTLA- 4, the secretion of immunosuppressive factors including TGF-β and IL- 10, and the recruitment of Tregs and MDSCs, which inhibit cancer immunity.

MHC-I proteins in humans are classified into classical and non-classical HLA-I subtypes, commonly referred to as HLA-I [53]. The classical HLA-I molecules, HLA-A, HLA-B, and HLA-C, enhance cellular antigen presentation and contribute to immunosurveillance and cancer immunotherapy. Loss of HLA-I function has been linked to immune evasion and disruptions in immune activity [54–56], affecting approximately 60–90% of individuals

before therapy and reducing their responsiveness to immunotherapy [57]. Additionally, non-classical HLA-I molecules have been implicated in immune evasion in cancer [58]. Downregulation, decreased diversity, or complete loss of HLA molecules can result in immune escape. Non-classical HLA-I molecules, such as HLA-E and HLA-G, serve as reliable prognostic indicators due to their immunosuppressive roles. Increased expression or genetic variation in classical HLA-I molecules can enhance immunotherapy outcomes. Furthermore, specific HLA types exhibit higher affinity for tumor antigens that mimic self-antigens [59]. Certain HLA-I genotypes, particularly those with high heterozygosity at HLA-I loci, and specific HLA supertypes, such as HLA-B44 or HLA-B62, are associated with improved survival rates in patients with cancer receiving immune checkpoint blockade (ICB), whereas HLA-B* 15:01 impairs the recognition of neoantigens by CD8+ T cells [60]. Additional details can be found in Section S1 and Table S1.

Cancer immunotherapy strategies

Oncolytic virus therapy

Basics

The use of viruses as experimental tools to induce cell death or dysregulation has been investigated [61]. The concept of using viruses to eliminate cancer cells was introduced in the 1990 s, leading to the development of oncolytic viruses (OVs). OVs replicate within cancer cells and induce lysis and immunogenic cell death (ICD). Although some OVs, such as T-VEC, have received Food and Drug Administration (FDA) approval for clinical use, many others are still undergoing preclinical investigation. The distinction between OVs and gene therapy lies in the fact that gene therapy vectors cannot replicate within infected cells.

OVs are classified into two categories: naturally occurring and genetically modified. In 2015, the FDA approved T-VEC, the first OV, for the treatment of metastatic melanoma. T-VEC is based on oncolytic herpes simplex virus type 1 (oHSV- 1) and contains several genetic modifications aimed at enhancing its oncolytic effectiveness [61, 62]. Additionally, Japan approved the first OV targeting glioma in 2021, DELYTACT (oHSV- 1 with G47Δ) [63]. OVs are used for the targeted treatment of cancer cells and can be engineered to express transgenes that function through four distinct mechanisms: oncolysis, vascular collapse, anticancer immune response, and the expression of therapeutic transgenes to inhibit tumor growth [64].

Despite the advantages of OV-based therapies, several limitations hinder their widespread clinical application [65]. The primary challenge is the systemic delivery of OVs. Furthermore, improving the distribution of OVs while managing antiviral and innate immune responses is essential [66]. Achieving clinical efficacy through OVs alone is difficult, and combination therapies with additional treatment modalities are recommended. Addressing these challenges could enhance the clinical use of OVs in cancer immunotherapy [67, 68]. Further details are provided in Section 3 of the Supplementary Material.

Clinical importance

Third-generation oHSVs are designed to specifically target TAAs, such as HER2, while evading natural receptors, thereby enhancing both safety and efficacy. These viruses achieve significant yields in modified Vero cells and replicate effectively in human cancer cell lines, suggesting their potential to generate lasting immunity against metastatic cancers [69].

An engineered measles virus (MV) that is resistant to neutralization by anti-measles antibodies has been developed. This retargeted MV maintains its growth kinetics, receptor specificity, and cytotoxic activity, presenting a promising approach for systemic cancer therapy in measles-immune individuals. The use of epidermal growth factor receptor (EGFR)-retargeted MVs highlights their potential in systemic cancer therapy [70].

An innovative strategy utilizes anti-adenoviral immune responses for cancer immunotherapy by employing a bifunctional adaptor that directs antibodies to tumor sites. This approach reduces tumor growth, extends patient survival, and activates tumor-specific CD8+ T cells via natural killer (NK) cells. Furthermore, it enhances the efficacy of PD- 1 checkpoint inhibition. The combination of oncolytic adenoviruses with PD- 1 blockade significantly improves treatment outcomes and prolongs survival in patients undergoing therapy [71]. Targeting oncolytic adenoviruses with polysialic acid enhances tumor infection, reduces off-target effects, promotes CD45-positive immune cell infiltration, and strengthens tumor reduction, durability, and T-cell responses, thereby improving cancer therapy outcomes [72].

A Phase 1b clinical trial enrolled 15 patients with treatment-resistant CRC who received Pexa-Vec, an oncolytic vaccinia virus with immunological properties. The study aimed to determine the maximum tolerable dose and assess the pharmacokinetics, pharmacodynamics, and anticancer efficacy of Pexa-Vec. Each patient received at least two doses, with an average of four doses in total. No dose-limiting toxicities were observed, and the most common adverse events were flu-like symptoms. Further studies are necessary to evaluate the therapeutic effectiveness of Pexa-Vec in this patient population [73].

Pexa-Vec functions as both an oncolytic agent and an immunotherapy by selectively infecting and destroying cancer cells through viral lysis while simultaneously

generating tumor-specific immunity. Studies have been conducted in both adult and pediatric patients, including a dose-escalation study that assessed the safety of intratumoral administration. The primary adverse effects were sinus fever and tachycardia. Imaging studies suggested potential anticancer biological effects, and two patients demonstrated strong immune responses following treatment [74].

Adoptive cell therapy

Basics and principles

Due to the remarkable success of chimeric antigen receptor T (CAR-T) cell therapy in treating hematological cancers, adoptive cell therapy (ACT) has garnered significant attention. ACT involves harvesting immune cells from patients, expanding and genetically modifying them, and subsequently reinfusing them to combat cancer or infections, as opposed to relying on chemotherapy. Among the primary ACT methods, CAR-T cell therapy has been approved and has demonstrated significant efficacy in blood cancers [75]. Other notable methods include tumor-infiltrating lymphocyte (TIL) therapy and TCR-engineered T-cell (TCR-T) therapy. Additionally, novel CAR-engineered immune cell therapies, including CAR-NK cells, CAR-macrophages, CAR-gamma delta T (γδT) cells, and CAR-NKT cells, have emerged. Each of these approaches presents distinct advantages and challenges, yet clinical trials are advancing rapidly across all modalities [76].

Despite the success of CAR-T cell therapy, many patients experience limitations following autologous CAR-T cell therapy, which was the first clinically implemented and commercially available approach for treating aggressive B-cell cancers. Moreover, NK cells have been introduced for ACT [77]. However, several challenges remain unresolved. Patients with rapidly progressing diseases who require urgent treatment face difficulties due to the complex and time-consuming production process, which presents large-scale manufacturing challenges. Additionally, patients who have undergone recent intensive chemotherapy or who have extremely low white blood cell counts may not qualify for CAR-T cell therapy, as their own cells are required for treatment.

At the clinical level, CAR-T cell therapy may lead to severe side effects, including cytokine release syndrome (CRS) and neurotoxicity, necessitating rigorous monitoring and hospitalization. By targeting antigens independently of human leukocyte antigen (HLA) molecules, NK cells reduce the risk of graft-versus-host disease (GvHD) in allogeneic applications. In contrast, T cells require genetic modifications to eliminate their native TCR to prevent GvHD. High levels of NK cells can reduce the cancer development [78]. Further details can be found in Section 4 of the Supplementary Material.

Clinical studies and importance

On February 16, 2024, the U.S. FDA granted accelerated approval for lifileucel (Amtagvi), an adoptive immune cell therapy utilizing autologous ex vivo-expanded TILs for adult patients with advanced or unresectable melanoma that had progressed after treatment with ICIs. In cases where patients had BRAF V600 mutations, the therapy was approved for use following BRAF/MEK inhibitor treatment.

The clinical trials supporting this approval underscore the complexities involved in therapy production, patient selection criteria, and the necessity of a pretreatment lymphodepletion protocol. Lifileucel (Amtagvi) was administered as a single infusion, followed by up to six doses of high-dose IL- 2, with potential adverse effects occurring at each stage of therapy.

In early 2024, expert consensus guidelines were published, outlining best practices and patient care strategies for ACT using autologous ex vivo-expanded TILs. A global TIL Working Group has been established to streamline regulatory approval for these therapies in clinical practice. This approval marks a significant milestone in the field of ACT, demonstrating the potential of autologous ex vivo-expanded TILs while also highlighting the challenges associated with the implementation of this complex, time-intensive, and potentially costly immunotherapy [79].

Lymphodepletion, also known as lymphodepletion conditioning, is a critical component of ACT, a form of immunotherapy used in cancer treatment. This process involves a temporary reduction in the number of existing lymphocytes before introducing modified or selected immune cells, such as TILs or CAR-T cells. Lymphodepletion eliminates native lymphocytes, thereby creating space within the immune system for the infused therapeutic cells to expand and function effectively. This phenomenon is sometimes referred to as "establishing space" within the immune niche. Without lymphodepletion, the infused cells may compete for essential resources, including cytokines, growth factors, and physical space, thereby restricting their proliferation and diminishing their therapeutic potential.

A novel therapeutic approach for metastatic melanoma has been developed that involves the adoptive transfer of carefully selected tumor-specific T lymphocytes, particularly those targeting overexpressed self-antigens. In this approach, T cells are administered following nonmyeloablative conditioning treatment. The transplanted T cells undergo in vivo proliferation, demonstrating sustained functional activity and tumor-specific migration.

This strategy has resulted in the regression of metastatic melanoma and the initiation of autoimmune melanocyte destruction, offering new possibilities for treating cancer and various infectious diseases [80].

The immune system includes Tregs and MDSCs, which suppress the activity of adoptively transferred cells. Lymphodepletion reduces these suppressive populations, thereby improving the functionality of therapeutic cells. This effect is particularly important within the TME, where immunosuppressive factors often hinder the effectiveness of infused cells. Effector cells derived from naïve CD8+ T cells have demonstrated superior antitumor immunity compared to those generated from central memory T cells, challenging the previous assumption that central memory cells were more advantageous. Naïve-derived effector cells exhibit a rapid decline in CD62L expression while avoiding terminal differentiation markers such as KLRG- 1, thereby enhancing their proliferative capacity and cytokine production upon transfer. This suggests that engineering tumor-specific TCRs into naïve T cells may improve the effectiveness of adoptive immunotherapy.

The role of CD4+ T cells in CD8+ T cell responses challenges the hypothesis that a lack of CD4+ T cells enhances treatment efficacy for persistent tumor or self-antigens. Adding CD4+CD25– T helper (Th) cells with tumor-targeting CD8+ T cells has been shown to induce both tumor regression and autoimmunity in CD4-deficient environments. However, the presence of CD4+CD25+ Tregs reduces treatment efficacy. Successful immunotherapy relies on Th cells that produce IL- 2, as Th cells lacking IL- 2 are unable to support CD8+ T cell functionality. This underscores the essential role of Th cells in overcoming immune tolerance to self-antigens and counteracting Treg-mediated suppression [81, 82].

Lymphodepletion also stimulates the release of homeostatic cytokines, such as IL- 7 and IL- 15, which are critical for the survival, expansion, and persistence of infused T lymphocytes. Under non-lymphodepleted conditions, these cytokines are often limited due to competition with native lymphocytes. By increasing the availability of homeostatic cytokines and reducing the influence of Tregs and MDSCs, lymphodepletion before ACT enhances antitumor responses. In the pmel- 1 mouse model, a strong correlation was observed between the degree of total body irradiation and ACT success. Higher radiation doses increased the proportion of tumor-reactive CD8+ T cells relative to suppressive cell populations, including CD4+ Tregs and Gr1+ MDSCs, as well as natural cytokine sinks such as CD8+ and NK cells. Augmented lymphodepletion also elevates systemic inflammatory markers and LPS levels, which enhance tumor treatment efficacy, although careful risk-benefit assessments are necessary. Additionally, IL- 15, which promotes the longevity of memory CD8+ T cells and inhibits apoptosis, has been shown to enhance the in vivo antitumor effectiveness of adoptively transferred CD8+ T cells in tumor-bearing hosts [83, 84]. Lymphodepletion improves the lifespan of infused cells, which is crucial for therapeutic efficacy, as these persistent cells continuously eliminate cancer cells, thereby reducing the likelihood of recurrence.

ACT employing autologous TILs has been effective in treating metastatic melanoma, leading to objective cancer regression in approximately 50% of patients. Additionally, donor lymphocytes have proven beneficial in immunosuppressed patients with post-transplant lymphomas. Recent advancements in genetic engineering have further expanded the capabilities of ACT by enabling the retargeting of T cells to recognize specific tumor antigens, thereby broadening their applicability to various cancer types. These developments include improved antigen targeting, modifications to enhance T cell effectiveness, and the identification of critical T cell subsets that optimize tumor destruction [85, 86].

Tumors often undergo an immunosuppressive epithelial-mesenchymal transition (EMT) that enables immune evasion. Lymphodepletion can help reprogram the immune system, break immune tolerance, and enhance the ability of infused cells to recognize and attack tumors more effectively. Lymphodepletion is typically achieved through chemotherapeutic agents, such as cyclophosphamide and fludarabine, or, in some cases, radiation therapy. These treatments are administered immediately before the infusion of therapeutic cells.

Clinical research has demonstrated that lymphodepletion significantly improves the efficacy of ACT. In CAR-T cell therapy for hematological malignancies, including leukemia and lymphoma, lymphodepletion is associated with higher response rates. Additionally, in TIL therapy for solid tumors, lymphodepletion has been shown to enhance tumor regression and improve patient outcomes.

ICIs: clinical insight

The FDA has approved ipilimumab, a monoclonal antibody developed by Bristol Myers Squibb that targets CTLA- 4, for the treatment of metastatic melanoma [87]. However, tremelimumab has failed to demonstrate success in multiple late-phase clinical trials [88, 89]. A phase III randomized clinical trial involving 655 patients with advanced metastatic melanoma did not show a significant survival advantage compared to standard-of-care chemotherapy. Similarly, in the DETERMINE phase IIb trial, tremelimumab did not improve overall survival (OS) as a second- or third-line treatment for recurrent

malignant mesothelioma, although the FDA granted it orphan drug designation in April 2015 for mesothelioma therapy [90]. Currently, no evidence suggests that tremelimumab is effective in cancer treatment [87].

During the initial phase of T cell activation, there is an increased expression of the co-inhibitory receptor CTLA- 4, which was identified as the first negative regulator of T cell activation [91, 92]. CTLA- 4 inhibits the ligands (CD80/CD86) that T lymphocytes use to obtain costimulatory signals through two mechanisms: (1) it facilitates the trans-endocytosis and degradation of these ligands [93], and (2) it transmits inhibitory signals that prevent T cell proliferation and IL- 2 production [94], leading to T cell tolerance via anergy induction [95]. The regulatory effects of CTLA- 4 differ between CD4+ and CD8+ T lymphocytes, although both cell types express it. CTLA- 4 primarily suppresses effector CD4+ T cell responses during the priming of naïve cells [96], whereas its regulatory influence on CD8+ T cells is more pronounced in memory cells rather than primary cells [92, 97].

Inducible T-cell COStimulator (ICOS) plays a crucial role in the context of anti-CTLA- 4 therapy, particularly in enhancing the efficacy of CTLA- 4 inhibition. Anti-CTLA- 4 therapy upregulates ICOS expression and increases CD4+ T cell populations. ICOS is essential for T-bet expression in CD4+ T cells, particularly through the PI3 K signaling pathway. T-bet functions as a transcription factor in Th1 cell differentiation and enhances anticancer immunity. Studies have shown that ICOS deletion in mice leads to reduced T-bet expression [98].

A case study of a patient with metastatic melanoma treated with ipilimumab, an anti-CTLA- 4 antibody, demonstrated a notable reduction in tumor progression following treatment. Analysis of blood and tumor tissues revealed an increase in T cells targeting Melan-A, a melanoma-associated antigen. Additionally, an autoimmune skin rash infiltrated by Melan-A-specific cytotoxic T cells was observed, suggesting a potential link between treatment-induced autoimmunity and antitumor effects [99].

Another study evaluated the efficacy of cadonilimab, a bispecific antibody that concurrently targets PD- 1 and CTLA- 4, in inhibiting immune checkpoints with a single agent. This Phase II clinical trial involved patients with lung cancer who had experienced disease progression following chemotherapy. Patients received cadonilimab either as monotherapy or in combination with standard second-line chemotherapy. Cadonilimab demonstrated the potential to moderately enhance anticancer immune responses, both alone and in combination with chemotherapy. However, the overall response rates (ORRs) were modest, and the median progression-free survival (PFS) and OS durations were limited [100].

Another study examined the combination of toripalimab, an anti-PD- 1 antibody, and HBM4003, an innovative anti-CTLA- 4 heavy-chain-only antibody, for treating solid tumors such as melanoma. This Phase I clinical study found that the combination therapy was well tolerated, with only mild to moderate side effects. Notably, patients with mucosal melanoma who had not previously received anti-PD- 1/PD-L1 treatment exhibited promising responses. A high baseline proportion of Tregs relative to CD4+ T cells in the tumor was associated with an improved response to combination therapy [101].

For further details, please refer to Section 5 of the Supplementary Materials. Tables S2 and S3 provide additional information on cancer therapeutics.

Recent research has demonstrated that ICB can facilitate the recruitment and expansion of previously inactivated or naïve T cell clones within the TME. Immunotherapies targeting inhibitory checkpoint receptors on T cells have significantly advanced cancer treatment. However, it remains uncertain whether the T cell response to checkpoint inhibition is driven by the reactivation of pre-existing TILs or by the recruitment of new T cells. Researchers conducted paired single-cell RNA and TCR sequencing on 79,046 cells derived from site-matched tumors of patients with basal or squamous cell carcinoma, both before and during anti-PD- 1 therapy. By analyzing TCR clones and their transcriptional profiles, they identified a correlation between tumor recognition, clonal expansion, and T cell dysfunction. This dysfunction is characterized by the clonal expansion of CD8+CD39+ T cells, which exhibit chronic activation and exhaustion. The expanded T cell clones did not originate from pre-existing tumor-infiltrating T cells but instead comprised new clonotypes not previously identified within the tumor. Clonal replacement was particularly evident in exhausted CD8+ T cells and was observed in patients with basal and squamous cell carcinomas [102].

Although ICB therapies have revolutionized cancer treatment, many patients with metastatic melanoma continue to succumb to the disease. To investigate the underlying mechanisms, researchers analyzed the transcriptomes of 16,291 immune cells from 48 melanoma tumor samples obtained from patients undergoing checkpoint inhibitor therapy. Two distinct states of CD8+ T cells associated with either tumor regression or progression were identified. In a separate cohort, the presence of the transcription factor TCF7 in CD8+ T cells correlated with improved clinical outcomes. This study explored the clonal and epigenetic characteristics of various T cell states, suggesting that targeting specific factors within exhausted T cells could enhance anticancer immune responses [103].

T cells within murine tumors differentiate into two distinct chromatin states: a flexible dysfunctional state that allows potential T cell rescue and a rigid dysfunctional state resistant to reprogramming. Researchers identified unique surface markers associated with each chromatin state, enabling the differentiation between reprogrammable and non-reprogrammable PD1 hi dysfunctional T cells in diverse T cell populations within mouse tumors. Similar surface markers were detected in human PD1 hi tumor-infiltrating CD8+ T cells, suggesting their relevance in human cancer immunotherapy [104].

In chronic viral infections, CD8+ T cells frequently exhibit dysfunction and express the inhibitory receptor PD- 1. To improve immunotherapies aimed at restoring T cell function, scientists examined CD8+ T cells in mice infected with chronic lymphocytic choriomeningitis virus. Following PD- 1 inhibition, a unique subset of virus-specific CD8+ T cells expanded. These cells expressed PD- 1 along with costimulatory markers such as ICOS and CD28 and displayed a gene profile akin to that of CD4+ T follicular helper cells, memory precursors, and stem cell progenitors, yet distinct from TH1 cells and terminally exhausted CD8+ T cells. This subset, primarily located in lymphoid organs, exhibits stem cell-like properties, including self-renewal and the ability to differentiate into exhausted CD8+ T lymphocytes. The proliferative response to PD- 1 inhibition predominantly originates from this subset, which relies on the transcription factor TCF1 for expansion and maintenance [105].

In both chronic infections and cancer, continuous antigen exposure and inflammatory stimuli lead to diminished T cell functionality, a phenomenon termed "exhaustion." Exhausted T cells exhibit reduced effector functions, express multiple inhibitory receptors, and possess unique transcriptional profiles. This exhaustion often contributes to the failure to control chronic diseases and tumors. Restoring exhausted T cell function can reinvigorate immune responses [106].

The expression of PD- 1 on circulating CD8+ T cells serves as a marker for tumor-specific lymphocytes targeting neoantigens in patients with melanoma. A customized screening approach identified neoantigen-reactive T cells in the blood of three out of four patients, particularly within the CD8+PD- 1+ subset. Although present in limited numbers, these cells displayed tumor antigen specificities and TCR repertoires similar to those of TILs, indicating that circulating CD8+PD- 1+ T cells reflect the immune response within the tumor. This discovery offers a non-invasive method to identify antitumor T cells unique to each patient, facilitating the development of personalized therapies using neoantigen-reactive lymphocytes or engineered TCRs [107].

ICB therapies have transformed cancer treatment; however, many patients with metastatic melanoma do not achieve durable responses. To identify characteristics associated with treatment success or failure, researchers analyzed the transcriptomes of 16,291 immune cells from 48 melanoma tumor samples from patients receiving checkpoint inhibitor therapy. Two distinct states of CD8+ T cells were associated with either tumor regression or progression. The transcription factor TCF7 was identified as a marker of positive clinical outcomes in a separate group of patients receiving checkpoint inhibitors. This study explored the epigenetic landscape and clonality of various T cell states, indicating that targeting new combinations of factors in exhausted T cells may enhance anticancer immunity [103].

The immune surveillance score (ISS) and the advanced ISS (ISS10) serve as prognostic markers for improved outcomes in patients with hepatocellular carcinoma (HCC) receiving combination immunotherapy, such as atezolizumab with bevacizumab or nivolumab with ipilimumab, compared to sorafenib. High ISS10 responders exhibit a more favorable immune microenvironment, characterized by increased antitumor macrophages and activated T cells. This suggests that ISS10 may enhance patient stratification and aid in the development of personalized treatment strategies for HCC [108].

HCC recurs in 70–80% of cases following curative resection or ablation, with the liver's immune environment playing a crucial role in recurrence. Immunosuppressive pathways mediated by vascular endothelial growth factor (VEGF) and PD-L1 contribute to this process. The combination of atezolizumab (a PD-L1 inhibitor) and bevacizumab (a VEGF inhibitor) has significantly improved OS, PFS, and response rates in patients with unresectable HCC. Dual inhibition of PD-L1 and VEGF may reduce recurrence by fostering a TME that is more conducive to immune activation. IMcourage 050 (NCT04102098) is a randomized, open-label, Phase III clinical trial evaluating atezolizumab plus bevacizumab versus active monitoring in patients with high-risk HCC following curative resection or ablation, with recurrence-free survival as the primary endpoint. Clinical Trial Registration ID: NCT04102098 [109]. PD- 1 blockade and immune regulation therapy have been applied to various tumors, including melanoma [110], solid tumors [111], urothelial carcinoma [112], breast cancer [113] and lung cancer [114], among others. Figure 3 illustrates immune resistance mechanisms and associated therapeutic targets.

Cytokines

Cytokines play a crucial role in cancer immunotherapy by regulating immune responses and enhancing the

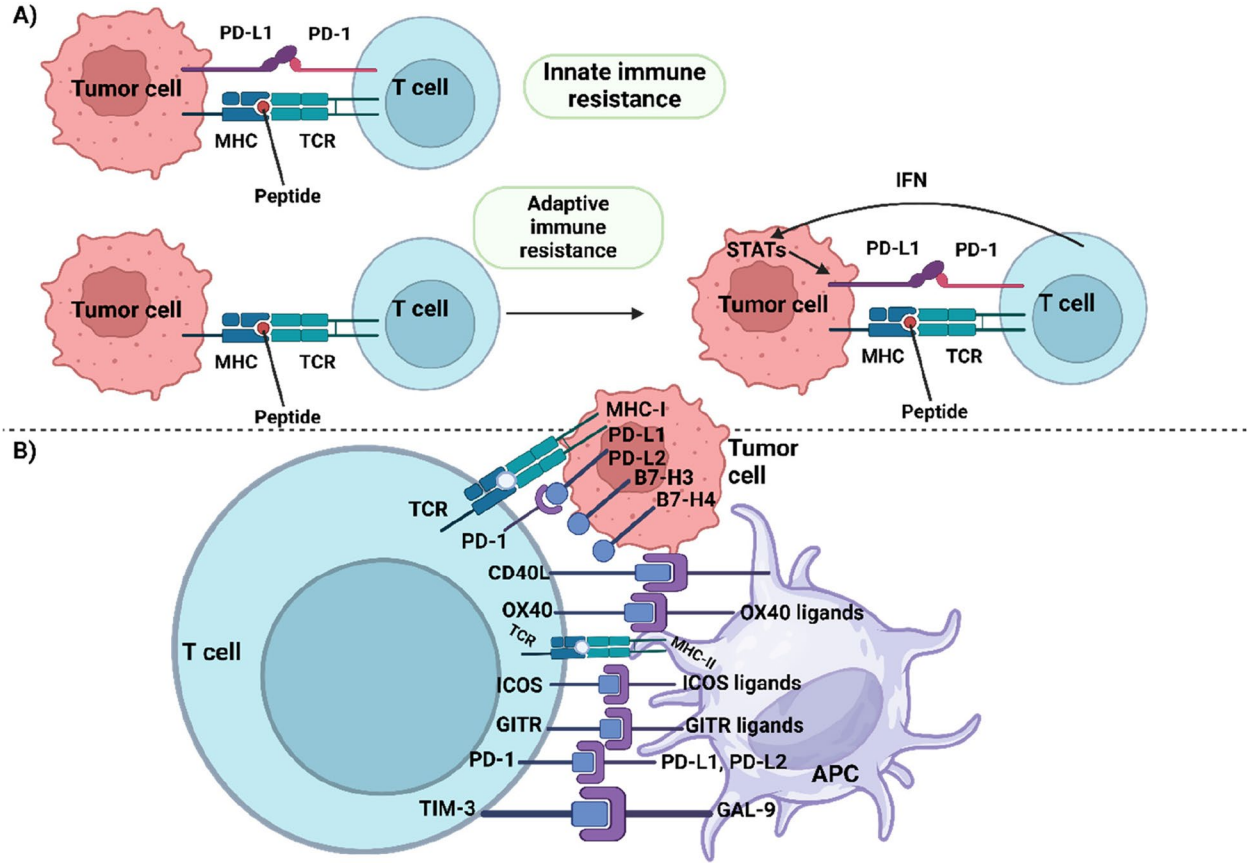

Fig. 3 A diagram illustrating the progression of immune resistance and the potential therapeutic targets. **A** This illustration is centered on PD-L1, but it also pertains to various types of immune checkpoint inhibitors, such as PD-L2, which is referred to as B7-DC. In several cancers, the activation of oncogenic pathways can elevate PD-L1 levels in a manner that is not dependent on inflammatory signals in the TME. Additionally, it has been demonstrated that the overexpression of AKT and STAT3 leads to elevated levels of PD-L1. Nonetheless, there is an absence of PD-L1 expression in various cancer types, and its expression may arise due to inflammatory factors produced by the active immune responses against cancer. The varied expression of PD-L1 seen in different tumor regions with TIL infiltration indicates that PD-L1 expression arises from immune responses in the TME [115]. **B** The process of anti-cancer immunity includes multiple checkpoints [116]. Various types of co-receptors exist on cell surfaces that can either activate or inhibit immune responses. The majority of these receptors rely on TCR activity to recognize antigens presented by MHC molecules on APCs, delivering either inhibitory or stimulatory signals. These interactions have been noted in the peripheral regions or in secondary lymphoid tissues. Several receptors have specific motifs such as UVKM for CTLA- 4 and KIEELE for LAG3, while other inhibitory receptors exhibit ITIMs and/or ITSMs within their intracellular domains. Utilizing antibodies for checkpoint treatments to modify T cell inhibitory signals such as PD- 1 and CTLA- 4 can stimulate prolonged immune responses in individuals. Additional measures can be taken to enhance the effectiveness of immunotherapy in patients. One approach involves the use of PD- 1 and CTLA- 4 blockade alongside various antagonists of inhibitory receptors on T cells, such as TIM- 3, LAG- 3, TIGIT, and BTLA. Another approach is to combine ICB with the agonist of co-stimulatory receptors on T cells, such as CD27, 4 - 1BB, OX40, and GITR. The ultimate approach may involve using ICBs while promoting tumor antigen recognition through vaccines and activating dendritic cells with CD40 agonists. *(Created by Biorender.com)*

identification and destruction of tumor cells. In 1986, IFN-α became the first cytokine to receive FDA approval for cancer treatment, followed by IL- 2 in 1992. Despite these advancements, the development of cytokine-based therapies has been challenging. Cytokines are essential for initiating immune responses to external triggers; however, their short half-life and narrow therapeutic window, combined with significant toxicity risks, limit their widespread application [117]. Although cytokines directly activate immune cells such as T cells and NK cells, enhancing the immune system's ability to fight cancer, their clinical use is constrained by low efficacy and dose-limiting toxicities. Cytokines such as GM-CSF, IL- 2, IL- 7, IL- 12, IL- 15, IL- 18, and IL- 21 have been explored in clinical trials for their potential to boost immune responses against cancer. Current research focuses on improving cytokine therapy by enhancing targeted delivery methods, engineering cytokines with improved properties, and combining them with other immunotherapies, such as checkpoint inhibitors, to reduce toxicity while

increasing efficacy [118]. Further information is available in Section 6 of the Supplementary Materials.

IL- 15 was first identified in the culture supernatants of the HUT102 and Cv1/EBNA cell lines, where it was found to promote the proliferation of the cytokine-dependent T cell line CTLL- 2 [119]. NK cells, NKT cells, γδT cells, IL/C1 cells, intraepithelial lymphocytes, and innate immune cells expressing CD103+, CD56+, and CD44+, along with memory CD8+ T cells, contribute to the production of IL- 15. This cytokine, a member of the 4 alpha-helix-bundle family, has a molecular weight of 14–15 kDa [120–131]. Although IL- 15 protein production is regulated at the transcriptional level, most control occurs during translation [132]. Transcription of IL- 15 can be induced by type I and II IFNs, CD40 engagement, and TLR signaling [119, 133]. Various IL- 15 agonists have been developed, including IL- 15 N72D mutein [134], a heterodimer of IL- 15 and IL- 15Rα (hetIL- 15) [135], RLI (a fusion protein combining IL- 15 with the cytokine-binding Sushi domain of IL- 15Rα) [136, 137], and N- 803 [138, 139].

Clinical studies have evaluated the efficacy of IL- 15 in cancer immunotherapy. ALT- 803, an IL- 15 super-agonist, has shown promise when combined with nivolumab for lung cancer treatment. In a non-randomized Phase I clinical trial involving 21 patients, this combination therapy exhibited no dose-limiting toxicities, though some adverse effects, such as injection site reactions and flu-like symptoms, were observed. The most common side effects included lymphocytopenia and fatigue. In the second phase of treatment, patients received 240 mg of intravenous nivolumab every 2 weeks alongside 20 μg/kg of ALT- 803 subcutaneously [140].

Chemokines

Chemokines regulate immune cell trafficking and tissue distribution through interactions with specific chemokine receptors [141–144]. Some chemokines and their receptors facilitate the recruitment of antitumor immune cells, while others promote tumor progression by attracting immunosuppressive cells. Additionally, chemokines are essential for the regulation of DCs and T cells [144–148]. Consequently, the chemokine superfamily plays a complex and multifaceted role in tumor immunity.

The chemokine receptors CCR2 and CCR1 exhibit intricate and sometimes contradictory roles within the TME and cancer immunotherapy. CCR2, which is involved in monocyte recruitment, has been implicated in both tumor progression and suppression. Some studies have shown that inhibiting CCR2 signaling reduces pulmonary metastases and enhances antitumor immunity by preventing monocyte recruitment, as demonstrated with the angiotensin receptor blocker losartan [149].

CXCR2, a chemokine receptor associated with neutrophil recruitment and inflammation, has been extensively studied. In pancreatic ductal adenocarcinoma (PDAC), CXCR2 blockade significantly reduces metastasis and improves immunotherapy efficacy by limiting MDSC infiltration and increasing T cell infiltration into tumors [150]. Similarly, in non-alcoholic steatohepatitis-associated HCC, CXCR2 inhibition enhances the effectiveness of immunotherapy by mitigating the immunosuppressive TME [151]. Additionally, targeting ESE3/EHF transcription factors with nifurtimox reduced CXCR2+ neutrophil infiltration, addressing PDAC resistance to chemotherapy and immunotherapy [152]. These findings underscore the significance of CXCR2 in tumor immunity and its potential as a therapeutic target in cancer treatment.

CCR7, a chemokine receptor involved in lymphocyte migration and localization to lymph nodes, has also emerged as a promising target. In chronic lymphocytic leukemia (CLL), anti-CCR7 immunotherapy has demonstrated preclinical efficacy in high-risk patients [153]. Moreover, overexpression of CXCR4 and CCR7 in NK92 cells enhances their migration and antitumor activity in a human colon cancer model [153], suggesting that modifying CCR7 levels could improve immune cell targeting of tumors. Furthermore, the Bruton's tyrosine kinase inhibitor ibrutinib has been found to regulate CCR7 expression and function in CLL, thereby influencing the efficacy of CAP-100, a novel therapeutic anti-CCR7 antibody [154]. These findings highlight the intricate interplay between CCR7 signaling and various therapeutic strategies, necessitating further research to optimize treatment approaches.

The role of CCR4 in tumor-induced immunosuppression has also been investigated. In hepatitis B-associated HCC, intratumoral stem-like CCR4+ TREGs contribute to the immunosuppressive microenvironment [155]. Table 1 provides an overview of the roles of cytokines and chemokines in cancer immunotherapy.

Combination immunotherapy

Chemotherapy

Combination immunotherapy incorporating chemotherapy has demonstrated promising immunological and clinical responses in various cancers. Intravenous bevacizumab and oral metronomic cyclophosphamide were administered, followed by autologous whole-tumor lysate immunization combined with anti-angiogenic therapy, to assess responses in patients with recurrent cancer [193]. Among these patients, two exhibited partial responses, two experienced stable disease, and two showed disease

Table 1 The role of cytokines and chemokines in cancer immunotherapy

Cytokine/Chemokine	Cancer	Remark	Reference
IL- 12	Glioblastoma	The delivery of IL- 12 mRNA by biomimetic calcium carbonate nanostructures cab improve necroptosis-mediated immune responses	[156]
IL- 15	-	Polymeric micelles can deliver IL- 15/IL- 2 to induce NK cells	[157]
IL- 12	Prostate cancer	Improving anti-cancer immunity through tumor-localized IL- 12 in form of collagen binding domain-IL- 12 fusion protein	[158]
IL- 12	-	DCs generating IL- 12 can mediate immunotherapy The IL- 12 production from DCs was dependent on the sensing IFN-γ	[159]
IL- 12	Glioblastoma	CAR-T cell combination a single local dose of IL- 12 can improve immune responses and increasing T cell infiltration	[160]
IL- 12 IL- 27	Melanoma	Lipid nanostructures can provide intratumoral delivery of IL- 12 and IL- 27 mRNA to enhance infiltration of immune cells such as NK cells and T cells	[161]
IL- 12	Melanoma	Upon the administration of a collagen-binding domain fused to IL- 12 (CBD-IL- 12), they can accumulate in the tumor site	[162]
IL- 12	Melanoma	Combining T cells engineered with mRNAs to express single-chain IL- 12 (scIL- 12) or an IL- 18 decoy-resistant variant (DRIL18)	[163]
IL- 12	-	Delivery of IL- 12-mRNA by lipid nanostructures Stimulation of immunogenic cell death Induction of danger sensors Regulation of immune cells by IL- 12	[164]
IL- 21	-	The synergistic cooperation of IL- 21 with IL- 7 in enhancing expansion and function of T cells	[165]
IL- 12	-	Non-canonical MAVS suppresses IL- 12 to impair DC-mediated immunity	[166]
IL- 12	Melanoma	A combination of IL- 7 and IL- 12 promotes the function of T cells	[167]
IL- 12	-	Loading IL- 12 on serum albumin nanostructures and conjugation to CAR-T cells for the increase in the secretions of CCL5, CCL2 and CXCL10 recruiting CD^{8+} CAR T cells	[168]
IL- 12	Leukemia and neuroblastoma	IL- 12 provides the reprogramming of CAR-expressing natural killer T cells to long-lived Th1-polarized cells	[169]
IL- 21	-	LDH suppression along with IL- 21 improves the anti-cancer immunity mediated by CD^{8+} T cells	[170]
IL- 21	-	IL- 21 improves the function of NKT cells in adoptive immunotherapy	[171]
IL- 21	-	Improving anti-cancer activity of CAR-T cells	[172]
IL- 15	R/R B-cell malignancies	Increasing number of CAR-T cells	[173]
IL- 15	Solid tumors	Both the single-agent regimen of NIZ985 and its combination with spartalizumab demonstrated good tolerability. The recommended dose for expansion (RDE) was established at 1 μg/kg administered three times weekly. In tumor types known for their resistance to immune checkpoint inhibitors (ICIs), the combination treatment exhibited antitumor activity	[174]
IL- 15	-	Delivery of IL- 15 mRNA and ultrasound-targeted microbubble destruction promote ROS generation to mediate ER stress-induced immunogenic cell death	[175]
IL- 15	Triple-negative breast cancer	A combination of cetuximab and IL- 15 can improve the function of NK cells and DCs	[176]
IL- 15	Pancreatic cancer	Combination of NK cell therapy and IL- 15-expressing OV and PD-1 blockade Addition of PD- 1 blockade antibodies can improve the prolonged activation of immune cells, enhancing the tumor suppression	[177]
CCR7	Leukemia	Upregulation of CCR7 in patients The application of anti-CCR7 monoclonal antibody can improve the eradication of cancer cells through complement-induced mechanism	[178]

Table 1 (continued)

Cytokine/Chemokine	Cancer	Remark	Reference
CCR7	Head and neck squamous cell carcinoma	Development of a hybrid nanovaccine utilizing tumor-derived exosomes (TEX) with DCMV Targeting lymph nodes to induce immune responses	[179]
CXCR4	-	Upregulation of CXCR4 on exhausted CD^{8+} T cells Blocking CXCR4 improves the potential of cancer immunotherapy	[180]
CXCR4	Gastric cancer	TFF2-MSA as CXCR4 agonist is able to induce receptor completely and can target MDSCs Intervention with the generation of MDSCs	[181]
CXCR4, CXCL12, CXCR7	Pancreatic cancer	The expression of CXCR4 and CXCL12 in tumor cells was associated with shorter recurrence-free RFS in PDAC patients High levels of CXCL12 in tumor cells predicted worse CSS in these patients. In patients who underwent complete tumor removal (radical resection), high CXCL12 levels were linked to poor RFS and CSS.	[182]
CXCR4	Osteosarcoma and Ewing sarcoma	Improving the anti-cancer activity of NK cells through CXCR4 downregulation	[183]
CXCR4	Breast cancer	Upregulation of PD-L1 in the patient samples Low immune density results from overexpression of CXCR4	[184]
CXCR4	Breast cancer	Upregulation of CXCR4 Suppressing CXCR4 using plerixafor reduces fibrosis in TME Increased number of CTLs upon CXCR4 inhibition	[185]
CXCR4	Glioblastoma	Combination blockage of CXCR4 and PD- 1 to enhance the number of CD^{8+} T cells and decrease MDSCs	[186]
CXCR4 CXCL12	Glioma	Delivery of AMD3100 as CXCR4 antagonist by nanoparticles Modification of nanostructures with iRGD Induction of immunogenic cell death	[187]
CXCR4	Pancreatic cancer and colorectal tumor	Evaluating the tumor biopsies from patients with metastatic PDAC and MSS CRC who received AMD3100 (plerixafor), a CXCR4 inhibitor Stimulation of immune responses upon CXCR4 downregulation	[188]
CXCR2	Hepatocellular carcinoma	Upregulation of CXCR2 ligands Modification of CAR-T cells to express CXCR2 in improving their migration towards HCC cells	[189]
CXCR2	Different cancers including pancreatic cancer	The study designed and synthesized a series of benzocyclic sulfone derivatives as potential CXCR2 antagonists Inhibition of CXCR2 and reducing neutrophil infiltration	[190]
CXCR2	Pancreatic cancer	Secretion of CXCR2 ligands by pancreatic cancer cells Engineering CAR-NK cells for the expression of CXCR2 to improve their migration towards cancer cells	[191]
CXCR2	Gastric cancer	Secretion of CXCL8 by GCMSCs binding to CXCR2 on the surface of cancer cells Such interaction stimulates HK2 to enhance lactate production The accumulation of lactate in the TME can suppress immune reactions	[192]

progression. This treatment led to increased CD8+ T cell infiltration, elevated IgG and IgM seropositivity, a positive correlation between MHC-I expression and the number of TILs, and a reduction in Treg cell levels [194].

Cerullo et al. investigated three cyclophosphamide protocols—metronomic, maximum tolerated dose (MTD), and a combination of MTD and metronomic—in conjunction with oncolytic adenovirus in patients with resistant solid tumors. Their study revealed significantly improved disease control rates with cyclophosphamide compared to the virus alone ($p < 0.0001$). A reduction in Treg cells was observed in the metronomic cyclophosphamide group, while the antitumor effectiveness of CD8+ T cells was preserved [195]. Similarly, Liikanen et al. evaluated 17 patients with resistant solid tumors who received oncolytic adenoviruses, a low-dose pulse of temozolomide, and metronomic cyclophosphamide for Treg depletion. Objective effectiveness was observed in 67% of radiologically assessable treatments, with high-mobility group box 1 (HMGB1) levels positively correlated with antitumor T cell responses [196].

Checkpoint regulatory systems are maintained by ligands that inhibit T cell responses, preventing overactivity and potential host damage [197, 198]. In many cancers, tumor, stromal, or infiltrating immune cells produce these ligands in excess, thereby weakening the effectiveness of antitumor T cells. Monoclonal antibodies targeting immune checkpoints, such as CTLA- 4 and PD- 1, have been clinically approved and have shown efficacy. Numerous clinical trials have explored chemotherapy in combination with checkpoint blockade; however, many were designed to compare chemotherapy alone with chemotherapy plus checkpoint inhibitors, omitting a group receiving only immunotherapy. This trial design has hindered a comprehensive evaluation of chemotherapy's role in combination treatments. Preliminary results from the CheckMate 012 study, which assessed four combinations of platinum-based chemotherapy with the anti-PD- 1 antibody nivolumab, indicated that none of the combinations surpassed the median PFS achieved with nivolumab alone [199, 200]. However, these findings were based on non-randomized comparisons, and detailed data remain unpublished. More information can be found here [198].

Gemcitabine, a standard-dose chemotherapeutic agent with immunomodulatory properties, exhibits various immune-related effects. It promotes tumor cell death and enhances CD8+ T cell cross-priming in preclinical studies [201]. Additionally, it restores the impaired cross-presentation of tumor antigens by DCs within the TME [202]. Administering gemcitabine before immunization or a CD40 agonist improved survival rates in mice undergoing chemoimmunotherapy [201, 203]. Likewise, the combination of gemcitabine and cisplatin following immunotherapy with an adenoviral vector producing IFN-α enhanced anticancer efficacy compared to monotherapy by increasing the number, activation, and trafficking of antigen-specific TILs [204].

An independent study demonstrated that while concurrent gemcitabine administration reduced antigen-specific peripheral T cell counts, it enhanced the efficacy of a DC-based vaccine by increasing T cell trafficking and sensitizing tumor cells to T cell-mediated killing [205]. This peripheral immune suppression was overcome by administering gemcitabine after two rounds of immunization. Moreover, preclinical animal studies have demonstrated that gemcitabine significantly reduces MDSCs [204, 206–208].

Figure 4 illustrates the immune-modulating effects of various chemotherapeutic agents. Further details on the combination of chemotherapy or radiotherapy with immunotherapy are available in Section 7 of the Supplementary Materials.

Radiotherapy

Tumor radiation activates multiple immunopotentiating mechanisms; however, research has rarely examined these processes or their individual contributions to enhancing immunotherapy. Significant findings have linked alterations in the TME to the effectiveness of immunotherapy. Localized radiation has been shown to increase Fas expression, thereby significantly enhancing the efficacy of adoptively transferred T lymphocytes in targeting carcinoembryonic antigen. This approach improves Fas-dependent cytotoxic T cell function, reducing tumor growth rates in subcutaneous adenocarcinoma mouse models. Similar findings from various experiments indicate that targeted irradiation of subcutaneous tumors enhances Fas expression, thereby boosting the effectiveness of cancer vaccines. These results demonstrate a notable increase in CD8+ CTLs within the tumors, leading to tumor regression. Additional recognized effects include increased vascular density and an abscopal effect, wherein distant, non-irradiated tumors also show regression [210].

Various studies have investigated the complex signaling interactions between inflammatory and stromal cells within the PDAC microenvironment, with the goal of improving PDAC response to immune therapies [211–213]. Poor PDAC outcomes are frequently linked to its propensity to metastasize to the liver. Liver metastases exhibit resistance to immunotherapy due to liver-resident macrophages, which enhance the removal of CD8+ T cells targeting the tumor [214, 215]. Consequently, the risk of developing immunoreactivity is significant when the tumor is aggressive or metastatic. This suggests that radiation could serve as an effective strategy for overcoming this immunosuppressive mechanism. More information on immunotherapy can be found here [213, 216].

T cell clones in both the bloodstream and tumor tissue have gained research attention. After radiation therapy, expanded and contracted clones were detected in the peripheral blood of responders on day 22. Radiation therapy increased tumor-derived KPNA2 gene expression, which encodes karyopherin α2, as indicated by the expanded clone [217, 218]. Further analysis revealed that the elevated clonotypes in peripheral blood samples were primarily enriched in tumors, suggesting a correlation between the tumor and blood sample repertoires following radiation therapy [219]. Notably, the combination of radiation therapy with PD- 1 blockade facilitates the movement of expanded clones from the treated tumor to the untreated tumor and the surrounding bloodstream. This strategy could mitigate adaptive resistance driven by the PD- 1/PD-L1 pathway, thereby strengthening a broader polyclonal T cell response [218, 220].

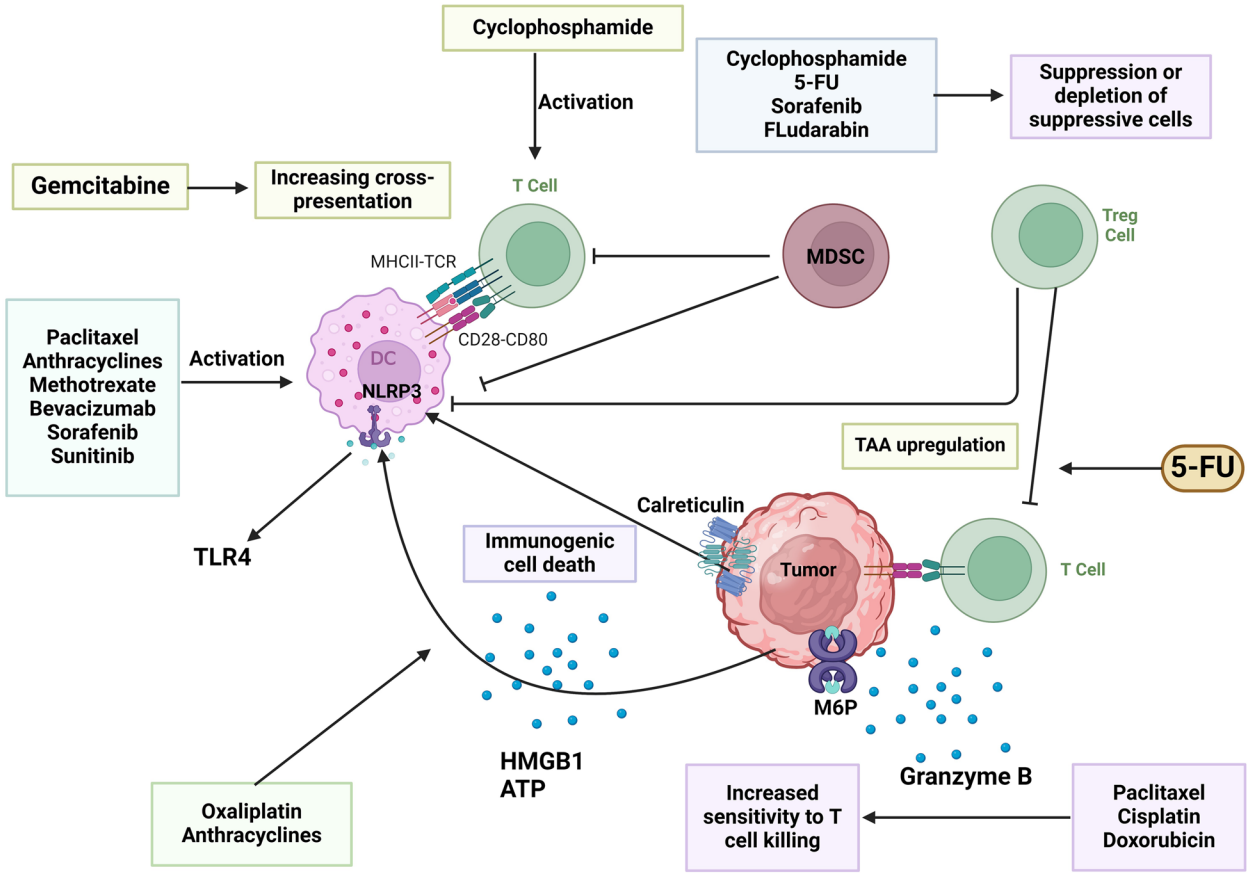

Fig. 4 The modulation of the immune system through chemotherapeutic agents. Various types of anti-cancer agents can target immune cells, potentially generating a synergistic effect in cancer immunotherapy. The presence of calreticulin along with the release of HMGB1 and ATP may lead to immunogenic cell death that facilitates DC activation by influencing NLRP3 and TLR4. Several chemotherapy medications can directly stimulate DCs. The heightened cross-presentation may result from gemcitabine, and several of them can inhibit or eliminate the immunosuppressive cells [209]. *(Created by Biorender.com)*

The integration of radiotherapy and immunotherapy has proven beneficial in triggering ferroptosis in cancer cells by downregulating SLC7 A11, which reduces cystine uptake and enhances lipid peroxidation [221]. Low-dose radiation therapy can modify the immunosuppressive TME, which is typically characterized by limited T cell infiltration and poor response to immunotherapy. This alteration may enhance the efficacy of immunotherapy by increasing tumor immunogenicity and facilitating better T cell infiltration. Consequently, low-dose radiotherapy has been shown to improve cancer immunotherapy outcomes [222].

Radiotherapy and immunotherapy work synergistically to eliminate tumor-supporting erythroid progenitor cells, known as "Ter cells," through adaptive immunity. These cells promote tumor growth by releasing artemin, a neurotrophic peptide that activates the RET signaling pathway. The combination of radiotherapy and immunotherapy effectively targets and eliminates these cells, further inhibiting tumor growth [223]. Additionally, the DNA exonuclease Trex1 plays a role in regulating radiation-induced tumor immunogenicity, suggesting that modifying Trex1 function could enhance the immune response triggered by radiation and improve the effectiveness of immunotherapy [224].

Nanostructures containing selenium have been shown to facilitate the delivery of doxorubicin (DOX) to tumor sites, enhancing chemotherapy. Radiation promotes DOX release and accelerates chemotherapy. Furthermore, radiation enhances the oxidation of nanoparticles to selenium by integrating chemotherapy and immunotherapy, thereby increasing NK cell activity [225]. Figure 5 illustrates the significance of combining radiotherapy with immunotherapy.

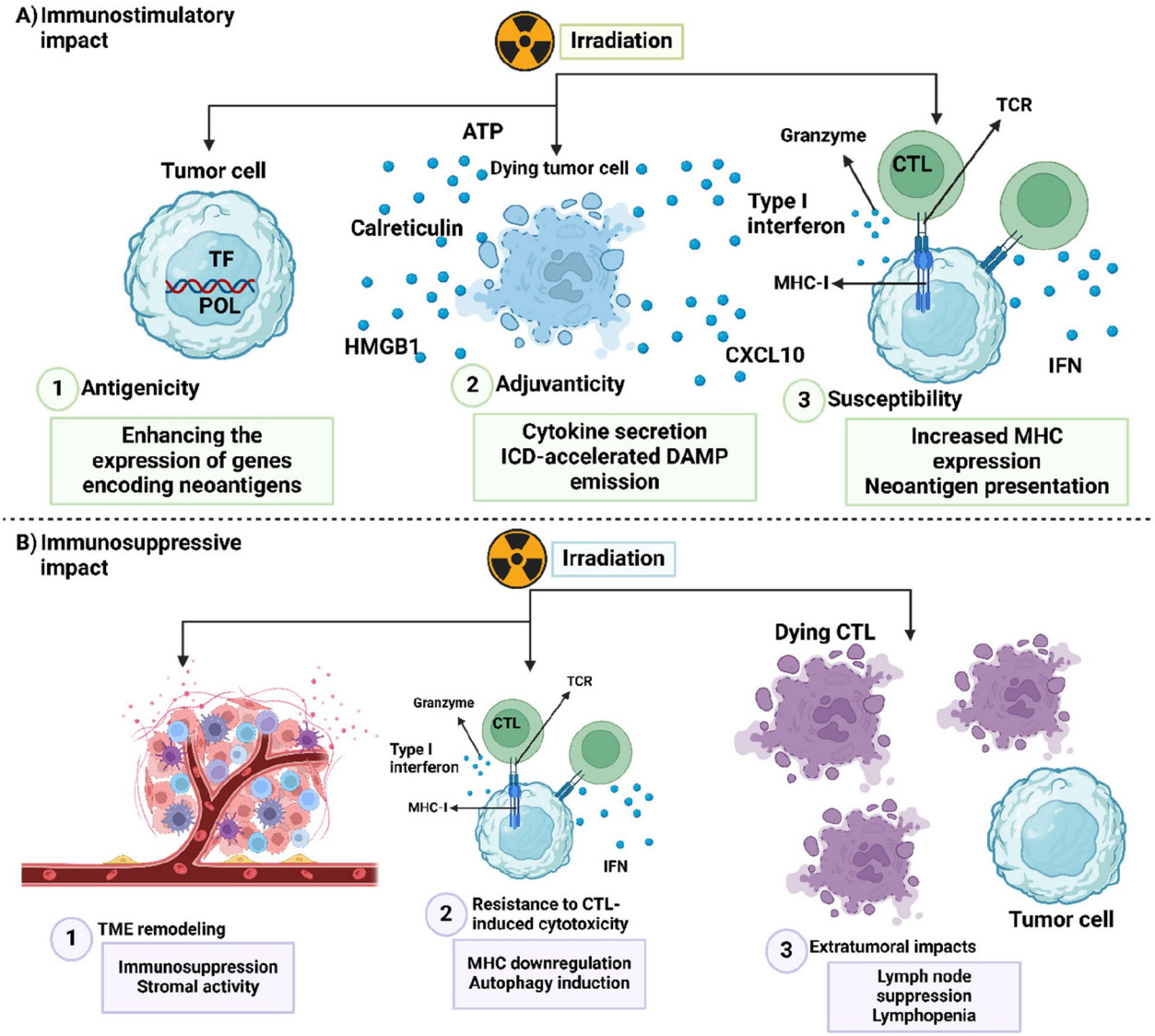

Fig. 5 The reasoning behind integrating radiotherapy and immunotherapy for cancer eradication [226]. It is important to recognize that radiotherapy has a dual role, making it essential to implement new strategies that harness the synergistic effects of radiotherapy. **A** Radiotherapy might have an immunostimulatory effect by enhancing the levels of neoantigen-encoding genes, boosting immunogenic cell death, and facilitating neoantigen presentation on MHC class I molecules. **B** Radiotherapy might also exert an immunosuppressive effect depending on the radiation dosage, fractionation schedule, and treatment area. The hypoxia might enhance TME remodeling to encourage the M2 polarization of macrophages while promoting the infiltration of Treg cells and activating CAFs. Conversely, there could be a decrease in MHC expression and an increase in autophagy, combined with suppression of the lymph nodes. Additional details regarding the role of radiotherapy in stimulating the immune system are available in this review [227]. *(Created by Biorender.com)*

Personalized immunotherapy

Currently, there are three primary methods of T cell-based cancer immunotherapy: active vaccination, adoptive cell transfer therapy, and ICB. These approaches have demonstrated significant clinical effectiveness and have garnered considerable attention in cancer immunotherapy. A comprehensive understanding of the mechanisms underlying antitumor immune responses, known as the "Cancer-Immunity Cycle," is essential for advancing this treatment strategy. Tumors employ various mechanisms to evade antitumor immunity, some of which arise from the selection of cancer cells exhibiting immunosuppressive traits through a process known as cancer immunoediting. In addition to this selective mechanism, antitumor immune responses can be suppressed through various pathways that differ among individuals. This variability

underscores the need for personalized cancer immunotherapy, which involves (1) identifying the limiting factors for each patient, (2) developing and integrating strategies to overcome these barriers, and (3) advancing the next phase of the "Cancer-Immunity Cycle."

Cancer cells possess genetic alterations that serve as markers for immune system recognition and tumor elimination. Neoantigens, which are altered proteins exclusively expressed in cancer cells, are recognized by the immune system. Advances in next-generation sequencing have facilitated the mapping of the genetic basis of human cancers, enabling the identification of potential neoantigens specific to individual tumors. As a result, immunotherapies must be tailored to target specific immunosuppressive pathways and recognizable neoantigens [228]. However, intratumoral heterogeneity, characterized by genetically diverse subpopulations within a tumor, poses a significant challenge for personalized cancer treatment. Developments in next-generation sequencing have allowed for genome comparisons across multiple tumor sites within the same patient. Studies have revealed variations in genotypes and phenotypes at different tumor locations in both hematological and solid malignancies, driven by distinct somatic mutations and alterations in DNA copy number. This heterogeneity suggests that a single biopsy may not accurately represent the entire tumor, potentially leading to treatment failure and disease recurrence. Moreover, tumor heterogeneity may reduce the reliability of prognostic biomarkers in clinical applications. Mechanisms such as antigen loss or downregulation in response to immunological pressure further complicate therapeutic efficacy. In cases where HLA expression is downregulated, CAR-T cells may demonstrate greater efficacy than TCR-T cells. Therefore, a thorough understanding of tumor clonal evolution is crucial for addressing genetic variations across tumor sites and throughout treatment [229].

Recent advances in cancer immunotherapy have focused on augmenting antitumor immune responses mediated by CTLs. Adoptive transfer therapy using TILs has demonstrated promising results, particularly in patients with melanoma, with clinical trials reporting a 22% complete response rate and a 56% objective response rate. However, adverse effects, including neutropenia and capillary leak syndrome, have been observed. Cancer vaccines, including peptide and DC-based vaccines targeting neoantigens or shared tumor antigens, have exhibited therapeutic efficacy. A phase II trial evaluating an oncoantigen peptide vaccine for esophageal cancer demonstrated significantly improved 5-year survival rates, particularly among patients with tumors lacking CD8+ T cell infiltration or PD-L1 expression. Personalized neoantigen vaccines have been investigated in several phase I trials, showing promise for use in melanoma and glioblastoma. Patients receiving these vaccines exhibited neoantigen-specific T cell responses and prolonged PFS, especially when combined with anti-PD- 1 therapy. Although neoantigen vaccines appear feasible for tumors with lower mutational burdens, such as glioblastoma, challenges remain, as some patients continue to experience disease progression. Adverse events associated with these vaccines are generally mild, with grade 1–2 injection site reactions and flu-like symptoms being the most common. Serious toxicities occur in fewer than 10% of patients [230].

Factors affecting cancer immunotherapy

Tumor type

The effectiveness of immunotherapy is significantly influenced by tumor type, as each cancer exhibits distinct biological and molecular characteristics that impact immune recognition and response. An essential factor is the tumor's antigen profile, which varies across different cancer types. Tumors with high mutational burdens, such as melanoma, lung cancer, and microsatellite instability-high (MSI-H) tumors, often generate numerous neoantigens, making them more responsive to immune therapies, particularly ICIs. In contrast, tumors with lower mutational burdens, such as pancreatic and certain breast cancers, produce fewer neoantigens, leading to a weaker immune response to immunotherapy. Additionally, the TME plays a crucial role in determining the success of immunotherapy. Some cancers, such as melanoma and lung cancer, exhibit a "hot" TME, characterized by high levels of immune cell infiltration, which enhances responsiveness to ICIs. Conversely, tumors that exhibit a "cold" TME, such as pancreatic cancer, glioblastoma, and ovarian cancer, demonstrate limited immune cell infiltration and elevated levels of immunosuppressive components, including Tregs and MDSCs, which hinder the effectiveness of immune therapies.

TME heterogeneity

The TME is a complex and dynamic ecosystem composed of tumor cells, immune cells, stromal cells, blood vessels, ECM components, and soluble factors. TME heterogeneity refers to variations in cellular composition, molecular signaling, and immune cell presence within different regions of a single tumor, as well as differences between primary tumors and metastatic sites. This variability significantly affects responses to immunotherapy, as the immunological landscape within tumors can vary greatly. In some regions, a tumor may exhibit extensive immune infiltration characterized by activated T cells and DCs, making it more susceptible to ICB or other immunotherapeutic interventions. However, in other regions, the TME may display immunosuppressive characteristics,

as indicated by increased levels of MDSCs, Tregs, and tumor-associated macrophages (TAMs), which suppress the activation and function of effector immune cells. Furthermore, spatial variations in oxygen and nutrient availability can lead to hypoxic regions, which enhance immunosuppressive factors such as VEGF and hypoxia-inducible factor- 1 alpha, thereby reducing the efficacy of immunotherapy. Tumors exhibiting diverse immunological and stromal conditions pose significant treatment challenges, as immune-resistant regions may persist even when other areas respond to therapy.

Gut microbiota

Recent studies have highlighted the role of gut microbiota in modulating the efficacy of cancer immunotherapy, particularly ICIs that target the PD- 1/PD-L1 pathway. Three independent studies have provided insights into this relationship in patients with melanoma and other cancers. Gopalakrishnan et al. found that individuals who responded to anti-PD- 1 treatment exhibited greater gut microbiome diversity and higher abundances of Ruminococcaceae and Faecalibacterium, whereas non-responders showed reduced microbial diversity and increased levels of Bacteroidales [231]. Matson et al. identified several bacterial species that were more prevalent in responders, including *Bifidobacterium longum*, whereas *Ruminococcus obeum* and *Roseburia intestinalis* were enriched in non-responders [231]. It was reported that responders exhibited heightened microbiome diversity, with *Akkermansia muciniphila* being associated with better treatment outcomes, and found that antibiotic use during immunotherapy reduced its efficacy [231]. Collectively, these studies emphasize the importance of gut microbiota composition and diversity in shaping responses to anti-PD- 1 therapy.

Local immunity in the digestive system is supported by pattern recognition receptors (PRRs) and bacterial metabolites such as short-chain fatty acids (SCFAs). PRRs recognize pathogen-associated molecular patterns and promote DC maturation, which in turn facilitates the differentiation of naïve T cells into Tregs and Th17 cells. Systemic immune responses are influenced by microbiome priming; a balanced microbiome enhances immune function and vaccine efficacy, whereas dysbiosis weakens mucosal barriers and promotes systemic inflammation [232]. The gut microbiota plays a crucial role in modulating responses to various cancer immunotherapies, including ACT, TLR agonists, and ICB. Antibiotics such as ciprofloxacin and vancomycin can disrupt the microbiota, thereby affecting the efficacy of ACT through mechanisms associated with bacterial LPS, TLR4 signaling, and type 1 conventional DCs [233]. Similarly, beneficial bacteria produce SCFAs that enhance the functionality of CD8+ T cells and CAR-T cells by inhibiting histone deacetylases (HDACs) and stimulating IL- 12 production [233]. Intratumoral TLR9 agonists, such as CpG-oligodeoxynucleotides (CpG-ODNs), depend on gram-negative bacteria to activate myeloid cells and promote TNF and IL- 12 secretion, thereby enhancing antitumor immunity [233]. In ICB therapies, gut microbiota composition is correlated with patient outcomes, with bacterial families such as Ruminococcaceae, Lachnospiraceae, and Bifidobacteriaceae being associated with favorable responses to anti-PD- 1/PD-L1 treatment [233]. However, antibiotic-induced dysbiosis has been shown to impair ICB efficacy. Despite these associations, variations in findings across studies underscore the need for further investigation at the subspecies or strain level to identify specific bacterial genes or pathways that influence immunotherapy outcomes. Understanding these complex interactions may enable microbiota-targeted strategies to enhance the effectiveness of immunotherapy [233].

Research in both murine models and patients with metastatic melanoma has demonstrated that specific T cell responses against *Bacteroides thetaiotaomicron* and *Bacteroides fragilis* are linked to improved responses to CTLA- 4 inhibition [234]. This study employed a clustering approach based on stool genus composition and genomic sequencing of bacterial 16S ribosomal RNA to identify three distinct microbiome clusters: one primarily dominated by *Alloprevotella* or *Prevotella* and two additional clusters consisting of various *Bacteroides* species [234]. To assess the functional relevance of these microbiome clusters, fecal microbiota transplantation (FMT) was performed from human donors to germ-free (GF) mice. FMT was conducted 2 weeks before tumor inoculation in GF mice, followed by treatment with an anti-CTLA- 4 antibody [235]. Mice that received fecal microbiota transplants from cluster C patients exhibited a significant response to CTLA- 4 inhibition, whereas those that received transplants from cluster B patients showed no anticancer effects [235].

Neoantigens

Neoantigens are aberrant proteins produced exclusively by tumor cells through nonsynonymous mutations, distinguishing them from normal cellular proteins. These antigens exhibit high immunogenicity and play a pivotal role in activating the immune system. Unlike TAAs, which are found in both normal and malignant cells, neoantigens are unique to cancer cells. The process of identifying neoantigens involves several key steps: obtaining a tumor biopsy specimen, detecting mutated genes and abnormal proteins via sequencing, employing computational models to predict antigenic proteins, and using mass spectrometry techniques for immunological

confirmation. Neoantigen-based therapies have demonstrated considerable success in eliciting immune responses, particularly in patients with tumors characterized by high mutation rates, such as melanoma [236].

The advent of high-throughput cancer genome sequencing has facilitated the identification of somatic mutations that lead to the emergence of neoantigens. These antigens are distinct to individual tumors and arise due to random mutations induced by DNA damage or repair defects. Certain cancers with high mutational burdens, such as MSI-H tumors, may harbor shared neoantigens originating from mutations in specific genomic loci. The identification of neoantigen targets typically involves whole-exome or RNA sequencing of metastatic tumors. The number of neoantigens varies considerably by tumor type, ranging from a minimal presence in astrocytomas to abundant quantities in melanoma and lung cancer [237]. A comprehensive study utilizing genomic data from 221 PDAC samples revealed several critical findings: nearly all PDAC samples contained potentially targetable neoantigens, tumor-infiltrating T cells were present but exhibited diminished activation, and markers associated with effective antigen presentation were inversely correlated with cytotoxic T cell activity. These results suggest that T-cell activation is profoundly suppressed in PDAC, even in tumors containing tumor-specific neoepitopes [238].

Neoantigens play an essential role in cancer immunotherapy, particularly in CAR-T cell therapy and ICB targeting PD- 1/PD-L1. In CAR-T cell therapy, targeting neoantigens allows T cells to selectively attack tumor cells while sparing healthy tissues. One notable example is the tight junction protein claudin 6, which is expressed in various solid tumors but is largely absent in normal adult tissues, making it an attractive therapeutic target. In ICB therapy, tumor mutational burden (TMB) serves as a predictive biomarker, with a higher TMB correlating with an increased probability of neoantigen formation and enhanced responses to ICIs. For instance, patients with NSCLC who exhibit a high TMB experience improved survival rates following treatment with PD- 1/PD-L1 inhibitors. However, despite the general correlation between high TMB and positive immunotherapy responses, some patients develop resistance through the loss of previously recognized neoantigens or the emergence of new neoantigens with enhanced major histocompatibility complex (MHC) binding affinity, potentially facilitating immune evasion. These findings underscore the dynamic nature of neoantigens and their critical role in determining immunotherapy efficacy [239].

Inhibition of PD- 1 enhances CD8+ T cell activity, particularly against mutation-associated neoantigens (MANAs); however, various factors within the TME can impair these responses. Single-cell transcriptomic studies have revealed functional impairments in TILs, where MANA-specific TILs exhibit unique transcriptional profiles characteristic of tissue-resident memory cells but display reduced responsiveness to IL- 7 signaling. In non-responsive tumors, MANA-specific TILs demonstrate diminished ligand-dependent signaling and upregulation of inhibitory receptors. Some tumor-associated mutations, such as those in the TP53 tumor suppressor gene, present additional challenges due to intracellular localization. Nevertheless, peptides derived from these mutations, including the p53R175H variant, can be displayed by HLA molecules, rendering them potential targets for immunotherapy. A bispecific antibody, H2, was engineered to bind specifically to the p53R175H peptide-HLA complex and direct T cells to eliminate cancer cells, demonstrating efficacy both in vitro and in vivo. Similarly, efforts targeting oncogenic RAS mutations have resulted in the development of single-chain diabodies that activate T cells to recognize and destroy cancer cells expressing mutant RAS peptides on HLA molecules. These approaches highlight the potential of targeting recurrent neoantigens derived from common oncogenic driver mutations, offering a strategy applicable to a broad range of patients with cancer. Moreover, advancements in the identification and quantification of tumor-derived peptides bound to HLA molecules through immunoprecipitation and mass spectrometry are crucial for refining targeted immunotherapies and neoantigen-based cancer vaccines. Collectively, these developments illustrate the evolving landscape of cancer immunotherapy, underscoring the importance of neoantigen targeting, T-cell engineering, and precision therapeutic strategies to overcome challenges posed by tumor heterogeneity and immune evasion [240–244].

The unique neoantigen repertoire of an individual patient, known as the "neoantigenome," presents several challenges in the development of personalized cancer immunotherapies. One of the primary hurdles is the precise identification and prediction of neoantigens, necessitating extensive genomic and transcriptomic analyses to differentiate tumor-specific mutations from normal genetic variations. This process is technically complex and computationally demanding. Furthermore, not all predicted neoantigens exhibit immunogenic properties, and identifying which neoantigens elicit robust immune responses remains a significant challenge. Tumor heterogeneity and the dynamic nature of the TME further complicate this process, as neoantigen expression may change over time or differ between primary and metastatic tumor sites. Additionally, the significant costs and time required to develop personalized neoantigen

vaccines limit their widespread clinical implementation. Finally, immune evasion strategies, such as impaired antigen presentation and the presence of immunosuppressive signals within the TME, may diminish the efficacy of neoantigen-based therapies, necessitating combination approaches to overcome resistance.

Mutations

Immune evasion is a hallmark of cancer, as tumors exploit immune checkpoint proteins such as PD- 1, PD-L1, and CTLA- 4 to escape destruction by T cells. ICIs function by reactivating T-cell activity; however, their efficacy is contingent on the presence of immunogenic neoantigens presented by MHC molecules. TMB is positively correlated with improved ICI outcomes, as a higher TMB increases the likelihood of producing immunogenic neoantigens. However, TMB alone has limitations as a predictive biomarker, with response rates of approximately 45% in TMB-high tumors due to factors such as neoantigen clonality, tumor molecular markers, and variations in the host immune environment. Given the complexity of immune responses—including T cell trafficking, cytokine balance, and MHC-TCR interactions—TMB should be considered in conjunction with additional biomarkers to enhance the prediction of ICI efficacy [245].

PD-L1 expression and TMB are both used as independent biomarkers to predict responses to ICB. While PD-L1 has demonstrated some utility as a biomarker, its inconsistent and heterogeneous expression, along with test variability, limits its predictive accuracy. TMB has emerged as an alternative biomarker, with higher TMB consistently associated with better outcomes in patients undergoing ICB, as demonstrated in clinical trials such as Checkmate 026 and IMvigor211. Patients with both high TMB and elevated PD-L1 expression tend to derive greater benefit from ICIs; however, TMB and PD-L1 levels are not correlated. In combination immunotherapy (such as anti-PD- 1 plus anti-CTLA- 4 therapy), high TMB appears to exert a greater influence on therapeutic response than PD-L1 expression, suggesting that TMB identifies immunogenic tumors in which CTLA- 4 plays a regulatory role in T-cell activation. These findings underscore the potential of integrating TMB and PD-L1 expression for improved patient selection in ICB while also highlighting the complexity of immune responses and the necessity for comprehensive biomarker strategies [246].

A bioinformatics approach was developed to detect tumor-specific antigens, or neoantigens, arising from single nucleotide variants (SNVs) in tumor tissues, demonstrating their potential use in cancer vaccines. This method involves sequencing tumor DNA, identifying tumor-specific SNVs via variant calling, and predicting peptides with high binding affinity for common HLA class I alleles in specific populations, such as those in Costa Rica's Central Valley. This approach identified 28 non-silent SNVs in 17 genes on chromosome one, generating 23 high-affinity peptides for HLA class I alleles. This study represents the first in silico exploration of a cancer vaccine based on DNA sequencing data of HLA alleles. Human cancers exhibit a variety of somatic mutations, some of which can be presented on MHC class I molecules and recognized as "non-self" by the immune system. A streamlined method integrating whole-exome sequencing, transcriptome analysis, and mass spectrometry has been introduced to identify and model neoantigens, circumventing the labor-intensive nature of conventional techniques for detecting immunogenic mutant peptides. This approach has been validated in murine tumor models, demonstrating that the predicted immunogenic peptides elicit therapeutic T-cell responses. Peptide-MHC dextramers allow for direct observation of T-cell responses, facilitating personalized cancer vaccines and real-time evaluation of their pharmacodynamics in patients. This pipeline has proven effective in identifying neoantigens and advancing personalized cancer immunotherapy [247, 248].

A fusion protein comprising an antibody and cytokine (scFv_RD_IL- 15) was engineered to selectively enhance IL- 15 activity at tumor sites by incorporating an IL-15Rα fragment, aiming to mitigate systemic toxicity while improving anticancer efficacy in a murine lung metastasis model. Additionally, SGN- 00101 (HspE7), a therapeutic vaccine combining heat shock protein 65 with the HPV 16 E7 oncoprotein, was evaluated for the treatment of cervical intraepithelial neoplasia grade III. In a study involving 64 women, the vaccine demonstrated potential efficacy, with 22.5% achieving complete pathological response and 55% exhibiting partial responses. However, it remains uncertain whether these outcomes resulted from natural regression or the vaccine itself. Cross-reactivity with non-HPV 16 infections was observed, and local inflammation was associated with the strength of immune responses. While these approaches present promising therapeutic opportunities, further research is required to enhance their efficacy and identify patient subgroups most likely to benefit from them [249, 250].

A study analyzing SNVs in genes associated with the PD- 1 axis investigated their predictive and prognostic significance in patients with advanced melanoma receiving PD- 1 inhibitor therapy. Among the SNVs examined, the PD-L1 +8293 C/A genotype was linked to a lower risk of immune-related adverse events (irAEs) compared to the C/C genotype. Additionally, a decreasing trend in irAE occurrence was noted for the PD1.5 T allele. No significant association was found between these SNVs and

treatment efficacy. However, the PD1.7 C/C genotype correlated with improved OS, suggesting that PD1.5 and PD-L1 +8293 SNVs could serve as potential predictive biomarkers for irAEs, while PD1.7 SNVs may have prognostic value for survival. Further validation is needed to confirm these findings [251].

CRC typically develops via two primary genetic instability pathways. While most CRCs exhibit chromosomal instability, approximately 15% are categorized as MSI-H tumors due to defects in DNA mismatch repair (MMR). MSI-H CRCs accumulate insertion and deletion mutations within microsatellite sequences and are frequently associated with Lynch syndrome. These tumors generally have favorable prognoses and rarely metastasize. MSI-H CRCs contain unique tumor antigens that elicit strong immune responses, leading to various immune evasion strategies. This review explores novel molecular mechanisms underlying the etiology, immunogenicity, and immune evasion of MSI-H CRCs. It also examines alterations in HLA presentation and considers how immune evasion, while protecting against localized immune responses, might inadvertently restrict a tumor's metastatic potential [252].

MSI CRCs exhibit a significant neoantigen mutation burden due to deficient DNA MMR, resulting in extensive immune infiltration and immune evasion mechanisms. A study investigated the role of high endothelial venules (HEVs), specialized blood vessels that facilitate lymphocyte trafficking, in MSI CRCs. Analysis of HEV density in MSI CRCs ($n = 48$) and microsatellite-stable CRCs ($n = 35$) revealed significantly elevated HEV densities in MSI tumors, particularly in cases linked to Lynch syndrome. Notably, Lynch syndrome-associated CRCs harboring B2M mutations exhibited the highest HEV densities, suggesting a potential relationship between lymphocyte recruitment and immune evasion. These findings underscore the role of lymphocyte trafficking in antitumor immunity in MSI CRCs and highlight the impact of tumor immunoediting [253]. Figure 6 illustrates the factors influencing the efficacy of cancer immunotherapy.

Immunotherapeutics

Small molecules and synthetic drugs

Basics

Recent research has demonstrated that small-molecule inhibitors have the potential to revolutionize cancer immunotherapy by targeting various mechanisms involved in tumor immune evasion and resistance. One approach focuses on modifying the immunosuppressive TME, as exemplified by toosendanin, which reprograms macrophages to enhance antitumor immunity in glioblastoma [254]. Another strategy involves directly inhibiting tumor proliferation while improving the efficacy of existing immunotherapies, as seen with small-molecule MYC inhibitors [255]. Additionally, targeting specific immune checkpoints such as AhR using BAY 2416964 [256] or Tim- 3 with small-molecule inhibitors [257] can amplify T cell-driven antitumor responses. Moreover, the co-delivery of small molecules targeting both calcium channels and CD47 through nanomedicine presents a promising method to enhance immunotherapy in lung cancer [258]. The development of small-molecule antagonists that disrupt PD- 1/PD-L1 interactions offers another avenue for immune checkpoint inhibition in NSCLC and melanoma [259].

These diverse strategies highlight the adaptability of small-molecule inhibitors in addressing the limitations of existing immunotherapies and improving treatment outcomes for various cancer types. Research into small-molecule inhibitors continues to be a promising area for developing novel strategies to enhance cancer immunotherapy. For example, inducing gasdermin D (GSDMD) expression in tumor cells through a small-molecule agonist can trigger pyroptosis, an inflammatory form of cell death that strengthens antitumor immunity while minimizing systemic toxicity [260]. Similarly, stimulating the P2X7 receptor using a small molecule enhances antitumor immune responses and boosts immunotherapy efficacy in lung cancer [261]. Another approach involves small-molecule MHC-II inducers, which increase cancer cell recognition by the immune system and reprogram tumor metabolism to support antitumor immunity [262]. In multiple myeloma, a combination of small-molecule inhibitors targeting HDAC and Akt has been shown to suppress tumor growth and enhance immunotherapy efficacy [263]. Additionally, small-molecule inhibitors of PTPN2 have been found to sensitize resistant melanomas to anti-PD-1 immunotherapy [264]. Targeting hematopoietic progenitor kinase 1 with a novel small-molecule inhibitor further strengthens antitumor immunity [265]. Finally, small-molecule degraders of protein tyrosine phosphatases, including PTP1B and TCPTP, represent a promising strategy for modulating T-cell activity to improve cancer immunotherapy outcomes [266].

Clinical importance

These strategies demonstrate the potential of small-molecule inhibitors to enhance antitumor immune responses and overcome therapeutic resistance across different cancer types. Numerous small-molecule immunomodulators have been identified, with several making significant progress in clinical trials. A comprehensive analysis of these immunomodulators categorizes them according to their molecular targets [267].

The integration of small-molecule inhibitors with other immunotherapeutic strategies, such as ICIs or adoptive

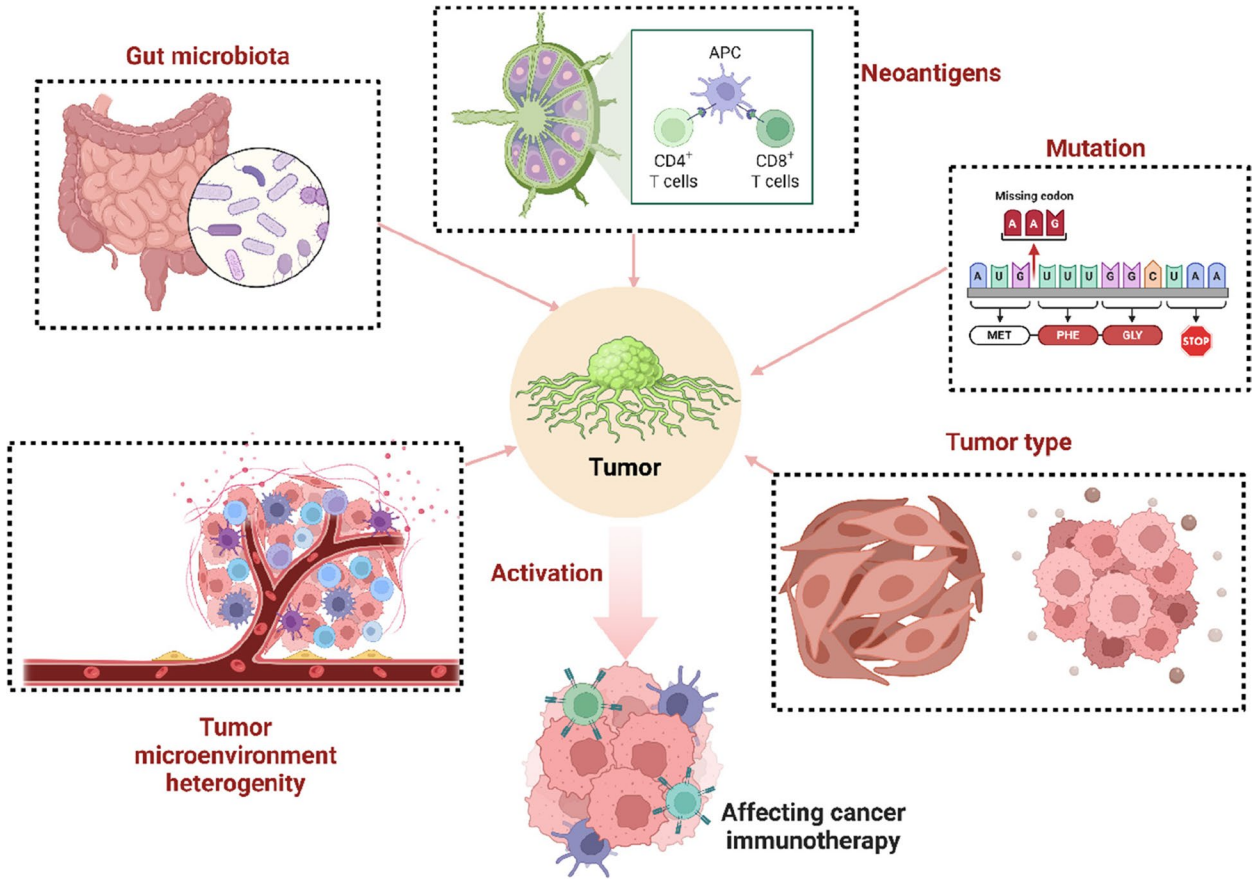

Fig. 6 The main elements involved in the modulation of immunotherapy effectiveness. The effectiveness of immunotherapy is influenced by a complicated interaction of factors that are both intrinsic and extrinsic to the tumor. At the heart of this process is the TME, which differs in immune cell infiltration and immunosuppressive components. Tumor classification and molecular subtypes influence mutational burden and neoantigen generation, with cancers exhibiting high TMB (melanoma, NSCLC) demonstrating improved responses to ICIs. Neoantigens, arising from somatic mutations, play essential roles as targets for T cell-driven anti-tumor immunity. The gut microbiome regulates systemic immune responses, affecting immunotherapy results by means of microbial variety and metabolite generation. Alterations in genes that control antigen presentation, immune checkpoints, and oncogenic pathways also influence immune evasion and resistance to therapy. Moreover, the heterogeneity of the tumor microenvironment and mechanisms of immune evasion (like PD-L1 overexpression and MHC downregulation) result in differing responses. Research is underway on combination therapies aimed at these various factors to address resistance and improve treatment effectiveness. This illustration emphasizes the complex nature of immunotherapy responses and the necessity for tailored treatment approaches. *(Created by Biorender.com)*

T-cell therapy, offers a synergistic approach to strengthening immune responses and mitigating resistance mechanisms [268]. By simultaneously targeting multiple signaling pathways or immune checkpoints through combination therapy, the breadth and durability of anti-tumor immune responses may be enhanced, resulting in improved therapeutic outcomes. Additionally, combining small-molecule inhibitors with conventional cancer treatments such as chemotherapy or radiotherapy enables a multi-faceted attack on tumor cells, leading to more robust and sustained responses [269]. The strategic design of combination therapies that harness the advantages of diverse treatment modalities holds significant potential for advancing cancer immunotherapy and addressing critical challenges, including immune evasion and tumor heterogeneity [270]. Figure 7 illustrates the molecular targets of small molecules in cancer immunotherapy.

Antibodies

Antibodies play a crucial role in cancer immunotherapy by enabling precise immune responses against tumor cells. A bispecific antibody fusion protein, PPAB001, was developed to target both CD24 and CD47. This antibody inhibits both CD47/SIRPα and CD24/Siglec-10 interactions, enhancing macrophage-mediated phagocytosis of

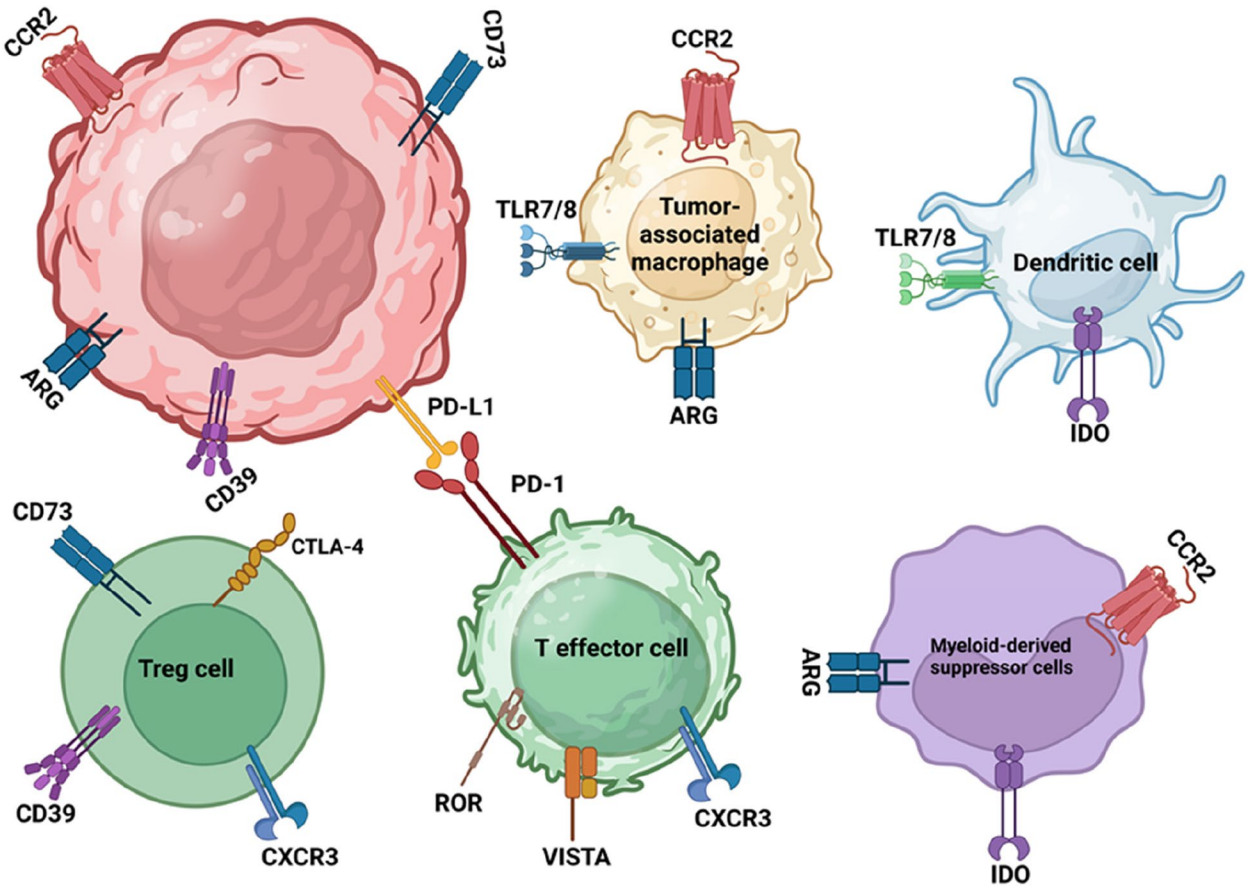

Fig. 7 The targets of small molecules in the field of cancer immunotherapy. Tumor cells are encased by various immune cells, including Tregs, Teffs, MDSCs, TAMs, and DCs. Scientists are exploring various proteins and receptors found on tumor and immune cells as potential targets for cancer immunotherapy. The targets encompass PD-1/PD-L1, RORγt, chemokine receptors, and TGF-β, linked to the adaptive immune response; Sting and TLR, associated with the innate immune response; and IDO, arginase, and A2 A adenosine receptor, which are relevant to the tumor microenvironment. The most promising and therapeutically developed targets consist of immune checkpoint proteins like PD-L1 (found on tumor cells), PD-1 (located on effector T cells), and CTLA4 (present on Tregs). Additional targets being examined in immuno-oncology encompass IDO/TDO and arginases, which play a role in the inherent processes of cancer cells [271]

cancer cells [272]. Additionally, the development of antibody agonists aims to trigger immune receptor signaling by locally depleting large receptor-like protein tyrosine phosphatases (RPTPs), such as CD45. Since RPTPs regulate immune responses, antibodies can potentially inhibit their interaction with immune receptors during immune cell activation [273].

Trispecific antibodies have also been engineered to target three distinct molecules: CD19, CD3, and CD28. These antibodies bind to CD3 and CD28 on T cells, facilitating their interaction with CD19-expressing tumor cells, which enhances T cell activation and immune responses. This trispecific antibody induces stronger T cell activation than antibodies targeting only CD3, as it benefits from co-stimulation through CD28 [274]. Another bispecific antibody, IMM2902, was designed to target both CD47 and HER2. IMM2902 functions through two pathways: first, it inhibits CD47 to disrupt the "do not eat me" signal, enhancing macrophage-mediated phagocytosis. Second, antibodies such as trastuzumab target HER2 to suppress its oncogenic signaling [275].

Another antibody, NILK-2301, was designed to connect CEACAM5 and CD3, bringing T cells closer to CEACAM5-expressing tumor cells. This enhances T cell recognition and immune response, promoting cytokine release and tumor cell destruction [276]. Preclinical studies support the use of antibodies for cancer immunotherapy [277, 278].

Several antibodies have demonstrated promising clinical applications in cancer immunotherapy. Daratumumab (Darzalex) targets CD38, a protein found on myeloma and various hematological cancers. This antibody activates the complement system, triggers NK cell activity,

enhances macrophage-mediated tumor cell phagocytosis, and promotes apoptosis, leading to tumor cell elimination. Daratumumab has effectively reduced myeloma cells and remained potent even in the presence of bone marrow stromal cells, which often protect tumor cells from treatment. It has demonstrated efficacy at low concentrations, minimizing adverse effects [279].

Sabatolimab, an antibody that inhibits TIM-3 (a marker of exhausted T cells), has shown safety and efficacy in a Phase Ib clinical trial. The trial also determined optimal dosing when used alongside decitabine and azacytidine [280]. Ivonescimab, a novel bispecific antibody, is currently being evaluated in a Phase 1b clinical trial for advanced or metastatic NSCLC in patients who have not received prior immunotherapy. Ivonescimab targets both PD-1, an immune checkpoint protein, and VEGF, a growth factor involved in angiogenesis, aiming to simultaneously enhance immune responses against cancer cells and disrupt tumor vascularization. The primary objective of the trial is to assess the safety and tolerability of ivonescimab, while the secondary objective is to evaluate preliminary efficacy data [281].

Peptides

Peptide-based proteolysis-targeting chimera nanoparticles (PT-NPs) have been designed to selectively degrade the immune checkpoint protein PD-L1, which normally inhibits T cell activation. PT-NPs enhance T cell-mediated tumor destruction by promoting PD-L1 degradation [282]. Another strategy involves peptide-reprogrammed small-molecule nanoassemblies that accumulate inside tumor cells, improving chemotherapy and immunotherapy efficacy. These nanoassemblies deliver drugs and stimulate immune responses within the TME [283].

Peptide nanotubes loaded with the STING agonist c-di-GMP have been studied for their ability to improve melanoma immunotherapy. These nanotubes efficiently deliver c-di-GMP to cancer cells, triggering the STING pathway and inducing a robust antitumor immune response [284]. Additionally, a superantigen mutant linked with an iRGD peptide has been shown to enhance tumor targeting and T cell infiltration. This fusion protein specifically binds to cancer cells and stimulates T cells, improving their recruitment to tumor sites and strengthening antitumor immunity [285].

A novel cyclic peptide targeting LAG-3, an immune checkpoint protein, has been developed. This peptide enhances antigen-specific CD8+ T cell responses, improving tumor cell destruction. It also rejuvenates exhausted T lymphocytes and promotes tumor clearance by inhibiting LAG-3 [286]. Another study described a polymer chimera combining a stapled oncolytic peptide with an anti-PD-L1 peptide. This construct merges the tumor-killing activity of the oncolytic peptide with the immune checkpoint-blocking effects of the anti-PD-L1 peptide. The approach significantly enhanced the antitumor immune response in CRC by facilitating ICD and blocking PD-L1-mediated immune suppression [287].

A separate study investigated a novel peptide-based nanoagonist that selectively activates the cGAS-STING pathway. This nanoagonist efficiently delivers STING agonists to cancer cells, triggering a strong innate immune response and improving ICB therapy [288]. Furthermore, a newly developed cyclic peptide inhibitor was designed to disrupt PD-1/PD-L1 interactions. By directly blocking this pathway, the peptide enhances T-cell activation and immune responses against cancer cells [289].

Nanocomplexes co-assembled with a peptide neoantigen (Adpgk) and a TLR9 agonist (CpG ODN) have been studied for CRC immunotherapy. These nanocomplexes efficiently deliver both the neoantigen and TLR9 agonist to immune cells, improving antigen presentation and eliciting a strong antitumor immune response [290].

Vaccines

Basics

Vaccines have become essential components of cancer immunotherapy in both basic research and clinical applications, as they enhance the immune system's ability to recognize and eliminate cancer cells. The key advantage of cancer vaccines is their potential to induce lasting immune responses. Vaccine development is based on the identification and validation of TAAs and neoantigens. Understanding the immune mechanisms involved in tumor recognition allows vaccines to be used as models to explore interactions between immune cells, such as DCs and NK cells.

Various platforms have been established to enhance the efficacy of cancer vaccines, including peptide-based vaccines, RNA/DNA vaccines, and virus-like particles. Adjuvant formulations have been developed to improve immunogenicity, and research into the TME has helped address immunosuppressive factors that limit vaccine effectiveness. Beyond preclinical research, advancements in clinical applications have led to the development of different vaccine types. Prophylactic vaccines such as those for HPV and HBV significantly reduce the risk of related cancers, including cervical and liver cancers. Therapeutic vaccines, designed to elicit immune responses in patients, target TAAs to control tumor progression or recurrence. Examples include sipuleucel-T for prostate cancer and neoantigen-targeted vaccines for melanoma and lung cancer.

The integration of cancer vaccines with ICIs, chemotherapy, and radiotherapy has demonstrated improved patient survival. Personalized medicine approaches,

supported by genomic and proteomic technologies, facilitate the creation of individualized vaccines tailored to specific tumor profiles.

Significant progress has been made in the clinical setting, with numerous studies evaluating vaccine efficacy and patient immune responses [291–302]. Cancer vaccines have been tested in multiple tumor types, including biliary tract cancer [303], melanoma [304], prostate cancer [305], CRC [306], ovarian cancer [307], bladder cancer [308], HPV-associated cancers [309], and HCC [310]. Figure S1 illustrates the mechanisms of action of vaccines in cancer immunotherapy.

Clinical applications

A personalized neoantigen-pulsed DC vaccine has been developed for lung cancer treatment. The vaccine is created using patient-specific neoantigens, which stimulate DCs that are later injected into the patient to induce an immune response. The therapy has been well tolerated, with mild to moderate side effects. The ORR was 25%, while the disease control rate reached 75%. The median PFS and OS were recorded at 5.5 and 7.9 months, respectively [311]. While these findings provide valuable insights, the study had a limited sample size (12 patients), and the long-term effectiveness of the vaccine remains to be determined.

A similar personalized neoantigen vaccine has been developed for melanoma treatment, designed to elicit an immune response against patient-specific tumor antigens. The vaccine demonstrated strong immunogenicity by stimulating T cells, leading to promising clinical outcomes. Four of six patients remained cancer-free at 25 months post-vaccination, while the two patients with tumor recurrence were treated with anti-PD-1 therapy, resulting in complete tumor regression [312]. These findings suggest that personalized neoantigen vaccines can effectively trigger anticancer immune responses in melanoma, particularly when combined with checkpoint inhibitors such as anti-PD-1. However, long-term efficacy requires further investigation.

The FixVac RNA vaccine (BNT111), which targets four TAAs commonly associated with melanoma, has been evaluated in patients with advanced melanoma, particularly those who had disease progression after checkpoint inhibitor therapy. The vaccine activated the immune system to recognize and eliminate melanoma cells, leading to durable objective responses, including tumor regression or elimination in certain patients. Notably, the vaccine demonstrated promising results when administered alone or in combination with PD-1 checkpoint inhibitors, highlighting its potential for improving clinical outcomes through combined immunotherapy strategies [313].

A small Phase I study evaluated a personalized mRNA vaccine for metastatic gastrointestinal cancers. The vaccine instructs the body to produce tumor-specific neoantigens to stimulate an immune response. While the vaccine successfully induced T cell responses to neoantigens and was well tolerated, none of the four patients exhibited tumor shrinkage. Further research with larger patient cohorts and combination therapies is required to enhance the efficacy of mRNA vaccines for gastrointestinal cancers [314].

HPV vaccines have received considerable attention for their role in preventing cervical cancer and other HPV-associated malignancies [315]. In a Phase II neoadjuvant study, the response to tecemotide (L-BLP25), a therapeutic vaccine derived from MUC1, was evaluated in patients with early-stage HER2-negative breast cancer. The vaccine was designed to stimulate an immune response against the overexpressed MUC1 protein in breast cancer. Patients received the vaccine before surgery to assess its impact on tumor response to standard treatments. Although the vaccine was well tolerated and did not increase toxicity, it did not significantly improve pathological complete response rates or residual cancer burden. These findings underscore the challenges in developing effective cancer vaccines and highlight the need for further research on tecemotide in different clinical settings or in combination with other therapies [316]. Additional clinical studies on cancer vaccines are presented in Table 2. Figure S1 provides a schematic representation of vaccines used in cancer immunotherapy.

Despite promising developments, cancer vaccines face several challenges. Tumor heterogeneity, both among patients and within individual tumors, complicates vaccine design because cancer cells express different antigen levels. Additionally, tumors employ immune evasion strategies such as downregulating antigen presentation, upregulating immune checkpoint molecules (PD-L1), and creating an immunosuppressive TME that hinders immune responses. Other issues include poor immune recognition of tumor antigens and the limited presence of immunogenic neoantigens. Effective vaccine delivery to immune cells remains a critical challenge in optimizing cancer immunotherapy.

Gene therapy approaches

Recent advancements in cancer immunotherapy have incorporated genetic tools to regulate key gene expression, offering deeper insights into tumor immunology. However, genetic approaches still face challenges, including off-target effects, suboptimal pharmacokinetics, insufficient tumor site accumulation, and degradation by RNase enzymes, necessitating the use of nanoparticle-based delivery systems. Addressing these challenges through optimized nanoparticle administration has the potential to significantly improve cancer immunotherapy.

Table 2 The application of therapeutic factors in immunooncology

Therapeutic factor	Cancer	Remark	Reference
VISTA Small Molecule Inhibitors	-	Inhibition of VISTA, an immune checkpoint protein, may enhance T cell activation and anti-tumor immune responses	[317]
ENPP1 Inhibitors	-	Inhibition of ENPP1 may increase cyclic GMP-AMP (cGAMP) levels, leading to activation of the STING pathway and enhanced anti-tumor immunity	[318]
Physachenolide C (natural product)	-	Targeting BET proteins may modulate the expression of genes involved in immune regulation and enhance the efficacy of immunotherapy	[319]
Poly(ADP-ribose) Polymerase (PARP) and PD-L1 Inhibitor Conjugates	-	Dual inhibition of PARP and PD-L1 may synergistically enhance anti-tumor activity by combining immunotherapy with a DNA damage response inhibitor	[320]
PD-L1/EGFR Dual Inhibitors	Glioblastoma	Dual inhibition of PD-L1 and EGFR may overcome resistance to anti-PD-L1 therapy and enhance anti-tumor immunity in glioblastoma	[321]
Thermosnsitive composites	-	Combines photothermal therapy with lonidamine to induce pyroptosis (inflammatory cell death) in tumor cells, potentially enhancing anti-tumor immunity.	[322]
Cocktail of small molecule inhibitors	-	Increasing DC maturation for the anti-cancer immunity	[323]
1-methyl- 1H-pyrazolo[4,3-b]pyridine derivatives	-	Inhibition of the PD- 1/PD-L1 interaction, an important immune checkpoint, may enhance T cell activation and anti-tumor immune responses	[324]
PIK- 93	-	TME modulation in improving ICB therapy	[325]
β-catenin suppressors	-	Suppression of β-catenin signaling may enhance anti-tumor immunity, potentially by affecting the TME or immune cell function	[326]
99 mTc-labeled small molecule	-	Development of a novel imaging agent for visualizing PD-L1 expression in tumors, which could aid in patient selection and treatment monitoring for immunotherapy	[327]
Small-molecule inhibitor of PD- 1/PD-L1 interaction	-	Inhibition of the PD- 1/PD-L1 interaction, an important immune checkpoint, with demonstrated anti-tumor efficacy in vivo	[328]
M335 (STING agonist)	-	Activation of the STING pathway leads to the production of type I interferons and other cytokines, promoting anti-tumor immunity	[329]
Alphataxin	Renal cancer	Increases tumor-infiltrating CD^{4+} T cells and, in combination with anti-PD- 1 therapy, suppresses tumor growth and metastasis	[330]
STAT3 inhibitor	Glioma	Reverses immune tolerance by inducing co-stimulatory molecules on macrophages and microglia, stimulating cytokine production, and promoting effector T cell proliferation	[331]
Vascular Adhesion Protein- 1 (VAP- 1) inhibitors	-	Reduces the accumulation of myeloid cells in the tumor microenvironment, leading to attenuated tumor growth	[332]
SB- 3 CT (MMP2/MMP9 inhibitor)	-	Modulates tumor immune surveillance by regulating PD-L1 expression	[333]
Isoxazole-containing biphenyl derivatives	-	Targets the PD- 1/PD-L1 immune checkpoint, potentially enhancing T cell activation and anti-tumor immunity	[334]
Resorcinol biphenyl ether analogs	-	Inhibits PD- 1/PD-L1 interaction with potentially reduced toxicity compared to other inhibitors	[335]
Tigilanol tiglate	-	Induces ICD in tumor cells and enhances the response to immune checkpoint blockade in both treated and distant tumors	[336]

Table 2 (continued)

Therapeutic factor	Cancer	Remark	Reference
Benzo[d]isothiazol-based small molecule inhibitors	-	Targets the PD- 1/PD-L1 interaction, potentially enhancing T cell activation and anti-tumor immunity	[337]
Benzimidazoles	-	Acts as potent inhibitors and degraders of VISTA, an immune checkpoint protein, potentially enhancing T cell activation and anti-tumor immunity	[338]
ANXA1-derived peptide (A11)	Several cancers	Targets PD-L1 for degradation, inhibiting tumor immune evasion and enhancing CD^{8+} T cell activation. Synergistic antitumor effect with PD- 1 monoclonal antibodies	[339]
Peptide inhibitors of VISTA/PSGL- 1 interaction	-	Blocks the interaction between VISTA and PSGL-1, potentially enhancing anti-tumor immunity by inhibiting VISTA's immunosuppressive function	[340]
Dual-targeting D-peptide	-	Blocks both CD24/Siglec- 10 and PD- 1/PD-L1 interactions, enhancing macrophage-mediated phagocytosis of tumor cells and CD^{8+} T cell activation. Synergizes with radiotherapy	[341]
Peptide-MHC-restricted antibodies	-	Repurposes existing antibodies to specifically target tumor antigens presented by MHC molecules, potentially leading to more precise and effective immunotherapy	[342]
PD-L1 and VEGFR2 dual-targeted peptide	-	Targets both PD-L1 and VEGFR2, potentially combining immune checkpoint inhibition with anti-angiogenesis. Shows synergistic effects with radiotherapy	[343]
Oral peptide blocking PD- 1/PD-L1 (delivered via fish oil-based microemulsion)	-	Efficiently delivers an oral peptide that blocks PD- 1/PD-L1 and induces ferroptosis (iron-dependent cell death) in tumor cells	[344]
Toxoplasma gondii GRA8-derived peptide	Colorectal cancer	Improves tumor targeting and shows anti-tumor activity in colorectal cancer	[345]
PD-L1 targeted peptide	-	Demonstrates potent antitumor and immunomodulatory activity by targeting PD-L1	[346]
Cyclic peptide-based PROTAC	Cervical cancer	Induces intracellular degradation of a palmitoyltransferase, leading to decreased PD-L1 expression in cervical cancer cells	[347]
Peptide neoantigens + STING and TLR4 agonists (cancer nanovaccine)	-	Co-delivers peptide neoantigens with STING and TLR4 agonists to enhance anti-tumor immune responses	[348]
CD47/SIRPα blocking peptide	-	Blocks the CD47-SIRPα interaction, enhancing macrophage-mediated phagocytosis of tumor cells. Shows synergistic effects with radiotherapy	[349]
Chimeric peptide-engineered nanomedicine	Breast cancer	Uses a self-delivery nanomedicine with a chimeric peptide to enhance photodynamic therapy and promote macrophage polarization for breast cancer immunotherapy	[350]
Macrocyclic peptide blocking CD47-SIRPα	-	Blocks the CD47-SIRPα interaction, enhancing macrophage-mediated phagocytosis of tumor cells	[351]
Covalent inhibitor of K-Ras(G12 C)	-	Induces MHC class I presentation of haptenated peptide neoepitopes, making the tumor cells more susceptible to immunotherapy	[352]
LHRH-R targeted lytic peptide (EP- 100)	Ovarian cancer	Enhances the efficacy of immune checkpoint blockade by targeting and killing LHRH-R-positive ovarian cancer cells, leading to increased tumor-infiltrating lymphocytes	[353]
Peptide-AIEgen nanocomposite	-	Mediates a cascade amplification of the cancer immunity cycle, leading to enhanced anti-tumor immune responses and improved immunotherapy outcomes	[354]
Self-assembled peptide	-	Enables effective cancer immunotherapy by blocking CD47, leading to enhanced macrophage-mediated phagocytosis of tumor cells	[355]

Table 2 (continued)

Therapeutic factor	Cancer	Remark	Reference
Trivalent peptide hydrogel vaccine	-	Acts as a supramolecular vaccine that effectively activates the immune system against cancer	[356]
DEC- 205 binding peptide	-	Used to develop a dendritic cell-targeting nanovaccine for enhanced antigen presentation and T cell activation	[357]
Patched 1-interacting peptide	Pancreatic cancer	Represses fibrosis in the tumor microenvironment of pancreatic cancer, improving the effectiveness of immunotherapy	[358]
SMAC peptide-doxorubicin conjugated prodrug	-	Combines a cancer cell-specific and pro-apoptotic SMAC peptide with doxorubicin in a prodrug format for synergistic cancer immunotherapy	[359]
Peptide-antibody self-assembly	-	Blocks both CD47 and CD24 signaling, enhancing macrophage-mediated phagocytosis and anti-tumor immune responses	[360]
Anti-PD-L1 peptide-conjugated prodrug nanoparticles	-	Combining PD-L1 blockade with the induction of immunogenic cell death through a targeted nanoparticle delivery system	[361]
TGF-β siRNA (synchronous delivery to stromal and tumor cells)	Triple-negative breast cancer	Elicits robust antitumor immunity by comprehensively remodeling the tumor microenvironment, including reducing immunosuppressive cells and increasing T cell infiltration	[362]
Shikonin and IDO- 1 siRNA (codelivered via hybrid micelles)	-	Enhances immunotherapy by remodeling the immunosuppressive tumor microenvironment, potentially by inhibiting IDO- 1 activity and increasing T cell infiltration	[363]
PD-L1 siRNA and Imatinib	Melanoma	Promotes the cancer-immunity cycle, leading to enhanced anti-tumor immune responses	[364]
YTHDF1 siRNA	Hepatocellular carcinoma	Boosts antitumor immunity by inhibiting the EZH2-IL- 6 axis, potentially leading to decreased tumor growth and improved survival	[365]
Chromatin remodeling factors (identified via genome-wide CRISPR screens)	-	Identified chromatin remodeling factors that play a role in T cell exhaustion, potentially opening up new avenues for improving T cell persistence and anti-tumor immunity	[366]
CRISPR-engineered T cells	Refractory cancer	Demonstrates the feasibility and safety of using CRISPR-engineered T cells to target cancer in patients with refractory malignancies	[367]
E3 ligase Cop1 (identified via in vivo CRISPR screens)	-	Identifies Cop1 as a regulator of macrophage infiltration into tumors, suggesting it could be a potential target for cancer immunotherapy	[368]
Sodium bicarbonate nanoparticles	-	Amplifies cancer immunotherapy by inducing pyroptosis (inflammatory cell death) and regulating lactic acid metabolism in the tumor microenvironment	[369]
Platelet membrane-camouflaged magnetic nanoparticles	-	Enhances cancer immunotherapy by inducing ferroptosis (iron-dependent cell death) in tumor cells, potentially increasing immune recognition	[370]
Tumor microenvironment-responsive nanoparticles	-	Amplifies STING signaling, leading to increased production of type I interferons and enhanced anti-tumor immunity	[371]
Genetically edited nanoparticles	-	Activates macrophage-mediated cancer immunotherapy by delivering genetic material that enhances macrophage phagocytosis and anti-tumor activity	[372]
Elesclomol and copper nanoparticles (ROS-responsive)	-	Induces cuproptosis (copper-dependent cell death) in tumor cells, combined with anti-PD-L1 therapy for enhanced cancer immunotherapy	[373]

A study introduced siRNA-facilitated assembly method designed to simultaneously block "self" signals while enhancing "eat-me" signals on cancer cells. This method employs siRNA to suppress CD47, a "self" marker that prevents phagocytosis, while increasing the expression of calreticulin, an "eat-me" marker that promotes phagocytosis by immune cells. This dual approach improves immune system recognition and elimination of tumor cells [374].

Another study explored ultrasound-responsive nanocarriers for the delivery of siRNA and Fe_3O_4 nanoparticles to reprogram macrophages and inhibit M2 polarization, thereby improving immunotherapy for NSCLC. These nanocarriers delivered siRNA targeting STAT3, a transcription factor associated with M2 polarization, along with Fe_3O_4 nanoparticles that activated the IRF5 pathway to promote M1 polarization. This combination therapy effectively induced macrophages to adopt an antitumor phenotype, thereby enhancing NSCLC immunotherapy [375].

A follow-up study investigated a nanodrug combining siRNA targeting PD-L1 with birinapant, a SMAC mimic, to enhance tumor immunotherapy. This nanomedicine effectively co-delivered siRNA and birinapant to cancer cells, leading to reduced PD-L1 expression and apoptosis induction. This combined approach simultaneously improved antitumor immunity and triggered tumor cell death [376].

Another study examined lipid nanoparticles encapsulating siRNA to modulate the function of TAMs in cancer immunotherapy. These nanoparticles successfully delivered siRNA targeting genes involved in TAM polarization, shifting their function toward an antitumor phenotype and enhancing immune responses against tumors [377].

A novel siRNA delivery technique capable of crossing the blood-brain barrier and the blood-brain tumor barrier was developed to target gliomas for brain tumor immunotherapy. This method effectively delivered siRNA to glioma cells, inhibiting genes associated with tumor growth and immune evasion, ultimately strengthening antitumor immune responses within the brain [378].

Another study highlighted a nanoassembly of DOX-conjugated polyphosphoester and siRNA that enhanced anticancer immune responses mediated by both macrophages and T cells. This system delivered DOX to induce ICD while simultaneously providing siRNA to inhibit CD47, a key molecule in immune evasion. This approach effectively increased macrophage phagocytosis and T cell activation, resulting in a more robust antitumor immune response [379].

A dual-purpose nanovaccine, polyethyleneimine (PEI)-EGFR-PD-L1-siRNA, was developed for lung cancer treatment. This nanovaccine utilized PEI as a vehicle to deliver siRNAs targeting EGFR and PD-L1, silencing these genes to improve the antitumor immune response. EGFR served as a targeting agent, enhancing tumor-specific delivery [380].

A related study examined a dual siRNA-assembled nanoadjuvant designed to activate RIG-I/MDA5 signaling while simultaneously inhibiting the CD47-SIRPα checkpoint. This nanoadjuvant co-delivered siRNA targeting CD47 and LGP2, a negative regulator of RIG-I/MDA5 signaling. By blocking the CD47-SIRPα immune evasion pathway and activating innate immune responses, this approach significantly enhanced both innate and adaptive antitumor immunity [381].

In another study, supramolecular nanovehicles co-delivered a TLR7/8 agonist and anti-CD47 siRNA to improve tumor immunotherapy. These nanovehicles facilitated the delivery of a TLR7/8 agonist to activate innate immunity while simultaneously suppressing the "do not eat me" signal via CD47 siRNA, effectively enhancing both innate and adaptive immune responses against tumors [382].

Researchers have also explored ultrasound-sensitive nanocarriers incorporating siRNA and Fe_3O_4 nanoparticles to modulate macrophage polarization and enhance phagocytosis in lung cancer immunotherapy. These nanocarriers co-delivered siRNAs targeting STAT3, a transcription factor that drives M2 polarization, along with Fe_3O_4 nanoparticles to promote M1 polarization, thus reprogramming macrophages into an antitumor phenotype and improving immune responses [383].

A study investigated the direct delivery of celastrol and PD-L1 siRNA to the endoplasmic reticulum to enhance ICD and cancer immunotherapy. This approach utilized nanoparticles to deliver celastrol, which promotes immunogenicity, and PD-L1 siRNA to improve tumor immune recognition, ultimately strengthening the antitumor response [384].

CRISPR-Cas9 screening has identified COX2, a gene activated by KRAS, as a key driver of immunotherapy resistance in lung cancer. These findings highlight the potential of COX2 inhibition to improve immunotherapy efficacy in KRAS-mutated lung tumors [385].

Another study utilized in vivo CRISPR screening with a targeted antigen removal lentiviral vector system to explore immune dependencies in renal cell carcinoma, revealing the importance of tumor antigens in immune recognition and elimination [386].

In vivo epigenetic CRISPR screening identified Asf1a, a histone chaperone, as a promising immunotherapy target in KRAS-mutant lung adenocarcinoma, as it plays a key role in regulating immune responses within the TME [387].

An independent study combined in vitro modeling of CD8+ T cell exhaustion with CRISPR screening to investigate the role of the transcription factor BHLHE40 in T cell exhaustion, providing potential strategies to reverse this phenomenon and improve immunotherapy outcomes [388].

Multidimensional in vivo CRISPR screening identified Lgals2, a member of the galectin family, as a key immunotherapy target in triple-negative breast cancer (TNBC). Lgals2 suppresses antitumor immune responses, and its inhibition could enhance immunotherapy effectiveness [389].

A genome-wide CRISPR screen focused on CD8+ T cell function identified proline metabolism as a target for improving CAR-T cell therapy, suggesting that metabolic reprogramming could enhance CAR-T cell efficacy [390].

A versatile CRISPR-Cas13 d system has been developed for multiplexed transcriptome regulation and metabolic engineering of primary human T cells, allowing precise gene expression modulation and advancing the development of personalized immunotherapies [391].

A CRISPR activation screen revealed that BCL- 2 proteins and B3GNT2 contribute to cancer resistance against T cell-mediated cytotoxicity, identifying these proteins as potential therapeutic targets for improving T cell-based immunotherapies [392].

Nanoparticle-driven cancer immunotherapy

In recent years, nanoparticles have been widely utilized in cancer immunotherapy and TME remodeling [393–397]. One study demonstrated the use of ionizable lipid nanoparticles to integrate immune checkpoint inhibition into mRNA CAR T-cell development. These nanoparticles deliver mRNA encoding CAR and siRNA targeting PD- 1, allowing for the efficient generation of CAR T cells with enhanced antitumor activity by simultaneously blocking the PD- 1 immune checkpoint [398].

An independent study focused on developing macrophage-inspired multifunctional nanoparticles loaded with a TGF-β inhibitor for integrated cancer therapy. These nanoparticles mimic macrophages to deliver the inhibitor directly to the TME, reducing immunosuppression and enhancing antitumor immune responses through the combined effects of immunotherapy and targeted delivery [399]. Another study highlighted self-assembled coordination nanoparticles capable of activating the STING pathway, which plays a crucial role in innate immune responses. These nanoparticles induce type I IFN production and enhance antitumor immunity, demonstrating potential applications in cancer immunotherapy and vaccine development [400].

An alternative approach involves investigating injectable hydrogels loaded with RNA-encapsulating lipid nanoparticles for pancreatic cancer treatment. This hydrogel system delivers immune-stimulating RNA to the tumor site, altering the TME and enhancing antitumor immune responses [401]. Additionally, another study explored nanoparticles designed to modulate metabolic balance and enhance antibody-independent cancer radioimmunotherapy. By targeting tumor-specific metabolic changes, these nanoparticles improve radiation therapy effectiveness and boost antitumor immunity, resulting in a synergistic therapeutic effect [402].

Manganese-enriched zinc peroxide functional nanoparticles have been developed to enhance cancer immunotherapy by generating reactive oxygen species (ROS) within the TME. This strategy induces oxidative stress and immune-mediated cell death, amplifies antitumor immune responses, and increases the effectiveness of immunotherapy [403]. Macrophage-derived biomimetic nanoparticles have also been shown to enhance sonodynamic therapy (SDT) and immunotherapy, effectively suppressing tumor progression and metastasis. These macrophage-derived nanoparticles contain an acoustic sensitizer and catalase, which synergistically improve SDT by generating ROS and modulating the tumor immune environment. When combined with ICB, this approach successfully inhibits tumor growth and metastasis [404].

Another promising strategy involves the silencing of Siglec15 using nanoparticles and the repolarization of macrophages to improve cancer immunotherapy. These nanoparticles deliver siRNA targeting Siglec15, an immune checkpoint regulator, while inducing macrophage polarization from the M2 to the M1 phenotype. This dual approach reduces immunosuppression and enhances macrophage-driven cancer cell elimination [405].

Biomineralized nanoparticles loaded with two enzymes have been used to regulate tumor glycometabolism, initiate pyroptosis, and enhance effective antitumor immunotherapy. These nanoparticles simultaneously deliver enzymes that disrupt tumor metabolism and induce immunogenic pyroptosis, a form of programmed cell death that activates immune responses against tumors [406].

Another study explored STING-activating nanoparticles designed to restore the vascular-immune interface and enhance cancer immunotherapy. Activation of the STING pathway by these nanoparticles leads to tumor blood vessel normalization and increased immune cell infiltration into the TME, thereby improving immunotherapy efficacy [407].

Magnetic nanoparticles coated with cancer-erythrocyte hybrid membranes were developed for photothermal immunotherapy targeting ovarian cancer. These nanoparticles combine the photothermal properties of

magnetic nanoparticles with erythrocyte membrane shielding, improving tumor targeting while minimizing immune clearance. This combined approach enhances photothermal therapy and synergistically boosts anticancer effects when used alongside immunotherapy [408].

Ultrathin clay nanoparticles have been employed to enhance the combined effects of ferroptosis and cancer immunotherapy. Ferroptosis, an iron-dependent form of programmed cell death, triggers the release of damage-associated molecular patterns, which activate antitumor immune responses. When combined with immunotherapy, this strategy leads to a robust therapeutic effect [409]. Table 2 outlines the various types of immunochemotherapies.

Despite the promise of nanoparticles in cancer immunotherapy, several challenges must be addressed. A major obstacle is the precise targeting and transport of nanoparticles to tumor sites, as off-target interactions could lead to toxicity and reduced treatment effectiveness. Overcoming biological barriers, including clearance by the reticuloendothelial system, remains a key challenge, as nanoparticles are often removed before reaching their intended site of action.

Tumor heterogeneity further complicates nanoparticle design, as different cancers may require specific formulations to effectively deliver antigens, adjuvants, or immune modulators. Additionally, the scalability and cost-effectiveness of producing nanoparticles for clinical applications pose difficulties, particularly for personalized medicine approaches that require customized designs.

Despite these limitations, advancements in nanotechnology continue to offer promising solutions. Multifunctional nanoparticles capable of simultaneously delivering antigens, activating immune cells, and modifying the immunosuppressive TME have been developed. Nanoparticles can be engineered to carry mRNA or DNA encoding tumor-specific antigens, providing a versatile platform for eliciting strong antitumor immune responses. Furthermore, surface modifications with ligands or antibodies can enhance specificity for immune cells such as DCs or TAMs, thereby improving antigen presentation and T cell activation.

Future research should focus on integrating nanoparticles with other immunotherapies, including ICIs and cytokines, to overcome resistance mechanisms and enhance therapeutic efficacy. Emerging biomaterials and artificial intelligence-driven approaches may further refine nanoparticle design, allowing for real-time monitoring of drug release and immune responses. The integration of nanotechnology with precision medicine has the potential to revolutionize cancer immunotherapy by providing safer, more effective, and personalized treatment options, ultimately leading to prolonged remission and improved patient survival rates.

Adverse effects of cancer immunotherapy

Cancer immunotherapy enhances the immune system's ability to recognize and eliminate cancer cells, improving treatment effectiveness. However, it can also lead to severe adverse effects, including irAEs such as systemic inflammation, gastrointestinal toxicity, endocrinopathies, and pneumonitis [410–413]. Rare but serious toxicities, including cardiovascular complications (myocarditis), neurological disorders (neuropathies and encephalitis), and kidney failure, have also been documented [414–416]. ICIs can amplify T-cell responses against tumors, but they may also trigger irAEs, some of which are manageable and well-tolerated [417]. Reported irAEs include sepsis, neutropenia, immune thrombocytopenia following steroid tapering, colitis with gastrointestinal perforation, and interstitial pneumonia [418].

A meta-analysis of seven randomized controlled trials assessed the safety and tolerability of PD- 1/PD-L1 inhibitors in 3,450 patients with advanced cancer [419]. Compared to chemotherapy, PD- 1/PD-L1 inhibitors were associated with lower rates of common side effects such as fatigue, diarrhea, anorexia, nausea, and constipation. However, while Grade 1–4 adverse events were less frequent overall, some toxicities could be life-threatening [417].

As the use of ICIs increases, irAEs are being observed and recognized more frequently. The incidence and severity of irAEs depend on multiple factors, including the type of ICI used (anti-CTLA- 4 antibodies such as ipilimumab have higher irAE rates compared to PD- 1/PD-L1 inhibitors), the dosage, whether the therapy is used as a monotherapy or combination treatment, and cumulative exposure duration. Combination therapies that include CTLA- 4 inhibitors generally result in a higher incidence of irAEs compared to PD- 1 inhibitors or monotherapy approaches. Common irAEs include colitis, pneumonitis, dermatitis, endocrine disorders, arthralgia, arthritis, myalgia, muscle weakness, and Sicca syndrome, with varying frequencies based on the treatment regimen. Arthralgia occurs in 5–16% of patients receiving nivolumab, and the rate increases to 43% when nivolumab is combined with peptide vaccination therapies. Although autoimmune-related symptoms such as vasculitis and giant cell arteritis have been reported, they remain rare. Estimating the true prevalence of irAEs is challenging due to limited study populations, inconsistencies in grading systems that focus primarily on severe cases, and the exclusion of mild irAEs in clinical trials [420].

Sex-based differences in irAE susceptibility have also been reported. Men typically have a lower incidence of

endocrinopathies related to ICIs, particularly thyroid dysfunction, compared to women. However, ICI-induced hypophysitis appears more frequently in males. Additionally, ICI-induced Sicca/Sjögren's syndrome occurs more often in men than in cases of idiopathic primary variants. No significant sex differences have been observed in the frequency of hematological and gastrointestinal irAEs. However, neurological and vascular irAEs associated with ICIs appear to occur more frequently in men [421].

ICIs have revolutionized cancer treatment, significantly improving survival rates even in late-stage disease. However, a subset of patients (4–29%) exhibit paradoxical tumor growth after ICI therapy, a phenomenon known as hyperprogressive disease (HPD). HPD lacks a standardized clinical definition, and its biological mechanisms remain unclear. Studies investigating the TME and genetic traits of cancer cells have proposed various hypotheses to explain the negative effects associated with ICIs, necessitating further research [422].

The adverse effects of cancer immunotherapy, including irAEs and overall toxicity, can be minimized through strategies aimed at enhancing treatment precision and patient management. One approach involves the development of more targeted therapies, such as personalized cancer vaccines or nanoparticle-based drug delivery systems, which reduce off-target effects by directly targeting tumor antigens or immune cells within the TME. Additionally, combining immunotherapies with immune-modulating agents, such as low-dose corticosteroids or cytokine inhibitors, can effectively control excessive immune responses while maintaining antitumor efficacy.

Early recognition and management of irAEs through regular monitoring and biomarker evaluation allow for timely interventions, reducing the risk of severe complications. Advances in understanding irAE mechanisms, such as T-cell cross-reactivity and cytokine storms, are also contributing to the development of safer therapeutic approaches. These include engineered T cells with built-in "off-switches" and more precise delivery of ICIs. Furthermore, improved patient stratification based on genetic, immunological, and clinical characteristics can help optimize the balance between therapeutic benefits and adverse effects, ultimately improving the safety and outcomes of cancer immunotherapy.

Basic research

Molecular pathways

TRIB3, a stress-activated protein, reduces CD8+ T cell infiltration and promotes immune evasion in CRC by inhibiting the STAT1-CXCL10 pathway. By suppressing STAT1 activation and lowering CXCL10 expression, TRIB3 restricts CD8+ T-cell infiltration into the tumor, facilitating immune escape [423]. The PI3 Kβ signaling pathway has been identified as a key modulator of immune evasion in PTEN-deficient breast tumors by increasing the expression of immunosuppressive molecules and hindering T cell infiltration, thereby enabling immune escape [424]. Additionally, glycosylation of PD-L2 has been shown to enhance immune evasion and contribute to resistance against anti-EGFR therapies by strengthening the binding of PD-L2 to PD- 1, thereby reducing T-cell activation and worsening therapeutic outcomes [425].

Activation of mTORC1 has been linked to increased expression of B7-H3/CD276, an immune checkpoint protein that suppresses antitumor T-cell function, leading to immune evasion [426]. The loss of optineurin, an autophagy receptor, is associated with immune evasion in cancer by promoting palmitoylation-dependent lysosomal sorting and degradation of IFNGR1. This loss disrupts IFN-gamma signaling and contributes to immune suppression [427]. USP2, a deubiquitinase, facilitates tumor immune evasion by stabilizing PD-L1 through deubiquitination, enhancing its immunosuppressive function [428]. Mutations in KEAP1 associated with lung adenocarcinoma lead to immune evasion and immunotherapy resistance by disrupting the Nrf2-Keap1 pathway, resulting in increased expression of immunosuppressive molecules [429]. Similarly, the integrin αvβ6-TGFβ-SOX4 signaling pathway promotes immune evasion in TNBC by enhancing TGFβ signaling, which suppresses antitumor immune responses [430]. Biomarkers associated with cancer immunotherapy are detailed in Section 2 of the Supplementary Materials.

Abnormal R-loop formation has been identified as a contributing factor in immune evasion, cellular signaling, and metabolic alterations during cancer progression. R-loops are three-stranded nucleic acid structures that disrupt gene expression and DNA repair. Single-cell research has demonstrated that these atypical R-loops promote immune evasion while modifying cellular communication and metabolism [431]. A20, an anti-inflammatory protein, promotes immune evasion in CRC by increasing STC1 expression, which blocks the "eat-me" signal, thereby inhibiting macrophage-mediated phagocytosis of cancer cells [432]. Acetate, a metabolic byproduct, is associated with tumor metabolism changes and increased PD-L1 expression, promoting immune evasion via upregulation of c-Myc. Acetate alters tumor cell metabolism and increases PD-L1 expression, leading to immune suppression [433].

PRDM1/BLIMP1, a transcriptional repressor, has been identified as a key regulator of cancer immune evasion by modulating the USP22-SPI1-PD-L1 pathway in HCC cells. PRDM1/BLIMP1 influences USP22 and SPI1

expression, thereby controlling PD-L1 levels, leading to immune evasion through reduced T cell activation [434]. Similarly, EMSY, a transcriptional co-regulator, inhibits homologous recombination repair and IFN responses, facilitating immune evasion in lung cancer. EMSY impairs DNA repair mechanisms and IFN signaling, promoting tumor progression [435].

Dormantly dispersed tumor cells evade immune detection due to their low numbers; however, they remain viable targets for T-cell immunotherapies. This finding underscores the need to target dormant tumor cells in cancer treatment strategies [436]. ANXA1, a calcium-binding protein, promotes immune evasion in cancers by interacting with PARP1, which enhances Stat3-driven PD-L1 expression. ANXA1 engages with PARP1, activating Stat3 signaling and increasing PD-L1 expression, leading to immunosuppression [437].

Research on mammalian STING has shown that it functions independently of IFNs to regulate antiviral responses and contribute to tumor immune evasion. STING, a key component of innate immune defense, facilitates tumor immune evasion through non-IFN-dependent pathways [438]. RAD21 amplification has been identified as an epigenetic inhibitor of IFN signaling, promoting immune evasion in ovarian cancer. RAD21, a component of the cohesin complex, suppresses IFN signaling through epigenetic modifications, thereby facilitating immune evasion [439].

Multimodal combined perturb-CITE-seq screening has been used in patient-derived models to elucidate cancer immune evasion mechanisms. This screening approach has identified numerous genes and pathways associated with immune escape, providing promising targets for immunotherapy [440].

Noncoding RNAs

miR- 155 enhances the antitumor efficacy of CD8+ T lymphocytes by preventing senescence and functional exhaustion, processes commonly associated with terminal differentiation. This occurs through the epigenetic suppression of key components that promote terminal differentiation. miR- 155 indirectly enhances the function of PRC2 by upregulating Phf19, a factor associated with PRC2. This upregulation is achieved by reducing Ship1 levels, which inhibits Akt. Phf19 plays a crucial role in controlling a transcriptional pathway that significantly overlaps with miR- 155, preventing T-cell senescence and sustaining robust CD8+ T-cell responses against tumors. These effects depend on Phf19's ability to bind histones, which is critical for PRC2's recruitment to chromatin targets [441].

DC-based immunotherapy holds promise for cancer treatment, and miRNAs such as miR- 5119 can enhance its efficacy. In mouse models of breast cancer, miR- 5119 expression was reduced in splenic DCs, and restoring it using an miR- 5119 mimic decreased the levels of immunosuppressive molecules such as PD-L1 and IDO2. DCs engineered to express miR- 5119 mimics exhibited decreased T-cell depletion, improved CD8+ T-cell functionality, and triggered potent antitumor immune responses, marked by increased cytokine production and reduced T-cell apoptosis. Administering miR- 5119 mimic-engineered DC vaccines suppressed tumor growth in breast cancer mouse models, demonstrating a novel strategy for DC-based immunotherapy targeting breast cancer [442].

The long noncoding RNA LIMIT is crucial for tumor immunity as it enhances MHC-I expression and immunogenicity in both human and rat models. IFNγ stimulation induces LIMIT, which then activates the GBP gene cluster in cis. GBPs disrupt the HSP90-HSF1 interaction, leading to HSF1 activation and the transcription of MHC-I components, without affecting PD-L1 expression. RNA-guided CRISPR activation of LIMIT enhances GBP and MHC-I expression, thereby increasing tumor immunogenicity and improving checkpoint therapy efficacy. Inhibiting LIMIT, GBPs, or HSF1 reduces MHC-I expression, impairs anticancer immunity, and affects immunotherapy effectiveness. Clinically, LIMIT, GBP, and HSF1 signaling have been linked to MHC-I levels, tumor-infiltrating T cells, and responses to checkpoint blockade in patients [443].

LINK-A expression facilitates interactions between phosphatidylinositol-(3,4,5)-trisphosphate and inhibitory GPCR pathways, thereby reducing protein kinase A-mediated activation of the E3 ubiquitin ligase TRIM71. This leads to increased K48-polyubiquitination and the degradation of antigen PLC, along with tumor suppressors Rb and p53. Targeting LINK-A with locked nucleic acids or GPCR antagonists stabilizes PLC components, Rb, and p53, thereby enhancing the sensitivity of breast cancers to ICIs. In PD- 1 blockade-resistant TNBC, elevated LINK-A levels and reduced PLC expression have been observed [444].

CircHMGB2 (hsa_circ_0071452) expression is significantly upregulated in NSCLC tissues and serves as an independent prognostic marker for poor outcomes in patients with LUAD and LUSC. Although circHMGB2 has minimal impact on tumor cell proliferation, it significantly reshapes the TME by promoting immune exhaustion in antitumor responses, as demonstrated in both immunocompetent and humanized mouse models. CircHMGB2 acts as a sponge for miR- 181a- 5p, reducing its inhibition of CARM1 and consequently deactivating the type I IFN response in LUAD and LUSC. Elevated circHMGB2 expression decreases the efficacy of anti-PD- 1 therapy, whereas combining the CARM1 inhibitor

EZM2302 with an anti-PD- 1 antibody yields synergistic benefits in preclinical models [445].

In NSCLC cells and tissues, Circ-CPA4 and PD-L1 expression levels are elevated, whereas let- 7 miRNA expression is downregulated compared to normal bronchial epithelial cells and adjacent tissues. Knockdown of circ-CPA4 reduces NSCLC cell proliferation, migration, and EMT while increasing apoptosis by downregulating PD-L1 through let- 7 miRNA sponging. Exosomes derived from NSCLC cells containing PD-L1 enhance cancer stemness and confer cisplatin resistance. In a Transwell co-culture system using CD8+ T cells from human peripheral blood mononuclear cells, NSCLC cells suppressed CD8+ T cell activity in a PD-L1-dependent manner. Circ-CPA4 positively regulates exosomal PD-L1, and its knockdown restores CD8+ T cell activation in NSCLC cells [446].

Epigenetic factors

Tumorigenesis involves genetic mutations and epigenetic modifications, such as promoter hyperacetylation and aberrant DNA methylation, which may activate oncogenes or silence tumor suppressor genes. Global DNA hypomethylation and hypermethylation of CpG islands promote cancer progression. The TME undergoes epigenetic changes that establish an immunosuppressive state, leading to T cell exhaustion and immune evasion. "Hot" tumors exhibit better immune infiltration and therapeutic responses compared to "cold" tumors. Epigenetic drugs such as DNA demethylating agents and LSD1 inhibitors can reverse immune suppression by activating endogenous retroviruses, thereby triggering viral mimicry and enhancing IFN responses that bolster antitumor immunity. Combining these epigenetic drugs with checkpoint inhibitors, including anti-PD- 1, may rejuvenate T cell activity, reduce exhaustion, and improve treatment effectiveness by promoting robust immune responses in tumors [447].

Epigenetic mechanisms play a critical role in cancer progression, immune cell function, and tumor-immune interactions. Key immune-related genes (granzyme B, IFN-γ, FoxP3) and checkpoint proteins (PD- 1, CTLA- 4) are epigenetically regulated in both immune and tumor cells. Epigenetic therapies can reprogram the TME by inhibiting immunosuppressive cells (such as MDSCs and Tregs) while promoting antitumor immune cells, including T effector cells and antigen-presenting cells. These agents enhance tumor immunogenicity by increasing TAAs, neoantigens, and MHC components, as well as inducing ICD, which provides antigens for T cell activation and renders tumors more susceptible to immunotherapy. Consequently, epigenetic modulators hold great potential as components of combination therapies to enhance cancer immunotherapy efficacy [448].

Exosomes

Exosomes play a crucial role in facilitating intercellular communication during tumor immunoediting. In the elimination stage, tumor-derived exosomes (TEs) activate the immune system, while immune cell-derived exosomes exhibit strong tumor-suppressive effects. However, their role in cancer-immune system interactions during the balance phase remains unclear. In the escape phase, TEs contribute significantly by suppressing immune response cells, activating immunosuppressive cells, and promoting macrophage polarization within the TME. Despite challenges in isolation, purification, and clinical application, exosomes play a critical role in multiple tumor immunotherapy strategies, including cancer vaccines and advanced drug delivery systems, presenting promising opportunities for further research and therapeutic advancements [449].

Studies have highlighted the significance of exosome-mediated genetic reprogramming of TAMs in eliciting robust anticancer responses. Engineered exosomes carrying an antisense oligonucleotide targeting STAT6, a transcription factor that promotes M2 macrophage polarization, successfully transformed TAMs into an M1-like phenotype, significantly inhibiting tumor growth [450]. Multifunctional hybrid exosomes have demonstrated the potential to enhance cancer chemo-immunotherapy by activating the STING pathway. These exosomes, which encapsulate both a chemotherapeutic agent and a STING agonist, effectively eliminate tumor cells while stimulating innate immune responses, leading to synergistic anticancer effects [451].

The development of exosomes derived from OX40L-expressing M1-like macrophages has been explored as a novel cancer therapy. These exosomes, engineered to express OX40L—a costimulatory protein—enhance T cell activation and boost antitumor immunity [452]. Another study investigated exosomes derived from M1 macrophages that were modified to promote M1 polarization and selectively target the IL- 4 receptor to inhibit tumor growth. These exosomes convert TAMs into M1-like macrophages and suppress IL- 4 signaling, which is associated with M2 polarization, leading to substantial tumor suppression [453].

A follow-up study demonstrated the efficacy of DC-based immunotherapy using miR- 155-enriched TEs in a mouse model of CRC. These exosomes, carrying miR-155—a microRNA that enhances DC maturation and activation—effectively improved antitumor immunity and reduced tumor growth. Additionally, research has investigated the potential of local exosome inhibition to

enhance photothermal immunotherapy in breast cancer. Inhibiting exosome release in the TME improved the efficacy of photothermal therapy, suggesting that exosomes contribute to tumor immune evasion [454, 455].

DC-derived exosomes carrying tumor-specific neoantigens have been evaluated for personalized cancer immunotherapy. These exosomes effectively activate T cells and trigger personalized anticancer immune responses [456]. Furthermore, macrophage-tumor chimeric exosomes have been shown to cluster in lymph nodes and tumors, enhancing immune responses and modifying the TME. These chimeric exosomes, formed by the fusion of macrophages with tumor cells, effectively modulate the TME and activate immune cells, thereby strengthening antitumor immunity [457].

Cell death mechanisms

Autophagy in cancer-associated fibroblasts (CAFs) plays a critical role in immunochemotherapy resistance for pancreatic cancer. Suppressing autophagy in CAFs has been shown to decrease PD-L1 levels in tumor cells, thereby reducing adaptive immune resistance and enhancing cancer susceptibility to treatment [458]. In B cell malignancies, autophagy inhibition has demonstrated the ability to overcome natural resistance to CAR-T cell therapy. Blocking autophagy enhances the cytotoxic effectiveness of CAR-T cells against tumor cells, suggesting the potential for combination therapies [459]. Temporary systemic inhibition of autophagy has been found to permanently disrupt lung tumor cell metabolism and boost T cell-mediated tumor elimination, leading to improved tumor control [460]. In MSI-H CRC, the inhibition of ATG7 enhances antitumor immunity and increases the efficacy of ICB, making tumor cells more vulnerable to immune attacks [461]. Additionally, the expression of the autophagy gene Atg16 l1 in CRC cells suppresses antitumor immunity by reducing T-cell activity and facilitating immune evasion, indicating that targeting this gene could improve immune-driven tumor suppression [462]. Another study has revealed that selective autophagy of MHC-I molecules contributes to immune evasion in pancreatic cancer by reducing MHC-I levels, thereby diminishing tumor visibility to T cells [463]. Research has also demonstrated that c-MYC suppresses ferroptosis and promotes immune evasion in ovarian cancer via NCOA4-driven ferritinophagy. The activation of c-MYC stimulates ferritinophagy, degrading ferritin and reducing iron accumulation, thereby enhancing resistance to ferroptosis and evading immune responses. Targeting c-MYC or ferritinophagy has been proposed as a strategy to improve antitumor immunity [464].

Ferroptosis is a necrotic form of cell death that is driven by oxidative damage to phospholipid membranes in an iron-dependent manner. This pathway is initially linked to cysteine depletion, leading to a decrease in intracellular reduced glutathione (GSH), which triggers ferroptosis. GSH plays a protective role in ferroptosis through the enzymatic activity of GPX4, a selenoprotein that reduces peroxidized phospholipids and suppresses the arachidonic acid-metabolizing enzymes involved in phospholipid peroxidation. The intricate relationships among lipid, iron, and cysteine metabolism have been recognized as crucial regulators of this cell death pathway [465]. GPX4 is essential for protecting Tregs from lipid peroxidation and ferroptosis, thereby maintaining immune balance and enhancing anticancer immunity. Depleting GPX4 in Tregs disrupts their immunological stability, leading to ferroptosis upon TCR and CD28 activation. In GPX4-deficient Tregs, inhibiting lipid peroxidation or limiting iron availability prevents ferroptosis. Additionally, these cells exhibit increased mitochondrial superoxide levels and produce greater amounts of IL-1β, promoting TH17 responses. The depletion of GPX4 in Tregs hinders tumor growth and strengthens immune responses against cancer [466].

A self-amplifying iridium(III) photosensitizer that specifically targets the transferrin receptor, which is commonly overexpressed in cancer cells, has been shown to induce ferroptosis upon light activation, leading to ICD and improved antitumor immunity [467]. Additionally, triggering a hybrid apoptosis/ferroptosis pathway has been demonstrated to enhance ICD and improve the efficacy of PD-L1 checkpoint blockade immunotherapy by utilizing combined cell death pathways to maximize immune activation and therapeutic outcomes [468]. Later studies have focused on the development of an injectable Pickering emulsion gel that enhances ferroptosis-related tumor immunity by delivering iron oxide nanoparticles to tumors, thereby triggering ferroptosis and strengthening antitumor immune responses [469]. Furthermore, iron oxide@chlorophyll clustered nanoparticles have been used to eliminate bladder cancer via photodynamic immunotherapy-induced ferroptosis and immune stimulation, combining photodynamic therapy with ferroptosis induction for improved therapeutic outcomes [470].

Several studies have investigated the development of nanoparticles that enhance ferroptosis and boost immunotherapy. Cu-containing nanoparticles that self-assemble to trigger GSH depletion, enhance ferroptosis, and improve immunotherapy efficacy have been explored [471]. Transformable supramolecular self-assembled peptides designed to trigger ferroptosis and enhance cancer immunotherapy have demonstrated the ability to form nanostructures that boost both ferroptosis and immune responses [472]. Moreover, iridium(III) photosensitizers have been shown

to simultaneously induce pyroptosis and ferroptosis, improving synergistic multi-network tumor immunotherapy by activating inflammatory pyroptosis and ferroptosis pathways [473]. A novel nanoformulation has been developed to counteract immunosuppression while enabling self-amplifying anticancer ferroptosis immunotherapy, reducing immunosuppressive conditions and inducing ferroptosis in cancer cells [474]. Another innovative approach involves a responsive and non-traceable assembly of iron nanoparticles linked to 131I-labeled radiopharmaceuticals for ferroptosis-boosted radioimmunotherapy. This combination of ferroptosis induction with radiation enhances tumor cell elimination and bolsters antitumor immune responses [475]. Mefloquine, an antimalarial drug, has also been found to enhance the efficacy of anti-PD- 1 immunotherapy by inducing ferroptosis through the IFN-γ-STAT1-IRF1-LPCAT3 pathway, thereby improving the effects of checkpoint blockade treatments [476]. Additionally, NQO1, an enzyme involved in redox reactions, has been shown to enhance ferroptosis and activate antitumor immunity in KEAP1-deficient cancers that are resistant to immunotherapy, providing a potential strategy to overcome therapeutic resistance [477].

Necroptosis has been implicated in amplifying the "don't eat me" signal and inducing neutrophil extracellular traps, thereby promoting hepatic metastasis in pancreatic cancer. Necroptosis in pancreatic cancer cells elevates CD47 expression, which prevents macrophage-driven phagocytosis and facilitates the formation of metastases. Additionally, necroptotic cancer cells trigger inflammation and create a favorable environment for metastasis. Inhibiting necroptosis has been proposed as a strategy to prevent the spread of pancreatic cancer [478]. Cryo-nanocatalysts have been designed to improve the therapeutic efficacy of cryo-immunotherapy by promoting necroptosis and aiding in the targeted delivery of PD-L1 inhibitors. Combining cryo-nanocatalysts with cryotherapy triggers necroptosis in cancer cells and enhances the release of PD-L1 inhibitors, boosting antitumor immune responses [479].

Hypoxia-accelerated pyroptosis nanoinducers have been engineered to improve image-guided cancer immunotherapy. These nanoparticles selectively target hypoxic tumor regions, where they induce pyroptosis, thereby enhancing immune responses. Additionally, the nanoparticles improve image-guided therapy by providing real-time feedback on treatment effectiveness [480]. Intermetallic nanoparticles have been developed to induce both pyroptosis and disulfidaptosis in cancer cells, thereby amplifying antitumor immunity through a dual cell death approach [481]. Research has further explored mRNA lipid nanoparticles designed to trigger pyroptosis and convert immunologically "cold" tumors into ones responsive to checkpoint immunotherapy. These nanoparticles deliver mRNA encoding GSDMD, an essential protein in pyroptosis, to tumor cells, thereby enhancing the efficacy of checkpoint inhibitors [482].

Biodegradable upconversion nanoparticles have been investigated for their ability to induce pyroptosis in cancer cells. When exposed to near-infrared light, these nanoparticles release visible light, triggering pyroptosis and boosting antitumor immune responses [483]. Integration of aggregation-induced emission luminogens into covalent organic frameworks has been explored to enhance pyroptosis- and ferroptosis-triggered cancer immunotherapies. This strategy employs a combination of two distinct cell death processes to amplify antitumor immunity [484]. Additionally, extracellular vesicles engineered to carry GSDMD-N mRNA have been identified as effective tools for inducing pyroptosis in cancer cells, thereby bolstering immune responses against tumors [485].

Blocking SF3B1, a splicing factor, has been shown to improve the tumor immune microenvironment through pyroptosis and works synergistically with anti-PD-L1 therapy in ovarian cancer. SF3B1 inhibition triggers pyroptosis, thereby enhancing the effectiveness of checkpoint blockade therapy [486]. Moreover, self-harming Cu carriers have been developed to induce both pyroptosis and cuproptosis (Cu-triggered cell death), offering a promising strategy for tumor immunotherapy, particularly for targeting dormant and recurrent cancers. These carriers activate multiple cell death pathways to eliminate cancer cells and boost immune responses [487]. Table S4 summarizes basic research on cancer immunotherapy. For more information about immunotheray and related therapeutics, please refer to Tables S1-S4 in the "Supplementary Materials".

Conclusion, perspectives, and future challenges

Cancer immunotherapy has introduced novel possibilities for cancer treatment. However, like other therapeutic strategies, immunotherapy faces several challenges that must be addressed to enhance its effectiveness and broaden its application for tumor suppression. The current challenges in cancer immunotherapy can be summarized to several key factors. First of all, the effective of immunotherapy in targeting and suppressing sold tumors is restricted. Various immunotherapeutic approaches, such as CAR-T cell therapy, struggle to penetrate solid tumors and face significant obstacles in overcoming the immunosuppressive TME. Cancer immunotherapy can cause adverse effects, including CRS, along with various immune-related toxicities. These side effects pose challenges, particularly in combination cancer therapies. The large-scale production and commercialization

of personalized treatments, such as CAR-T cells, remain difficult. Resistance mechanisms continue to pose a significant challenge, as cancer cells can evade immune responses through various strategies, including antigen loss, upregulation of alternative immune checkpoints, and the modification of immune evasion pathways. Although substantial efforts have been made in biomarker discovery, there remains significant potential for identifying reliable and predictive biomarkers that can guide immunotherapy selection and improve patient outcomes. The studies are also encouraged to consider the tumor heterogeneity and this is a significant challenge for the clinical application of immunotherapeutics.

There are several promising directions for advancing the studies. Personalized medical strategies can be refined, allowing for the development and implementation of individualized therapies tailored to the specific tumor characteristics and immunological profile of each patient. Additionally, nanoscale delivery systems have been highlighted as a means to significantly enhance the effectiveness of cancer immunotherapy, although considerations such as efficacy, long-term biosafety, and scalability for large-scale production remain crucial. Given the growing recognition of the gut microbiota's influence on cancer immunotherapy outcomes, modifying the gut microbiome composition presents a potential strategy to improve treatment responses. Enhancing the sensitivity of tumors to immunotherapy by converting immunologically "cold" tumors into "hot" tumors could further optimize therapeutic efficacy. The integration of artificial intelligence into cancer immunotherapy holds significant potential to refine response predictions and advance personalized medicine. Furthermore, novel approaches targeting neoantigens and T cells may improve tumor suppression. Lastly, the development of more advanced animal models is essential to better replicate human tumor-immune system interactions, facilitating more accurate preclinical assessments and optimizing therapeutic strategies.

Supplementary Information

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Supplementary Material 1.

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Declarations

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