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REVIEW

The Benefits and Safety of Monoclonal Antibodies: Implications for Cancer Immunotherapy

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Abstract: Monoclonal antibodies (mAbs) have transformed cancer treatment by providing highly targeted and effective therapies that specifically attack cancer cells, thus reducing the likelihood of adverse events (AEs) in patients. mAbs exert their action through various mechanisms, such as receptor blockade, antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and inhibition of immune checkpoints (eg, PD-1, PD-L1, and CTLA-4). These therapies have led to significant improvements in the treatment of several cancers, including HER2-positive breast cancer, non-small cell lung cancer (NSCLC), and melanoma. The efficacy of mAb therapy in cancer treatment is influenced by various intrinsic and extrinsic factors, such as environmental exposures, psychosocial factors, infection status, ways of life, and tumor microenvironment (TME), all of which can impact immune responses and treatment outcomes. Notably, the therapeutic benefits of mAbs are often accompanied by immune-related AEs (irAEs), which can vary from mild to severe and affect multiple organ systems. The dual nature of mAbs—stimulating antitumor immune responses while also inducing immune-related side effects—presents a notable challenge in clinical practice. This review highlights the importance of proactive strategies for managing irAEs, such as early detection, corticosteroid use, targeted immunosuppressive treatments, and the urgent need for reliable predictive biomarkers to improve treatment outcomes. Advancements in the prevention, prediction, and management of irAEs are essential to enhance the safety and effectiveness of mAb-based therapies, ultimately aiming to improve cancer patient outcomes.

Keywords: monoclonal antibody, immune-related adverse event, immune checkpoint blockade, cancer immunotherapy, treatment strategy

Introduction

Cancer remains one of the most pressing global health challenges, contributing to a significant proportion of mortality worldwide. This has spurred extensive research into innovative therapeutic strategies to improve patient outcomes. Systemic therapy, which utilizes medications to target and eliminate cancer cells throughout the body, remains a cornerstone of modern oncology.[1] Among the various systemic treatments, targeted therapies—particularly monoclonal antibodies (mAbs)—have revolutionized cancer treatment due to their exceptional specificity and efficacy. mAbs are designed to precisely bind to molecular targets on cancer cells or within the tumor microenvironment (TME), thereby disrupting key pathways involved in tumor growth and metastasis.[2]

The term "monoclonal" refers to the derivation of these antibodies from a single hybridoma cell line, which is genetically engineered to produce antibodies targeting specific antigens.[3] This high specificity allows mAbs to selectively bind to receptors or proteins expressed on cancer cells.[4] As our understanding of the molecular mechanisms underlying

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cancer progression has advanced, the applications of mAbs in immunotherapy have expanded significantly, encompassing both hematologic malignancies and solid tumors.

Despite their impressive therapeutic potential, mAbs are not without limitations. Some mAbs can enhance immune activation, potentially leading to immune-related adverse events (AEs) (irAEs).[5,6] In some cases, these irAEs may affect multiple organ systems and result in severe clinical complications.[7] Consequently, robust management strategies are essential to optimize the therapeutic benefits of mAbs while mitigating their associated risks. This review aims to provide a comprehensive resource for researchers and clinicians, offering insights into the optimization of mAb-based treatment regimens to maximize efficacy while minimizing adverse effects. By addressing these challenges, we seek to advance the clinical application of mAbs and improve outcomes for cancer patients.

Major Types of mAbs

Most mAbs work in one of the following two ways: blocking signals that promote cancer cell growth or activating the immune system to attack cancer cells.[8]

mAbs That Block Oncogenic Signaling Pathways

Some mAbs bind to tumor cell surface antigens, such as growth factor receptors, to block oncogenic signaling pathways and inhibit tumor growth. Additionally, they can engage immune effector functions to enhance tumor clearance. mAbs targeting HER2, such as trastuzumab and pertuzumab, have dramatically improved the prognosis of patients with HER2-positive breast cancer. Pertuzumab binds to a distinct epitope on the HER2 receptor, which is different from that of trastuzumab. This binding prevents HER2 receptor dimerization, thereby enhancing the therapeutic effect of both antibodies. The combination of pertuzumab, trastuzumab, and chemotherapy has shown superior efficacy in the neoadjuvant setting. Furthermore, this therapeutic strategy significantly increased the pathological complete response (pCR) rate, which is a critical predictor of long-term survival for cancer patients.[9,10] Clinical studies[11,12] have demonstrated that adding pertuzumab to trastuzumab and docetaxel improves pCR rates from around 21% to 39% in patients with early-stage HER2-positive breast cancer.

mAbs Triggering the Immune System to Attack Cancer Cells (ICB mAbs)

The PD-1/PD-L1 axis (PD-1/PD-L1 pathway) plays a crucial role in immune regulation by preventing excessive T cell activation during acute infections. However, in chronic infections and cancer, sustained activation of this pathway leads to T cell exhaustion, enabling pathogens and tumor cells to evade immune surveillance.[13] To address this, mAbs targeting PD-1/PD-L1 have been developed to disrupt the interaction between PD-1 and PD-L1. By blocking this pathway, these therapies partially restore or enhance the function of exhausted T cells, allowing the immune system to effectively recognize and eliminate cancer cells.[14]

Anti-PD-1 agents, such as pembrolizumab[15] and nivolumab,[16] have been approved for adjuvant treatment in patients with stage III and stage III/IV melanoma. Both ICBs have demonstrated a significant prolongation of disease-free survival (DFS) in the adjuvant treatment of melanoma.[15,16] Notably, pembrolizumab is used both as monotherapy and in combination with chemotherapy for patients with PD-L1 expression levels $\geq 1\%$.[17]

ICBs have transformed the treatment landscape for melanoma. Pembrolizumab and nivolumab have shown durable responses and long-term survival benefits in advanced melanoma patients, often outperforming previous standard therapies like dacarbazine.[18] Pembrolizumab and nivolumab have also been approved for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). These agents have demonstrated improved survival outcomes, particularly in patients with PD-L1-positive tumors.[17] Despite these benefits, the response rate remains modest, highlighting the need for biomarkers to better predict which patients will benefit from ICB therapy.[19]

ICBs are also used in urothelial carcinoma, renal cell carcinoma, hepatocellular carcinoma, and several other malignancies. The FDA has approved these agents for a variety of indications based on the expression of PD-L1 or other biomarkers such as microsatellite instability-high (MSI-H) or high tumor mutational burden (TMB).[17,18]

NKG2A (KLRC1) has recently been added to the list of viable immune checkpoint targets. NKG2A is an inhibitory receptor that, when bound to its ligand HLA-E, suppresses the activation of nature killer (NK) cells and certain $CD8^+$

T cell populations.[20] Strategies have been developed to disrupt the NKG2A:HLA-E interaction, either directly or indirectly, to enhance NK cell activation against cancer.[20] Monalizumab, an anti-NKG2A mAb, prevents the interaction between NKG2A and HLA-E and has shown promising therapeutic potential in various cancers, such as NSCLC, colorectal cancer (CRC), and squamous cell carcinoma of the head and neck (SCCHN).[21]

Mechanisms of mAb Therapy in Oncology

mAbs have become a cornerstone in cancer therapy due to their ability to specifically target cancer cells while minimizing damage to normal tissues. These antibodies activate the immune system, which include the following.

Targeting Receptors and Blocking Signaling Pathways

Genetic, epigenetic, and somatic changes can disrupt the expression of growth factor receptors (GFRs), potentially driving cancer initiation and progression.[22] mAbs targeting these receptors are engineered to bind to specific antigens on tumor cell surfaces, such as the epidermal growth factor (EGF) receptor (EGFR). Upon binding, the IgG molecules form ordered hexamers that trigger the classical complement pathway by recruiting C1q. This activation leads to complement-dependent cytotoxicity (CDC), causing tumor cell lysis. The efficiency of CDC is influenced by factors such as antibody epitope, valency, and affinity. mAbs targeting validated solid tumor antigens, like EGFR, block tumor signaling while simultaneously enhancing complement activation, making them valuable tools in cancer therapy.[23] Anti-EGFR mAbs, for instance, can prevent the binding of transforming growth factor alpha (TGF-α) and EGF to their receptors, thereby inhibiting receptor tyrosine kinase activation.[24]

HER2 (ERBB2), a member of the EGFR family, has been found to amplify and/or overexpress in approximately 25–30% of human breast cancers,[25,26] which has been associated with aggressive disease and poor outcomes.[27] Under long-term or specific conditions, trastuzumab inhibits HER2-mediated signaling by disrupting HER2 receptor function and reducing ERK1/2 phosphorylation, thereby suppressing the MAPK pathway. It significantly suppresses the PI3K/AKT pathway by reducing AKT phosphorylation, either through inhibiting HER3 phosphorylation or activating PTEN. Additionally, trastuzumab specifically targets HER2, directly influencing HER2-mediated signaling while indirectly affecting other HER family members (Figure 1).[28]

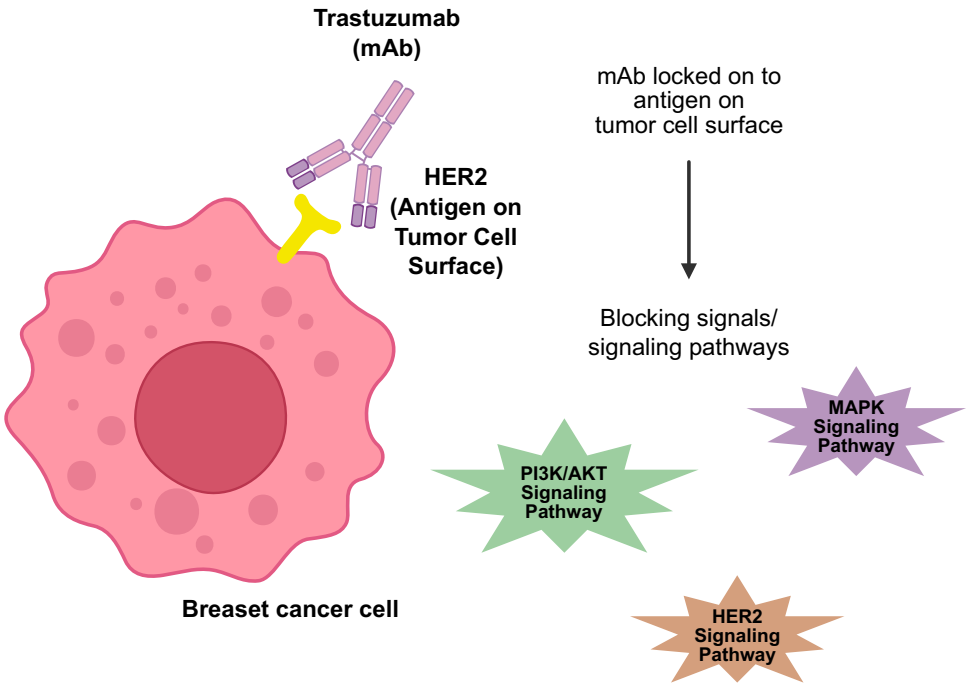

Figure 1 Mechanisms of monoclonal antibodies (mAbs) targeting receptors and blocking signaling pathways. This illustration takes trastuzumab as an example.

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Antibody-Dependent Cellular Cytotoxicity (ADCC)

Immunoglobulins, primarily formed by B cells, bind pathogens through their fragment antigen-binding (Fab) domains and activate immune responses via fragment crystallizable (Fc) receptors. The majority of these antibodies are IgG, which mediate effector functions through Fc gamma receptors (FcγR) on myeloid and NK cells. ADCC, a key Fc-dependent function of IgG, plays a crucial role in clearing viral infections and is primarily mediated by NK cells. NK cells engage ADCC by binding antibody-coated target cells through FcγRIIIa (CD16a), triggering the release of cytotoxic granzymes and perforins, which is an essential mechanism for killing tumor cells in immunotherapy.[29]

Building on this, ADCC involves NK cells using antibodies to target and kill tumor cells through the CD16A receptor. This receptor binds to the Fc portion of antibodies on tumor cells, initiating NK cell activation and forming an immunological synapse—an area of tight interaction between the NK cell and the target cell, facilitating effective cytotoxic responses.[30] Upon activation, NK cells not only release cytolytic molecules but also secrete key cytokines, including interferon (IFN)-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which help modulate the immune response by recruiting and activating other immune cells. However, CD16A's function can be limited by downregulation in the tumor microenvironment, due to ADAM17-induced cleavage, reducing its binding affinity and ADCC potency. To overcome this, researchers have developed the CD64/16A fusion receptor, which combines the high-affinity CD64 with CD16A's signaling domain, enhancing ADCC by preventing receptor cleavage and improving binding affinity for therapeutic antibodies.[31] This strategy, particularly with iPSC-derived NK cells, offers a versatile approach for targeting multiple tumor antigens and overcoming antigen escape, improving cancer immunotherapy.

Among the various antibody isotypes, IgG_1 and IgG_3 are particularly effective in mediating ADCC due to their high affinity for most FcγRs on immune cells.[32] When mAbs of the IgG_1 or IgG_3 subclass bind to their target antigens, their Fc regions interact with FcγRIIIa on NK cells, initiating the ADCC process. This cytotoxic mechanism, mediated by IgG_1 and IgG_3 antibodies, serves as a critical functional link between innate and adaptive immunity.[33]

Rituximab, a therapeutic mAb used in the treatment of B-cell non-Hodgkin lymphoma, exemplifies the clinical application of ADCC.[34,35] The Fc region of rituximab binds to the FcγRIIIa receptor on NK cells, triggering the deletion of CD20 (MS4A1)-expressing target cells. While NK cells are central to this process, their role may also involve indirect mechanisms, such as the production of IFN-γ. This cytokine can exert direct antitumor effects or enhance ADCC by upregulating high-affinity Fcγ receptors (eg, CD64) on other immune cells like granulocytes. The precise contribution of NK cells—whether direct or indirect—remains complex. However, ongoing clinical trials with next-generation anti-CD20 antibodies, designed to enhance FcγR binding and NK cell activation, are expected to further elucidate the clinical significance of ADCC in rituximab's therapeutic efficacy.[36]

Similarly, trastuzumab, a HER2-targeted mAb, can trigger immune-mediated mechanisms such as ADCC, recruiting NK cells to attack HER2-expressing cancer cells.[37] Phase III clinical trials have demonstrated that combining trastuzumab with chemotherapy significantly improves overall survival (OS) and DFS in HER2-positive breast cancer patients.[23] The success of trastuzumab has spurred the development of other HER2-targeted therapies, including pertuzumab and ado-trastuzumab emtansine (T-DM1), thereby expanding treatment options for this subset of breast cancer patients.[23] Nevertheless, the efficacy of ADCC can be influenced by factors such as target antigen density, FcγR expression levels on NK cells, and the immunosuppressive TME, which may limit its effectiveness in certain cancers, such as pancreatic cancer.[38]

Complement-Dependent Cytotoxicity (CDC)

CDC is another critical mechanism through which mAbs induce cell death. This process begins when a mAb binds to a specific antigen on the surface of a cancer cell, thereby activating the complement cascade—a series of protein interactions that culminates in the formation of the membrane attack complex (MAC). The MAC forms pores in the cell membrane, leading to cell lysis and death.[39,40] Complement activation can significantly enhance the efficacy of mAbs. For example, alemtuzumab, a mAb used in the treatment of chronic lymphocytic leukemia (CLL), exerts its therapeutic effects partly through CDC. Alemtuzumab targets the CD52 antigen on lymphocytes, and upon binding, it activates the complement system, leading to MAC formation and subsequent lysis of CLL cells.[41]

The initiation of complement activation via the classical pathway involves the binding of C1q (a recognition molecule) to the Fc region of the antibody. This interaction triggers a cascade involving the activation of C4, C2, and eventually C3, culminating in the assembly of the MAC. The effectiveness of CDC can be modulated by complement regulatory proteins such as complement factor H (CFH). In some CLL patients who do not respond to rituximab (another mAb targeting CD20), the addition of an anti-CFH antibody can enhance CDC, thereby improving therapeutic outcomes.[41]

Immune Checkpoint Inhibition

Immune checkpoints are critical regulatory molecules that act as gatekeepers of immune responses, playing a dual role in maintaining immune homeostasis and enabling tumor immune evasion. These surface molecules, including PD-1, CTLA-4, LAG-3, TIM-3, TIGIT, and BTLA, deliver inhibitory signals through specific tyrosine-based motifs (ITIM and ITSM), effectively suppressing immune cell activation. In cancer, tumor cells exploit these checkpoints to evade immune surveillance.[42,43] By blocking these checkpoints, immune checkpoint blockers (ICBs), also known as immune checkpoint inhibitors (ICIs), enable T cells to recognize and destroy cancer cells more effectively.[44]

PD-1, an inhibitory receptor located on T cells, interacts with its ligands, PD-L1 and PD-L2, which are frequently overexpressed on tumor cells. Binding of PD-1 to its ligands can inhibit T cell activation and function. In particular, PD-L1 can induce T cell apoptosis, suppress cytokine production, and promote T cell exhaustion, thereby reducing antitumor activity.[45,46] Moreover, PD-L1 on tumor cells can interact with B7 (B7-1, CD80) on T cells, further suppressing T cell activity.[44] The interaction between PD-1 and its ligands (PD-L1 or PD-L2) significantly weakens the immune response by decreasing the release of cytokines like interleukin (IL)-2, IFN-γ, and TNF-α. This suppression is mediated through the inhibition of the CD28 co-stimulatory signaling pathway, which is essential for T cell activation and proliferation. By interfering with CD28 signaling, PD-1 effectively reduces T cell activity, leading to lower cytokine production and impaired cell proliferation.[47] PD-1 is also expressed on various immune cells within the TME, including activated monocytes, dendritic cells (DCs), NK cells, T cells, and B cells.[48] As such, blocking the PD-1 pathway may contribute to enhancing antitumor immunity.[49]

The effectiveness of PD-1/PD-L1 inhibitors has been demonstrated in several clinical trials. For instance, in the KEYNOTE-021 trial,[50] pembrolizumab combined with standard chemotherapy showed higher objective response rate (ORR) and progression-free survival (PFS) in non-small-cell lung cancer (NSCLC) patients compared to chemotherapy alone. This led to the approval of pembrolizumab in combination with chemotherapy as a first-line treatment for advanced NSCLC by the FDA.[51,52] However, not all patients respond to PD-1/PD-L1-targeted therapies. Some tumors exhibit resistance or develop mechanisms to evade immune detection even when the PD-1/PD-L1 pathway is blocked. Additionally, the presence of PD-L1 on tumors does not always correlate with responsiveness to these therapies, indicating the need for better biomarkers to predict patient outcomes.[51,52]

CTLA-4 is thought to function early in immune response, primarily regulating T cell activation within lymph nodes.[53] It competes with the costimulatory receptor CD28 for binding to B7 molecules on antigen-presenting cells (APCs), thereby suppressing T cell activation.[54] The effectiveness of CTLA-4 blockade is influenced by several factors, such as regulatory T cells (Tregs), T cell infiltration, $CD8^+$ T cell activation, and the recruitment of tumor-associated macrophages (TAMs). Treg cells, a crucial subset of $CD4^+$ T cells, are essential for maintaining self-tolerance and preventing autoimmune diseases. These immune cells consistently express CTLA-4, which plays a key role in suppressing the activity of both $CD4^+$ and $CD8^+$ cytotoxic T cells within the TME.[55]

Antibody-Dependent Cellular Phagocytosis (ADCP)

ADCP is a critical mechanism by which mAbs mediate antitumor effects, primarily through the action of macrophages. In this process, the Fc region of the mAb binds to FcγRs on macrophages, while the Fab region attaches to specific antigens on the surface of tumor cells. This binding triggers the macrophages to engulf and digest the target cells, a process known as phagocytosis.[56,57]

ADCP is mediated through specific Fcγ receptors, such as FcγRI and FcγRIII, which are critical for the recognition and phagocytosis of antibody-opsonized cells. The effectiveness of this mechanism can be influenced by various factors,

including the type of FcγR expressed on the macrophages, the density of the target antigen, and the isotype of the mAb used. The internalization and degradation of the target cells are further facilitated by phagosome formation, acidification, and the generation of reactive oxygen species (ROS) within the phagolysosome.[58,59]

Furthermore, while ADCP contributes significantly to the therapeutic effects of mAbs, it also has complex implications for the immune environment. For instance, macrophages that have engaged in ADCP may suppress other immune responses, such as NK cell activity, potentially impacting the overall antitumor response.[58]

Kupffer cells are a type of tissue-resident macrophage located in the liver. These immune cells are significant players in ADCP to clear circulating tumor cells (CTCs) and prevent metastasis, particularly following mAb therapy. Depletion of Kupffer cells significantly reduces CTC clearance and increases the risk of liver metastasis. Specifically, mAb-mediated activation of FcγRI and FcγRIV on Kupffer cells enhances their ability to phagocytose tumor cells, as observed in models such as CC531s (rat colon carcinoma)[60] and B16F10 (mouse melanoma) cells.[60] Thus, enhancing ADCP by Kupffer cells could be a crucial strategy for preventing tumor recurrence and metastasis after primary tumor resection.

Factors Influencing the Efficacy of mAb Therapy for Cancer

The effectiveness of mAb therapy in cancer treatment is influenced by a wide range of factors, both intrinsic and extrinsic to the patient (Figure 2).

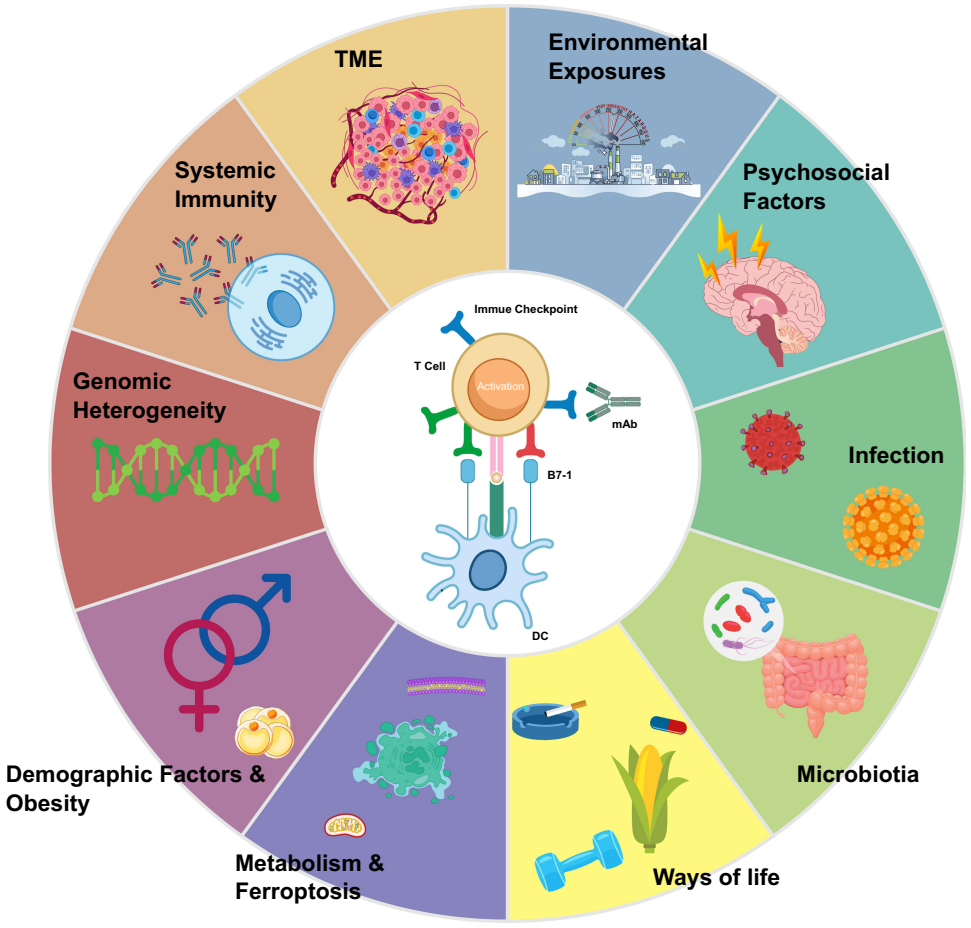

Figure 2 Major factors impacting response and resistance to monoclonal antibody (mAb) therapy for cancer.
Abbreviations: DC, dendritic cell; TME, tumor microenvironment.

Environmental Exposures

Environmental exposures can profoundly impact antitumor immunity and ICB effectiveness.[61] Liu, et al[62] conducted a cohort study and found that while general $PM_{2.5}$ exposure prior to immunotherapy was not significantly linked to NSCLC progression, long-term exposure to specific specific $PM_{2.5}$ components, such as black carbon and organic matter, significantly increased the risk of disease progression. Additionally, short-term exposure to ozone (O_3) was also linked to a higher risk of progression. These findings suggest the need for targeted measures to reduce specific pollutants to improve the prognosis of NSCLC patients undergoing PD-1/PD-L1 inhibitor immunotherapy.[62] Similarly, Gao, et al[63] also found that long-term exposure to $PM_{2.5}$ and its constituents, as well as short-term exposure to O_3, was positively associated with an elevated risk of adverse outcomes in immunotherapy.

Psychosocial Factors

Many studies have shown that psychological factors may influence the effectiveness of ICB treatment in advanced cancer patients. Perceived health status was positively associated with better treatment responses, while emotional distress, sleep difficulties, and worse health-related quality of life were linked to higher levels of soluble CTLA-4 (sCTLA-4) and pro-inflammatory cytokines like IL-6 and TNF-α.[64] In the Phase II PRADO trial,[65] pretreatment emotional distress was associated with reduced major pathologic responses, lower 2-year relapse-free survival (RFS), and decreased 2-year distant metastasis-free survival (DMFS), even after adjusting for known biomarkers like IFN-γ signature and TMB. Although preclinical studies suggest that emotional distress might impair antitumor immunity through β-adrenergic or glucocorticoid pathways, RNA sequencing did not clearly identify these mechanisms in patient samples. Moreover, a prospective study found that a significant proportion of metastatic melanoma patients experience psychological distress during ICB treatment, highlighting the need for integrated psycho-oncological support to potentially improve treatment adherence and outcomes.[66]

Infection

The impact of infections on ICB therapy is a critical consideration, particularly in patients with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infections. ICB therapy appears to be effective and well-tolerated in people living with HIV (PLWH) with advanced cancers, showing comparable efficacy and safety to the general population. Additionally, ICBs may contribute to reducing the HIV reservoir without compromising virologic control.[67] However, the risk of opportunistic infections in people living with HIV/acquired immune deficiency syndrome (AIDS) (PLWHIV) depends on their viro-immunological status, which can be managed with combination antiretroviral therapy to maintain viral suppression and CD4 counts above 200/mm^3.[68] In contrast, HBV infection poses a significant risk of reactivation during ICB therapy. HBV reactivation in patients receiving PD-1/PD-L1 inhibitors, even in the absence of immunosuppression, with pembrolizumab showing an elevated risk (odds ratio [OR] = 2.32, 95% confidence interval [CI]: 1.11–4.28, $p = 0.013$).[69] Retrospective analysis[70] indicated that the absence of antiviral prophylaxis is a significant risk factor for reactivation (OR = 17.50, 95% CI: 1.95–157.07, $p = 0.004$), while concurrent corticosteroid use does not appear to increase risk. Lymphocytes that express PD-1 seem to help manage viral control, whereas blocking PD-1/PD-L1 signaling can lead to a hyperinflammatory state, potentially disrupting the immune balance in latent hepatitis B infections and fostering viral replication.[71]

With regard to bacterial infections, the administration of antibiotics within the first 6 weeks after initiating ICB therapy is associated with a significantly reduced likelihood of therapeutic response. This effect is primarily attributed to antibiotic-induced disruption of the gut microbiome, which is essential in modulating immune responses to ICB.[72] Specifically, the odds of a positive response to immunotherapy are significantly lower when antibiotics are used during this critical period, as evidenced by a multivariate analysis showing an OR of 0.48 (95% CI: 0.29–0.80, $P = 0.01$).

Microbiota

Intratumoral microbes significantly influence the response to ICB therapy. Recent studies have demonstrated that a diverse range of microbial populations exist across different tumor types, suggesting that these microbes play unique roles in shaping the TME and, consequently, in determining the effectiveness of ICB therapy. For instance, the

composition of the tumor microbiome differs between responders and non-responders to immunotherapy, indicating that certain microbial communities may either enhance or suppress antitumor immune responses.[73] Intratumoral microbes can modulate the immune landscape by reducing immune cell infiltration and promoting a more immunosuppressive environment.[74] Furthermore, tumor-associated microbes can influence various aspects of cancer biology, such as tumor initiation, growth, invasion, and metastasis, thereby indirectly affecting the outcomes of ICB therapy.[75,76] Mechanistically, peptides derived from intratumoral bacteria can be presented on tumor cells via HLA molecules, potentially triggering T cell responses and altering the efficacy of ICB.[77]

Recent research has also revealed that the gut microbiome enhances antitumor immunity by downregulating the expression of PD-L2 and its binding partner, repulsive guidance molecule b (RGMb). Blocking the interaction between PD-L2 and RGMb may overcome microbiome-dependent resistance to PD-1 pathway inhibitors. In various mouse tumor models unresponsive to anti-PD-1 or anti-PD-L1 therapies alone—including germ-free mice, antibiotic-treated mice, and mice colonized with stool samples from non-responsive patients—combining anti-PD-1 or anti-PD-L1 antibodies with either antibody-mediated blockade of the PD-L2–RGMb pathway or conditional deletion of RGMb in T cells promoted antitumor responses.[78] The downregulation of the PD-L2–RGMb pathway can be considered as a specific mechanism by which the gut microbiota promotes responses to PD-1 checkpoint blockade and suggest a potential immunological strategy for treating patients who do not respond to PD-1 cancer immunotherapy.

Smoking, Nutrition, and Physical Activity

Smoking history appears to enhance the response to anti-PD-1 therapy in NSCLC patients, with former and current smokers showing higher response rates compared to non-smokers.[79] This may be linked to smoking-induced metabolic changes, particularly the enrichment of oxidative phosphorylation (OXPHOS) and mitochondrial-related pathways, which could influence immune responses to ICB therapy.

Research from the Diet and Immune Effects Trial (DIET) project[80] outlined that a high-fiber diet (targeting 50 g/day from whole foods) can modulate the gut microbiome, which is crucial for enhancing the response to ICB in melanoma patients. This dietary intervention has been shown to improve systemic and tumor immunity, metabolic profiles, and overall quality of life, while also reducing immunotherapy toxicity. Another study[81] on dietary fiber and probiotics revealed that higher fiber intake is associated with improved PFS in patients on ICB, whereas probiotic use may impair treatment response by altering the gut microbiome and reducing the frequency of IFN-γ-positive cytotoxic T cells in the TME. On the other hand, exercise can enhance the effectiveness of cancer immunotherapies by improving immune function. It mobilizes leukocytes, boosts cardiorespiratory fitness, and reduces dysfunctional T cells. Both acute and chronic exercise may improve responses to various immunotherapies, though optimal exercise parameters are still being studied.[82] Furthermore, a meta-analysis[83] underscored the combined benefits of physical activity and diet, demonstrating that such interventions can reduce body weight, fat mass, insulin levels, and inflammation, while improving lipid profiles and mental health outcomes in cancer patients. These findings collectively suggest that adopting a high-fiber diet, avoiding unnecessary probiotic supplements, and engaging in regular physical activity can create a favorable gut microbiome and systemic environment, thereby enhancing the effectiveness of immunotherapy and improving overall patient outcomes.

Metabolism and Ferroptosis

Ferroptosis and metabolic pathways significantly influence immune cell functionality. The development of tumors primarily relies on the buildup of mutated proto-oncogenes, which trigger metabolic reprogramming in tumor cells. This reprogramming enables the cells to adapt to challenging conditions like oxidative stress, promotes the rapid proliferation of cancer cells, and enhances their ability to invade, metastasize, and resist drugs.[84] Importantly, ferroptosis is considered a potential common outcome of many dysregulated metabolic pathways.[85] Ferroptosis is a type of non-apoptotic cell death marked by iron-dependent lipid peroxidation of cell membranes.[86]

Ferroptosis influences the TME through multiple pathways, including the polarization of macrophages and suppression of immune cell activity. For instance, in pancreatic cancer, ferroptotic tumor cells release lipid metabolites that promote M2 macrophage polarization, which is associated with immunosuppression and tumor progression.[87,88]

Additionally, ferroptotic cells can inhibit DCs, NK cells, and other immune cells by releasing lipid metabolites, thereby facilitating immune evasion.[88] The activation of the SMAD pathway in macrophages increases tumor susceptibility to ferroptosis, while IL-4 induced protein 1 (IL4I1), an amino acid oxidase, enhances immune evasion through tryptophan metabolism.[89] IL4I1 produces indole-3-pyruvate (I3P), which scavenges free radicals and suppresses oxidative stress, protecting tumor cells from ferroptosis.[88]

ICB therapy has shown promise in enhancing cancer treatment by targeting ferroptotic cells. In the presence of GSH, GPX4 can protect cells undergoing ferroptosis.[90] Administration of GPX4 inhibitors not only induces tumor cell death but also enhances antitumor immunity, particularly in triple negative breast cancer (TNBC). This combination of GPX4 inhibitors with anti-PD-1 therapy demonstrates superior therapeutic efficacy compared to monotherapy, suggesting that ferroptosis induction can sensitize tumors to immune checkpoint blockade.[91] Additionally, dietary polyunsaturated fatty acid (PUFA) supplementation may enhance anti-tumor immunity and overcome immunotherapy resistance, revealing the effect of Adenosine 5′-triphosphate citrate lyase's (ACLY) inhibition.[92]

IL-1β blockade has been shown to maintain iron-sulfur clusters and inhibit ferroptosis, which in turn synergizes with anti-PD-1 therapy to enhance tumor suppression, further underscoring the role of ferroptosis in modulating immune responses.[93] Additionally, biomineralized nanovaccines that induce ferroptosis, such as Fe@OVA-IR820, have been shown to trigger immunogenic cell death and amplify antitumor immunity when combined with CTLA-4 checkpoint blockade, offering a novel approach to treat refractory cancers.[94]

Demographic Factors and Obesity

Research indicates that age can influence the effectiveness and tolerability of mAb treatments targeting PD-1/PD-L1. Older patients may experience different outcomes compared to younger ones. Some studies suggest that older patients might have similar or even better tolerance to these therapies, although they may face different immune-mediated toxicities.[95]

Gender differences have also been noted in ICB therapy outcomes. These differences are influenced by tumor antigenicity, immune environment, genetic and epigenetic factors, and sex hormones.[96,97] Male patients typically show better responses, while females, particularly those with high TMB, may benefit more from combination therapies, such as ICB combined with chemotherapy.[97–99] Meta-analyses conducted by Botticelli, et al[100] and Pinto, et al[101] further support that males experience greater benefits from ICB treatment in terms of OS and PFS, while females may not experience the same level of benefit with ICB monotherapy.[98,99] Therefore, treatment strategies for females may need to focus on enhancing tumor antigenicity to improve immunotherapy responses.[97]

Although obesity is typically associated with cancer development and poorer prognosis, it has surprisingly been linked to better outcomes in some solid tumors (eg, melanoma and NSCLC) treated with ICBs.[102,103] A retrospective multi-cohort study on melanoma patients suggested that obesity (defined as a body mass index [BMI] > 30 kg/m^2) reduced the risk of death by nearly 40%, particularly in males, suggesting that metabolic factors and gender together may influence immunotherapy efficacy.[104]

Genomic Heterogeneity

Genomic alterations at the CD274 locus (encoding PD-L1) have been linked to increased PD-L1 expression in various cancers, including lung cancer, lymphoma, and gastric cancer. These alterations can result from genetic amplifications or epigenetic modifications, such as DNA methylation and histone modifications, which either enhance or suppress gene expression. These variations can significantly affect the efficacy of PD-1/PD-L1 inhibitors, as these therapies depend on the expression of PD-L1 on tumor and immune cells to function effectively.[105] Moreover, specific mutations in the CTLA-4 gene, such as the G199R mutation in its cytoplasmic domain, have been found to enhance protein-membrane interactions, leading to stronger inhibition of T cell activation,[106] which may alter the effectiveness of these inhibitors.

Additionally, homozygosity at HLA loci, which leads to reduced antigen presentation diversity, has been associated with decreased survival in cancer patients treated with ICB.[107] This finding reveals the broader implications of genetic variability on immunotherapy outcomes.

Systemic Immunity

Systemic immunity, encompassing both innate and adaptive immune responses, plays a pivotal role in determining patient outcomes. Systemic immune markers, like the neutrophil-to-lymphocyte ratio (NLR), offer valuable insights into the effectiveness of ICB therapies. Research has shown that an NLR of 2.0–3.0 is associated with optimal treatment outcomes, indicating that balanced systemic inflammation may be crucial for optimizing ICB response.[108] The emergence of autoantibodies during ICB therapy may compromise immune tolerance. 19.2% of ipilimumab-treated melanoma patients who were initially autoantibody-negative developed new autoantibodies, particularly antithyroid antibodies, which were significantly associated with thyroid dysfunction during subsequent anti-PD-1 therapy (OR = 9.96; 95% CI, 1.94–51.1).[109]

The expansion of ≥ 55 $CD8^+$ T cell clones in peripheral blood preceded the development of severe irAEs in patients receiving ipilimumab. This finding underscores the potential of $CD8^+$ T cell clonal expansion as a correlative biomarker for early detection and intervention.[110] Additionally, cytokine dysregulation further illustrates the systemic nature of irAEs. The cytokine toxicity (CYTOX) score, which integrates 11 proinflammatory cytokines, was predictive of severe irAEs (area under the curve [AUC] = 0.68 at baseline and 0.70 early during treatment), providing a tool for early management of toxicities.[111] Additionally, germline variants and baseline immune profiles, such as HLA-B allelic variations and TMEM162 mutations, have been identified as risk factors for irAEs, emphasizing the role of systemic genetic and immunological factors in shaping ICB outcomes.[112] Therefore, systemic immunity is not only a determinant of ICB efficacy but also a critical factor in managing treatment-related toxicities.

TME

The TME significantly influences the response to ICB therapy by harboring various non-immune stromal and immune cells that contribute to immune evasion and resistance mechanisms. Non-immune stromal cells, such as endothelial cells and cancer-associated fibroblasts (CAFs), can create physical barriers and secrete factors like TGF-β that modulate the extracellular matrix (ECM) and immune infiltration, ultimately affecting ICB efficacy.[113,114] Furthermore, tissue-specific stromal cells, such as reactive astrocytes in brain metastases, have been implicated in promoting immune evasion and resistance to ICBs by altering the immune cell milieu, such as reducing $CD8^+$ T cell activity and increasing immunosuppressive microglia.[115]

Immune cells within the TME, such as myeloid-derived suppressor cells (MDSCs), TAMs, and Tregs, are crucial in shaping the immune response to tumors and thereby affecting the outcomes of immune ICB therapy. VEGF and TGF-β are two potent regulators in promoting immune evasion within the TME. VEGF activates STAT3 signaling, which recruits and differentiates MDSCs, enhancing their immunosuppressive function, including the production of ROS and arginase-1 (ARG-1).[116,117] Similarly, TGF-β drives MDSC differentiation and upregulates immunosuppressive molecules like IL-10 and PD-L1, further inhibiting T cell activity.[118,119] Dual inhibition of VEGF and TGF-β using bispecific antibodies has shown synergistic effects in reducing MDSC-mediated immunosuppression and enhancing antitumor immunity in combination with PD-1 blockade.[118] These findings outline the potential of targeting VEGF and TGF-β pathways to mitigate MDSC-induced immune suppression and improve ICB treatment efficacy.

MDSCs and M2 TAMs, characterized by their immunosuppressive phenotypes and expression of checkpoint molecules like PD-L1, suppress effector T cell (Teff) activity and facilitate tumor immune evasion.[120,121] Additionally, recent findings suggest that B cells, particularly those within tertiary lymphoid structures (TLSs), may enhance ICB responses in certain cancers, although the mechanisms remain under investigation.[122,123]

irAEs Induced by mAb Therapies

The therapeutic efficacy of ICBs is often accompanied by irAEs, which, in the most severe cases, can be fatal. These side effects occur when an enhanced immune response mistakenly targets normal tissues, leading to inflammation and autoimmune-like symptoms.[124]

Introduction to irAEs

An irAE is an AE with characteristics of an immunologic reaction.[125] In the context of ICB therapy, these reactions occur when the heightened immune response, intended to target cancer cells, also mistakenly attacks normal tissues, leading to a spectrum of autoimmune-like symptoms.[126,127] It is estimated that irAEs affect around 20% of cancer patients undergoing immunotherapy. The risk increases with patients who are concurrently taking 2 immunotherapy drugs and have had a history of autoimmune disease.[128] These events can affect multiple organ systems, including the skin, gastrointestinal tract, and endocrine system, among others.

The severity of irAEs in patients undergoing cancer immunotherapy can range from mild to life-threatening. irAEs are classified by severity using the Common Terminology Criteria for Adverse Events (CTCAE),[129] with grades ranging from 1 to 5. Grade 1 refers to mild cases, where symptoms are either asymptomatic or minimal, requiring no treatment and detectable only through clinical or diagnostic means. Grade 2 indicates moderate severity, involving symptoms that require minor, localized, or noninvasive treatment and that interfere with age-appropriate instrumental activities of daily living (ADLs). Grade 3 involves severe or medically significant conditions that, while not immediately life-threatening, require hospitalization or extended hospital stays and may result in disability or impair self-care ADLs. Grade 4 is characterized by life-threatening outcomes that demand urgent medical intervention, and Grade 5 results in death due to the AEs. With the expanding approval of ICBs for various cancers, the prediction, detection, and management of irAEs have become crucial for optimizing patient outcomes.[127]

Major Mechanisms Leading to irAEs

irAEs are common and diverse, varying in incidence, timing, and severity. Exploring these mechanisms may help identify irAEs at early stage and develop targeted treatment strategies.[130]

T Cell Activation or Infiltration

The mechanisms behind irAEs are complex, primarily involving T cells activated by ICB therapy. These cells can cause inflammation in both tumor and normal tissues. Although the exact mechanisms underlying the development of irAEs remain incompletely understood, they are believed to result from bystander effects mediated by activated T cells.[131] In particular, tumors that exhibit cytotoxic T lymphocyte (CTL) infiltration before treatment may undergo heightened inflammation and increased tumor cell death following ICB administration.[131]

Moreover, ICB therapy can trigger a variety of inflammatory infiltrates in the tumor immune microenvironment (TIME), such as $CD8^+$ tumor-infiltrating lymphocytes (TILs), neutrophils, and plasma cells. It also upregulates specific immune checkpoint pathways, decreases the presence of immunosuppressive M2 macrophages, and encourages the development of organized tertiary lymphoid structures (TLS) within the tumor bed.[132,133] For instance, in the NEOSTAR trial,[134] combining ipilimumab with neoadjuvant chemotherapy and PD-1 blockade enhanced the expression of $CD8^+$ T cell activation markers while reducing markers linked to immunosuppression. Furthermore, the importance of $CD4^+$ T cells in ICB response is becoming more evident, with studies indicating that ICB influences $CD4^+$ T cell chemotaxis and supports TLS formation.[131,133] Certain patterns of T cell infiltration may be associated with unfavorable outcomes. $CD8^+$ $GZMB^+$ T cell infiltration correlates with improved OS in patients receiving combination GVAX + nivolumab therapy, while immune suppression mechanisms, such as IL-8 signaling in tumor-associated neutrophils (TANs), may limit T cell infiltration and response to therapy.[133]

Elevated Cytokine Levels

ICBs can lead to cytokine release syndrome (CRS), a severe reaction characterized by an overwhelming release of cytokines by activated T cells. This can cause extensive inflammation and damage to multiple organ systems. In the context of T cell-engaging therapies, CRS is initiated by the substantial release of IFN-γ from activated T cells or tumor cells themselves, subsequently leading to the activation of macrophages.[135] These activated macrophages then generate elevated levels of IL-6, IL-8, IL-10, and TNF-α,[136] leading to widespread inflammation affecting organs like the liver, lungs, and skin.[135,137] Other common symptoms include fever and hypotension. CRS has been well-documented in therapies like chimeric antigen receptor (CAR)-T cells but is increasingly recognized in ICB-treated patients.[138] CRS is

a relatively rare but severe irAE associated with ICBs, with an incidence of approximately 1–4.6% in clinical cohorts.[138,139] The pathophysiology of CRS involves the loss of immune homeostasis, where ICBs disrupt self-tolerance and consequently activate autoreactive T cells and B cells, as well as systemic inflammation.[138]

Grade 3–5 CRS is associated with severe complications, including cardiovascular, neurologic, pulmonary, and rheumatic involvement, which may lead to fatal outcomes despite treatment.[138] A recent study[138] revealed that patients with severe CRS tend to have a longer time to fever onset, lower platelet counts, and higher urea levels at presentation, which can serve as predictive biomarkers for severe outcomes. ICB rechallenge after mild CRS has been reported to be generally safe, but caution is advised due to the potential for recurrent or more severe irAEs.[139]

Risk Factors for irAEs

Several patient-related factors influence the risk and severity of cetuximab-induced oral mucositis. Among these, gender and age have emerged as significant determinants. Studies[140,141] indicate that female cancer patients are more likely to develop oral mucositis than their male counterparts, a phenomenon potentially linked to hormonal influences on inflammatory processes. Estrogen and other female hormones have complex regulatory effects on immune responses, which may heighten susceptibility to mucosal injury during cetuximab treatment. Additionally, older patients ($\geq$ 70 years old) exhibit a higher prevalence and severity of oral mucositis. While the exact mechanisms remain unclear, the increased fragility of aging tissues and reduced regenerative capacity may contribute to heightened toxicity in elderly patients.[142] Furthermore, elderly individuals often experience a greater burden of treatment-related irAEs, necessitating careful consideration of cetuximab therapy in this population.[141,143,144] Furthermore, given that high doses and prolonged treatment cycles are also associated with increased mucositis risk,[145,146] clinicians should evaluate the overall health status of elderly and female patients before initiating cetuximab-based regimens, particularly in combination with radiotherapy or chemotherapy.

Germline genetic alterations, which regulate the immune system, may also influence the occurrence of irAEs. A study involving 530 cancer patients treated with ICBs identified significant associations between certain HLA types and organ-specific irAEs.[147] Notably, HLA-DRB301:01 was linked to an increased risk of thrombocytopenia, while HLA-DPB104 :02 was associated with electrolyte imbalances such as hypokalemia and hyponatremia, as well as hematologic conditions like leukopenia and anemia.

In addition to HLA variants, a genome-wide association study (GWAS) has uncovered other germline genetic variants that may predispose patients to irAEs. A comprehensive study analyzing 1751 patients across 12 cancer types identified significant associations between irAEs and variants near the IL7 and IL22RA1 genes.[148] The variant near IL7, rs16906115, was notably associated with an increased risk of developing irAEs. This finding was further supported by replication in independent cohorts, suggesting a robust link between this genetic variant and irAE susceptibility. While these findings offer insights into genetic predispositions, further research is needed before personalized risk assessments based on genetic profiles can be implemented in clinical practice.[149]

Dual-Edged Sword Effects of Immune Activation Associated With mAbs in Cancer Treatment

The challenge of using mAbs in cancer treatment lies in balancing their antitumor efficacy with the management of irAEs. The dual-edged sword effects of immune activation associated with mAbs in cancer treatment are illustrated in Figure 3.

Enhancement of Body's Immune Response

The therapeutic potential of mAbs is closely tied to their ability to enhance the body's immune response against cancer. For instance, in metastatic melanoma, combining nivolumab with ipilimumab has shown superior ORRs and PFS compared to monotherapies.[150] This combination has become a promising treatment option for advanced melanoma, as well as other cancers like NSCLC and renal cell carcinoma (RCC). Likewise, radiotherapy can enhance the efficacy of anti-PD-1/PD-L1 therapies through multiple mechanisms. It promotes the infiltration of tumor-infiltrating lymphocytes

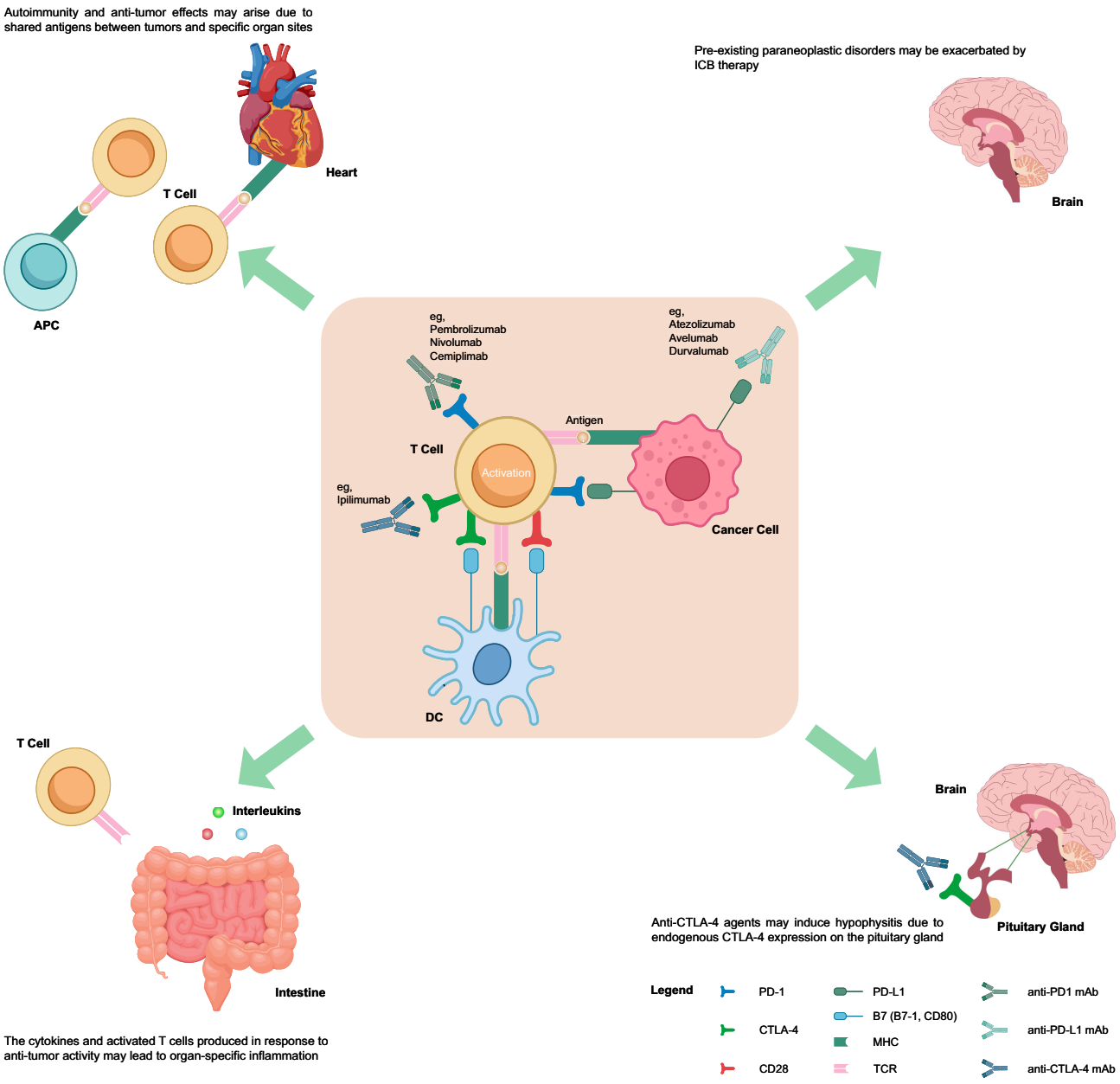

Figure 3 Dual-edged sword effects of immune activation associated with monoclonal antibodies (mAbs) in cancer treatment.
Abbreviations: APC, antigen-presenting cell; DC, dendritic cell; MHC, major histocompatibility complex; TCR, T cell receptor.

(TILs) and expands the T cell receptor (TCR) repertoire within the TME. Additionally, radiotherapy upregulates PD-L1 expression on tumor cells, providing more targets for immune checkpoint blockade, and increases MHC-I expression, helping to overcome resistance to anti-PD-1/PD-L1 therapy.[150] Moreover, cemiplimab, a fully human mAb targeting the PD-1 receptor, has demonstrated durable and significant benefits in treating advanced cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC), with a favorable safety profile. It is also approved for first-line treatment of patients with advanced NSCLC exhibiting high PD-L1 expression, demonstrating its versatility in managing various malignancies.[151,152]

However, activated T cells target both tumor and normal tissues, leading to therapeutic responses as well as toxicity. In a post-mortem study of two metastatic melanoma patients who developed fulminant myocarditis after receiving nivolumab plus ipilimumab, infiltrating T cells and macrophages were found in the myocardial tissue and cardiac conduction system. Furthermore, deeper analysis of the infiltrating T cells using TCR sequencing revealed common high-

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frequency TCRs in cardiac muscle, skeletal muscle, and tumor tissue, supporting this hypothesis.[153] Additionally, a recent prospective cohort study of 73 NSCLC patients treated with anti-PD-1 antibodies reported that 34.2% of patients developed dermatologic irAEs.[154]

Cancer cells often exploit immune checkpoints to escape detection by the immune system. One such checkpoint involves PD-1, a protein found on T cells. When PD-1 interacts with its ligands, PD-L1 and PD-L2, which are expressed on cancer cells and in the TME, it suppresses T cell activity, effectively allowing cancer cells to evade immune response.[19,155,156] Similarly, CTLA-4 competes with CD28 to bind CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells (APCs), further dampening T cell activation and fostering immune tolerance within the TME.[17,156,157]

Induction of Autoimmunity

irAEs can occur because inhibiting immune checkpoints enhances the immune response against tumors while also triggering an overactive response against normal tissues. This simultaneous occurrence of autoimmunity and antitumor effects can be attributed to shared antigens between tumors and specific organ sites. The spectrum of irAEs is broad, affecting multiple organ systems, including the skin, gastrointestinal tract, liver, endocrine glands, and others.[131,158]

Anti-CTLA-4 antibodies (eg, ipilimumab) are known to induce autoimmune-like reactions, including colitis, hepatitis, and endocrine disorders, due to the increased activation of naïve T cells.[159,160] Additionally, cytokines and activated T cells generated by the antitumor response can cause organ-specific inflammation. One crucial cytokine involved in this process is IL-6, a key player in the inflammatory response that is often elevated in patients undergoing ICB therapy. Elevated IL-6 levels have been implicated in the exacerbation of inflammatory responses and development of irAEs. IL-6 promotes the differentiation of T cells into Th17 cells, which contribute to autoimmunity and inflammation in various tissues.[131,161,162]

In the context of ICB therapy, gastrointestinal toxicity like diarrhea and colitis is closely linked to the immune system's activation. Although skin-related events (eg, rash, pruritus, and vitiligo) often appear first, self-reactive T cells can target multiple organ systems, including the gastrointestinal tract. Specifically, the differentiation and expansion of Th-17 cells within the gut mucosa have been implicated in the development of gastrointestinal-related immune AEs.[163]

On the other hand, tumors often express antigens that are also present in normal tissues, leading to the immune system targeting both cancer cells and healthy tissues. This cross-reactivity is a key reason why ICBs can induce irAEs. TCR clonotype analysis has identified shared T cell clones between tumors and irAE-affected tissues, suggesting that immune responses within the TME may contribute to both antitumor immunity and irAE development.[131,164]

Notably, several studies[131,165] have demonstrated that the occurrence of irAEs correlates with improved clinical outcomes. For instance, a retrospective analysis of patients treated with anti-PD-1 and anti-PD-L1 antibodies found that those who experienced irAEs had significantly longer OS and PFS compared to those who did not. Specifically, the median OS was not reached in patients with irAEs, compared to 8.21 months in those without, and the median PFS was 5.2 months versus 1.97 months.[131] Meanwhile, IL-6 was upregulated in tumor tissues from patients who did not respond to CTLA-4 ICB therapy, suggesting that IL-6 may contribute to resistance mechanisms against CTLA-4 blockade, highlighting its dual role in both adverse immune reactions and lack of therapeutic efficacy in some patients.[131]

Anti-CTLA-4 Therapy-Related Hypophysitis

CTLA-4 is expressed in specific pituitary cells.[166] Anti-CTLA-4 agents, such as ipilimumab and tremelimumab, can induce hypophysitis, a form of pituitary inflammation, through direct targeting of pituitary tissue and immune activation. As mAbs, CTLA-4 inhibitors may contribute to off-target toxicity through molecular mimicry, binding to unintended self-antigens expressed on anterior pituitary cells.[167] This interaction triggers the classical complement cascade, leading to immune-mediated pituitary damage.

Beyond complement activation, anti-CTLA-4 antibodies promote inflammatory cascades similar to type II hypersensitivity reactions, marked by C3d and C4d deposition. Lymphocytic infiltration follows, along with the development of pituitary-specific antibodies and hormone deficiencies, particularly affecting thyrotropin, follicle-stimulating hormone, and corticotropin-secreting cells. Mouse models further support this mechanism, demonstrating that repeated injections of a CTLA-4 blocking antibody lead to lymphocytic infiltration of the pituitary gland and circulating pituitary

antibodies.[166] Moreover, an autopsy study involving deceased patients treated with anti-CTLA-4 therapy has shown that severe hypophysitis is associated with high CTLA-4 expression in pituitary cells, accompanied by IgG-dependent complement fixation.[168]

In contrast, anti-PD-1 agents, like nivolumab, are less likely to activate the complement pathway and typically cause milder hypophysitis, characterized by corticotroph depletion without extensive necrosis or fibrosis.[169] The risk and severity of hypophysitis are higher with anti-CTLA-4 therapies, often occurring shortly after treatment initiation, whereas hypophysitis from other ICBs develops over a much broader timeframe.[167] Elevated pituitary CTLA-4 expression may predispose individuals to hypophysitis following anti-CTLA-4 therapy, although germline CTLA-4 mutations have not been linked to hypophysitis, indicating a unique mechanism of ICB-induced pituitary toxicity.[170]

Inhibition of EGFR and Mucositis

Cetuximab, which works by inhibiting EGFR, can also disrupt the proliferation and repair of normal mucosal cells, thereby increasing oral mucosal damage and inflammation. This adverse effect is particularly significant in treatments involving head and neck cancers, where the combination of cetuximab and radiotherapy has been shown to significantly elevate the incidence of oral mucositis. The incidence of oral mucositis can reach up to 44.7% when cetuximab is used in conjunction with radiotherapy.[146,171]

Impact of Pre-Existing Paraneoplastic Syndromes

Immunotherapy with ICBs, specifically targeting PD-1 or PD-L1, can have significant effects on patients with pre-existing paraneoplastic syndromes. These syndromes, which are autoimmune disorders associated with cancer, may not only worsen but also reveal new neurologic complications post-treatment.[172]

A systematic review analyzing 82 cases of ICB-induced encephalitis identified focal limbic or non-limbic encephalitis and meningoencephalitis as common presentations.[173] Paraneoplastic encephalitic syndrome, when undetected prior to the initiation of ICB therapy, may be triggered and presents with particularly severe outcomes. This type of syndrome is considered to have the worst prognosis among all encephalitis syndromes induced by ICBs. From a study analyzing adult patients treated with anti-PD-1 or anti-PD-L1 immunotherapy for solid tumors, it was found that up to 50% of patients with pre-existing paraneoplastic disorders experienced a worsening of symptoms following immunotherapy.[172] Another study[174] reported 14 cases of immune-related encephalitis in cancer patients treated with ICBs, highlighting the importance of early recognition and management. Pharmacovigilance research has also linked ICBs to encephalitis, underscoring the need for long-term monitoring of patients undergoing these treatments.

Treatment Strategy irAEs in Cancer Immunotherapy With mAbs

While mAbs have significantly improved outcomes for cancer patients, managing irAEs in cancer immunotherapy remains a dual challenge. Ensuring patient safety and optimizing therapeutic efficacy are crucial as the use of mAbs expands across various cancer types. Prompt identification and intervention are key to mitigating the impact of irAEs and improving overall treatment outcomes. For immune-related diarrhea or colitis induced by ICB therapy, corticosteroids are the first-line treatment starting at Grade 2 severity.[175] About 50% of patients respond to this intervention and achieve symptom resolution.[176–178] For Grade $\geq$ 3 irAEs, corticosteroids are widely utilized, with pulse therapy demonstrating particular efficacy in severe conditions such as pneumonitis and hepatitis.[179]

Effective management of these AEs also requires rigorous infection prophylaxis.[180] In patients undergoing ICB therapy, infection prevention involves comprehensive evaluation to exclude non-ICB causes of pneumonitis, such as infections or malignancies, often necessitating consultations with infectious disease and pulmonology specialists. Once non-ICB causes are excluded, high-dose steroids should be promptly initiated. However, data on optimal second-line immunosuppressive treatments for steroid-refractory pneumonitis remain limited. Outcomes in such cases are generally poor, with patients often succumbing to pneumonitis or secondary infections.[181] The diagnosis of ICB-induced pneumonitis relies on the exclusion of other potential causes, with chest computed tomography (CT) being the preferred

imaging modality.[182] Although pneumonitis typically responds to steroids within 72 hours, effective second-line treatments for steroid-refractory cases are still lacking.[181,182]

In cases where corticosteroids fail to control symptoms, persistent or worsening diarrhea/colitis may become life-threatening, necessitating more aggressive interventions. Infliximab, a monoclonal anti-TNF-α antibody, is commonly employed for steroid-refractory irAEs during ICB therapy. It has demonstrated efficacy in managing severe, steroid-resistant colitis associated with ipilimumab, as evidenced by multiple case studies.[175,180,181]

Vedolizumab, an integrin antagonist, selectively inhibits the migration of T cells into inflamed gastrointestinal tissues by blocking the interaction between α4β7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). It is currently indicated for treating ulcerative colitis and Crohn's disease[99] and has shown promise in managing ICB-induced diarrhea/colitis in case reports.[183–185] Vedolizumab offers more targeted immune suppression for gastrointestinal inflammation by specifically blocking T cell migration to the gut, thereby reducing systemic immunosuppression and potentially preserving antitumor immune responses. Similar to infliximab, early administration of vedolizumab within 10 days of colitis onset can improve outcomes and reduce symptom duration.[186] Achieving endoscopic or histologic remission with vedolizumab treatment is also critical for preventing relapse.

Infliximab is also approved for various autoimmune diseases, including ulcerative colitis and Crohn's disease.[186–188] Early administration of infliximab within 10 days of colitis onset can reduce symptom duration and enhance the success of steroid tapering.[186] Furthermore, treatment with ≥ 3 doses of infliximab and achieving endoscopic or histologic remission are associated with a lower risk of colitis relapse, underscoring the importance of endoscopic evaluation for predicting long-term outcomes.[175]

In CRS, elevated IL-6 levels serve as a key mediator of the proinflammatory response. Consequently, tocilizumab has emerged as a therapeutic option for managing CRS induced by mAb therapy in cancer patients. This humanized mAb effectively inhibits both the soluble and membrane-bound IL-6 receptor.[187] Tocilizumab is recommended for patients with ≥ Grade 3 CRS or ≥ Grade 2 CRS with comorbidities, as it can rapidly alleviate fever and hypotension.[138]

It is also essential to assess a patient's normal bowel habits before starting immunotherapy. Patients should be advised to inform their healthcare team about any changes in bowel patterns to enable early identification of colitis, which may develop before the next planned appointment. While diarrhea (an increase in bowel movement frequency) is the most common presentation, other colitis-related symptoms can also occur, as previously mentioned. The severity of diarrhea (measured by the increase in daily bowel movements compared to baseline) and presence or intensity of additional colitis symptoms help determine the grade of the gastrointestinal irAE. High-grade gastrointestinal irAEs may lead to serious complications, such as hemodynamic instability, ischemic bowel, perforation, or toxic megacolon, which can be life-threatening.[175] Additionally, healthcare providers should undergo specialized training on irAEs to effectively educate patients and adopt a multidisciplinary strategy to reduce the severity of these AEs.[179]

Close monitoring of irAEs is crucial for patients receiving ICB therapy, necessitating comprehensive pretreatment evaluations and continuous clinical and laboratory assessments throughout the treatment course.[188] In this context, ongoing research is focused on identifying reliable biomarkers that can predict the onset and severity of irAEs. The discovery of such predictive markers holds the potential to revolutionize irAE management by facilitating personalized treatment strategies that maximize the therapeutic benefits of ICBs while mitigating associated toxicities.[188,189] Currently, several novel biomarkers are under investigation for irAE diagnosis and prediction, including blood cell analysis, chemokines/cytokines, autoantibodies, and immune-cell subsets such as the T cell repertoire and fecal microbiome.[190] Peripheral blood biomarkers for irAEs—detected in serum, plasma, or whole blood—comprise underlying germline genetic factors (eg, specific HLA haplotypes),[183] mRNA levels (eg, CD177 and CEACAM1), and specific cytokine concentrations (eg, interleukins or interferons).[184]

Conclusion and Future Prospects

This literature review provides a comprehensive analysis of the role of mAbs in cancer therapy, emphasizing their mechanisms of action, clinical applications, and challenges associated with irAEs. The core findings underscore the remarkable success of mAbs in selectively targeting cancer cells through various mechanisms, including receptor blockade (eg, HER2), ADCC, CDC, and immune checkpoint inhibition (eg, PD-1/PD-L1 and CTLA-4). These therapies

have revolutionized cancer treatment, significantly improving patient outcomes across multiple malignancies. However, despite these advancements, a major challenge remains in balancing therapeutic efficacy with the risk of irAEs, which can range from mild to life-threatening. As the indications for mAbs continue to expand, the management of irAEs will remain a critical priority.

To address this challenge, future research should focus on developing predictive models and prophylactic strategies to mitigate irAEs while preserving antitumor immunity. In addition, investigating the role of the gut microbiome, systemic immunity, and cytokine profiles in irAE pathogenesis may lead to innovative interventions, such as microbiome modulation[131] or cytokine-targeted therapies.[163]

Another crucial area for future exploration is the identification and validation of robust biomarkers to predict therapeutic response and irAE risk. Despite promising findings, many candidate biomarkers require further validation in large-scale clinical trials before routine clinical application. Emerging approaches, including liquid biopsies, circulating tumor DNA (ctDNA), GWAS, and multi-omics analyses, could offer deeper insights into patient-specific responses, facilitating personalized treatment strategies. For instance, research has increasingly focused on single nucleotide polymorphisms (SNPs) to predict patient survival outcomes for specific mAbs. In the phase III MAX trial, VEGF-A rs25648 was associated with improved survival outcome, whereas VEGF-A rs699947 correlated with shorter PFS.[185] Additionally, VEGFR2 rs11133360 was linked to a reduced risk of severe hypertension. These findings underscore the potential of SNP profiling as a valuable tool for developing more individualized and effective treatment strategies.

Future research should also focus on elucidating the mechanisms underlying resistance to mAb therapy and developing combination strategies to overcome this challenge. Ongoing investigations are exploring the synergistic effects of combining mAbs with chemotherapy, targeted small molecules, or other immunotherapies. This approach aims to enhance therapeutic efficacy while minimizing the likelihood of resistance, ultimately leading to more durable and effective cancer treatments.

The prospect of mAb therapy in oncology is promising, with numerous opportunities to optimize therapeutic potential while mitigating associated risks. Advances in antibody engineering, combination therapies, personalized immunotherapy, and irAE management are expected to shape the next generation of cancer treatments. Through ongoing research, innovation, and collaboration, the primary objective is to enhance patient outcomes and position mAb therapies as safer and more effective treatments for a wider variety of cancer patients.

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