REVIEW ARTICLE

# Tumor Immunotherapy Resistance: Underlying Mechanisms and Emerging Strategies to Overcome Therapeutic Bottlenecks

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## Abstract

**This review presents a systematic synthesis of the principal tumor immunotherapy strategies and their corresponding resistance mechanisms. Immunotherapies—including antibody-based therapies, adoptive cell therapies, immune modulators, and novel approaches such as oncolytic viruses and cancer vaccines—work by stimulating or enhancing the patient's immune system to target cancer cells. Nevertheless, they commonly encounter resistance in clinical applications. Resistance mechanisms predominantly stem from tumor-intrinsic factors and tumor microenvironment (TME) factors. To surmount resistance, combination therapies and personalized treatment strategies grounded in TME profiling and biomarkers represent critical future directions.**

**Keywords**: tumor immunotherapy, resistance mechanisms, tumor microenvironment, combination therapy.

## 1 Introduction

Globally, cancer ranks as the second leading cause of death [1]. Over 100 distinct cancer types have been identified in humans. Breast cancer has the highest incidence rate, whereas lung cancer has the highest mortality rate [2]. Currently, various therapeutic methods are employed in cancer treatment. Recently, significant advancements have been made in tumor immunotherapy. The core idea is to reinstate the immune system's ability to combat cancer. Immunotherapy—which aims to harness the body's immune system to eliminate cancer cells—represents a significant breakthrough in cancer treatment. Several immunotherapy approaches, including monoclonal antibodies, immune-checkpoint inhibitors, cancer vaccines, adoptive cell transfer therapy, and oncolytic

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virus therapy, have shown encouraging results.

However, drug resistance persists as a continuous challenge. Despite the immune system's complex mechanisms to identify and eradicate tumor cells, tumor cells have inherent adaptations that enable them to evade the immune response, a process thoroughly explained by the concept of 'cancer immunoediting'. Consequently, tumors frequently advance to an immune-escape state, where they may even harness the immune system to promote metastasis [1]. Cancer immune evasion also represents a significant bottleneck restricting the effectiveness of existing therapies.

The failure of tumor immunotherapy can be ascribed to the combined effects of the tumor cells' inherent escape strategies and the immunosuppressive microenvironment [3]. Tumor cells hinder T cell recognition and activation by reducing major histocompatibility complex-I (MHC-I) expression—thereby disrupting antigen presentation—and by dynamically altering immune checkpoint molecules such as PD-L1. Simultaneously, TME establishes a complex immunosuppressive network [4]: T-cells not only show inadequate infiltration but also become functionally exhausted; stromal cells, like cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs), release inhibitory factors such as TGF-$\beta$ to establish an immunosuppressive milieu; abnormal vascular structures restrict immune cells infiltration; and metabolic reprogramming within tumors generates metabolites such as lactate and adenosine to further attenuate immune responses. Collectively, these factors form a complex barrier that results in immunotherapy failure.

This review initially conducts a systematic delineation of the principal immunotherapy strategies and their corresponding mechanisms of action. Subsequently, it centers on an in-depth analysis of the core causes of resistance. Resistance not only originates from intrinsic escape mechanisms, including deficiencies in antigen presentation and abnormal PD-L1 expression, but also from the multi-dimensional immunosuppressive network within TME, which encompasses T-cell exhaustion, activation of suppressive cells, and metabolic irregularities. Ultimately, it discusses possible strategies to overcome resistance, seeking to offer a theoretical basis and practical guidance to improve the success of immunotherapy.

## 2 Types and Principles of Tumor Immunotherapy

### 2.1 Antibody-Based Therapies

#### *2.1.1 Monoclonal Antibodies*

Monoclonal antibodies (mAbs) elicit anti-tumor effects via three principal mechanisms: (1) directly antagonizing activators and receptors implicated in cancer-cell proliferation and angiogenesis [5]; (2) mediating antibody-dependent cellular cytotoxicity (ADCC) by binding to tumor-associated antigens and inducing complement-dependent cytotoxicity (CDC) [6–8]; (3) activating immune cell responses through blockade of immune checkpoint receptors [9].

Immune cell activation is precisely regulated through the interactions between ligands and receptors, which can occur between immune cells themselves or between immune cells and tumor cells. T-cell activation begins when the T-cell receptor (TCR) recognizes neoantigens and is further influenced by immune checkpoint molecules [10]. Cancer cells can achieve immune evasion by increasing co-inhibitory signals or reducing co-stimulatory signals, thereby disrupting this balance [10, 11].

CTLA-4 was originally identified as a member of the immunoglobulin superfamily expressed on T cells [12], and subsequent functional studies established its role as a negative regulator of T-cell activation [13]. The CTLA-4/B7-1 and PD-1/PD-L1 pathways serve as key immune checkpoints that suppress T-cell activation during both the initial priming phase and the effector phase [14]. From a mechanistic perspective, the interaction of CTLA-4 with B7-1 and PD-1 with PD-L1 activates protein phosphatase 2A (PP2A) and Src homology region 2 domain-containing phosphatases (SHP2) respectively, leading to reduced TCR signaling and suppression of T-cell functions [15]. Beyond classical MHC-I molecules, non-classical MHC-I complexes such as HLA-G have also been implicated in tumor immune evasion [16]. Blocking other co-inhibitory receptors such as LAG-3 and TIM-3 (ligand: Galectin-9) [17] has also demonstrated anti-tumor effects in clinical trials. For example, using nivolumab (anti-PD-1) together with ipilimumab (anti-CTLA-4) resulted in a 58% overall survival rate at three years for patients with advanced melanoma [18].

#### *2.1.2 Bispecific Antibodies*

As a rapidly evolving form of immunotherapy, BsAbs can bind to two separate epitopes simultaneously. This dual-targeting feature permits them to redirect

cytotoxic effector cells, such as T cells and NK cells, to target tumors, while simultaneously blocking essential signaling pathways necessary for tumor growth and survival [19, 20]. BsAbs have multi-target capabilities compared to monospecific mAbs, offering unique benefits in dealing with highly heterogeneous tumors [21].

### 2.2 Adoptive Cellular Immunotherapy

#### *2.2.1 Chimeric Antigen Receptor T-Cell (CAR-T) Therapy*

This method involves altering T-cells genetically to produce chimeric antigen receptors that target specific antigens independently of MHC, enabling them to recognize and eliminate target cells. The design of CARs has undergone several generational evolutions:

- First-generation CARs consisted only of an extracellular domain for antigen binding and an intracellular CD3$\zeta$ signaling domain. The lack of co-stimulatory signals restricted their effectiveness against tumors.
- Second-generation CARs integrated one co-stimulatory domain in addition to CD3$\zeta$, facilitating the sustained proliferation, survival, and cytokine secretion of T-cells.
- Third-generation CARs include two separate co-stimulatory molecules to enhance their effectiveness and longevity.
- Fourth-generation CARs are engineered to inductively express functional transgene proteins for the purpose of enhancing anti-tumor activity or improving safety.
- Fifth-generation CARs utilize novel targeting systems, presenting new prospects for universal and programmable CAR-T therapies [22].

#### *2.2.2 T-Cell Receptor-Engineered T-Cell (TCR-T) Therapy*

Different from CAR-T therapy that uses an artificial receptor, TCR-T immunotherapy utilizes the natural receptors of T-cells to recognize tumor antigens displayed by MHC molecules. Nevertheless, the clinical application of TCR-T therapy is restricted by cancer immune evasion. To overcome these limitations, novel TCR-engineering technologies, including STAR, AbTCR, and ImmTAC, are currently in the process of development to augment the efficacy and applicability of TCR-T therapy. Concurrently, overcoming immune checkpoint-mediated resistance remains a key consideration in optimizing TCR-T approaches [23].

### 2.3 Tumor-Infiltrating Lymphocyte (TIL) Therapy

Tumor-infiltrating lymphocyte therapy represents a personalized cellular treatment modality for refractory solid tumors. Tumor-infiltrating lymphocytes are lymphocytes extracted directly from a patient's tumor tissue, with an innate ability to identify tumor neoantigens specific to the patient. Consequently, TIL therapy provides a highly individualized and targeted therapeutic option, which is distinguishable from conventional broad-spectrum therapies [24].

### 2.4 Immune System Modulators

Cytokines are vital immune mediators secreted by both immune and non-immune cells during stress, infection, or inflammation, aiding in swift and coordinated antigen-specific immune reactions. The discovery of interleukin-2 (IL-2) in 1976 established the groundwork for cytokine-based cancer treatment. IL-2 acts as a T-cell growth factor, facilitating the proliferation of T-cells both in vitro and in vivo, and high doses of IL-2 have been shown to cause tumor shrinkage in cases of metastatic cancer.

Interferon-alpha (IFN-$\alpha$) is another classic cytokine with direct anti-tumor effects that induce senescence and apoptosis and indirect immunostimulatory effects that stimulate dendritic cell maturation and strengthen T-cell cytotoxicity. Despite its clinical efficacy in malignancies such as melanoma and leukemia, high-dose IFN-$\alpha$ has restricted utility as monotherapy; notably, interferon receptor signaling itself drives upregulation of PD-L1 and PD-L2 on tumor cells [25], potentially counteracting its anti-tumor effects and providing a rationale for combined therapeutic strategies.

### 2.5 Other Novel Therapies

#### *2.5.1 Oncolytic Virus (OVs) Therapy*

Oncolytic viruses specifically multiply within and destroy cancer cells. Although OVs are capable of entering both normal and tumor cells, the deficiencies in antiviral signaling pathways, which are prevalent in tumors, establish a permissive milieu for viral replication. The resulting oncolysis not only destroys tumor cells directly but also releases tumor-associated antigens, danger-associated molecular patterns, and viral particles. This mechanism initiates a comprehensive anti-tumor immune reaction by activating antigen-presenting cells and virus-specific $CD8^+$T-cells [26].

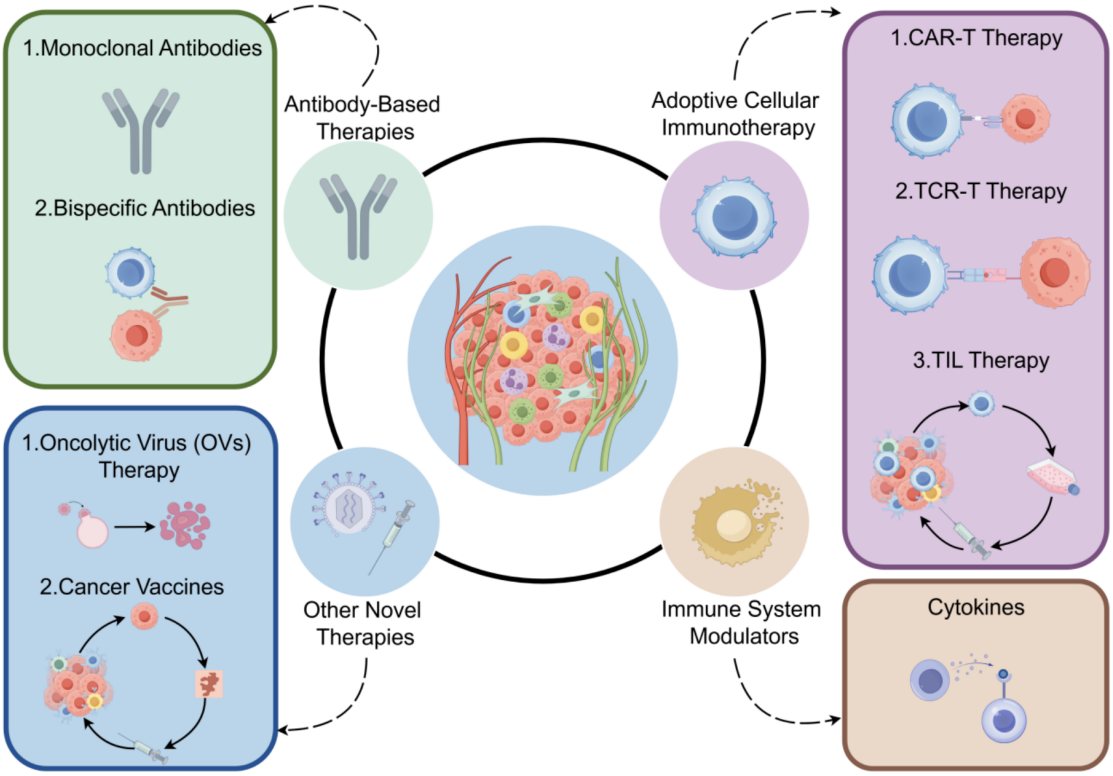


**Figure 1.** Overview of tumor immunotherapy strategies. The main approaches include antibody-based therapies, adoptive cellular immunotherapies, immune system modulators, and other novel therapies. Each strategy employs distinct mechanisms to enhance anti-tumor immunity.

#### *2.5.2 Cancer Vaccines*

Cancer vaccines for therapy aim to generate a robust, varied, and enduring group of tumor-specific $CD4^+$ and $CD8^+$ T-cells, including memory T-cells with stem-cell-like properties. Vaccines administer tumor antigens through cellular vectors, peptides, or nucleic acids, frequently in combination with adjuvants to comprehensively activate dendritic cells. After vaccination, dendritic cells (DCs) capture and process antigens, presenting them to $CD8^+$ and $CD4^+$ T-cells through MHC I and II. Through their T-cell receptors, naïve T-cells identify the MHC–antigen complex, and with additional co-stimulatory signals, they activate, proliferate, and transform into effector T-cells that travel to tumor locations to execute cytotoxic functions [27]. A schematic overview of these immunotherapeutic strategies is presented in Figure 1.

## 3 Mechanisms of Tumor Immunotherapy Resistance

Immunotherapy resistance can be broadly divided into two temporal categories: primary resistance, where tumors never respond to initial treatment due to pre-existing barriers, and acquired resistance, where tumors initially respond but later progress as new mechanisms emerge under therapeutic pressure. The following sections examine these two forms of resistance through two complementary dimensions—tumor-intrinsic factors and TME factors, distinguishing in each case the mechanisms that predate treatment from those that arise as its consequence.

### 3.1 Tumor-Intrinsic Factors

#### *3.1.1 Impaired Antigen Presentation*

In the context of tumor-intrinsic factors, primary resistance stems from pre-existing features such as defective antigen presentation (e.g., loss of MHC-I expression) and insufficient PD-L1 expression that collectively render tumor cells poorly immunogenic from the outset. Acquired resistance, by contrast, arises through treatment-induced adaptations, including acquired antigen presentation defects, epigenetic silencing, and metabolic rewiring, that enable tumor cells to evade an initially effective immune response. This section discusses these intrinsic mechanisms according to their temporal relationship with therapy.

The presentation of antigens is crucial for effective immune reactions against cancer. Cytotoxic T-cells are activated by MHC I molecules presenting tumor antigens, which aids in the destruction

of tumor cells; early evidence demonstrated that enhancing T-cell co-stimulatory signals through CTLA-4 blockade potentiates this antigen-driven anti-tumor response [28]. When the antigen presentation process is disrupted, it is linked to resistance to immunotherapy [29]. The mechanisms are as follows:

*Loss or Downregulation of MHC-I Molecules*

MHC-I plays a role in displaying antigens to cytotoxic T cells, so disruption in its components can weaken its ability to present neoantigens to TILs. Tumor cells employ multiple strategies to dysregulate MHC-I, thereby evading the immune system's attack [30]. Prior research has indicated that the $\beta$2-microglobulin (B2M) of MHC-I in melanoma becomes inactivated as a result of mutations, deletions, or loss of heterozygosity (LOH). Furthermore, B2M inactivation occurs more frequently in the group that does not respond to immune checkpoint blockade (ICB) therapy [31].

*Alterations in Antigen-Processing Activity*

MHC-I molecules intrinsically exhibit instability in the absence of peptide–antigen loading, and deficiency in antigen transport machinery such as TAP further compounds this instability by preventing stable MHC-I complex formation [32]. Consequently, tumor cells disrupt the process of presenting antigens by dysregulating the components of the antigen processing mechanism to evade the immune response. Empirical evidence indicates that several components of the antigen presentation mechanism are dysregulated in cancer. Earlier research has indicated that multiple components of the antigen processing machinery are dysregulated across diverse tumor types: loss of $\beta$2-microglobulin has been documented during melanoma metastatic progression [33], downregulation of HLA class I antigens has been associated with disease stage in ovarian carcinoma [34], and differential reduction of endoplasmic reticulum chaperones calnexin and calreticulin has been observed in metastatic melanoma [35], collectively demonstrating the breadth of antigen presentation defects that facilitate immune escape. Likewise, tumor cells evade the immune system owing to the insufficient expression of Tapasin [36, 37]. The lack of TAP is associated with problems in antigen presentation, which in turn impacts T cell activation. These antigen processing deficiencies operate within a broader immunosuppressive context, as the tumor microenvironment encompasses diverse cellular and non-cellular components that collectively impair immune cell function [38].

#### 3.1.2 *Insufficient PD-L1 Expression*

Patients with high PD-L1 expression and immune-cell infiltration demonstrate superior overall response rates (ORR) and progression-free survival (PFS) when treated with PD-1/PD-L1 blockade therapy [14]. Conversely, tumors characterized by low or undetectable PD-L1 levels frequently display resistance [39]. Studies confirm that low levels of PD-L1 are related to an unsatisfactory response to PD-1 inhibitors; for example, mutations in Janus kinase 1/2 (JAK1/2) lead to a loss of PD-L1 in melanoma and cause resistance to anti-PD-L1 treatment [40]. The relationship between PD-L1 expression and immunotherapy outcomes has evolved considerably as the field has advanced, with the clinical significance of PD-L1 as a predictive biomarker now well recognized across multiple tumor types [41]. Comprehensive assessment of PD-L1 expression across tumor cells and immune infiltrates, as well as emerging composite biomarker panels, has been reviewed in depth as a guide for patient stratification in immune checkpoint inhibitor therapy [42]. Therefore, evaluating PD-L1 is important for selecting patients and ensuring successful treatment.

Beyond insufficient PD-L1 expression, certain tumor genotypes can intrinsically program an immune-cold state that drives primary resistance to immunotherapy. The most well-characterized example is non-squamous NSCLC harboring co-mutations in STK11 and/or KEAP1. In these tumors, the immunosuppressive microenvironment is not merely a consequence of low tumor mutational burden or absent PD-L1, but rather an active consequence of oncogenic signaling. Mechanistically, STK11 loss suppresses STING-dependent innate immune sensing, impairing dendritic cell activation and subsequent T-cell priming, while KEAP1 mutations confer a cytoprotective, antioxidant program that blunts antitumor immunity and reinforces an immunosuppressive milieu [43, 44]. The resultant immune-cold phenotype, characterized by T-cell exclusion and a neutrophil-enriched stroma, defines a genomically distinct subset of NSCLC with de novo resistance to immune checkpoint blockade [45].

### 3.2 Tumor Microenvironment Factors

Similarly, the tumor microenvironment contributes to both forms of resistance. Primary resistance is often associated with an immune-excluded or immune-desert TME, characterized by poor T cell

infiltration, abundant immunosuppressive cells, a dense stromal barrier, and a gut microbiota composition that fails to support antitumor immunity at baseline. Acquired resistance involves dynamic TME remodeling under treatment pressure, including progressive T cell exhaustion driven by epigenetic and mitochondrial dysfunction, upregulation of alternative immune checkpoints, chemokine profile shifts, and dysregulated interferon signaling. This section examines the cellular and non-cellular components of the TME through this temporal lens, from tumor-infiltrating lymphocytes and B cells to metabolites and systemic modulators.

### 3.2.1 Cellular Components of TME

*Absence of Tumor-Infiltrating Lymphocytes*

Whether TILs are present or absent in TME can serve as a key marker of the immune response and the efficacy of immunotherapy [46]. Beyond classical lymphocyte-mediated recognition, phagocytic checkpoints such as the CD47–SIRP$\alpha$ axis represent an additional layer of immune evasion that shapes the overall immunological status of the tumor [47]. Tumor-infiltrating lymphocytes (TILs) within TME are essential for recognizing and targeting cancer cells. A lack of TILs might suggest that the tumor is an "immune desert type", which is marked by minimal immune response and is linked to cancers with poor outcomes [48]; notably, metabolic pathways such as $NAD^+$ metabolism sustain inducible PD-L1 expression on tumor cells, further entrenching this immune-excluded state [49]. Tumor mutational burden (TMB), DNA damage repair status, and expression of co-inhibitory ligands have emerged as key biomarkers for stratifying patients likely to respond to immunotherapy [50–54], while absence of TILs has also been associated with poor prognosis in colorectal cancer [30, 55], and genetic mechanisms of resistance to PD-1 blockade, including acquired mutations that impair T-cell recognition, have been characterized in detail [56]. In clinical settings, a lack of TILs is usually linked to a worse prognosis. Therefore, tumors with low TIL levels may exhibit greater aggressiveness and possess the ability to escape immune response [55]. Various studies have discovered different mechanisms linked to the prevention of cytotoxic T-cell infiltration into tumors, including metabolic control of immune checkpoint molecule expression—for instance, LAT2-mediated amino acid uptake regulates CD47 levels on tumor cells, enabling evasion of immune cell-mediated elimination [46]—as well as impaired antigen processing [29]. Increasing T-cell penetration into tumors to boost the success of anti-PD-L1 treatment continues to be a significant hurdle.

Thus, comprehending the mechanisms behind TILs deficiency in TME will aid in enhancing immune cell infiltration and creating targeted treatments. These approaches involve using medications to modify immunosuppressive environments or directly boosting the movement and function of TILs at tumor locations. Tailoring immunotherapy according to the presence or absence of TILs and altering the TME to enhance immune cell function are key areas of focus in immuno-oncology research, anticipated to improve cancer treatment outcomes. Nonetheless, inhibiting these mechanisms in cancer patients has not been extensively examined across various cancer types.

*T-Cell Dysfunction*

T cells within the tumor microenvironment frequently progress to a state of exhaustion—a hypofunctional condition characterized by sustained inhibitory receptor co-expression, impaired cytokine production, and diminished effector capacity—whose molecular and cellular underpinnings have been extensively characterized [57].

*a. Epigenetic Reprogramming* is pivotal to cancer development, progression, and immune system evasion. In contrast to gene mutations, epigenetic changes such as DNA methylation, histone modification, and chromatin remodeling can be reversed and are subject to dynamic regulation, rendering them promising targets for therapy. Notably, epigenetic dysregulation weakens antigen presentation and leads to T cell exhaustion, resulting in 'cold' tumors characterized by lymphocyte exclusion and enrichment of immunosuppressive cells. Among these, tumor-associated macrophages (TAMs) play a prominent role: CAR-T-cell-mediated depletion of immunosuppressive TAMs has been shown to promote endogenous antitumor immunity [58], and multiple therapeutic strategies targeting TAM polarization and survival are under active investigation [59].

*b. Mitochondrial Dysfunction* Effective cancer immunotherapy hinges upon the potent functionality of cytotoxic T cells. However, many tumors develop resistance to treatment due to T-cell exhaustion, a dysfunctional state characterized by decreased proliferation, weakened cytokine production, and lowered effector function. Mitochondria occupy the key position in T-cell metabolism and function, thereby playing a pivotal role at multiple stages of

the immune response. Tumor cell heterogeneity represents an additional layer of complexity: the rejection of immunogenic tumor clones is constrained by their clonal fraction within the tumor [60], tumor-cell-intrinsic factors underlie the heterogeneity of immune cell infiltration patterns [61], and UV-induced intratumoral heterogeneity in melanoma has been shown to diminish the overall immune response [62]. Furthermore, spatial analyses reveal that this heterogeneity drives distinct organizational patterns of the intratumoral immune landscape [63], collectively highlighting how tumor diversity impedes effective immune elimination.

*c. Spatial Metabolic Heterogeneity* In addition to tumor cell metabolism, the varied spatial metabolism of immune cells plays a crucial role in shaping anti-tumor immunity. Single-cell metabolic regulator analysis (scMEP) has identified cytotoxic T cells with tissue-specific metabolic inhibition in human colorectal cancer, showing metabolic differences compared with T cells confined to tumor-immune interface. The varied spatial metabolism highlights complex T-cell dysregulation in cancer. In parallel, systemic immune changes accompanying combination checkpoint blockade—such as early B cell alterations—can serve as predictive indicators of immune-related adverse events, underscoring the breadth of immune perturbations induced by these therapies [64].

*B cells and Tertiary Lymphoid Structures*
Beyond T cells, macrophages, and fibroblasts, the role of B cells and tertiary lymphoid structures represents a notable gap in the discussion of immunotherapy resistance. Regulatory B cells can promote an immunosuppressive microenvironment by secreting IL-10 and TGF-$\beta$, thereby inhibiting effector T cell function [65]. Furthermore, the functional maturation of TLS depends on specific signaling pathways. Sawada et al. [66] demonstrated that germinal center reactions within TLS require synergistic activation of STING and lymphotoxin-$\beta$ receptor pathways; without such signals, only immature lymphoid aggregates form, failing to produce IgG+ plasma cells and memory B cells essential for durable humoral immunity. Notably, Peyraud et al. [67] showed that even the presence of mature TLS in non-small cell lung cancer does not preclude primary resistance to immune checkpoint inhibitors, underscoring that TLS presence alone is insufficient to guarantee effective antitumor immunity. Together, these findings indicate that immunosuppressive B cell polarization, impaired TLS maturation, and functional incompetence of existing TLS represent underappreciated mechanisms of immunotherapy resistance.

*Cancer-Associated Fibroblasts (CAFs)*
In normal tissues, fibroblasts represent the predominant cell type within TME. These spindle-shaped cells are derived from the mesenchymal lineage. Within the extracellular matrix (ECM), a subset of fibroblasts persists in a quiescent or inactive state and does not actively engage in the production or renewal of ECM [68]. Nevertheless, these dormant fibroblasts may become activated under specific circumstances [69]. Activated fibroblasts diverge from resting cells in that their morphology and metabolism undergo alterations instigated by inflammatory stimuli, including wound healing signals, transforming growth factor-$\beta$ (TGF-$\beta$), interleukin-6 (IL-6), platelet-derived growth factor (PDGF), and hypoxia; the crosstalk between tumor cells and the TME is critical to this activation process and influences tumor progression. Reactive oxygen species (ROS) have the capacity to activate quiescent fibroblasts [68]. Upon activation, fibroblasts facilitate tissue remodeling by producing ECM components, secreting chemokines and cytokines, and creating forces at the tissue level. They are involved in encouraging epithelial cell differentiation, controlling immune reaction, and preserving tissue balance [69, 70].

In TME, activated fibroblasts transform into cancer-associated fibroblasts (CAFs), which play a crucial role in altering the extracellular matrix structure and may originate from normal fibroblasts. Growth factors such as TGF-$\beta$, PDGF, and FGF2 are secreted by immune and tumor cells to aid in their recruitment [70]. After being recruited, these CAFs can proliferate and expand, influenced by autocrine and paracrine involving other CAF populations [68]. TME can foster an immunosuppressive environment marked by a thick interstitium along with immunosuppressive cells and factors, often leading to limited initiation and infiltration of T cells [71]. TGF-$\beta$ is a key immunosuppressive cytokine that facilitates immune evasion and prevents the development of T-helper 1 (TH1) effector factor phenotypes [71].

CAFs are prevalent in TME and primarily produce TGF-$\beta$. High TGF-$\beta$ levels in CAFs are linked to T-cell exclusion in tumors and a weak response to the immune checkpoint inhibitor, atezolizumab [72]. TGF-$\beta$ prevents $CD4^+$ T lymphocytes from

multiplying by reducing IL-2 production and aids in converting naïve $CD4^+$ T lymphocytes into regulatory T cells (Tregs) [73, 74]. Furthermore, TGF-$\beta$ hinders the differentiation and antigen presentation of dendritic cells, thus blocking the effective activation of T cells [73]. Overall, TGF-$\beta$ significantly impairs anti-tumor immunity through affecting T cell function and differentiation, thereby stopping T cells from infiltrating tumors. Notably, certain immune cell populations can retain their antigen-presenting function even in the presence of TGF-$\beta$ and other immunosuppressive factors: CD40-activated B cells have been shown to be resistant to the suppressive effects of IL-10, TGF-$\beta$, and VEGF, suggesting their potential utility in circumventing the immunosuppressive TME [75]. Elucidating the function of TGF-$\beta$ in the immunosuppressive TME is pivotal to develop strategies to tackle the difficulties of cold tumors and enhance immunotherapy efficacy.

CAFs constitute a crucial element of the tumor matrix and exert a substantial promotional effect on tumor growth; this stromal dependency has been therapeutically exploited through tumor stroma-targeted antibody–drug conjugates that achieve localized anticancer drug release within the CAF-enriched matrix [76]. CAFs are mainly situated at the edge of the tumor and influence angiogenesis and metastasis by controlling ECM and secreting cytokines [77, 78]. This process turns the tumor boundary into an immune-cold area, which suppresses the immune response and hinders T cells from entering [77, 79]. CAFs mediate the exclusion and immunosuppression of T-cell by remodeling ECM, which serves as a physical obstacle [73]. Furthermore, CAFs secrete the C-X-C motif chemokine ligand 12 (CXCL12), which hinders T lymphocyte infiltration, as shown in a pancreatic cancer model [78, 80]. Moreover, CAFs can produce immunosuppressive molecules like TGF-$\beta$ and IL-6, which suppress T-cell activity [77].

*Tumor-Associated Macrophages (TAMs)*

Macrophages display remarkable plasticity and are subject to environmental influences. In the context of injury or infection, macrophages secrete pro-inflammatory factors, including tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-1 (IL-1), and nitric oxide, thereby triggering tissue remodeling and host defense. Tissue remodeling entails a critical transition between pro-inflammatory and anti-inflammatory macrophage subsets. Inadequate regulation of pro-inflammatory responses may result in autoimmune diseases or chronic inflammation [81].

Beyond their critical involvement in innate immune responses, macrophages play prominent roles in tumor immunity and represent important therapeutic targets; antibody-based strategies that modulate macrophage activity have emerged as a promising avenue in cancer immunotherapy [82]. Interestingly, in many types of cancer, tumor cells take advantage of these functions, using macrophages to aid their growth and development. Macrophages are vital in immune responses and tissue development due to their heterogeneity and diverse functions. However, their participation in cancer underscores the complex connection between the immune system and tumor cells.

Macrophage polarization is a key idea for categorizing on the basis of various surface markers triggered by particular environmental factors [83]. Macrophages are conventionally classified into M1 and M2 types. However, recent studies have shown that they actually exhibit a continuous spectrum of activation states across diverse disease and tissue-specific context, with M1 and M2 being the two ends of this spectrum [83]. M1 macrophages are regarded as classically activated, and they generate inflammatory substances that are essential for host protection and tumor eradication [82]. On the contrary, M2 macrophages release anti-inflammatory cytokines, primarily inhibiting inflammatory processes [84]. This M2 population is linked to immunosuppression in TME, aiding in tumor blood vessel formation, ECM remodeling, and wound healing [84]. TAMs are occasionally called M2-polarized macrophages, but it's critical to recognize that distinct TAM subsets are distributed along the M1-M2 polarization spectrum in this context [85]. As a crucial determinant of enhanced tumor activity, the exact positioning of TAMs within tumor tissues has been confirmed, wherein these cells are mainly distributed in the perivascular microenvironment or at the forefront of tumor invasive growth. Antibody-mediated targeting strategies can exploit this positioning to redirect TAM immunosuppressive activity toward antitumor functions [82]. Monocytes are mobilized to the invasive front, where they further differentiate into macrophages under the stimulation of signals from stromal and tumor cells. A variety of cytokines, chemokines, and growth factors play essential roles in stimulating monocyte recruitment, differentiation, and survival [68, 86].

TAMs exhibit diverse receptors, such as those from the TAM receptor tyrosine kinase family, including Tyro3, Axl, and MerTK. The immunosuppressive effects of TAMs in TME are largely regulated by these receptors. Recent studies have emphasized the importance of the TAM receptor tyrosine kinase family in promoting tumor activity [87–89]. Furthermore, the engagement of the cytokine CSF-1 with its receptor (CSF-1R) promotes the conversion of bone marrow cells into the immunosuppressive M2 macrophage phenotype. Using CSF-1R inhibitors to target TAMs has proven to be efficient to reduce the number of TAMs and consequently boosting the infiltration of effector lymphocytes, like $CD8^+$ T cells [90]. Targeted TAM therapy, by controlling the population and immunosuppressive function of TAMs, is expected to become a favorable approach for enhancing anti-tumor immune responses and increasing the effectiveness of cancer immunotherapy [91].

### 3.2.2 Non-Cellular Components of TME

*Chemokines*

Chemokines impact the immune response in TME by attracting immune cells, controlling tumor growth, and facilitating angiogenesis and metastasis [92]. CXCL9 and CXCL10 are capable of recruiting Th1 cells into TME, thereby inhibiting proliferation and reducing angiogenesis via interferon-$\gamma$ (IFN-$\gamma$) [93]. The infiltration of Th1 cells is linked to a positive prognosis in individuals with pancreatic and colon cancers [94]. CCL4 can recruit antigen-presenting dendritic cells (DCs) [95]. Conversely, chemokines such as CCL2 and CXCL8 (IL-8) can recruit MDSCs [95], which support tumor growth by generating angiogenesis factors, including transforming growth factor beta, platelet-derived growth factors (PDGFs), fibroblast growth factors (FGFs), and epidermal growth factors (EGFs) [96]. For instance, substances secreted by triple-negative breast cancer cells can trigger the production of CCL5 and VEGF in lymphatic endothelial cells, enhancing angiogenesis and metastasis [97].

*Abnormal Vascular Microenvironment*

The structure and function of blood vessels are altered by vascular endothelial growth factor, resulting in abnormal tumor vascular systems with reduced expression of endothelial cell adhesion molecules [98]. Lymphocyte infiltration into TME relies on adhesion molecules like ICAM-1, VCAM, and e-selectin, which are expressed by endothelial cells [99]. The deficiency of these molecules will impede T cell adhesion and transendothelial migration. For example, VEGF signaling in ovarian cancer promotes the infiltration of myeloid-derived suppressor cells (MDSCs), and anti-VEGF treatment can reverse this phenomenon [100]. Disrupted vascular function can also restrict the delivery of immunotherapy drugs. Endothelial cells in tumors that express PD-L1 and Fas ligands can deactivate cytotoxic T lymphocytes and promote the induction of Tregs [101]. The IL-6, TGF-$\beta$, VEGF and other factors secreted by these cells can inhibit T cell survival/activation and induce tumor-associated macrophages to polarize towards the immunosuppressive phenotype [100]. Moreover, hypoxia upregulates VEGF via hypoxia-inducible factor-1$\alpha$ (HIF-1$\alpha$), further aggravating immunosuppression [102].

*Dysregulated Interferon Signaling*

The interferon signaling pathway plays a vital role in triggering the immune response against tumors. Activated T cells express interferons when they interact with tumor antigens via MHC Class I-TCR complexes. The expression of PD-L1 in tumor cells and other cells within TME is driven by the type I interferon signaling pathway, which in turn suppresses the anti-tumor immune response [103]. Tumors impede interferon production or disrupt its signal transduction within TME through multiple mechanisms, including the subversion of pattern recognition receptor pathways that are essential for innate immune sensing and the initiation of antiviral and antitumor inflammatory responses [104]. This involves reducing the expression of interferon receptors to stop dendritic cells from activating T cells and/or increasing the infiltration of Treg cells. Disabling interferon receptors leads to changes in downstream signaling pathways, including the JAK-STAT pathway. Reduced interferon signaling is likely to lead to reduced activation of immune cells, decreased antigen presentation, as well as a general decline in immune response. Tumors that originally react positively to immunotherapy may undergo adaptive changes by creating ways to block interferon signaling, and it has been noted that JAK1/2 mutations can nullify this signaling, which gives rise to acquired drug resistance [105]. In summary, this indicates that drug resistance arises from the dysregulation of the interferon signaling pathway. This ability to adapt and resist drugs can result in tumor recurrence, manifested as a reduced sensitivity of the tumor to immunotherapy.

*Metabolites*

Cancer cells have developed metabolic adaptations as a key strategy to escape immune detection [106]. As

cancer advances from a premalignant state to invasive disease, metabolic changes emerge, which facilitate cancer cells in evading immune surveillance [106]. A variety of studies have shown that cancer cells undergo metabolic alterations when nutrients are present, which weakens immune responses [107].

It is noteworthy that metabolic alterations (such as increased glycolysis [108] and reduced oxidative phosphorylation [109]) can affect immune cell function and promote immune escape [110]. Moreover, numerous studies have demonstrated that cancer cells generate metabolites such as lactic acid [111], kynurenine [112], adenosine [113], and acetate [115], which are associated with the impaired functions of natural killer cells and cytotoxic T cells, as well as antigen-presenting cells, thus inhibiting the immune response against tumors. The ectoenzymes CD39 and CD73 play a pivotal role in this process by catalyzing the extracellular conversion of ATP to immunosuppressive adenosine within the tumor microenvironment [114]. The efficacy of anti-CTLA-4 therapy depends in part on Fc-mediated depletion of tumor-infiltrating regulatory T cells within the microenvironment [116]. Notably, combination immune checkpoint blockade can also perturb humoral immunity, as evidenced by early B cell changes that presage autoimmune complications [64].

Moreover, the struggle for metabolic resources in TME plays a vital part in the resistance to immunotherapy, with both T cells and tumor cells vying for glucose and oxygen. This competition in metabolism might speed up cancer progression and limit the display of MHC Class I antigens [117–119]. Additional studies have shown that immune checkpoint blockade (ICB) antibodies aimed at cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) can restore glucose in TME, facilitating T-cell glycolysis and interferon-$\gamma$ (IFN-$\gamma$) production [117, 120]. The critical role of metabolic restriction in modulating T cell activity within tumors is prominently emphasized by these results. Furthermore, the expression of immune checkpoint molecules is controlled by metabolic checkpoints, including HIFs and mTOR, which in turn exerts an additional regulatory effect on the activity of immune cells in the TME [119].

In an effort to furnish further evidence supporting the association between metabolism and immunosuppression, a mechanistic investigation demonstrated that acetate, a metabolite enriched in the tumor microenvironment, reprogrammes tumor metabolism and drives PD-L1 upregulation through c-Myc activation, thereby promoting immune evasion [115]. Chang et al. [121] extended this notion by showing that L-asparaginase, conventionally employed in the treatment of leukemia, engenders an unfavorable TME through the consumption of asparagine. In compassionate-use trials for patients with metastatic nasopharyngeal carcinoma, this combination therapy alongside pembrolizumab led to decreased tumor burden and prolonged progression-free survival [121].

Taken together, existing research underscores the complex interplay between the metabolic processes of tumor cells and immune cells, which is pivotal in driving immune evasion as well as therapeutic resistance to immunotherapy [118, 122–124]. Moreover, other cells in the TME, such as CAFs, also play a role in this metabolic reprogramming, affecting the success of immunotherapy [125].

*Gut Microbiota*

Beyond the local tumor microenvironment factors discussed above, the gut microbiota has emerged as a systemic hub that remotely shapes antitumor immunity and contributes to immunotherapy resistance. The gut microbiota influences treatment outcomes through multiple mechanisms that converge on the TME. Specific bacterial taxa, such as *Akkermansia muciniphila*, *Bifidobacterium spp.*, and *Faecalibacterium*, produce short-chain fatty acids and tryptophan metabolites that enhance $CD8^+$ T cell effector function, promote dendritic cell maturation, and strengthen intestinal barrier integrity [126]. Conversely, dysbiosis—characterized by the loss of butyrate-producing commensals and expansion of opportunistic pathobionts—disrupts the gut barrier, facilitates lipopolysaccharide translocation, and fuels systemic chronic inflammation, thereby driving the expansion of regulatory T cells and myeloid-derived suppressor cells that establish an immunosuppressive TME [126, 127]. Furthermore, inter-individual variation in baseline microbiota composition has been linked to the risk of immune-related adverse events and to an "efficacy–toxicity coupling effect," wherein patients harboring specific phyla may simultaneously experience better antitumor responses and higher toxicity, highlighting the importance of microbiota-based patient stratification [127]. Collectively, the gut microbiota represents a therapeutically modifiable component of the TME, offering microbiota-directed strategies to overcome

immunotherapy resistance.

## 4 Potential Therapies to Overcome Immunotherapy Resistance

As summarized in Figure 2, resistance to immunotherapy arises from a complex interaction of tumor-cell adaptations, TME immunosuppression, and host immune status [128]. To address this bottleneck, multi-pronged strategies focusing on combination therapies and precision medicine are being actively explored.

### 4.1 Personalized Immunotherapy

Personalized neoantigen vaccines embody the principle of precision immunotherapy by tailoring interventions to the unique mutational landscape of each patient's tumor. Braun et al. [129] recently provided key evidence for this strategy in a phase I trial in clear cell renal cell carcinoma, a tumor type with low mutational burden. By integrating whole-exome and RNA sequencing, the authors constructed individualized neoantigen panels targeting key driver mutations—including VHL, PBRM1, and BAP1—which resulted in 77.8% of patients generating T cell responses that recognized autologous tumor cells, with no disease recurrence at a median follow-up of 40.2 months. These findings offer initial evidence that individually tailored immune interventions can overcome the limited efficacy of conventional vaccines targeting non-specific antigens.

However, two major bottlenecks remain. First, current prediction algorithms prioritize neoantigen peptides of which only approximately 6% are ultimately recognized by patient T cells [130], highlighting that accurate identification of individualized neoantigens—the very foundation of precision immunotherapy—requires substantial improvement. Second, data from Braun et al. [129] themselves reveal that while the vaccine induced highly specific T cell immunity, it concurrently triggered systemic upregulation of immunosuppressive molecules such as PD-1, VEGFA, and LAG3. This demonstrates that precise immune activation provokes a set of universal immunosuppressive feedback mechanisms, indicating that vaccine precision alone is insufficient to guarantee therapeutic efficacy. Therefore, the development of personalized vaccines must evolve from "precise targeting" to "precise combination"—tailoring the addition of immune checkpoint inhibitors or anti-angiogenic agents according to the suppressive pathways upregulated in each patient, thereby achieving comprehensive and dynamic precision immunotherapy.

### 4.2 Combined Immunotherapy

Tumor immunotherapy is increasingly moving away from using a single biomarker like PD-L1 for patient selection, towards personalized treatment approaches that consider the tumor's immune microenvironment. The body's immune response to tumors is dynamic and variable, and the complex regulatory network of immune checkpoints and their ligands makes it challenging to accurately predict therapeutic efficacy using just one indicator.

The clinical optimization of lifileucel, the first tumor-infiltrating lymphocyte (TIL) therapy approved for solid tumors, offers an instructive paradigm for combination immunotherapy. In the pivotal C-144-01 study, 5-year follow-up data showed that lifileucel monotherapy produced durable responses (median duration of response, 36.5 months; 5-year overall survival, 19.7%) in patients with advanced melanoma refractory to anti-PD-1 and targeted therapy, yet the objective response rate (ORR) was 31.4% [131]. Notably, when lifileucel was combined with the PD-1 inhibitor pembrolizumab as frontline therapy, the ORR rose to 65.2% with a complete response rate of 30.4% [131]. This marked improvement—from 31.4% to 65.2%—establishes combination with immune checkpoint inhibitors as a central strategy for advancing TIL therapy. The mechanistic rationale is underscored by Katsikis et al. [130], who delineated the multiple barriers confronting antitumor T cells within the tumor microenvironment—including immunosuppression, T cell exclusion, and PD-1-driven T cell exhaustion—regardless of how they were induced, positioning immune checkpoint inhibitors as the most mechanistically grounded partner for combination regimens. Together, these clinical and mechanistic insights point to a converging direction: the synergistic combination of adoptive cell therapy and immune checkpoint blockade is emerging as a critical next dimension in solid tumor immunotherapy.

## 5 Discussion

Tumor immunotherapy signifies a paradigmatic transformation in cancer therapy, which is focused on stimulating the body's immune response to eliminate cancerous growths. This review has thoroughly outlined key strategies, such as adoptive cell therapies and immune-checkpoint inhibitors, and explored the significant clinical issue of therapeutic resistance.

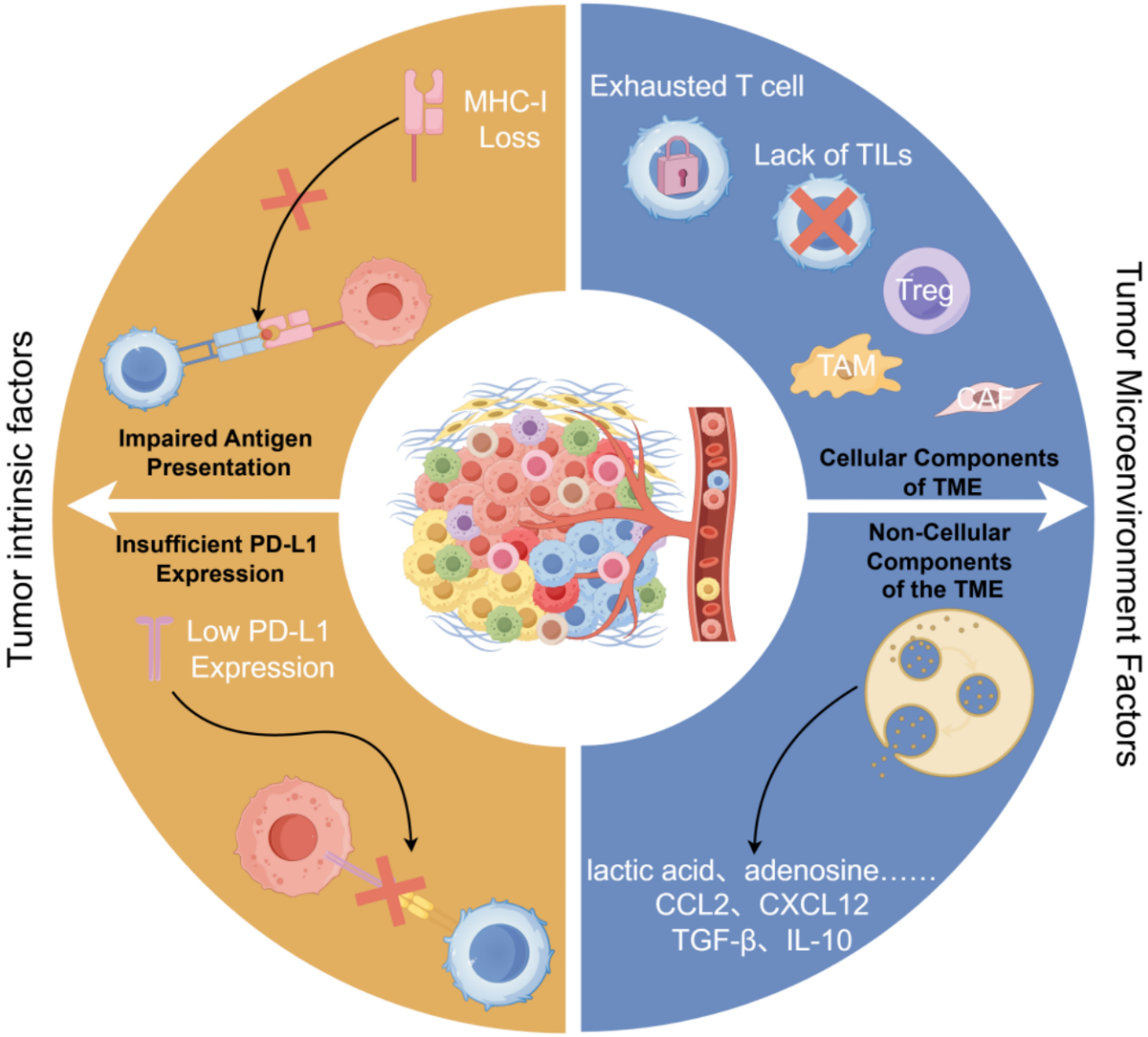


**Figure 2.** Mechanisms of resistance to tumor immunotherapy. Resistance arises from both tumor-intrinsic factors (e.g., MHC-I loss, low PD-L1) and extrinsic immunosuppression within TME (TME). Key cellular components include exhausted T cells, tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), and regulatory T cells (Tregs). Non-cellular factors such as abnormal vasculature, immunosuppressive metabolites, and dysregulated cytokine networks further hinder immune attack.

Evidently, resistance arises from a complex interplay between the inherent adaptations of tumor cells and the multi-layered immunosuppressive network of the TME.

From the perspective of tumor cells themselves, they directly evade T-cell recognition by down-regulating or losing MHC-I molecules and disrupting antigen processing and presentation mechanisms, which constitutes the basis of "immune neglect". Meanwhile, tumor cells modulate the levels of immune checkpoint molecules dynamically. They can either lead to primary drug resistance due to insufficient expression or induce acquired drug resistance under therapeutic stress through up-regulation of expression, glycosylation modification, or by taking advantage of senescence and other states. These intrinsic mechanisms cause tumor cells to attenuate the initiation and efficacy of immune responses at the source.

Conversely, as a functional entity, the immunosuppressive characteristics of TME represent another significant factor contributing to drug resistance. This encompasses the following aspects: 1) Functional impairments of immune effector cells, such as inadequate T-cell infiltration, functional exhaustion, and metabolic dysregulation; 2) The

accumulation of immunosuppressive cells such as TAMs, CAFs, Tregs, and MDSCs creates an immunosuppressive environment by secreting factors like TGF-$\beta$. Abnormal physicochemical microenvironments, such as structurally disorganized and functionally defective vascular systems that impede immune cell infiltration, hypoxia, acidosis, and disrupted interferon signaling pathways, collectively constitute a series of barriers.

Confronted with this intricate challenge, the future direction for overcoming drug resistance is bound to move towards multi-mechanism joint intervention and highly individualized strategies. Combination therapy aims to reverse immunosuppression via synergistic effects. For example, the combination of ICI and anti-angiogenic drugs can improve T-cell infiltration. Combined with epigenetic drugs, it can reverse T-cell exhaustion and reprogram immunosuppressive cells. When combined with targeted metabolic or cytokine therapies, it can ameliorate the metabolic state of TME. A more advanced strategy is to develop novel immunomodulators or optimize cell therapies. It is important to recognize that certain combination therapies intended to enhance treatment response or overcome resistance may unintentionally elevate the risk of immune-related adverse events. Therefore, a thorough understanding of the mechanisms underlying each treatment challenge remains essential for making informed and rational decisions when selecting appropriate combination therapies—decisions that aim to maximize patient benefits while minimizing risks, both now and in the future.

However, the optimization of the combined protocol cannot rely solely on experience; it must be based on a precise analysis of the drug resistance mechanism. The focus of future research should lie in the utilization of advanced technologies like single-cell multi-omics, spatial transcriptomics, and liquid biopsy to conduct dynamic and real-time monitoring of the immune microenvironment and molecular typing of patients during the treatment process. This not only enables the identification of different immunophenotypes such as “hot tumors”, “cold tumors” or “immune rejection type” tumors, but also accurately identifies the dominant drug resistance pathways, thereby tailoring subsequent treatment strategies for patients and achieving a true transformation from a “one-size-fits-all” approach to a “tailored policy for each individual”. For example, for tumors with MHC-I loss, drugs that restore MHC-I expression can be used in combination or MHC-non-restrictive therapies can be adopted instead; for tumors mainly characterized by T-cell depletion, the combination of epigenetic regulators or mitochondrial function agonists can be given priority.

In summary, drug resistance in tumor immunotherapy represents a dynamic, real - time feedback, and systemic challenge. The resolution does not solely rely on the development of novel targets and medications. Rather, comprehensively grasping the dynamic interplay between tumors and the immune system is of vital importance. Based on this understanding, a personalized treatment system capable of real - time feedback and precise intervention should be established. Only by closely integrating the in - depth insights from basic research with the individualized requirements of clinical practice can drug resistance be effectively surmounted, ultimately extending the survival duration of patients and enhancing their quality of life.

## 6 Conclusion

Tumor immunotherapy has witnessed remarkable progress; however, resistance persists as a significant constraint. Resistance arises from complex tumor-intrinsic mechanisms and an extensively immunosuppressive microenvironment. Future research ought to focus on clarifying the specific molecular and cellular basis of resistance and utilizing high-throughput technologies for dynamic monitoring and precise classification. Through rational combination therapies and highly personalized treatment strategies, it might be possible to reverse or prevent resistance, transforming immunologically "cold" tumors into "hot" ones, thus improving patient outcomes. Ultimately, transitioning to an individualized treatment paradigm based on real-time mechanistic analysis and precise intervention is crucial for surmounting immunotherapy resistance and enhancing its effectiveness.

## Data Availability Statement

Not applicable.

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## Conflicts of Interest

Shaoquan Zheng served as an Editor-in-Chief, and Jieying Liang served as an Associate Editor of the *Oncology Communications* at the time of manuscript submission. To ensure the integrity of the peer-review process, neither Shaoquan Zheng nor Jieying Liang was involved in the editorial handling, peer review, or decision-making process for this manuscript, which was handled independently by another editor. The remaining authors declare no conflicts of interest.

## AI Use Statement

The authors used AI for language polishing during the preparation of this manuscript.

## Ethical Approval and Consent to Participate

Not applicable.

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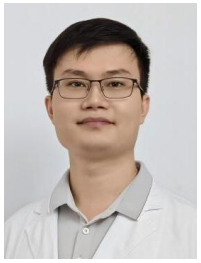

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