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Mechanisms of Resistance to Cancer Immunotherapy: A Host–Tumor Interaction Perspective; A Review Article

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, yet a substantial proportion of patients develop primary or acquired resistance. Understanding the mechanisms underlying this resistance is critical for improving therapeutic outcomes. This review comprehensively examines resistance mechanisms to cancer immunotherapy through a host–tumor interaction perspective, integrating tumor-intrinsic factors, the immunosuppressive microenvironment, and systemic host characteristics.

Main Findings: Resistance arises from multiple interconnected mechanisms: (1) tumor-intrinsic defects, including impaired antigen presentation, aberrant oncogenic signaling (MAPK, PI3K/AKT/mTOR, and WNT/β-catenin pathways), and metabolic reprogramming; (2) tumor-extrinsic factors, including immunosuppressive immune cells (MDSCs, Tregs, and M2 macrophages), physical barriers, and metabolic competition; and (3) systemic host factors, including gut microbiome composition and HLA polymorphisms. These mechanisms collectively create a formidable barrier to effective antitumor immunity.

Conclusions: A comprehensive understanding of this multimodal crosstalk is essential for developing effective strategies to overcome resistance. Rational combination therapies targeting multiple nodes within the cancer-immunity cycle, informed by patient-specific resistance profiles, represent a promising approach to improve immunotherapy efficacy and expand the population of responders.

1 | Introduction

Over the past decade, cancer immunotherapy, particularly the use of immune checkpoint inhibitors (ICIs), has emerged as a transformative treatment modality, fundamentally altering the prognosis for patients with a wide array of advanced cancers [1]. By targeting inhibitory pathways that restrain T-cell activity, such as those mediated by cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), ICIs can unleash the body's own immune system to

Abbreviations: APM, antigen processing and presentation machinery; B2M, beta-2-microglobulin; CAF, cancer-associated fibroblast; CAR-T, chimeric antigen receptor T cell; CI cycle, cancer-immunity cycle; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DAMP, damage-associated molecular pattern; DNMT, DNA methyltransferase; ECM, extracellular matrix; EZH2, enhancer of zeste homolog 2; FAP, fibroblast activation protein; FMT, fecal microbiota transplantation; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; HLA, human leukocyte antigen; ICI, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon-gamma; IL, interleukin; JAK, Janus kinase; LAG-3, lymphocyte activation gene 3; LOH, loss of heterozygosity; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MSI-H, microsatellite instability-high; mTOR, mammalian target of rapamycin; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SCFA, short-chain fatty acid; TAM, tumor-associated macrophage; TAP, transporter associated with antigen processing; TGF-β, transforming growth factor-beta; TIL, tumor-infiltrating lymphocyte; TIM-3, T-cell immunoglobulin and mucin domain-containing-3; TLR, Toll-like receptor; TMB, tumor mutational burden; TME, tumor microenvironment; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; VISTA, V-domain Ig suppressor of T-cell activation.

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recognize and eliminate malignant cells, leading to durable responses and improved long-term survival in a subset of patients [2]. Since the landmark approval of ipilimumab in 2011, the field has expanded exponentially, with ICIs now approved for more than 50 cancer types and indications [3].

Despite these unprecedented successes, the clinical benefit of ICIs is not universal. A substantial number of patients display primary resistance, where their tumors are inherently nonresponsive to treatment from the outset. Others experience acquired resistance, where an initial positive response is followed by tumor relapse and progression after a variable period of disease control [4]. Objective response rates vary significantly across different cancer types, ranging from as high as 40%–70% in malignancies such as melanoma, Hodgkin's lymphoma, and microsatellite instability-high (MSI-H) tumors to as low as 10%–25% in many common solid tumors such as pancreatic cancer, prostate cancer, and glioblastoma. This heterogeneity in response underscores the complex biological barriers that limit the efficacy of immunotherapy and highlights the urgent need to understand the mechanisms underlying resistance [5].

Initial research into resistance mechanisms focused heavily on tumor-cell-intrinsic factors, such as the loss of neoantigens or defects in antigen presentation machinery. However, it is now increasingly clear that resistance is a multifactorial phenomenon orchestrated by a dynamic and bidirectional crosstalk between the tumor and the host. This intricate host–tumor interaction spans multiple biological scales, from the molecular landscape of the cancer cell to the cellular composition of the tumor microenvironment (TME) and systemic factors unique to each patient [6]. The tumor does not exist in isolation but is embedded within a complex ecosystem that includes stromal cells, blood vessels, extracellular matrix components, and a diverse array of immune cells. Moreover, systemic factors such as the composition of the gut microbiome, genetic polymorphisms in the host immune system, and even lifestyle factors can profoundly influence the response to immunotherapy [7].

This review aims to provide a comprehensive analysis of the mechanisms of resistance to cancer immunotherapy, framed within the context of the host–tumor interactome. We will first outline the cancer-immunity cycle as a conceptual framework for understanding how antitumor immunity can fail at multiple steps. We will then delve into the specific tumor-intrinsic and tumor-extrinsic mechanisms of resistance, emphasizing their interconnectedness and the ways in which they collectively create a formidable barrier to effective immune-mediated tumor control. Finally, we will discuss current therapeutic strategies and future perspectives aimed at overcoming these resistance pathways, with a focus on rational combination approaches that target multiple nodes within the host–tumor interaction network to broaden the reach and impact of cancer immunotherapy.

2 | The Cancer-Immunity Cycle: A Framework for Resistance

The effective eradication of cancer cells by the immune system can be conceptualized as a cyclical process known as the cancer-immunity cycle, first described by Chen and Mellman. This elegant framework divides the antitumor immune response into seven sequential steps that, when functioning properly, create a self-amplifying loop of tumor destruction. The cycle begins with the release of cancer cell antigens after tumor cell death. These antigens are then captured by dendritic cells (DCs) and other antigen-presenting cells (APCs), which migrate to draining lymph nodes to present the processed antigens to naive T cells via MHC molecules. Upon recognition of tumor antigens, T cells become activated and undergo clonal expansion. The activated effector T cells then traffic through the bloodstream to the tumor site, where they must extravasate from blood vessels and infiltrate the tumor parenchyma [8, 9]. Finally, the effector T cells recognize and bind to cancer cells displaying their cognate antigens on MHC Class I molecules, leading to the targeted killing of tumor cells. This killing releases additional tumor antigens, thereby propagating the cycle and amplifying the immune response [10].

ICIs primarily act to reinvigorate this cycle at specific checkpoints that have evolved to prevent autoimmunity but are coopted by tumors to evade immune destruction. Anti-CTLA-4 antibodies, such as ipilimumab, function primarily during the priming and activation phase of T cells in the lymph nodes, blocking the inhibitory signal delivered when CTLA-4 on T cells binds to B7 ligands on APCs. This blockade enhances T-cell activation and promotes the expansion of tumor-reactive T-cell clones. In contrast, anti-PD-1/PD-L1 antibodies work predominantly at the effector phase within the TME, preventing the engagement of PD-1 on T cells with its ligand, PD-L1, on tumor cells or myeloid cells, thereby restoring the cytotoxic function of exhausted T cells [10, 11].

Resistance to ICIs arises when one or more steps in this cycle are fundamentally broken or severely impaired, rendering the tumor nonresponsive to checkpoint blockade. For instance, if a tumor has a low mutational burden and consequently generates few neoantigens, the initial step of antigen release may be insufficient to prime a robust T-cell response. If the TME is devoid of functional DCs or if these cells are rendered tolerogenic by immunosuppressive signals, antigen presentation will be compromised. Physical barriers created by dense stromal tissue can prevent T-cell infiltration, whereas metabolic competition and the production of immunosuppressive metabolites can inhibit T-cell function even if they successfully reach the tumor. Therefore, the cancer-immunity cycle provides a valuable framework for categorizing and understanding the diverse mechanisms of resistance, which can be broadly divided into tumor-intrinsic factors that affect the cancer cells themselves and tumor-extrinsic factors that involve the microenvironment and systemic host characteristics [12].

2.1 | The Host–Tumor Nexus: A Central Hub of Resistance

Central to this review is the concept of the "host–tumor nexus," which we define as the dynamic molecular and cellular interface where tumor-intrinsic factors and host-related mechanisms converge to determine the outcome of antitumor immunity.

Rather than viewing these mechanisms as independent processes, the nexus framework emphasizes their interdependence. This nexus operates at multiple biological scales and is organized around several key hubs, including the direct tumor–immune cell interface, the metabolic competition between tumor and immune cells, the complex cytokine/chemokine signaling network, and the systemic–tumor interface where factors such as the gut microbiome exert their influence. Understanding resistance through this lens highlights that effective therapeutic strategies must target multiple hubs simultaneously to disrupt the interconnected network of immune evasion [13, 14].

3 | Tumor-Intrinsic Mechanisms of Resistance

Tumor-intrinsic resistance encompasses a range of alterations within the cancer cells themselves that enable them to evade immune recognition and attack (Figure 1). These mechanisms can be broadly categorized into defects in antigen presentation, aberrant oncogenic signaling, metabolic reprogramming, and epigenetic silencing [15].

3.1 | Impaired Antigenicity and Antigen Presentation

Effective T-cell-mediated tumor rejection requires that cancer cells present tumor-associated antigens, particularly neoantigens arising from somatic mutations, on their surface via major histocompatibility complex (MHC) Class I molecules. A failure in any step of this pathway, from neoantigen generation to peptide presentation, represents a key mechanism of immune escape and resistance to immunotherapy [16].

3.1.1 | Low Neoantigen Burden

The quantity and quality of neoantigens are critical determinants of tumor immunogenicity. Tumors with a low tumor mutational burden (TMB), such as certain pediatric malignancies and some adult cancers such as prostate cancer and glioblastoma, generate fewer neoantigens and are thus less visible to the immune system. Consequently, these tumors are often referred to as immune-cold tumors. Immune-cold tumors are characterized by a paucity of tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, and a generally noninflamed, immunosuppressive microenvironment that limits the efficacy of checkpoint blockade [17].

In contrast, tumors with high TMB, such as melanoma, non-small-cell lung cancer (NSCLC) associated with tobacco exposure, and mismatch repair-deficient (dMMR) tumors, are more likely to respond to checkpoint blockade [9]. However, it is now understood that not all mutations are equally immunogenic, and the quality of neoantigens—their ability to bind MHC molecules and be recognized by T cells—may be more important than sheer quantity. Thus, some high-TMB tumors fail to respond, suggesting that TMB is an imperfect biomarker. This strong correlation led to the tissue-agnostic approval of pembrolizumab for any solid tumor with high TMB, a landmark decision in personalized medicine [18].

3.1.2 | Defects in Antigen Processing and Presentation Machinery (APM)

Even in tumors with a high neoantigen load, resistance can arise from defects in the APM. This complex machinery includes the proteasome, which degrades intracellular proteins into peptides; the transporter associated with antigen processing (TAP), which

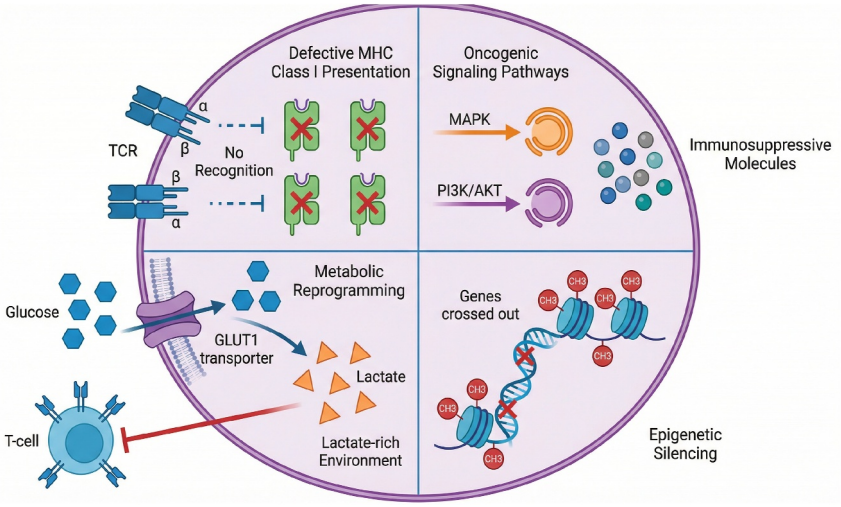

FIGURE 1 | Tumor-intrinsic resistance mechanisms. Cancer cells employ multiple intrinsic mechanisms to evade immunotherapy. (1) Defective antigen presentation occurs through loss of MHC Class I molecules or impaired neoantigen generation, preventing T-cell recognition. (2) Aberrant oncogenic signaling through MAPK and PI3K/AKT pathways promotes immune evasion by producing immunosuppressive molecules and downregulating immune-related genes. (3) Metabolic reprogramming, particularly aerobic glycolysis, depletes glucose and produces lactate, creating a hostile environment for T cells. (4) Epigenetic modifications, including DNA methylation and histone modifications, silence immune-related genes such as those encoding chemokines and antigen presentation machinery.

translocates peptides into the endoplasmic reticulum; and the MHC Class I heavy chain and β2-microglobulin (B2M), which form the peptide-MHC-I complex. Loss-of-function mutations in the B2M gene are a well-documented mechanism of acquired resistance, leading to a complete loss of MHC-I surface expression and rendering tumor cells invisible to CD8+ T cells [19]. Similarly, downregulation of other APM components, such as TAP1, TAP2, or the immunoproteasome subunits, through genetic or epigenetic mechanisms, can impair antigen presentation and contribute to resistance [20].

3.1.3 | Impaired Interferon Signaling

The interferon-gamma (IFN-γ) signaling pathway is a central regulator of antitumor immunity. IFN-γ, secreted by activated T cells and NK cells, induces the expression of numerous genes involved in immune surveillance, most notably by upregulating MHC Class I expression on tumor cells. Genetic defects in the IFN-γ pathway, such as loss-of-function mutations in the receptors (IFNGR1/2) or the downstream signaling molecules (JAK1, JAK2, and STAT1), can render tumor cells insensitive to IFN-γ, allowing them to evade immune recognition and resist immunotherapy [21].

3.2 | Aberrant Oncogenic Signaling Pathways

Oncogenic pathways that drive tumor growth and survival can also actively promote an immunosuppressive state and mediate resistance to immunotherapy. These pathways not only confer a growth advantage to cancer cells but also reshape the TME to favor immune evasion.

3.2.1 | MAPK Pathway

The mitogen-activated protein kinase (MAPK) pathway, frequently activated through mutations in BRAF or RAS genes, is a key driver of immune evasion. MAPK signaling increases the production of immunosuppressive cytokines such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), which can inhibit DC maturation and promote the recruitment of immunosuppressive myeloid cells. Furthermore, MAPK pathway activation has been associated with reduced T-cell infiltration into tumors and an increase in the expression of PD-L1, creating a more immunosuppressive microenvironment [22].

3.2.2 | PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR pathway is another critical oncogenic signaling cascade that is frequently dysregulated in cancer. Aberrant activation of this pathway contributes to resistance by promoting the expression of PD-L1 on tumor cells, increasing the production of immunosuppressive factors such as transforming growth factor-beta (TGF-β), and inhibiting T-cell function and infiltration [14]. The mTOR pathway also regulates the metabolism of both tumor cells and immune cells, and its hyperactivation in tumors can create a metabolically hostile environment that suppresses T-cell activity [23].

3.2.3 | WNT/β-Catenin Pathway

Activation of the WNT/β-catenin signaling pathway has emerged as a potent driver of immune exclusion in tumors. Tumors with active WNT/β-catenin signaling often exhibit a lack of T-cell infiltration, a phenotype referred to as an "immune desert." This phenotype is characterized by the physical exclusion of T cells from the tumor parenchyma, where immune cells may be present in the surrounding stroma but fail to infiltrate the tumor bed, rendering the core of the tumor immunologically ignorant. Mechanistically, WNT/β-catenin signaling in tumor cells has been shown to inhibit the production of chemokines, such as CCL4, that are necessary for the recruitment of conventional Type 1 dendritic cells (cDC1s) and, subsequently, T cells into the tumor [24]. In non-small-cell lung cancer and melanoma, oncogenic MAPK signaling, loss of antigen presentation machinery, and immunosuppressive myeloid infiltration frequently coexist, collectively driving resistance to immune checkpoint blockade [6].

3.3 | Metabolic Reprogramming

Cancer cells undergo profound metabolic changes to support their rapid proliferation. This metabolic reprogramming not only fuels tumor growth but also creates a TME that is hostile to infiltrating immune cells, particularly T cells.

3.3.1 | Aerobic Glycolysis (Warburg Effect)

A hallmark of cancer metabolism is the preferential use of glycolysis for energy production, even in the presence of oxygen, a phenomenon known as the Warburg effect. This high rate of glucose consumption by tumor cells leads to a glucose-depleted TME. T cells, particularly activated cytotoxic T cells, rely heavily on glycolysis to meet their bioenergetic demands. When glucose is scarce, T cells are unable to sustain their effector functions, leading to T-cell exhaustion or anergy. Moreover, the glycolytic byproduct, lactate, accumulates in the TME and creates an acidic environment that further suppresses T-cell function [25].

3.3.2 | Hypoxia

The rapid proliferation of cancer cells often outpaces the formation of new blood vessels, leading to regions of hypoxia within the tumor. Hypoxia is a potent driver of immune evasion and resistance to immunotherapy. Under hypoxic conditions, tumor cells upregulate hypoxia-inducible factors (HIFs), which transcriptionally activate genes involved in angiogenesis, metabolic adaptation, and immune suppression. Hypoxia has been shown to promote the downregulation of MHC Class I molecules on tumor cells and to promote the recruitment and activation of immunosuppressive cell types such as MDSCs and TAMs [26].

3.4 | Epigenetic Alterations

Epigenetic modifications, including DNA methylation and histone modifications, play a critical role in regulating gene expression. In cancer, aberrant epigenetic changes can silence genes involved in antitumor immunity, creating an "immune-cold" phenotype that is resistant to ICIs. DNA methylation and histone modifications: Hypermethylation of CpG islands in the promoter regions of genes involved in antigen presentation, chemokine production (e.g., CXCL9 and CXCL10), and IFN-γ signaling can lead to their transcriptional silencing. Similarly, repressive histone modifications, catalyzed by enzymes such as histone deacetylases (HDACs) and the histone methyltransferase EZH2, can compact chromatin and prevent the expression of immune-related genes. EZH2-mediated silencing of genes involved in antigen presentation and T-cell chemotaxis has been implicated in resistance to immunotherapy. The reversibility of these epigenetic modifications makes them attractive therapeutic targets. For instance, epigenetic silencing of IFN-γ pathway components can render tumors immune-cold, a phenotype that may be reversed by epigenetic modulators, thereby restoring sensitivity to ICIs. Clinical trials combining these agents with checkpoint blockade are ongoing [18, 27].

3.4.1 | Integrative Synthesis

Tumor-intrinsic mechanisms do not operate in a vacuum. They actively shape the tumor microenvironment, creating a self-reinforcing loop of immune evasion. For example, the metabolic reprogramming of tumor cells toward glycolysis results in a lactate-rich, acidic environment. This lactate is not merely a waste product; it is a key signaling molecule that fuels the immunosuppressive functions of MDSCs and TAMs, directly linking an intrinsic metabolic shift to the establishment of an extrinsic cellular barrier. Similarly, epigenetic silencing of chemokine genes within the tumor cell prevents the recruitment of effector T cells, creating an "immune desert" that is impervious to immunotherapy. This intricate crosstalk underscores that targeting only the tumor cell is often insufficient; a successful therapeutic strategy must also address the immunosuppressive niche that the tumor cell cultivates [3].

4 | Tumor-Extrinsic and Host-Related Mechanisms of Resistance

Although tumor-intrinsic factors are critical, resistance to immunotherapy is frequently driven by factors outside the cancer cell, originating from the complex TME and the host's systemic environment (Figure 2).

4.1 | The Immunosuppressive Tumor Microenvironment

The TME is a complex ecosystem composed of cancer cells, stromal cells, and a diverse array of immune cells. In many tumors, this environment is profoundly immunosuppressive, actively preventing effective antitumor immune responses.

4.1.1 | Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are a heterogeneous population of immature myeloid cells that expand dramatically in cancer and exert potent immunosuppressive effects. They suppress antitumor immunity through multiple mechanisms, including the depletion of amino acids essential for T-cell function (e.g., arginine), the production of reactive oxygen species (ROS), and the promotion of regulatory T cell (Treg) expansion [20]. Their abundance in the TME and peripheral blood is strongly correlated with poor outcomes in patients receiving immunotherapy [28]. Therapeutic strategies targeting MDSCs, such as inhibitors of CXCR2 (e.g., navarixin) or CSF-1R (e.g., pexidartinib), are in clinical trials. Regulatory T cells (Tregs): Tregs are a specialized subset of CD4+ T cells that play a critical role in maintaining immune homeostasis. However, their accumulation in the TME contributes to immune suppression and resistance to immunotherapy. Tregs suppress antitumor immunity through the secretion of immunosuppressive cytokines (e.g., IL-10 and TGF-β), the expression of inhibitory receptors such as CTLA-4, and the modulation of DC function. Tumor-associated macrophages (TAMs): Macrophages in the TME are often polarized toward an M2-like phenotype. These M2-like TAMs promote tumor growth, angiogenesis, and immune suppression. Agents targeting TAMs, such as CSF-1R inhibitors (which block macrophage survival and differentiation) and CD40 agonists (which can repolarize TAMs to an antitumor M1 phenotype), are under active investigation. They secrete factors such as VEGF and immunosuppressive cytokines such as IL-10 and TGF-β, and

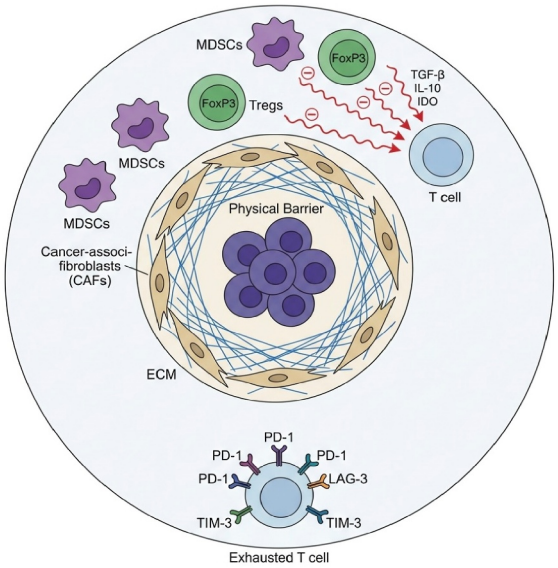

FIGURE 2 | Tumor-extrinsic resistance mechanisms. The immunosuppressive tumor microenvironment creates multiple barriers to effective antitumor immunity. Myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) secrete inhibitory cytokines (TGF-β, IL-10, and IDO) that render cytotoxic T cells anergic and dysfunctional. Cancer-associated fibroblasts (CAFs) produce dense extracellular matrix (ECM) that physically restricts T-cell infiltration into the tumor core. Exhausted T cells upregulate compensatory immune checkpoints (LAG-3 and TIM-3) beyond PD-1, leading to sustained T-cell dysfunction despite PD-1 blockade.

they express high levels of PD-L1, contributing to T-cell exhaustion [29].

4.1.2 | Cancer-Associated Fibroblasts (CAFs)

CAFs are a major component of the tumor stroma and play a multifaceted role in tumor progression and immune evasion. CAFs secrete extracellular matrix proteins, creating a dense, fibrotic stroma that acts as a physical barrier to T-cell infiltration. They also secrete a variety of cytokines and growth factors, including TGF-β and CXCL12, which can promote tumor growth and immune suppression [20]. Therapeutic agents targeting CAF-related pathways, such as inhibitors of FAP (e.g., sibrotuzumab) or TGF-β, are in clinical development.

4.1.3 | Compensatory Upregulation of Alternative Immune Checkpoints

After treatment with PD-1 or CTLA-4 blockade, tumors can adapt by upregulating alternative immune checkpoint molecules on T cells, such as LAG-3, TIM-3, and TIGIT. The coexpression of multiple inhibitory receptors on T cells is a hallmark of T-cell exhaustion, and the blockade of a single checkpoint may be insufficient to fully restore T-cell function [12].

4.2 | Systemic Host Factors

Beyond the tumor and its immediate microenvironment, systemic factors inherent to the host play a crucial role in shaping the response to immunotherapy.

4.2.1 | The Gut Microbiome

The composition of the gut microbiome has emerged as a key modulator of systemic immunity and the efficacy of ICIs. Dysbiosis, an imbalance in the microbial community, has been linked to poor ICI response, whereas enrichment of specific bacterial taxa, such as *Akkermansia muciniphila*, *Bifidobacterium* species, and *Faecalibacterium prausnitzii*, is associated with enhanced antitumor immunity and improved clinical outcomes. Mechanistically, the microbiome influences systemic immunity through the production of metabolites such as short-chain fatty acids (SCFAs), modulation of immune cell maturation, and by providing microbe-derived adjuvants that can prime the immune system [30]. Recent preclinical and clinical advances have shown that interventions such as fecal microbiota transplantation (FMT) from responder to nonresponder patients can restore ICI sensitivity, highlighting the translational significance of this axis [7].

4.2.2 | Host Genetics (HLA Genotype)

The diversity and heterozygosity of an individual's human leukocyte antigen (HLA) Class I genes are critical determinants of the breadth of the neoantigen repertoire that can be presented to T cells. Studies have shown that a higher degree of HLA heterozygosity is associated with improved survival in patients treated with ICIs, likely because it allows for the presentation of a wider array of tumor antigens.

4.2.3 | Integrative Synthesis

The extrinsic and host-related factors form a complex, interactive network that ultimately determines the fate of the antitumor immune response. The immunosuppressive cells within the TME, such as MDSCs and Tregs, are not merely passive inhabitants but are actively recruited and shaped by tumor-intrinsic oncogenic pathways. For example, MAPK signaling in tumor cells can drive the production of cytokines that recruit MDSCs. In turn, these extrinsic factors can exert selective pressure on the tumor, promoting the outgrowth of tumor cell clones with enhanced resistance mechanisms, such as those that have lost MHC expression. This bidirectional crosstalk highlights the need for therapeutic strategies that can disrupt multiple components of this resistance network simultaneously [31].

4.3 | Functional Heterogeneity of TME Populations

It is crucial to recognize that major TME components (e.g., TAMs, CAFs, MDSCs, and Tregs) are not homogeneous populations. Recent advances from single-cell and spatial profiling have revealed that these cell types exist in multiple functional states that can differentially influence immunotherapy resistance. For instance, tumor-associated macrophages (TAMs) exist along a spectrum from proinflammatory (M1-like) to immunosuppressive (M2-like) phenotypes, with most tumors containing a mixture of states. Similarly, distinct subsets of cancer-associated fibroblasts (CAFs) have been identified, including those that physically exclude T cells versus those that secrete immunosuppressive cytokines. This functional heterogeneity, shaped by the local microenvironment, means that targeting these populations requires a nuanced understanding of their context-dependent roles [32].

5 | Summary of Resistance Mechanisms and Therapeutic Targets

To provide a consolidated overview, Table 1 summarizes the key resistance mechanisms discussed, their classification, the type of resistance they mediate, and the potential therapeutic strategies being explored.

6 | Combination Strategies to Overcome Resistance: A Cancer-Immunity Cycle Framework

Rational combination approaches that target multiple, complementary nodes within the cancer-immunity cycle offer the greatest promise for overcoming resistance (Figure 3). We organize these strategies according to the specific steps of the cycle they aim to repair.

6.1 | Enhancing Antigen Release and Presentation (Steps 1–2)

To address a lack of tumor antigenicity, therapies that induce immunogenic cell death, such as certain chemotherapies and radiation therapy, can be combined with ICIs. This increases the pool of tumor antigens available for presentation. Furthermore, therapeutic cancer vaccines (e.g., personalized neoantigen vaccines) are designed to directly boost the presentation of tumor-specific antigens, enhancing T-cell priming when combined with checkpoint blockade [33].

6.2 | Enhancing T-Cell Priming and Activation (Step 3)

For tumors where T-cell priming is insufficient, dual checkpoint blockade (e.g., anti-CTLA-4 + anti-PD-1) has proven effective by

TABLE 1 | Summarizes the key resistance mechanisms.

Mechanism	Category	Resistance type	Evidence level	Potential therapeutic strategies (examples)
Antigen presentation defects				
Low tumor mutational burden (TMB)	Intrinsic	Primary	Clinical	Neoantigen vaccines, chemotherapy/radiotherapy
B2M/HLA mutations	Intrinsic	Acquired	Clinical	NK cell-based therapies, T-cell redirecting therapies
IFN-γ pathway defects (JAK1/2)	Intrinsic	Acquired	Clinical	STING agonists, Type I IFN therapy
Oncogenic signaling				
MAPK pathway activation	Intrinsic	Primary/ acquired	Clinical	BRAF/MEK inhibitors (e.g., dabrafenib and trametinib)
PI3K/AKT/mTOR pathway activation	Intrinsic	Primary/ acquired	Clinical	PI3K inhibitors (e.g., alpelisib), mTOR inhibitors
WNT/β-catenin pathway activation	Intrinsic	Primary	Preclinical/ clinical	WNT inhibitors (e.g., porcupine inhibitors)
Metabolic reprogramming				
Glycolysis/lactate production	Intrinsic	Primary	Preclinical/ clinical	Lactate dehydrogenase (LDH) inhibitors, MCT inhibitors
Hypoxia	Intrinsic/ extrinsic	Primary	Preclinical/ clinical	HIF inhibitors, antiangiogenic agents (e.g., bevacizumab)
Epigenetic silencing				
DNA/histone modifications	Intrinsic	Primary	Preclinical/ clinical	DNMT inhibitors (e.g., azacitidine), HDAC inhibitors (e.g., vorinostat)
Immunosuppressive TME				
Myeloid-derived suppressor cells (MDSCs)	Extrinsic	Primary/ acquired	Clinical	CXCR2 inhibitors (e.g., navarixin), CSF-1R inhibitors
Regulatory T cells (Tregs)	Extrinsic	Primary/ acquired	Clinical	Anti-CTLA-4 (depletion), CCR4 antagonists
M2-like tumor-associated macrophages (TAMs)	Extrinsic	Primary	Clinical	CSF-1R inhibitors (e.g., pexidartinib), CD40 agonists
Cancer-associated fibroblasts (CAFs)	Extrinsic	Primary	Preclinical/ clinical	FAP inhibitors (e.g., sibrotuzumab), TGF-β inhibitors
Alternative checkpoints				
Upregulation of LAG-3, TIM-3, and TIGIT	Extrinsic	Acquired	Clinical	Dual checkpoint blockade (e.g., anti-LAG-3 [relatlimab])
Systemic host factors				
Gut dysbiosis	Host	Primary	Clinical	Fecal microbiota transplantation (FMT), probiotics
HLA genotype (low heterozygosity)	Host	Primary	Clinical	(No direct therapy), biomarker for stratification

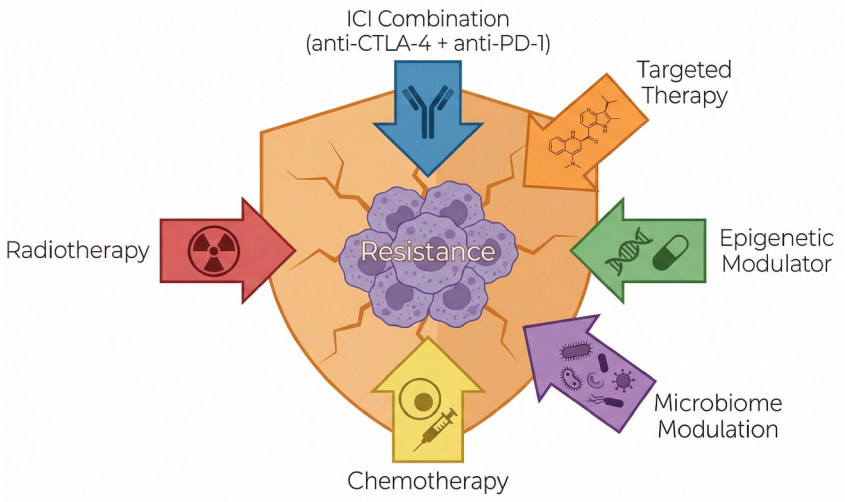

FIGURE 3 | Combination strategies to overcome immunotherapy resistance. A multipronged therapeutic approach is required to overcome the complex resistance mechanisms. Combination strategies include dual immune checkpoint inhibitor (ICI) combinations targeting CTLA-4 and PD-1; integration with targeted therapies that inhibit oncogenic pathways; chemotherapy and radiotherapy to induce immunogenic cell death; epigenetic modulators to restore the expression of silenced immune genes; and microbiome modulation to enhance systemic antitumor immunity. These complementary approaches work synergistically to dismantle the resistance shield and restore effective antitumor immune responses.

blocking two distinct inhibitory signals. Additionally, agonistic antibodies targeting costimulatory molecules (e.g., CD40 and OX40) can further enhance T-cell activation [33, 34].

6.3 | Overcoming T-Cell Infiltration Barriers (Step 4)

In "immune-desert" tumors, strategies are needed to promote T-cell trafficking. This includes therapies targeting the fibrotic stroma created by CAFs (e.g., FAP inhibitors) or agents that modulate chemokine signaling to attract T cells. Antiangiogenic therapies (e.g., anti-VEGF) can also facilitate T-cell infiltration by normalizing tumor vasculature.

6.4 | Targeting the Immunosuppressive Microenvironment (Steps 5–7)

Once T cells infiltrate the tumor, their function can be stifled by the TME. Strategies to counter this include therapies that deplete or reprogram immunosuppressive cells, such as CSF-1R inhibitors to target TAMs and CXCR2 antagonists to block MDSC recruitment. Metabolic modulators (e.g., IDO inhibitors) can also alleviate the metabolically hostile environment.

6.5 | Targeting Tumor-Intrinsic Resistance Pathways

Combining ICIs with targeted therapies that inhibit oncogenic pathways (e.g., BRAF/MEK inhibitors in melanoma) can simultaneously reduce tumor growth and reverse pathway-driven immune evasion. As discussed, epigenetic modulators (DNMTis and HDACis) can also be used to reverse the silencing of immune-related genes within the tumor cells themselves [35].

6.5.1 | Limitations of Current Regimens

Although promising, combination therapies significantly increase the risk of immune-related adverse events (irAEs) and financial toxicity. Furthermore, acquired resistance to combination therapies remains a challenge, often involving the emergence of tumor clones with complete loss of antigen presentation machinery (e.g., B2M mutations), representing a terminal resistance mechanism.

6.6 | Epigenetic and Microbiome Modulation

The reversibility of epigenetic modifications makes them attractive therapeutic targets. Epigenetic modulating agents, such as DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis), can enhance tumor immunogenicity by reversing the silencing of immune-related genes, including those involved in antigen presentation (e.g., MHC Class I) and T-cell recruitment (e.g., chemokines). This can effectively convert an immune-cold tumor into an immune-hot phenotype. Crucially, clinical data now support this strategy; for instance, the combination of azacitidine (a DNMTi) with nivolumab has demonstrated improved patient outcomes in certain hematologic malignancies. Similarly, combinations of HDAC inhibitors with ICIs have shown promise in early clinical trials by enhancing T-cell infiltration and function. These findings provide clinical validation for targeting the epigenome to overcome immunotherapy resistance [36].

6.6.1 | Microbiome Modulation

Given the critical role of the gut microbiome in modulating immunotherapy response, strategies to favorably alter the microbiome are being actively pursued. These include fecal

microbiota transplantation (FMT) from responders to non-responders, probiotic supplementation, and dietary interventions [7].

6.6.2 | Limitations of Current Regimens

Although promising, combination therapies significantly increase the risk of immune-related adverse events (irAEs) and financial toxicity. Furthermore, acquired resistance to combination therapies remains a challenge, often involving the emergence of tumor clones with complete loss of antigen presentation machinery (e.g., B2M mutations), representing a terminal resistance mechanism.

7 | Biomarkers for Patient Stratification: Mapping to Resistance Mechanisms

Identifying robust predictive biomarkers is essential for personalizing immunotherapy. The future lies in integrating biomarkers that map onto distinct resistance pathways.

7.1 | Biomarkers of Antigenicity

Tumor mutational burden (TMB) and specific neoantigen signatures serve as proxies for tumor immunogenicity. Low TMB or a lack of high-quality neoantigens predicts resistance due to a failure in Step 1 of the cancer-immunity cycle.

7.2 | Biomarkers of Antigen Presentation

Mutations in the antigen presentation machinery (APM), such as loss-of-function mutations in B2M, can be detected in ctDNA and predict resistance by indicating a failure in Step 2 of the cycle [37].

7.3 | Biomarkers of T-Cell Infiltration

Gene expression signatures (e.g., IFN-γ signature) and spatial profiling can classify tumors as "immune inflamed" versus "immune desert." This classification directly reflects whether T-cell infiltration (Step 4) is a key barrier and can guide the use of therapies aimed at overcoming T-cell exclusion [37].

7.4 | Biomarkers of Microenvironmental Suppression

The abundance of specific immunosuppressive cell populations (e.g., MDSCs and Tregs) or the expression of alternative checkpoints (e.g., LAG-3 and TIM-3) can indicate resistance driven by the TME (Steps 5–7).

7.5 | Systemic Biomarkers

Gut microbiome features (e.g., high diversity and the presence of favorable taxa) and host HLA genotype can predict systemic immune fitness and the capacity to mount an effective anti-tumor response.

By integrating these multimodal biomarkers, a comprehensive picture of an individual's resistance profile can be assembled, enabling the rational selection of tailored combination therapies [38].

8 | Conclusion

Resistance to cancer immunotherapy is a complex, multifactorial challenge arising from the dynamic dialog within the host–tumor nexus. This review has framed resistance not as a series of isolated defects but as a deeply interconnected network of tumor-intrinsic, microenvironmental, and systemic host factors that can disrupt the cancer-immunity cycle at any step. The main findings underscore that a "one-size-fits-all" approach to immunotherapy is insufficient. Key limitations in the current field include an incomplete understanding of the temporal evolution of resistance and the substantial heterogeneity of immune responses across different cancer types and patients. In future research, the focus must be on developing and applying advanced multiomics and spatial profiling technologies to create high-resolution maps of the resistance landscape in individual patients. This will enable the identification of dominant resistance nodes and inform the rational design of personalized combination therapies. Clinically, this implies a shift away from empirical combinations toward biomarker-guided strategies. The clinical implications are significant: By prospectively identifying resistance mechanisms, we can select therapies that directly target those vulnerabilities, thereby improving efficacy while minimizing unnecessary toxicity. The goal is to develop curative therapeutic strategies by integrating novel immunotherapies, targeted agents, and host-modulating approaches into rational combinations that can overcome the formidable challenge of resistance and extend the benefits of immunotherapy to all patients with cancer.

Author Contributions

Mohammed Elmujtba Adam Essa conceived and designed the study. Mohammed Elmujtba Adam Essa, Abdelkareem A. Ahmed, and Hamid Noori performed the literature search, data extraction, and quality assessment. Mohammed Elmujtba Adam Essa performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to the interpretation of the data and critical revision of the manuscript. All authors read and approved the final manuscript.

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