Volume 4, Issue 2, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

OVERCOMING IMMUNOTHERAPY RESISTANCE IN CANCER: MOLECULAR MECHANISMS, PREDICTIVE BIOMARKERS, AND EMERGING THERAPEUTIC STRATEGIES

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DOI: https://doi.org/10.5281/zenodo.18490858

Keywords

Article History
Received: 05 December 2025
Accepted: 20 January 2026
Published: 05 February 2026

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Abstract

The treatment of various cancers has been transformed through cancer immunotherapy, which has been able to produce lasting and, in some instances, curative responses even in the face of the more traditional therapies of surgery, radiotherapy, and chemotherapy. The incumbent modalities, which are immune checkpoint inhibitors, adoptive cell therapies, cancer vaccines, cytokine-based platforms, and oncolytic viruses, have achieved unprecedented clinical efficacy, specifically in melanoma, lung cancer, and hematologic malignancies. Despite these developments, long-term clinical efficacy is only attainable in a small group of patients, with primary and acquired resistance being the most significant obstacles in achieving long-term effectiveness and expansive clinical implementation.

The phenomenon of immunotherapy resistance is a complicated and dynamic interplay of tumor-intrinsic changes, immune evasion strategies, and immunosuppressive tumor microenvironmental conditions, which are also caused by host-related factors, including microbiome composition and genetic diversity.

Volume 4, Issue 2, 2026

Frontier in Medical & Health Research

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The current and novel predictive biomarkers, including tumor-based, immune-associated, genomic, transcriptomic, and liquid biopsy, are subjectively discussed in their role to narrow patient stratification and precision immunotherapy. Moreover, new treatment approaches that can overcome resistance are also mentioned, such as rational combination regimens, inhibition of new immune checkpoints and costimulatory pathways, metabolic and epigenetic reprogramming, microbiome-based interventions, and neoantigen-based personalized therapies. Together, these observations provide the map for improving the sustainability, efficiency, and individualization of cancer immunotherapy and define immunotherapy resistance as an opportunity to be addressed instead of an unavoidable disadvantage.

Introduction:

Cancer is a multidimensional and complex illness, which is the unchecked proliferation and division of the abnormal body cells (Kumari 2024). These cells may infiltrate and destroy neighboring tissues and organs and can potentially move to the other parts of the body via the blood or lymphatic system, a process called metastasis (Khalaf et al., 2024). Cancer occurs due to genetic and epigenetic changes that interfere with the usual mechanisms of cell division, survival, and differentiation, with uncontrolled proliferation, invasion, and metastasis (Ashraf et al., 2022). It ranks among the causes of death in the world, as it has no control of growth, invasion, and metastasis. Cancer is a mammoth disease burden in the world: around 19-20 million new cases and about 9.7-10 million deaths were reported each year in 2020-2022, which is approximately one in six deaths worldwide, costing about USD 3303.81 in low- or middle-class income countries (Bray et al., 2024; Morgan et al., 2023; Ashraf et al., 2025). It is already the major cause of death before 70 years of age in most countries and is expected to be the predominant cause of premature deaths in the world in this century (Jamison et al., 2024). The demographic aging, population increase, and growing nature of lifestyle- and environment-based risk factors like smoking, obesity, physical inactivity, and chronic infection are the factors that are stimulating the rising cancer burden. As a result, this rate would rise significantly; 35 million new cases will be estimated annually by 2050, which would create a serious urgent situation and necessitate effective prevention, early diagnosis, and better treatment approaches.

The mainstream cancer treatments existing in the market today are mostly comprised of surgery, radiotherapy, and chemotherapy, which are the three fundamental pillars of cancer treatment in the world (Zafar et al., 2025). Surgery is still a crucial and possibly a curative treatment option in most early-stage solid tumors, but a significant percentage of patients are now diagnosed with locally advanced or with metastatic disease, meaning that surgery cannot cure them (Liu et al., 2024; Wu et al., 2024). Positive surgery margins and undetected micrometastatic disease often recur after resection, and access and expertise disparities further restrict results in all parts of the world (Sparrer et al., 2025). Radiotherapy is highly used in curative and palliative contexts, as it is associated with better local tumor control in cancerous conditions in the rectum and gastrointestinal tract and cardiotoxicity, which is limited by radioresistance development due to tumor hypoxia and inherent tumor biology (Wu et al., 2023). As a treatment method, chemotherapy still remains a cornerstone against many cancers, but it is not tumor specific and instead destroys quickly dividing healthy cells, thereby causing significant systemic toxicity (Cavalcanti et al., 2021; Swanton et al., 2024). Its clinical use is also constrained by drug resistance, low bioavailability, and incomplete tumor elimination, which lead to recurrence and poor survival of cancers like lung, breast, pancreatic, and advanced gastric cancer.

Immunotherapy of cancer has evolved to include initial cytokine-based therapeutic approaches and

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

the development of therapies based on therapeutic vaccines to include immune checkpoint therapy (ICI) blockers, chimeric antigen receptor (CAR)-T-cells, oncolytic viruses, and rational combination therapy to achieve breakthroughs and longer-lasting responses in melanoma, lung cancer, and other malignancies (Said & Ibrahim, 2023; Zhu et al., 2021; Afzal et al., 2025). ICIs targeting Programmed Cell Death Protein-1 (PD-1) and Programmed Death-Ligand 1 (PD-L1) and Cytotoxic T-Lymphocyte-Associated Antigen 4 (CTLA-4) have become the new standard of care in various solid tumors, whereas CAR-T cell therapy has seen its most successful application in hematologic malignancies; vaccines and cytokines are mainly adjunct or niche therapies (Noor et al., 2025; Zhang et al., 2025). Notwithstanding these progressions, it is observed that close to 20-40% of patients respond to ICIs with lasting clinical benefit, whereas above 60-70% of patients are primary non-responders or ultimately relapse, which makes therapeutic resistance the main limitation of immunotherapy (Wang et al., 2025; Vitale et al., 2025). The overall survival and complete remission rates are significantly reduced by resistance despite the traditional understanding of it as immunotherapy-sensitive cancer (Aldea et al., 2021; van Elsas et al., 2020). Primary (intrinsic) resistance is typified by a lack of meaningful response despite an adequate exposure to treatment and is usually correlated with low tumor mutational burden, low neoantigenicity, an uninflamed or cold tumor microenvironment (TME), and a prevailing immunosuppressive cell or cytokine network (Perez-Ruiz et al., 2020; Vitale et al., 2025). In comparison, adaptive resistance occurs during treatment, when an initially effective immune response is suppressed by the activation of immune-evasion strategies, e.g., by switching alternative checkpoints or PD-L1 induced by interferon-g (and others), etc. (Aldea et al., 2021; Kim et al., 2022). Secondary (acquired) resistance is a subsequent response or acquired disease containment and is associated with tumor antigen loss, impairments of antigen presentation machinery, mutations in IFN-gamma signaling, T-cell exclusion, remodeling of the TME metabolism and stroma, and gut microbiota alterations, which are important factors that highlight the complexity and dynamic nature of immunotherapy resistance (Kluger et al., 2023; Saleh and Elkord, 2020).

In the article, the multifactorial nature of cancer immunotherapy resistance is discussed by uniting the existing knowledge of its underlying molecular and cellular mechanisms, especially tumor-intrinsic changes, immune evasion mechanisms, and the immunosuppressive tumor microenvironment. It also discusses known and new predictive biomarkers, which can stratify patients, predict therapeutic response, and make decisions on individual treatment. Lastly, the review identifies new and emerging therapeutic approaches, such as combination immunotherapies, modulation of the tumor microenvironment, metabolic and microbiome-associated factors, and next-generation cellular and biologic strategies to overcome resistance and enhance the duration and breadth of immunotherapy responses in cancer of varying types.

Overview of Cancer Immunotherapy Modalities:

Antitumor T-cell responses are suppressed and can be replenished with the help of the ICIs targeting CTLA-4 and the PD-1/PD-L1 axis, which has transformed the treatment of cancer (Zabeti Touchaei & Vahidi 2024). In the lymphoid organs, CTLA-4 takes over early T-cell priming through competence with the costimulatory receptor, CD28, but in the peripheral tissues and tumor microenvironment, PD-1 signaling suppresses the functions of effector T-cells, which promotes T-cell exhaustion and immune escape (Cheng et al., 2024; Hong and Maleki Vareki, 2022). Monoclonal antibodies targeting these checkpoints have now shown durable clinical efficacy in a variety of solid and hematologic cancers, and further trials of complementary stages of T-cell activation (combined with monoclonal antibodies) have shown superior responses, but with more toxicity and immune-related toxicity (Pophali et al., 2024; Johnson et al., 2022). Simultaneously, adoptive cell therapies (ACT) denote another type of immunotherapeutic approach that includes the ex vivo cloning or genetic modification of the

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ISSN: (e) 3007-1607 (p) 3007-1593

tumor-surveillance T cells, like CAR-T cells or tumor-infiltrating lymphocytes, and their reinfusion to enhance the antitumor immunity (Liu et al., 2025; Gazzoni et al., 2025). Collectively, ICIs and ACT emphasize the key role of T-cell-mediated immunity in cancer cell control and additionally point to the resistance, toxicity, and lack of efficacy issues in some tumor settings.

Adoptive cell therapies include a number of T-cell-based approaches that aim at maximizing antitumor immunity by ex vivo manipulation and transplantation of tumor-responsive lymphocytes (Nguyen & Youn 2025). Genetically engineered chimera antigen receptor (CAR)-T cells are genetically engineered to express engineered synthetic receptors to mediate HLA-independent recognition of tumor surface antigens, which allow powerful cytotoxicity and long-term memory responses and have demonstrated remarkable complete response rates in refractory B-cell malignancies but are limited by toxicities, such as cytokine release syndrome and neurotoxicity, and lower efficacy in solid tumors because of antigen heterogeneity and immunosuppressive checkpoint signaling (Abbasi et al., 2023; Katiyar et al., 2023). T-cell receptor-engineered T cells (TCR-T), on the other hand, use high-affinity, HLA-restricted receptors that retain physiological TCR signaling and enable targeting of intracellular and neoantigens, introducing reliance on antigen processing and HLA compatibility (Mehta et al., 2025; Dolton et al., 2023). Tumor-infiltrating lymphocyte (TIL) therapy is based on the proliferation of autologous, tumor-resident T cells, which are inherently enhanced in terms of tumor specificity and have proven to have a durable clinical efficacy in melanoma but have been explored in other solid tumors; the approach is limited by the complexity of manufacture, as well as functional suppression by immune checkpoints within the tumor microenvironment (Wiertsema et al., 2025; Barras et al., 2024).

Activation of the immune system can be achieved in relation to tumor-associated antigens or patient-specific neoantigens to provide long-lasting antitumor immunity using a wide range of platforms: peptide-based, nucleic acid-based, dendritic cell (DC) vaccines, whole-cell vaccines, and viral or oncolytic vectors (Papavassiliou et al., 2025; Mukerjee et al., 2025) Although prophylactic viral vaccines, including those applied against HPV and HBV, have been extremely successful in preventing cancer caused by virus exposure, therapeutic cancer vaccines have not been equally successful in the clinic, with DC-based and neoantigen-based approaches demonstrating higher T-cell priming and immunogenicity in preclinical models and in early clinical trials (Ahmed et al., 2025; Aggeletopoulou et al., 2025). Tumor-cell autologous vaccines offer a wide range of antigens and are undergoing further clinical trials, but viral vectors and oncolytic viruses have the added advantage of serving as immune adjuvants (Fan et al., 2023). Simultaneously, cytokine-based cancer immunotherapy has now developed into the next generation of engineered cytokines targeting antitumor efficacy without systemic adverse events, similar to how prior methods used IL-2 and IFN-a, albeit with high toxicity (Yi et al., 2024; Zhang et al., 2025). Among them, it is worth mentioning modified versions of IL-2, IL-12, and IL-15 with better tumor-targeting properties and therapeutic control of the ability of pro-tumor cytokines, including IL-6 and some IL-12 family members, and demonstrating a complicated but promising role in the formation of effective and strong anticancer immune responses (Cini et al., 2023; Balkhi et al., 2025).

The oncolytic virus (OV)-based therapeutic approach can be regarded as a special category of cancer immunotherapy, which includes direct cell killing of tumors and a significant stimulation of immune response (Tian et al., 2022). OVs specifically infect and replicate in malignant cells, which induces immunogenic cell death and the release of tumor antigens and danger-associated molecular patterns that facilitate antigen presentation and transform immunologically "cold" tumors into hot tumors (Khosravi et al., 2024; Zhang et al., 2025). A prime example of clinical validation of this approach is the oncolytic herpes simplex virus T-VEC that expresses GM-CSF and is approved by the FDA as an in situ

Frontier in Medical & Health Research
Volume 4, Issue 2, 2026
ISSN: (e) 3007-1607 (p) 3007-1593

tumor vaccine and has proven effective in melanoma (Volovat et al., 2024). Numerous viruses, including herpes simplex virus, adenovirus, vaccinia virus, reovirus, vesicular stomatitis virus, measles virus, and poliovirus, are also being actively investigated, with a range of these being engineered to produce immunostimulatory cytokines or chemokines such as IL-12, IL-15, IFN-α, or GM-CSF to promote local antitumor immunity with reduced systemic toxicity (Ma et al., 2023; Lei et al., 2025). OVs offer a powerful biological rationale to be combined with immune checkpoint inhibitors and other immunotherapies, and indeed a large number of clinical trials are in progress, with the ability of OVs to restructure the tumor microenvironment, increase CD8+ T cell and natural killer cell infiltration, and upregulate immune checkpoint molecules such as PD-L1 (Nadafi et al., 2025; Shakiba & Rahman, 2024).

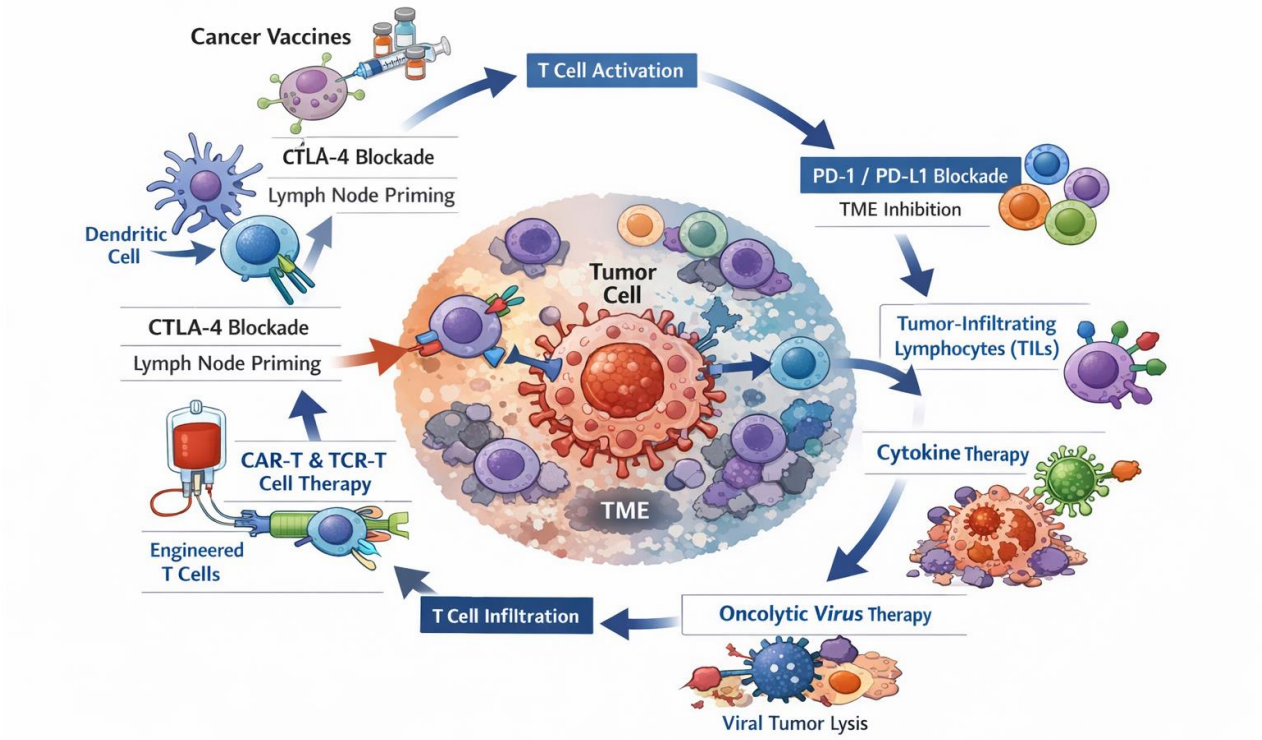

Figure 1: Introduction to cancer immunotherapy modalities and their action in the cancer-immunity cycle.

It is also shown in the diagram as different therapeutic immunotherapies, such as immune checkpoint blockers (CTLA-4 and PD-1/PD-L1 blockage), CAR-T/TCR-T/T cell therapeutics, tumor-infiltrating lymphocytes (TILs), cytokine therapy, cancer vaccines, and oncolytic virus therapy. All the modalities also promote the development of antitumor immunity through T-cell activation, infiltration, and tumor cell killing in the tumor microenvironment (TME).

Classification of Immunotherapy Resistance:

The resistance to immunotherapy is generally divided into two categories: primary (innate) and acquired (secondary or adaptive) resistance, depending on the time and longevity of clinical response. Primary resistance is defined as the lack of a significant tumor response after having started immunotherapy, and the tumor progresses too early despite sufficient drug exposure (Pan et al., 2022). This is clinically characterized by the development of progression during or in the immediate after treatment with immune checkpoint inhibitors, defined by the Society for

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ISSN: (e) 3007-1607 (p) 3007-1593

Immunotherapy of Cancer (SITC) (Xu et al., 202; Atkins et al., 2023). Primary resistance is induced by the reason of the prior-existing tumor and microenvironment factors that hinder effective antitumor immunity, such as low tumor mutational burden and neoantigen load, defective antigen presentation machinery, defects in interferon-γ signaling, non-inflamed or cold tumor immune microenvironment, and dominance of immunosuppressive cells and cytokines, which all negate T-cell activation and infiltration (Guan et al., 2025).

Conversely, acquired resistance emerges when the patient already shows a clinical response to treatment, whether partial or complete, and/or stable control of the disease, which is then followed by the subsequent tumor expansion as a result of, or independent of, treatment (Labrie et al., 2022). This type of resistance occurs via immune editing and adaptive tumor evolution, such as loss or alteration of tumor antigens, mutations in interferon-γ signaling pathways or antigen presentation machinery (e.g., JAK1/2 or b2-microglobulin), and compensatory increase in other inhibitory checkpoints (e.g., LAG-3, TIM-3, and TIGIT), and progressive remodelling of the immunosuppressive tumor microenvironment (Zhang et al., 2025; Baldi et al., 2025). Notably, apparent resistance should be differentiated from pseudoprogression, a condition that is associated with temporary enlargement or emergence of the tumor as a result of immune cell infiltration and inflammation and is followed by tumor regression or stabilization (Young et al., 2023; Dercle et al., 2023). Since the phenomenon of pseudoprogression is present in a few patients and differs depending on the type of cancer, immune-adapted response criteria, including iRECIST and confirmatory imaging or biopsy, will be necessary to distinguish between actual resistance and immune-related radiologic changes (Petrell et al., 2025).

Molecular Mechanisms Underlying Immunotherapy Resistance:

Cancer cell-intrinsic oncogenic programs and extrinsic tumor microenvironmental signals interact dynamically and reciprocally to drive tumor progression, which determines malignant growth, immune evasion, and resistance to therapy (De Visser & Joyce, 2023). Intrinsic changes, e.g., oncogenic drivers, e.g., myelocytomatosis oncogene (MYC) and Kirsten Rat Sarcoma viral oncogene homolog (KRAS); aberrant signaling pathways (PD-L1, TRAIL-R, HIF-1); metabolic rewiring; and epigenetic reprogramming not only promote proliferation, survival, epithelial-mesenchymal transition (EMT), metastasis, and stemness but also actively remodel (Goenka et al., 2023; Wang et al., 2023; Chen et al., 2021). Quite ironically, cell-autonomous inflammatory and apoptotic routes, which are generally considered tumor suppressive, are also utilized to aid tumor evolution and create a pro-oncogenic, immunosuppressive TME. Meanwhile, the non-malignant elements of TME, such as immunosuppressive immune cells, M2-polarized Tumor-Associated Macrophages (M2-TAMs), Myeloid-Derived Suppressor Cells (MDSCs), dysfunctional T cells, cancer-associated fibroblasts, endothelial cells, extracellular matrix, hypoxic and metabolically unfavorable conditions, and tumor-associated microbiota, complement malignant phenotypes through supporting EMT and invasion (Zhang et al., 2024; Rajesh et al., 2025). Examples of such convergence include EMT and immune evasion, both driven by intrinsic programs of cancer cells on the one hand and external cues like tumor growth factor (TGF-Beta), interleukin (IL-6), low oxygen tension, and stromal-immune crosstalk on the other hand (Goenka et al., 2023). This intrinsic-extrinsic network is especially close-knit in cancer stem cell niches and explains the resistance to treatment, which has a great justification to combinatorial therapeutic approaches that concomitantly hit tumor-intrinsic signaling and the crucial TME elements to produce enduring clinical responses.

Tumor progression is driven by a dynamic, reciprocal interplay between cancer cell–intrinsic oncogenic programs and extrinsic signals from the tumor microenvironment (TME), collectively shaping malignant growth, immune escape, and therapeutic resistance (De Visser & Joyce, 2023).

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ISSN: (e) 3007-1607 (p) 3007-1593

Intrinsic alterations, including oncogenic drivers such as myelocytomatosis oncogene (MYC) and Kirsten Rat Sarcoma viral oncogene homolog (KRAS), aberrant signaling pathways (PD-L1, TRAIL-R, HIF-1), metabolic rewiring, and epigenetic reprogramming, not only promote proliferation, survival, epithelial–mesenchymal transition (EMT), metastasis, and stemness, but also actively remodel the immune landscape to favor immune evasion (Goenka et al., 2023; Wang et al., 2023; Chen et al., 2021). Paradoxically, cell-autonomous inflammatory and apoptotic pathways, traditionally viewed as tumor suppressive, can be co-opted to support tumor evolution and establish a pro-oncogenic, immunosuppressive TME. In parallel, non-malignant TME components—including immunosuppressive immune cells, M2-polarized Tumor-Associated Macrophages (M2-TAMs), Myeloid-Derived Suppressor Cells (MDSCs), dysfunctional T cells, cancer-associated fibroblasts, endothelial cells, extracellular matrix, hypoxic and metabolically hostile conditions, and tumor-associated microbiota—reinforce malignant phenotypes by promoting EMT, invasion, angiogenesis, immune suppression, and pre-metastatic niche formation (Zhang et al., 2024; Rajesh et al., 2025). Processes such as EMT and immune evasion exemplify this convergence, arising from both intrinsic cancer cell programs and extrinsic cues such as tumor growth factor (TGF-β), interleukin (IL-6), hypoxia, and stromal-immune crosstalk (Goenka et al., 2023). This tightly coupled intrinsic–extrinsic network is particularly evident in cancer stem cell niches and underlies resistance to therapy, providing a strong rationale for combinatorial therapeutic strategies that simultaneously target tumor-intrinsic pathways and key TME components to achieve durable clinical responses.

The combination of cell-intrinsic differentiation programs and host-level contextual pressures results in immune dysfunction during chronic infection, cancer, and aging (Belk et al., 2022; Moller et al., 2022). Chronic exposure to antigens and inflammatory stimuli results in the T-cell exhaustion phenotype, with all these phenotypes manifested as a progressive loss of effector functions, expression of several inhibitory receptors (PD-1, CTLA-4, TIM-3, LAG-3, TIGIT) in the steady state, and a unique transcriptional and epigenetic program that inhibits reinvigoration, especially in terminally exhausted phenotypes (Sun & Dong 2025; Zhang et al., 2024). Similar inappropriate programs are not limited to T cells but also include NK cells because TIGIT marks exhausted tumor-infiltrating subsets and aging immune compartments, where senescent T cells get progressively accumulated and contribute to chronic low-grade inflammation (inflammaging) and loss of immune responsiveness (Atkins et al., 2023; Lin et al., 2025). These intrinsic programs are also influenced and enhanced by host-related factors, such as aging-related immunosenescence with loss of naive lymphocyte pools; chronic antigen exposure as a result of persistent viral infection or tumor-promoting checkpoint signaling; and CD8+ T-cell exhaustion (Gao et al., 2025; Zhang et al., 2025). Simultaneously, the maturation of immune responses to become inflammatory and senescent due to microbiome dysbiosis in later age and high risk in early life or socioeconomic adversity favors immune development toward inflammatory and increased susceptibility to infections, including COVID-19 (Yassin et al., 2025)

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ISSN: (e) 3007-1607 (p) 3007-1593

Table: Mechanisms of Resistance to Cancer Immunotherapy

Category	Key Factors	Effect on Immunity	References
Tumor-intrinsic	Antigen loss, defective antigen presentation, epigenetic silencing	Reduced T-cell recognition	(Zhang et al., 2024; Rajesh et al., 2025)
Immune checkpoint dysregulation	PD-1, CTLA-4, TIM-3, LAG-3, TIGIT upregulation	T-cell exhaustion	(Wang et al., 2023; Chen et al., 2021)
Tumor microenvironment	Tregs, MDSCs, TAMs, hypoxia, metabolic stress	Suppressed effector function	(Vitale et al., 2025)
Metabolic reprogramming	Glycolysis, amino acid and lipid metabolism	Epigenetic and functional immune suppression	(Belk et al., 2022)
Epigenetic alterations	DNA methylation, histone modifications, ncRNAs	Silencing of immune effector genes	(Kumar et al., 2025

Predictive Biomarkers of Immunotherapy Response and Resistance:

The discovery and therapeutic use of biomarkers have become the focus of cancer immunotherapy development, especially with the broad use of ICIs (Holder et al., 202). Biomarkers have become significant to predict patient responsiveness, oversee therapeutic effects, and predict adverse events involving immunity (Mino-Kenudson et al., 2022). Approaches to predicting tumors with clinically approved tumor-based biomarkers, including PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI), have their strong sides in predicting tumors in specific application settings, although their effectiveness is generally restricted by intratumor heterogeneity and sampling problems (Goswami et al., 2024). Immune-related biomarkers such as peripheral blood immune cell ratios, soluble immune checkpoints, and microenvironment tumor characteristics are receiving interest as dynamic and least invasive biomarkers of antitumor immunity and toxicity risk (Sidali et al., 2025). Together, the new evidence is in favor of a multifactorial model of biomarkers, which combines tumor-intrinsic and host immune parameters and improves the stratification of patients and clinical outcomes in cancer immunotherapy (Stenmark Tullberg et al., 2023). Precision-targeted therapy is already underway using genomic biomarkers like actionable Epidermal Growth Factor Receptor gene (EGFR) mutations, whereas the cancer-type-specific long non-coding RNA (lncRNA) and circular RNA (circRNA) biomarkers are already moving towards becoming functional drivers and valuable diagnostic and prognostic biomarkers (Davalos and Esteller, 2023; Wang et al., 2022). Because epigenetic changes, especially an aberrant pattern of DNA methylation, are very stable, tumor-specific, and can be detected at very early stages of the disease, they can be used to detect cancer, provide molecular subtyping, and predict response to treatment, with the added benefit of reversibility using epigenetic drugs (Jung et al., 2020; Ilango et al., 2020). In addition to these layers, transcriptomic methods, in particular single-cell RNA sequencing, reveal intratumoral

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ISSN: (e) 3007-1607 (p) 3007-1593

heterogeneity, subclones that resist therapy, and immune-evasion programs that cannot be observed in bulk analyses (Le et al., 2025). Using these insights on a wider scale, liquid biopsy methods offer non-invasive assessments of the available circulation of tumor DNA, tumor cells, tumor-derived RNAs (miRNAs, lncRNAs, circRNAs, etc.), tumor-trained platelets, and tumor-derived metabolites, all of which are indications of the tumor genomic, epigenomic, and transcriptomic map (Ren et al., 2024; Toden & Goel, 2022). The exceptional stability and specificity to cancer of non-coding RNAs circulating in exosomes, which package exosomes, make them potent early detection, prognosis, minimal residual disease, therapy monitoring, and resistance detection agents in many malignancies, including lung, colorectal, breast, prostate, and liver cancers, although their widespread use in clinical practice has been hampered due to issues in assay standardization, sensitivity, and specificity (Furlano et al., 2026).

Emerging Therapeutic Strategies to Overcome Resistance:

The combination immunotherapy is increasingly designed to bypass resistance by combining a range of cancer-immunity cycle multiomics. PD-1/PD-L1 or CTLA-4 blockade in combination with chemotherapy, targeted agents, or radiotherapy is an improved combination that has demonstrated a higher response rate in cancer types like melanoma, lung cancer, and triple-negative breast cancer, but with a higher likelihood of immune-related toxicities (Zhu et al., 2021; Yap et al., 2021). In addition to these, next-generation strategies of multi-immunotherapy involve immune checkpoint blockade with CAR-T cells, cancer vaccines, oncolytic viruses, cytokine or IL-2 agonists, STING agonists, and innate immune activators to turn immunologically "cold" tumors into "hot" ones (Chyuan et al., 2021). The rational combination design is designed to address different phases of the cancer-immunity cycle, such as antigenicity of tumor cells, immune priming, and the release of immune surveillance by the immune system, and reduce the unnecessary toxicity (Jin et al., 2023). One of the key areas of interest is the TME, in which the immunosuppressive components of the immune system (including regulatory T cells, myeloid-derived suppressor cells, tumor-associated macrophages, hypoxia, abnormal vasculature, and metabolic stress) cause therapeutic failure; new approaches aim to enumerate immunosuppressive cells, reset their programs, or use nanoparticle or biomimetic delivery systems to deliver immunomodulators to the TME (Chyuan et al., 2021; Zhu et al., 2021). Novel inhibitory checkpoints (such as LAG-3, TIM-3, TIGIT, BTLA, and VISTA) and costimulatory pathways (such as OX40, 4-1BB, GITR, ICOS, CD226, and CD2) are in development with agonist antibodies, mRNA therapies, and nanotechnology-based therapies, frequently combined with PD-1/PD-L1 blockade, to enhance sustained T- and NK-cell antitumor immunity (Luo et al., 2025; Zhang et al., 2024).

Epigenetic pathways, like DNA methylation, histone and chromatin remodeling, and non-coding RNAs, are key to controlling immune-related genes, immune checkpoints (PD-1, CTLA-4, TIM-3, LAG-3, and TIGIT), and immune effector molecules, including granzyme B, IFN-γ, IL-2, IL-12, FoxP3, and Stimulator of Interferon Genes (STING) in both tumor and immune compartments and thus shape antitumor immunity and therapeutic response (Kumar et al., 2025; Xu et al., 2023). The processes are closely connected with metabolic reprogramming in the tumor microenvironment that transforms the glycolysis, amino acid, and lipid metabolism and results in metabolites (e.g., α-ketoglutarate, S-adenosylmethionine, and lactate) that directly change the epigenetic states and promote immunosuppression (Sun et al., 2025; Zhang et al., 2024). Reprogramming of histone and DNA changes in T cells can be achieved by targeting important metabolic nodes, e.g., methionine transport or glycolytic, to restore T cell effector function and increase immune checkpoint blockade responsiveness (Qiu et al., 2024; Zheng et al., 2022). Based on these findings, the next-generation precision immunotherapy uses genomic, transcriptomic, and immunoprofiling

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ISSN: (e) 3007-1607 (p) 3007-1593

data to personalize treatment, utilizing neoantigen-based vaccines and TCR-engineered T cells based on tumor sequencing; swiftly versatile mRNA vaccine platforms that can target multiple neoantigens, including in immunologically cold tumors like brain cancers; and biomarker-directed immune checkpoint inhibitor approaches that combine PD-L1 expression, tumor mutational burden, neoantigen load, and epigenetic sign to rationally design synergistic combinations such as ICIs with epigenetic or metabolic modulators (Trivedi et al., 2024; Sun et al., 2025).

Future Perspectives:

The next generation of cancer immunotherapy is to address tumor-immune interaction resistance by a more comprehensive, integrative model on genetic, epigenetic, metabolic, and microenvironmental scales. Recent developments in multi-omics technologies, such as single-cell and spatial transcriptomics, epigenomic profiling, proteomics, and metabolomics, will permit mapping intratumoral heterogeneity and dynamic immune states at high resolution, which will allow prediction of resistance and therapeutic adaptation in real time. Further growth of liquid biopsy architecture will facilitate non-invasive liquid disease treatment response, clonal dynamics, and minimal residual illness monitoring. In therapy, effective development will rely on rationally formulated combination regimens that combine various, non-redundant cancer-immunity cycle steps and reduce toxicity, such as immune checkpoint blockade combined with metabolic, epigenetic, microbiome-modulating, and tumor-microenvironment-directed therapies. Meanwhile, the personalized immunotherapies, including neoantigen-based vaccinations, TCR-engineered and next-generation cellular therapies, and scalable mRNA platforms, are likely to extend efficacy to immunologically cold, heterogeneous, and treatment-refractory tumors. Taken together, all of these advances will move immunotherapy to indeed precision-guided, adaptive treatment paradigms that are specific to the tumor and host immune landscapes.

Conclusion:

Immunotherapy of cancer has completely revolutionized oncology, as it has been able to produce lasting or even curative responses. Nevertheless, primary and acquired resistance are still a major issues that contributes to the effectiveness of immunotherapy. A multifaceted and dynamic interplay of elements, such as tumor-intrinsic changes, immune evasion, metabolic and epigenetic reprogramming, and the impact of immunosuppressive tumor microenvironment and host-related factors, has led to this resistance being the focus of this review to shed light on the molecular mechanisms of resistance and the new treatment options to restore effective antitumor immunity. Notably, resistance is not to be seen as an unsolvable problem but an issue that can be overcome by biological means. It is possible to address it using integrated biomarker-based approaches and properly designed treatment plans.

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Frontier in Medical & Health Research

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