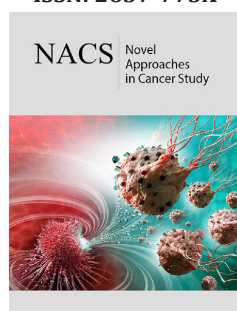


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Cancer Immun-surveillance and Immune Evasion: Mechanisms of Tumor Control, Metastatic Dormancy, and Immunotherapy

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Abstract

The immune system plays a central role in detecting and controlling cancer; this process is called cancer immun-surveillance. Both innate and adaptive immunity help identify and destroy abnormal cells, but tumors that survive this process often develop ways to avoid the immune system and continue growing. Research increasingly shows how tumors and their surrounding microenvironment interact, modulating the balance between immune defense and immune suppression. Immune cells such as cytotoxic T cells, natural killer cells, dendritic cells, macrophages, and regulatory T cells each shape this balance differently through antigen recognition, cytokine signaling, and immune regulation. A further translational consideration is the NAD⁺-dependent deacetylase SIRT1, which links cellular metabolism, stress responses, inflammation, and immune regulation. Because SIRT1 can have tumor-suppressive or tumor-promoting effects depending on tumor type, disease stage, cellular compartment, and molecular context, SIRT1-directed strategies require careful biomarker selection rather than a uniform activation or inhibition approach. Its potential relationship to immune-cell function, checkpoint signaling, treatment resistance, and circulating biomarkers is discussed as an emerging area for investigation. This review looks at how anti-tumor immunity works at the molecular and cellular level, focusing on antigen presentation via MHC molecules and the activation of tumor-targeting immune cells. This review examines the major mechanisms by which tumors evade immune control, including disrupted antigen presentation, immune checkpoint signaling, immunosuppressive cytokines, metabolic reprogramming, and the development of a tolerogenic tumor microenvironment. It also explores how the immune system maintains metastatic cells in a dormant state, the factors that trigger their reactivation, and current and emerging immunotherapies, including checkpoint blockade, adoptive cell transfer, CAR T-cell therapy, cancer vaccines and combination strategies designed to overcome therapeutic resistance. These insights point toward next-generation immunotherapies that could achieve lasting remission and prevent metastasis.

Introduction

Our understanding of cancer as a disease has changed dramatically over the past century [1]. Rather than viewing it as uncontrolled cell growth driven by mutations, we now recognize cancer as a continuous exchange between malignant cells and the immune system [2]. The immune system normally identifies and eliminates abnormal cells, but cancer cells can develop methods to slip past this defense, enabling them to grow uncontrollably and ultimately form life-threatening tumors [3].

Cancer immun-surveillance or the idea that immunity might protect against cancer actually dates back over a century, in 1891, surgeon William Coley noticed that some tumors shrank after patients suffered acute infections, leading him to try using bacterial toxins (Coley's toxins) to provoke an immune response against cancer [4]. Around the same time,

Paul Ehrlich proposed that the immune system must tolerate the body's own tissues, a concept he called "horror autotoxicus" [5]. Because of ideas like this, most scientists assumed for decades that tumors would appear invisible to the immune system because tumors are made of the body's own cells [6]. Early immunotherapy attempts, which often produced inconsistent results, only reinforced this assumption [6].

The controversy surrounding cancer immunosurveillance continued until the 1990s, until a combination of experimental evidence from animal models and human patients finally established the concept [7]. Studies using immunodeficient mouse strains: mice lacking T, B, and NKT cells (RAG2^{-/-} mice), mice deficient in interferon- γ or its receptor, and mice lacking perforin-mediated cytotoxic function consistently demonstrated higher rates of both spontaneous and carcinogen-induced tumors compared to their wild-type counterparts; these findings provided evidence that a functional cancer immunosurveillance process indeed exists and acts as an extrinsic tumor suppressor [8]. Researchers also found something more complicated: immunity doesn't just suppress tumors; it can also shape them in ways that help them survive; this led to a more refined model called cancer immunoediting [9].

Proposed by Robert Schreiber and colleagues, cancer immunoediting describes three phases or the "three Es": elimination, equilibrium, and escape [9]. In Elimination, the immune system detects and destroys transformed cells before a tumor forms [10]. If some cells survive, they enter Equilibrium, where the immune system holds the tumor in check, sometimes for years, while also un-attentionally selecting for less detectable cancer cell variants [10,11]. Eventually, in Escape, these immune-edited tumors build an immunosuppressive environment around themselves, evade detection entirely, and grow into clinically apparent disease [12].

Inspired by the "three Es", a new model has been proposed to classify the mechanisms through which cancer cells evade tumor-targeting immunity; this model, known as the "three Cs," contains camouflage, coercion, and cyto-protection [13]. Camouflage refers to the ability of malignant cells to hide from immune effector cells, avoiding being localized or recognized as transformed, this strategy

that can result from defects in antigen processing and presentation, limited secretion of chemotactic factors, or the creation of stromal barriers preventing immune infiltration [14]. Coercion describes how cancer cells that fail at camouflage can actively suppress the activity of immune effector cells, including DCs, NK cells and CD8⁺ CTLs (killer T cells), while promoting the activity of immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells (MDSCs) [15]. Cytoprotection entails the ability of malignant cells to protect themselves from immune cytotoxicity, resisting the effector molecules which are normally released upon immune cell activation [16].

The mechanisms by which tumors evade immune surveillance: altered antigen presentation, upregulation of immune checkpoint molecules such as PD-L1 and CTLA-4, recruitment of immunosuppressive regulatory cells, and metabolic reprogramming of the tumor microenvironment, represent critical vulnerabilities that can be therapeutically targeted [17]. This insight has driven the development of a new generation of cancer immunotherapies, including immune checkpoint inhibitors, adoptive T-cell therapies and cancer vaccines, which have fundamentally altered the treatment pattern for many malignancies [18]. The first immune checkpoint inhibitor, ipilimumab (an anti-CTLA-4 antibody), received FDA approval in 2011, followed by pembrolizumab (an anti-PD-1 antibody) and nivolumab (an anti-PD-1 antibody) in 2014 [19].

Despite these advances, some challenges are still present; primary and acquired resistance to immunotherapy is widespread, driven by the same mechanisms of immune evasion that allow tumors to continue growing [20]. T-cell exhaustion within the tumor microenvironment represents a central mechanism of adaptive resistance, compromising constant immunotherapeutic efficiency [21]. Diffused cancer cells that remain in a state of immune-controlled latency before eventually escaping to cause disease recurrence represent a daunting clinical challenge [22]. Understanding the biology of these dormant cells, their transcriptional and metabolic profiles, and the immune mechanisms that maintain their inactivity is essential for developing therapies capable of eradicating these tumors and preventing long-term relapse [22] (Figure 1).

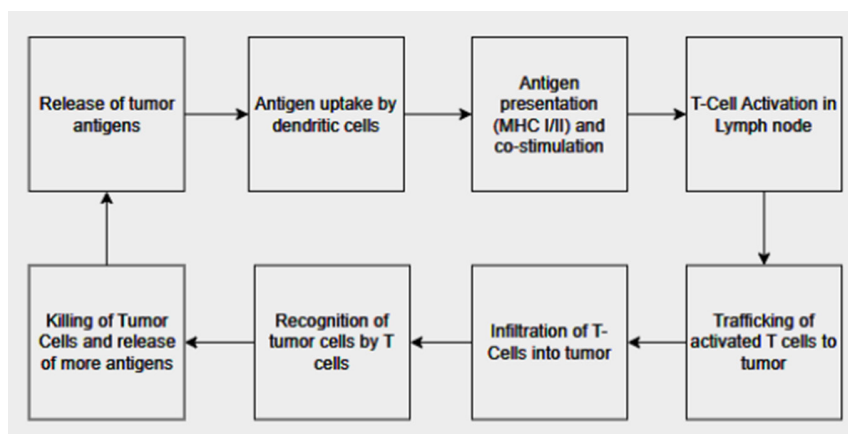


Figure 1: The Cancer-Immunity Cycle.

Anti-Tumor Immunity and Immune Recognition

The immune system uses a network of innate and adaptive responses to recognize and eliminate malignant cells [23]. Innate immunity provides rapid, non-specific defense, while adaptive immunity offers antigen-specific, long-lasting protection [2]. These two branches function interdependently, with innate responses bridging to adaptive immunity through antigen presentation and cytokine signaling [24].

Innate immunity acts as the first line of defense against cancer, acting within minutes to hours without prior exposure [25]. Innate immune cells recognize tumor cells through pattern recognition receptors that detect stress-associated molecular patterns [26]. NK cells serve as first responders against malignant cells; unlike T cells, NK cells do not require antigen-specific recognition, which allows rapid cytotoxic responses [27]. NK cell activity is regulated by a balance between activating and inhibitory receptors [28]. Inhibitory receptors, such as KIRs in humans, recognize self-MHC class I molecules and prevent NK activation against healthy cells; this mechanism allows NK cells to eliminate tumor cells that have stopped MHC class I expression, which is a common strategy for immune evasion [29]. Upon activation, NK cells kill tumor cells through perforin/granzyme exocytosis, FasL/TRAIL-mediated apoptosis and antibody-dependent cell-mediated cytotoxicity (ADCC) [30]. NK-derived IFN- γ enhances dendritic cell antigen presentation and promotes Th1 polarization, facilitating CD8+ T cell responses [31]. However, tumors prevent NK function through the release of NKG2D ligands, upregulation of PD-L1, and production of TGF- β and IL-10 [32].

Tumor-associated macrophages (TAMs) are among the most abundant immune cells in the tumor microenvironment [32]. Macrophages range along a spectrum from anti-tumor M1 to pro-tumor M2 phenotypes [33]. M1 macrophages are triggered by IFN- γ and LPS, produce IL-12, TNF- α and reactive oxygen/nitrogen species, intervening direct tumor destruction and efficient antigen presentation [34]. M2 macrophages, induced by IL-4, IL-10 and IL-13, promote tumor progression through IL-10 and TGF- β secretion, arginase-1-mediated T cell suppression and VEGF-driven angiogenesis [35]. Within tumors, TAMs primarily exhibit M2-like phenotypes and correlate with a poor prognosis in cancer [36]. The tumor microenvironment promotes M2 polarization through hypoxia, IL-10, TGF- β , CSF-1 and lactate accumulation [37]. TAMs also express PD-L1 and CD47, suppressing T cells and evading phagocytosis [38]. Dendritic cells (DCs) are the most powerful antigen-presenting cells and serve as the critical bridge between innate and adaptive immunity [39]. Conventional DC type 1 (cDC1), characterized by CD141 or CD103/CD8 α are specialized for cross-presentation of tumor antigens to CD8+ T cells and correlate with a good prognosis [40]. cDC2 cells present antigens to CD4+ helper T cells [41]. Plasmacytoid DCs (pDCs) produce type I interferons but can acquire immunosuppressive functions in the tumor microenvironment [42]. DCs provide co-stimulatory signals (CD80/CD86, CD40) required for T cell activation; however, tumors impair DC function through VEGF, IL-10, TGF- β and lactate, while PD-L1 expression on DCs directly inhibits T cells [43].

Neutrophils, the most abundant circulating leukocytes, exhibit context-dependent roles in cancer; tumor-associated neutrophils polarize into anti-tumor N1 and pro-tumor N2 phenotypes [44]. The neutrophil-to-lymphocyte ratio serves as a prognostic biomarker, with high NLR correlating with a poorer prognosis [45]. Innate lymphoid cells (ILCs) lack antigen-specific receptors but contribute to tissue immunity [46]. ILC1 produces IFN- γ and may exert anti-tumor effects, ILC2 produces type 2 cytokines and ILC3 produces IL-17A and IL-22, often associated with tumor-promoting inflammation; their roles in cancer remain under active investigation [47].

Adaptive immunity provides antigen-specific, self-renewing immunity against cancer through T and B lymphocytes [48]. CD8+ CTLs are the primary effectors of adaptive anti-tumor immunity; they can recognize peptide-MHC class I complexes through their T cell receptor [49]. Intratumoral CD8+ T cell infiltration correlates with a good prognosis for all types of cancer, and therapies that enhance CD8+ T cell activity, such as immune checkpoint inhibitors, have demonstrated significant clinical benefit in patients with metastatic melanoma [50]. CTL generation requires three signals: TCR engagement with peptide-MHC, co-stimulation and cytokine signals [51]. Activated CTLs kill tumor cells through perforin/granzyme exocytosis and FasL/TRAIL pathways, while producing IFN- γ and TNF- α [52]. A number of effector cells differentiate into long-lived memory T cells, providing durable protection against recurrence; however, the tumor microenvironment induces T cell exhaustion, characterized by progressive loss of effector function and sustained expression of inhibitory receptors [53]. Exhausted T cells are a sign of chronic antigen exposure and a major mechanism of immunotherapy resistance [54].

CD4+ helper T cells coordinate anti-tumor immunity without direct cytotoxicity [55]. They recognize MHC class II-presented antigens on professional APCs [56]. Th1 cells produce IFN- γ , IL-2 and TNF- α , supporting CTL generation and macrophage activation and are associated with favorable prognosis [3]. Th2 cells promote M2 polarization and are generally pro-tumorigenic [20]. Th17 cells have context-dependent roles, contributing to either inflammation-driven tumor promotion or CTL recruitment [21]. T follicular helper cells support B cell responses and tertiary lymphoid structure formation, associated with improved outcomes [57]. Regulatory T cells are potent immunosuppressors that maintain homeostasis but impede anti-tumor immunity [58]. Regulatory T cells suppress through IL-10, TGF- β , IL-2 consumption, CTLA-4, and LAG-3, and high Treg infiltration correlates with a poor prognosis [59].

B cells are increasingly recognized for their roles in anti-tumor immunity through antibody production, antigen presentation, and cytokine secretion [60]. Tumor-specific antibodies mediate complement-dependent cytotoxicity and ADCC via NK cells and macrophages [61]. Tumor-infiltrating B cells and tertiary lymphoid structures are associated with good prognosis and immunotherapy response [62]. B cells also present antigens to CD4+ T cells and secrete cytokines [63]. Regulatory B cells produce IL-10 and TGF- β , suppressing anti-tumor responses and correlating with poor outcomes [64].

Immunological memory provides long-lasting protection against tumor recurrence; memory T cells remain for decades and increase rapid recall responses [65]. Tissue-resident memory T cells in tumors are associated with a favorable prognosis and checkpoint blockade response [66]. Progenitor exhausted T cells expressing TCF1 maintain self-renewal capacity and respond to checkpoint inhibitors, representing a key reservoir for durable immunotherapy responses [67]. Cancer vaccines aim to generate memory responses for long-term protection [68]. The equilibrium phase of immunoediting represents immune-mediated tumor dormancy maintained by memory-like responses and understanding this state is essential for preventing metastatic recurrence [69].

Mechanisms of Tumor Immune Evasion

Despite the immune system's capacity to recognize and eliminate malignant cells, tumors use a range of strategies to escape immune destruction [70]. These mechanisms allow cancer cells to survive immune pressure, progress to clinically detectable disease, and resist immunotherapy [71]. Tumor antigen presentation on MHC molecules is essential for T cell recognition, and its disruption is a primary evasion strategy [72]. Loss or downregulation of MHC class I expression occurs frequently in advanced cancers, preventing CD8⁺ T cell recognition [73]. This results from mutations in β 2-microglobulin, defects in antigen processing machinery or epigenetic silencing [74]. Heterogeneous neoantigen expression allows tumor subclones lacking immunogenic mutations to escape detection [75]. MHC class II downregulation impairs CD4⁺ T cell recognition, while upregulation of non-classical MHC molecules HLA-G and HLA-E engages inhibitory receptors on NK and T cells [76].

Immune checkpoints maintain self-tolerance but are abused by tumors to suppress anti-tumor immunity [77]. The PD-1/PD-L1 axis is the most extensively characterized pathway, where tumor PD-L1 engages PD-1 on T cells, inducing exhaustion and apoptosis [78]. PD-L1 overexpression is driven by oncogenic signaling or adaptive resistance to IFN- γ [79]. CTLA-4 competes with CD28 for CD80/CD86 binding, delivering inhibitory signals that dampen T cell activation; its blockade has demonstrated clinical benefit in metastatic melanoma [11]. Additional checkpoints including LAG-3, TIM-3, TIGIT and VISTA are co-expressed on exhausted T cells and contribute to PD-1/PD-L1 resistance [23].

Tumors secrete and induce cytokines that reshape the microenvironment to favor immune evasion [2]. TGF- β inhibits T cell proliferation, suppresses NK function, promotes Treg differentiation and triggers EMT and metastasis [14]. IL-10 suppresses APC function, inhibits pro-inflammatory cytokines and promotes Treg expansion [80]. VEGF inhibits DC maturation, suppresses T cell movement and mobilizes immunosuppressive cells [80].

Altered tumor metabolism creates an immunosuppressive microenvironment [81]. High glycolytic activity leads to lactate accumulation and acidification, which suppresses T cell proliferation, cytokine production, and cytotoxicity, while decreasing NK and DC

function [82]. Tumors compete with immune cells for glucose and amino acids including L-arginine and tryptophan [83]. Tryptophan depletion by IDO promotes T cell inactivity and Treg differentiation, while arginase-1 from MDSCs and M2 macrophages depletes L-arginine required for T cell function [84]. Hypoxia induces HIF-1 α , promoting immunosuppression and immunotherapy resistance [85].

SIRT1 provides an additional metabolic and epigenetic link between tumor-cell adaptation and immune regulation [86]. SIRT1 is a NAD⁺-dependent deacetylase that acts on histone and non-histone substrates, including transcription factors involved in stress responses, metabolism, inflammation, DNA repair, apoptosis, and cellular senescence [86]. In cancer, its function is context dependent: SIRT1 may protect normal cells from genomic injury while, in established tumors, increased SIRT1 activity can support survival, metabolic adaptation, migration, metastasis, or resistance to therapy [86,87]. This duality is important when considering SIRT1 as a therapeutic target because both SIRT1 activation and inhibition have been proposed in different disease settings [87]. Recent reviews also describe SIRT1-mediated regulation of immune responses across T cells, macrophages and other immune populations, suggesting that SIRT1 may influence the tumor immune microenvironment in addition to acting directly within malignant cells [86].

The TME actively suppresses anti-tumor immunity through multiple mechanisms [88]. Dense stromal barriers, including CAFs and extracellular matrix, physically exclude immune cells [17]. CAFs produce TGF- β and IL-6, promoting angiogenesis and metastasis [89]. Tumor-derived exosomes carry PD-L1, FasL and TGF- β , systemically suppressing immune responses [21]. The TME establishes chronic inflammation and physical/metabolic barriers that prevent effector immune cell infiltration and persistence, contributing to primary immunotherapy resistance [90].

Regulatory T cells (Tregs) accumulate in the TME via tumor-derived chemokines [91]. Tregs are suppressed through IL-10 and TGF- β secretion, IL-2 consumption via CD25, CTLA-4 and LAG-3 expression and adenosine production [92]. High Treg infiltration correlates with poor prognosis and checkpoint blockade resistance [93].

Myeloid-derived suppressor cells (MDSCs) expand in response to tumor factors and effectively suppress T cell responses [94]. MDSCs suppress through arginase-1-mediated L-arginine depletion, IDO-mediated tryptophan depletion, ROS production and IL-10/TGF- β secretion [95]. MDSCs also promote Treg differentiation, angiogenesis, metastasis and their accumulation correlate with poor outcomes and immunotherapy resistance [96].

Tumor-associated macrophages promote evasion through M2 polarization [97]. M2 TAMs produce IL-10 and TGF- β , express arginase-1 and PD-L1/CD47 and promote angiogenesis and tissue remodeling [98]. The CSF-1/CSF-1R pathway is critical for TAM survival, and its blockade is currently being explored therapeutically [99]. TAMs recruit Tregs and MDSCs while excluding effector T

cells [100]. These evasion mechanisms, taken together, are a major reason immunotherapy often falls short [101]. Still, each one is a potential drug target and combining therapies to act on multiple pathways at once may be the best way to beat resistance [102].

From a therapeutic perspective, SIRT1 should therefore be viewed as a potential context-dependent modifier of immune escape rather than as a universally oncogenic or tumor-suppressive factor [86]. SIRT1 inhibition could be relevant in tumors in which SIRT1 supports survival, immune evasion, or treatment resistance,

whereas SIRT1 activation could theoretically be beneficial in settings in which SIRT1 preserves genomic stability or limits damaging inflammation [86]. Combination strategies pairing SIRT1 modulation with checkpoint blockade are particularly interesting because they could target both tumor-intrinsic resistance and the immunosuppressive microenvironment [103]. However, clinical evidence remains insufficient to establish SIRT1 modulators as standard immunotherapies, and future studies should determine which tumor types, immune-cell states and molecular profiles are most likely to benefit [103] (Figure 2).

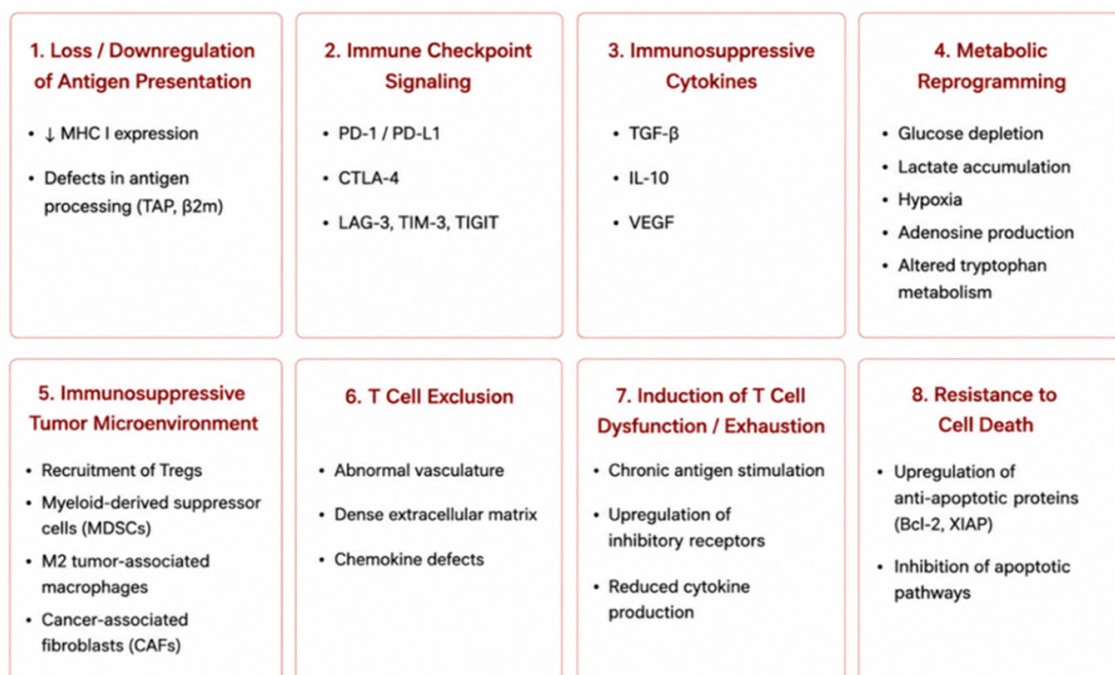


Figure 2: Mechanisms of Tumor Immune Evasion.

Immune Regulation of Metastasis and Cancer Immunotherapy

The relationship between the immune system and metastasis is complex, encompassing both the control of scattered cancer cells and the therapeutic strategies designed to mobilize immunity against cancer [104]. This section examines immune-mediated control of dormant metastases, mechanisms of metastatic reactivation, and the landscape of immunotherapeutic approaches targeting metastatic cancer [105].

Disseminated tumor cells (DTCs) can spread to distant organs and remain in a state of immune-controlled dormancy for years or even decades before reactivating to form clinically detectable metastases [106]. This dormant state represents the equilibrium phase of cancer immunoediting, where the immune system contains tumor growth in a minimal, non-proliferative delay [107]. Preclinical mouse models have revealed that immune-controlled dormant metastases possess a unique differentiated phenotype, with distinct transcriptional profiles compared to active metastases [108]. These dormant lesions are characterized by upregulation

of genes such as Ch25h and differential expression of microRNAs including mir-142-3p [109].

The microenvironment of dormant metastases is fortified with T lymphocytes and neutrophils; CD8+ T cells are essential for enforcing tumor dormancy, and their depletion can trigger rapid metastasis [72]. NK cells also contribute to the maintenance of dormancy by eliminating DTCs that attempt to proliferate [110]. The equilibrium between immune-mediated elimination and tumor cell survival determines whether DTCs are cleared, maintained in a dormant state, or progress to overt metastasis [111].

The transition from dormancy to active metastasis occurs when the balance between immune control and tumor cell outgrowth is disrupted [112]. Mechanisms contributing to metastatic reactivation include: the loss of immune surveillance changes in the tumor microenvironment, and tumor-intrinsic alterations [113]. Loss or downregulation of MHC class I expression on DTCs allows them to escape from CTL recognition [37]. Upregulation of immune checkpoint molecules such as PD-L1 on dormant cells can suppress local T cell responses and promote reactivation [42].

Changes in the metastatic environment also increases reactivation [114]. The composition of the extracellular matrix, the presence of inflammatory signals and the recruitment of immunosuppressive cells can disrupt the dormancy-maintaining microenvironment [115]. Tumor-derived factors including TGF- β and VEGF promote angiogenesis and create a metastatic outgrowth tolerant environment [64]. Tumor-intrinsic alterations, including the acquisition of proliferative mutations and epigenetic changes, can override immune-mediated growth arrest [19]. The Ch25h gene has been identified as a critical regulator of dormancy and its downregulation is associated with metastatic reactivation [23]. Understanding the molecular switches that control the dormancy-reactivation transition is essential for developing therapies that can prevent metastatic recurrence [2]. Mathematical modeling suggests that the relationship between cancer cells and immunomodulatory cells governs the timing and likelihood of immune escape from dormancy [116].

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of metastatic cancer by enabling T cell-mediated anti-tumor immunity [11]. PD-1/PD-L1 inhibitors, including pembrolizumab and nivolumab, block the PD-1 pathway, restoring T cell function and promoting the killing of tumor cells [117]. CTLA-4 inhibitors, such as ipilimumab, block the CTLA-4 checkpoint and enhance T cell priming in lymph nodes [116]. The clinical capacity of ICIs has been demonstrated across multiple types of cancer, with long-lasting responses observed in many patients [118]. Combined PD-1 and CTLA-4 blockade has shown improved outcomes compared to monotherapy in melanoma, renal cell carcinoma and other cancers; however, only a subset of patients responds to ICI therapy [119]. Biomarkers such as PD-L1 expression, tumor mutational burden, and microsatellite instability status help predict response but remain imperfect [120]. Cold tumors with low T cell infiltration and an immunosuppressive microenvironment are generally resistant to ICI therapy [12]. Strategies to convert cold tumors into hot, T-cell-inflamed tumors are currently a major focus of research [121].

SIRT1 may also warrant investigation as a complementary biomarker [87]. Tissue SIRT1 expression has been associated with clinicopathologic features and outcomes in several cancers, although published findings are heterogeneous and SIRT1 biology is strongly tumor-type dependent [87]. The measurement of circulating or plasma SIRT1 is therefore best considered a hypothesis-generating approach rather than an established clinical test [87,103]. Prospective studies could assess whether plasma SIRT1 levels correlate with tumor burden, immune phenotype, treatment response or acquired resistance, while simultaneously measuring tissue SIRT1, PD-L1, immune-cell infiltration and other validated biomarkers [103]. Such multimodal analyses could clarify whether SIRT1 provides information that is independent of, or complementary to, existing predictors [87].

Adoptive cell transfer involves collecting a patient's own T cells, expanding them *ex vivo* and reinfusing them to target tumor cells [122]. Tumor-infiltrating lymphocyte therapy involves the isolation and expansion of T cells from resected tumors, followed

by their reinfusion after lymphodepletion [87]. TIL therapy has demonstrated long-lasting responses in patients with metastatic melanoma and is being investigated in other cancer types [17].

Chimeric antigen receptor T-cell therapy represents a major advance in adoptive cell therapy [123]. CAR T cells are engineered to express synthetic receptors that recognize tumor-associated antigens without MHC restriction, allowing targeting of a broad range of tumors [124]. CAR T-cell therapy has shown much success in hematological malignancies with CD19-targeted CAR T cells achieving remissions in B-cell leukemias and lymphomas; however, CAR T-cell capacity in solid tumors is still limited by the immunosuppressive tumor microenvironment, the lack of tumor-specific antigens, and the challenges of T cell trafficking and persistence [92].

T-cell receptor (TCR) engineered T-cell (TCR-T) therapy is an alternative ACT strategy that can target intracellular antigens [125]. TCR-T therapy has shown clinical activity in melanoma, synovial sarcoma and other cancers, but challenges include MHC loss and toxicity towards other cells [116]. Cancer vaccines aim to stimulate the immune system to recognize and attack tumor antigens [118]. Vaccines can be classified as prophylactic or therapeutic [124]. Therapeutic cancer vaccines have historically shown limited efficacy, but recent advances in neoantigen discovery have restored interest in this approach [85].

Personalized neoantigen vaccines use next-generation sequencing to identify patient-specific neoantigens arising from somatic mutations [88]. These vaccines, typically formulated as synthetic long peptides or RNA, are designed to prime and expand neoantigen-specific T cells [89]. Clinical trials have demonstrated that personalized neoantigen vaccines can generate powerful, poly-specific T cell responses and show clinical activity in melanoma and glioblastoma [21].

Combining immunotherapy with conventional treatments such as chemotherapy, radiotherapy, and anti-angiogenic agents can enhance anti-tumor immunity [22]. Chemotherapy and radiotherapy induce immunogenic cell death, releasing tumor antigens and creating a favorable microenvironment for immune responses [61]. Anti-angiogenic agents normalize tumor vasculature, improving T cell trafficking and reducing immunosuppression [126].

Bispecific antibodies are engineered to simultaneously engage T cells and tumor cells, bringing them into close proximity to facilitate tumor cell elimination [64]. Bispecific T cell engagers have shown activity in hematological malignancies and are being explored in solid tumors [127]. Antibody-drug conjugates combine the targeting specificity of antibodies with the cytotoxicity of chemotherapeutic drugs [20]. Oncolytic viruses selectively replicate in tumor cells, inducing direct killing and immune activation [128]. Nanotechnology-based approaches are being developed to improve the delivery and targeting of immunotherapies [129].

Resistance to immunotherapy remains a major clinical challenge and can be classified as primary, adaptive, or acquired [130]. Primary resistance occurs when patients fail to respond to initial therapy, often due to the absence of pre-existing T cell

responses or cold tumors [131]. Adaptive resistance occurs when tumors initially respond to therapy but upregulate immune evasion mechanisms, such as PD-L1 upregulation in response to IFN- γ [132]. Acquired resistance develops over time, often due to tumor evolution and the emergence of resistance mutations [133].

The immunosuppressive tumor microenvironment is a major driver of resistance [134]. The presence of Tregs, MDSCs and M2 macrophages in the TME suppresses T cell function and promotes immune evasion [135]. T cell exhaustion, depicted by prolonged expression of inhibitory receptors including PD-1, CTLA-4, LAG-3 and TIM-3, limits the efficacy of checkpoint blockade [136]. Loss of tumor antigen expression or MHC class I downregulation enables immune escape [82]. Mutations in IFN- γ signaling pathways impair T cell-mediated killing and confer resistance to PD-1 blockade [137].

SIRT1 may intersect with several of these resistance mechanisms through its effects on metabolism, stress adaptation, inflammatory signaling, apoptosis and immune-cell function [86]. Recent literature has specifically examined SIRT1-mediated cellular immune responses in cancer and suggests that altering SIRT1 activity can change the balance between anti-tumor and immunosuppressive responses [86]. In addition, emerging work links SIRT1 to redox homeostasis and senescence, processes that can affect tumor persistence and therapeutic sensitivity [103]. These observations support investigation of SIRT1 as part of rational combination strategies, but they do not justify assuming that inhibition is beneficial in every cancer [86]. The direction of SIRT1 modulation should be determined experimentally for each tumor and immune context [103].

Strategies to overcome resistance include combining therapies that target multiple immune evasion pathways, using epigenetic modulators to restore antigen presentation and developing bispecific antibodies that bypass MHC restriction [138]. Understanding the mechanisms of resistance is essential for the rational design of combination therapies and the identification of biomarkers that predict responses [139].

Conclusion and Future Perspectives

Despite the impact immunotherapies have had only a fraction of patients see lasting benefit [138]. Most patients with solid tumors show primary resistance to checkpoint inhibitors from the start, especially those with cold tumors marked by sparse T cell infiltration and an immunosuppressive microenvironment [140]. Even patients who initially respond often develop acquired resistance over time, driven by things like loss of antigen presentation, upregulation of alternative checkpoints, or the emergence of resistance mutations [80]. Immune-related adverse events add another layer of difficulty: severe toxicities can affect multiple organs and often require immunosuppressive treatment that undercuts the therapy's anti-tumor effect [18]. We also still lack reliable predictive biomarkers; PD-L1 expression and tumor mutational burden, the current standards are far from perfect at predicting who will respond [141]. On top of this, the high cost of these therapies and limited access in resource-poor settings widen existing gaps in cancer care [142]. And because tumors are constantly evolving to dodge immune control, the tumor-immune interface itself is a moving target that makes therapeutic design difficult [143] (Figure 3).

Therapy	Target / Focus	Mechanism of Action	Examples
 Immune Checkpoint Inhibitors	PD-1, PD-L1, CTLA-4, LAG-3	Block inhibitory signals and restore T cell activity	Pembrolizumab, Nivolumab, Atezolizumab, Ipilimumab
 Adoptive Cell Transfer (TIL Therapy)	Tumor-infiltrating lymphocytes	Expand tumor-reactive T cells ex vivo and reinfuse	Lifileucel, other TIL products
 CAR T-Cell Therapy	Tumor antigens (CD19, BCMA, etc.)	Engineered T cells with chimeric antigen receptors to recognize and kill tumor cells	Tisagenlecleucel, Axicabtagene ciloleucel, Idecabtagene vicleucel
 Cancer Vaccines	Tumor antigens / neoantigens	Stimulate adaptive immune response and memory	Sipuleucel-T, mRNA vaccines, peptide / neoantigen vaccines
 Cytokine Therapy	Cytokines (IL-2, IFN- α , IL-15)	Enhance proliferation and activation of immune cells	Aldesleukin (IL-2), Interferon- α , IL-15 agonists
 Oncolytic Virus Therapy	Tumor cells	Viruses selectively infect and lyse tumor cells, enhancing anti-tumor immunity	Talimogene laherparepvec (T-VEC)

Figure 3: Current and Emerging Cancer Immunotherapies.

Looking ahead, the field is moving toward personalized, precision-based approaches that account for each patient's specific tumor biology and immune profile [19]. One promising strategy is personalized neoantigen vaccines, which use next-generation sequencing to pinpoint a patient's unique mutations and build a custom vaccine that trains T cells to recognize them [144]. Early clinical results in melanoma and glioblastoma look encouraging and pairing these vaccines with checkpoint inhibitors may boost their effect further [145]. Cell therapies are also becoming more individualized with neoantigen-reactive TIL therapies and personalized TCR-T products gaining traction [146]. Meanwhile, single-cell sequencing and computational biology are helping researchers pick better target antigens and predict who's likely to respond to treatment [147].

Future SIRT1 studies could benefit from the same precision-medicine framework [86]. Rather than measuring SIRT1 as an isolated variable, investigators could integrate SIRT1 protein abundance and enzymatic activity with NAD⁺ metabolism, immune-cell composition, checkpoint expression, tumor mutational features and treatment history [86]. Single-cell and spatial approaches may be especially useful for distinguishing SIRT1 activity in malignant cells from its activity in T cells, macrophages, dendritic cells and other components of the tumor microenvironment [87]. Longitudinal plasma sampling could further determine whether circulating SIRT1 changes during therapy and whether those changes precede radiographic or molecular evidence of response or progression [103].

The next generation of immunotherapies is pushing well past traditional checkpoint inhibitors [148]. Researchers are now testing new checkpoint targets like LAG-3, TIM-3, TIGIT, VISTA and LAG-3 blockade combined with PD-1 inhibition has already won FDA approval [149]. Bispecific antibodies and T cell engagers (BiTEs), which link tumor antigens directly to T cells, are proving effective in blood cancers and are now being adapted for solid tumors [150]. Antibody-drug conjugates take a different approach, pairing an antibody's precision with a toxic payload to hit tumor cells directly [61]. Oncolytic viruses are being engineered to replicate selectively inside tumor cells, triggering immunogenic cell death and kicking off a broader anti-tumor immune response [151]. And on the cytokine side, engineered IL-2 variants and IL-15 super agonists aim to boost T cell and NK cell activity without the toxicity that's plagued earlier cytokine therapies [152].

Nanotechnology is opening up new delivery options as well [153]. Nanoparticles can be designed to carry antigens, adjuvants, or immune-modulating drugs straight to tumors or lymph nodes, improving efficacy while limiting systemic side effects [154]. Lipid nanoparticles, which proved themselves in COVID-19 mRNA vaccines are now being repurposed for cancer immunotherapy [155]. CRISPR-Cas9 and similar gene-editing tools are letting scientists engineer immune cells that function better and resist the tumor microenvironment's suppressive signals [19]. And synthetic biology is enabling CAR T cells with built-in "logic gates" that can tell tumor cells apart from healthy tissue, which is a step that could make CAR T therapy considerably safer [61].

Beating treatment resistance will likely take a combination approach that hits several evasion mechanisms at once, rather than relying on any single strategy [151]. Pairing PD-1/PD-L1 inhibitors with CTLA-4 inhibitors has already improved outcomes in several cancers and combinations involving other checkpoints are under active investigation [153]. Combining immunotherapy with targeted therapies that interfere with oncogenic signaling can turn cold tumors hot, drawing in more T cells and easing immunosuppression [156]. MAPK inhibitors in melanoma and EGFR inhibitors in lung cancer are good examples of targeted drugs that can prime tumors for checkpoint blockade [19].

There's also a lot of work going into directly tackling the immunosuppressive tumor microenvironment [157]. Anti-CCR4 or anti-CD25 antibodies can deplete regulatory T cells while sparing effector T cells [2]. CSF-1R inhibitors can clear out M2 macrophages and nudge the remaining ones toward a more tumor-fighting M1 state [82]. Anti-CD47 antibodies block tumors' signals, freeing macrophages to attack them [138]. Other strategies target myeloid-derived suppressor cells by blocking their recruitment, differentiation or function [139]. IDO and arginase inhibitors aim to counter the metabolic suppression these cells impose on T cells [20]. Epigenetic drugs, HDAC inhibitors and DNA methyltransferase inhibitors can also help by restoring antigen presentation and making tumors more visible to T cells [158].

Metabolism itself is becoming a target for boosting immunotherapy [85]. Altering the gut microbiome, whether through fecal transplants or probiotics has been shown to improve checkpoint inhibitor responses [90]. Dietary changes that shift systemic metabolism are being studied as a complementary strategy [159]. On the cell therapy side, researchers are engineering CAR T cells to resist the suppressive tumor environment directly, for instance, by having them secrete IL-12 or express a dominant-negative TGF- β receptor [148]. There's also growing interest in off-the-shelf, allogeneic CAR T and NK cell products, which could make these therapies faster to manufacture and easier to access [149].

At the end of the day, the goal is durable remission and preventing cancer from coming back [160]. Long-lived memory T cells are what make lasting protection against recurrence possible [150]. Patients who achieve complete responses to checkpoint inhibitors can often stay in remission for years: a sign that real immunological memory has taken hold [161]. Tumors containing tissue-resident memory T cells tend to have better outcomes, underscoring just how important local immune surveillance is [162].

Stopping metastasis means catching disseminated tumor cells while they're still dormant [163]. This dormant phase, when the immune system is actively holding cancer cells in check, represents a real window for intervention [164]. Therapies that tip this immune-dormancy balance could wipe out these cells before they wake up and form detectable metastases [18]. That might mean vaccines that prime memory responses against shared tumor antigens, or immunotherapies designed to keep T cells active against lingering disease [154]. Liquid biopsies and circulating tumor DNA monitoring add another layer, potentially flagging recurrence early enough to act on it [141].

Bringing immunotherapy into the adjuvant and neoadjuvant settings is one of the biggest opportunities for preventing recurrence [142]. Neoadjuvant immunotherapy has produced encouraging pathologic response rates in melanoma and lung cancer [143]. Adjuvant immunotherapy after surgery, like pembrolizumab in melanoma, has shown it can clear residual disease and cut recurrence risk [15]. Combining immunotherapy with radiotherapy or chemotherapy around the time of surgery can also trigger immunogenic cell death and rally a stronger systemic immune response [69].

The relationship between cancer and the immune system has taken a century to unravel, and we're still learning [114]. From William Coley's early experiments to today's checkpoint inhibitors, our grasp of tumor immunology has reshaped oncology itself [43]. Perhaps the biggest shift has been realizing that cancer isn't just about cells growing out of control: it's also a disease of evading the immune system, and that reframing has changed how we treat it [110].

Tumors have developed remarkably sophisticated ways to dodge the immune system, even as the immune system retains real power to find and kill malignant cells [99]. Mapping out these evasion tactics: disrupted antigen presentation, checkpoint signaling, immunosuppressive cytokines, metabolic reprogramming and a hostile tumor microenvironment has given researchers concrete targets to aim for [165]. The existence of immune-controlled dormant metastases is a reminder of just how much immune surveillance matters in keeping disseminated disease in check, and why we need therapies that can sustain that control long-term [96].

Checkpoint inhibitors, adoptive cell therapies, and cancer vaccines have already changed outcomes for some patients, but real challenges remain [166]. Resistance, both primary and acquired, along with immune toxicities and the absence of good biomarkers, still limits how broadly these therapies can be used [167]. That said, progress in genomics, single-cell technology, and computational biology is moving fast enough that these obstacles feel increasingly solvable [133]. The path forward looks personalized: treatments tailored to each patient's specific tumor and immune biology [168]. New checkpoints, bispecific antibodies, engineered cell therapies, and nanotech delivery systems are all expanding what's possible [169]. But getting past resistance will take smart combination strategies that hit multiple evasion pathways at once, reshape the tumor microenvironment and strengthen immune function together [59]. Moving immunotherapy earlier, into adjuvant and neoadjuvant care, also holds real promise for stopping metastasis before it starts [170-173].

Ultimately, the goal is a durable, immune-driven control of cancer [77]. If we can fully harness the immune system, cancer could shift from being a fatal diagnosis to a manageable one, with durable remission and in many cases, cure within reach [116]. Getting there will take continued collaboration between basic immunology, translational research and clinical work, so that these gains eventually reach every patient with cancer [117].

Conflicts of Interest

The authors declare no conflicts of interest.

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