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The interplay between immune cells and the tumor microenvironment: from immunosurveillance to immunotherapy

Loris Brunner [1], Élise Chappuis [2], Alessio Rosselli [2,*]

1 Department of Clinical Research, Tumor Immunology, University of Bern, CH-3008 Bern, Switzerland
2 Division of Clinical Pathology, Institute of Pathology, University of Bern, CH-3008 Bern, Switzerland

* Address for Correspondences:
Alessio Rosselli
Division of Clinical Pathology, Institute of Pathology, University of Bern, CH-3008 Bern, Switzerland
E-mail: alessiorosselliii@gmail.com

Abstract

The immune system constitutes a highly coordinated network of cellular and molecular components that protect the host from infection, tissue injury, and malignant transformation. Immune cells, encompassing innate and adaptive lineages, serve as core effectors of this system. Innate immune cells, including macrophages, DCs, and NK cells, initiate rapid, nonspecific responses while shaping subsequent adaptive immunity. Adaptive immune cells, primarily T lymphocytes and B lymphocytes, mediate antigen-specific responses and long-term immunological memory. Within the tumor microenvironment (TME), these populations exhibit context-dependent functions, with cytotoxic subsets exerting tumor control and regulatory subsets facilitating immune evasion. TAMs, Tregs, and MDSCs exemplify immunosuppressive mechanisms, whereas cytotoxic $CD8^+$ T cells, NK cells, and DCs drive anti-tumor immunity. Cancer immunotherapy has harnessed these mechanisms, employing immune checkpoint inhibitors targeting PD-1, PD-L1, or CTLA-4, adoptive cell therapies such as chimeric antigen receptor T cell (CAR-T) therapy and tumor-infiltrating lymphocyte (TIL) therapy, as well as therapeutic cancer vaccines. Advances in single-cell RNA sequencing and spatial transcriptomics have revealed extensive cellular heterogeneity and spatial organization within the TME, uncovering mechanisms of immune suppression and therapeutic resistance.

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Integrating these high-dimensional approaches with rationally designed combination therapies provides a framework for personalized immunotherapy. This review presents a comprehensive overview of immune cell roles in tumor progression, immune evasion, and therapeutic intervention, highlighting strategies to exploit the immune landscape for durable clinical benefit.

KEYWORDS

Immune cells, Tumor microenvironment, Immunotherapeutic, Personalized therapy

Introduction

The immune system is a sophisticated and tightly regulated network of cellular and molecular components that collectively safeguard the host against infection, tissue injury, and malignant transformation(1). Immune cells serve as its core functional units and are broadly classified into innate or adaptive lineages. Innate immune cells, such as macrophages, dendritic cells (DC), and natural killer (NK) cells, form the first line of defense by initiating rapid but relatively nonspecific responses. They are responsible for pathogen recognition, antigen processing, and the activation of inflammatory cascades(2, 3). In contrast, adaptive immune cells, primarily T lymphocytes and B lymphocytes, generate highly specific responses to diverse antigens. T cells exert cytotoxic effects and orchestrate cellular immunity, whereas B cells secrete antibodies that provide durable humoral protection(4, 5). The coordinated interplay between innate and adaptive compartments enables both immediate defense and long-term immunological memory, processes indispensable for host survival.

The relationship between immune cells and cancer is particularly complex. Tumor progression represents a multistep process that is profoundly shaped by the tumor microenvironment (TME). Within this niche, immune cells exert dual and often opposing functions(6). Evidence has shown that interactions among immune components and tumor cells within the TME govern immune evasion strategies and determine tumor immunogenicity. Tumor-associated macrophages (TAMs), for example, may differentiate into M1-like or M2-like phenotypes depending on local cues, thereby influencing angiogenesis, invasion, or immune suppression(7). Tregs together with MDSCs further suppress cytotoxic T cell activity, which promotes immune escape and fostering therapeutic resistance(8). Conversely, anti-tumor immunity is strengthened and positively correlated with positive clinical responses when cytotoxic CD8 T cells, NK cells, or dendritic cells are activated(9).

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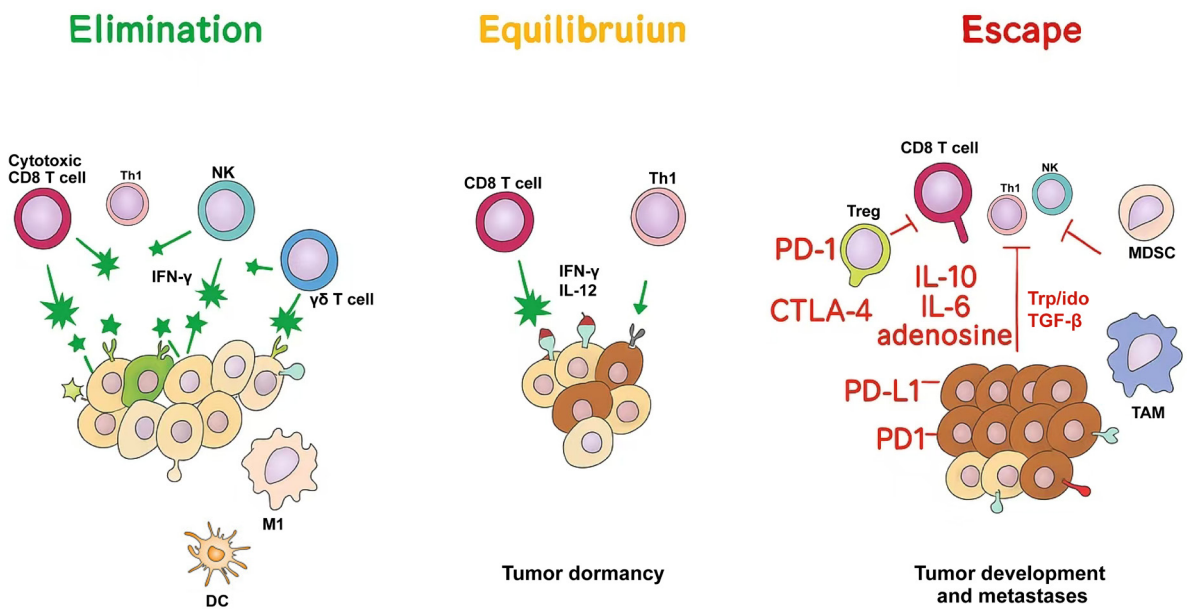

FIGURE 1
Immune mechanisms in cancer.

Cancer immunity is a dynamic game between tumors and the immune system, primarily consisting of three phases: elimination, equilibrium, and escape. During the elimination phase, DCs ingest and present tumor antigens, activating $CD4^+$ cells and $CD8^+$ cytotoxic T cells. These cells, in collaboration with NK cells, γδT cells, and M1 macrophages, kill highly immunogenic tumor cells through effector mechanisms such as IFN-γ and perforin/granzyme. Subsequently, in the equilibrium phase, the immune system relies on factors such as IFN-γ and IL-12 to suppress the growth of remaining tumor cells over a long period of time, rendering the tumor dormant. However, under continued pressure, some tumor cells gradually adapt to the immune environment through antigen loss or downregulation of MHC class I. Finally, in the escape stage, the tumor microenvironment is reshaped into an immunosuppressive state, with massive infiltration of Treg cells, MDSCs, and TAMs, which secrete inhibitory molecules such as IL-10, IL-6, TGF-β, and adenosine. At the same time, the function of effector T cells is weakened through PD-1/PD-L1, CTLA-4 signals, and IDO-mediated tryptophan depletion, allowing the tumor to break through immune surveillance and progress and metastasize. DCs: Dendritic cells; NK cells: Natural killer cells; MDSCs: Myeloid-derived suppressor cells.

Immunotherapy has become a pivotal strategy in therapy for cancer, complementing or even replacing conventional modalities such as surgery, chemotherapy, or radiotherapy. Targeting PD-1, PD-L1, or CTLA-4 immune checkpoint inhibitors have demonstrated durable clinical efficacy across multiple malignancies. Adoptive cell transfer approaches, including CAR-T therapy and TIL therapy, have shown remarkable success in hematologic cancers and are being actively explored for solid tumors(10). Cancer vaccines further expand therapeutic options. Moreover, unprecedented insights into tumor immunological heterogeneity have been made possible by developments in high-dimensional technologies like spatial transcriptomics and single-cell RNA sequencing, shedding light on immune evasion mechanisms and therapeutic resistance, thereby guiding the rational design of next-generation immunotherapies(11).

The goal of this study is to present a thorough summary of the diverse function of immune cells in the TME, tracing their

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contribution from immune surveillance to immune evasion and ultimately to immunotherapeutic intervention. By emphasizing recent advances in immune–tumor interactions and their clinical relevance, we seek to highlight the therapeutic potential of targeting the immune landscape in cancer.

Innate immune cells in tumors

Innate immune cells are the first line of defense against pathogens and transformed cells. Unlike adaptive immunity, which relies on antigen specificity and memory formation, innate immunity functions through germline-encoded pattern recognition receptors (PRRs) that rapidly detect damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs)(12). This system orchestrates immediate protective responses and shapes subsequent adaptive immunity. In cancer, innate immune cells play a multifaceted role, dependent on the cellular environment, functioning as both tumor promoters and suppressors, tumor stage, and microenvironmental factors. Among the innate immune cell population, macrophages are highly plastic and exhibit functional heterogeneity. ROS and proinflammatory cytokines are produced by classically activated M1-like macrophages, supporting tumor clearance(13). In contrast, alternatively activated M2-like macrophages promote tissue remodeling, angiogenesis, and immunosuppression. These TAMs often present an M2-like phenotype in the TME, thereby promoting tumor progression and impairing antitumor immunity(14, 15). DCs are essential for antigen presentation and T cell priming, but may lose their immunostimulatory capacity in tumors, leading to impaired cross-priming and a tolerant phenotype(16). NK cells are innate system cytotoxic lymphocytes that have the ability to destroy altered cells directly without first sensitizing them. However, their function is often impaired in solid tumors due to chronic exposure to immunosuppressive cytokines and downregulation of activating ligands on tumor cells(17). Similarly, neutrophils, once considered mere bystanders, are now recognized as active regulators of the TME. Tumor-associated neutrophils (TANs) can promote extracellular matrix remodeling, migration, and immunosuppression(18). In addition, immune evasion is encouraged by MDSCs, a diverse population of immature myeloid cells that proliferate in cancer and inhibit both innate and adaptive immune responses(19). Understanding the dynamic and often conflicting roles of innate immune cells is essential to unravel tumor-immune interactions.

Macrophages

Macrophages, which have great flexibility and context-dependent actions, are essential elements of the innate immune system. In the TME, they differentiate into TAMs, which often exhibit dual roles in either promoting or suppressing tumor development. Their functional phenotype is shaped by local cues, leading to polarization into classically activated M1-like or alternatively activated M2-like subtypes(20). M1-like macrophages are frequently triggered by microbial stimuli such as LPS or IFN-γ. They generate proinflammatory cytokines that improve antigen presentation and encourage cytotoxic T cell responses, including TNF-α, IL-12, and NO(21). M1-TAMs have been shown to be associated with tumoricidal activity, angiogenesis inhibition, and good prognosis in certain cancers. In esophageal squamous cell carcinoma, reduced lymph node metastases and an improved clinical stage were substantially correlated with a high density of M1-TAMs in tumor nests and stroma(22). In ovarian cancer, M1-TAMs inhibit tumorigenesis, invasion, and metastasis by regulating the TME(23). In contrast, M2-like macrophages are stimulated by IL-4, IL-10, or IL-13 and are characterized by the expression of arginase-1, CD206, and IL-10(24). The TME is usually dominated by pro-tumor M2-type TAMs, which promote angiogenesis, immunosuppression, and metastasis. For example, the abundance of M2 macrophages in bladder cancer is negatively correlated with chemotherapy response(25). In breast cancer, studies have found that M2-TAMs accelerate proliferation and migration by reducing the expression of interferon regulatory factors(26). Similarly, M2-TAMs dominate the TME and help cancer cells escape by

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suppressing immune responses. Their substantial infiltration is strongly linked to a bad prognosis for a number of malignancies, such as triple-negative breast cancer and colorectal cancer(27). In vivo, TAMs typically exhibit a mixed M1/M2 phenotype, which is affected by tumor-derived signals, metabolic state, and hypoxic conditions(28). Given their abundance and plasticity, TAMs are attractive targets for therapeutic reprogramming.

Dendritic cells (DCs)

DCs are expert antigen-presenting cells that serve as a crucial link between adaptive and innate immunity. By capturing tumor antigens and presenting them to T cells, they play a crucial role in triggering anti-tumor T cell responses. Within the TME, DC activity is tightly regulated by local signaling cues, metabolic stress, and immunosuppressive mediators. Immature DCs display strong phagocytic capacity but remain inefficient in activating T cells(29). Upon exposure to tumor-associated antigens and maturation stimuli such as Toll-like receptor ligands or type I interferons, DCs upregulate costimulatory molecules (e.g. CD80, CD86), secrete cytokines (e.g. IL-12), and migrate to lymphoid tissues, where they present peptide-MHC complexes to CD4⊠ and CD8⊠ T cells, initiating robust cytotoxic responses(30).

Multiple DC subsets exhibit distinct functions, with their distribution and activity varying across cancer types. Conventional DCs, particularly cDC1, are indispensable for cross-presenting antigens to CD8⊠ T cells and are essential for anti-tumor immunity(31). A good prognosis for breast cancer has been linked to high cDC1 infiltration(32). In contrast, plasmacytoid DCs (pDCs) have also been identified in breast cancer, where their infiltration strongly correlates with poor prognosis, for instance in cases with MAL2 overexpression, suggesting an immunosuppressive function(33). Recently, two novel subsets, CD1C⊠CD141⊠ DCs and CD1C⊠_B DCs, were reported in oral squamous cell carcinoma, with the potential to reshape the local immune landscape(34).

DCs thus exert dual roles: promoting immune activation against cancer while maintaining tolerance to self-antigens. Their functional state ultimately determines the efficacy of anti-tumor immunity. Owing to this central antigen-presenting capacity, DCs have become a cornerstone of cancer immunotherapy. DC-based vaccines, in particular, are being developed to deliver tumor antigens within immunogenic environments(35), aiming to reinvigorate T cell-mediated anti-tumor responses.

NK cells

NK cells are cytotoxic innate lymphocytes that play a pivotal role in immune surveillance against virally infected and malignant cells. Unlike T cells, NK cells recognize targets in an antigen-independent manner, primarily through a balance of activating and inhibitory signals mediated by germline-encoded receptors(36). A defining feature of NK cell recognition is their ability to detect cells with reduced or absent major histocompatibility complex class I (MHC I) expression, a phenomenon frequently observed during tumorigenesis(37). This “missing self” mechanism enables NK cells to eliminate tumor cells that escape cytotoxic T lymphocyte-mediated immunity. Clinical evidence indicates that high NK cell infiltration within tumors correlates with favorable prognosis in multiple malignancies, including colorectal cancer and leukemia, thereby driving interest in NK cell-based immunotherapies(38, 39).

Activated NK cells employ diverse strategies to exert anti-tumor effects. The release of cytolytic granules containing granzymes and perforins causes direct cytotoxicity by causing target cells to undergo apoptosis(40). Additionally, NK cells generate cytokines like IFNγ, which influence the immune system and increase the activity of T cells, macrophages, and other effector cells(41). Experimental studies have further demonstrated that co-culture of NK cells with ovarian cancer cells leads to enhanced cytotoxicity and increased apoptosis when angiopoietin-like protein 3 (ANGPTL3) is overexpressed, suggesting that ANGPTL3 augments NK cell-mediated anti-tumor responses(42). Despite their potent cytolytic capacity, NK cells are often functionally impaired within the TME. Hypoxia and tumor-derived substances including prostaglandin E2 and TGF-β inhibit NK cell function by downregulating activating receptors like NKp30 and NKG2D, while also limiting infiltration, survival, and effector functions(43). Consequently, strategies to restore NK cell activity and enhance their persistence in tumors represent promising therapeutic approaches.

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Myeloid-derived suppressor cells (MDSCs)

Within the TME, MDSCs are a diverse population of immature myeloid cells with strong immunosuppressive properties. They arise from disrupted myelopoiesis under chronic inflammatory conditions, a process driven by tumor-derived factors such as GM-CSF, VEGF, and IL-6(44). MDSCs exert immunosuppressive effects primarily through the depletion of essential amino acids such as L-arginine and L-cysteine, the production of ROS and NO, and the upregulation of immune checkpoint molecules(45, 46). These activities impair T cell growth, induce apoptosis, and promote the differentiation of Tregs, thereby creating an immunosuppressive niche conducive to tumor progression(47). Beyond T cell inhibition, MDSCs engage in interactions with other TME elements, including NK cells, DCs, and TAMs, modulating their activity to favor tumor growth and metastasis.

Emerging evidence highlights the dynamic plasticity of MDSCs, allowing them to adapt to diverse tumor-derived signals and microenvironmental cues. In breast cancer tissue, early-stage MDSCs have been discovered as a newly defined subpopulation that possesses stronger immunosuppressive capacity than classical MDSCs. They accumulate in the TME and significantly suppress immune responses. The increase in these cells is directly correlated with poor patient prognosis(48). In animal models of osteosarcoma, MDSCs promote tumor progression in the TME through immunosuppressive mechanisms, such as suppression of T cell function(49). Research is focusing on targeting MDSCs as a therapeutic strategy, such as using the drug atovaquone to reduce the number of MDSCs to increase the immunotherapy's effectiveness and improve anti-tumor activity(50). In summary, MDSCs constitute a central barrier to effective antitumor immunity. Their multifaceted interactions with immune and stromal components of the TME underscore their importance as both biomarkers of disease progression and therapeutic targets.

Adaptive immune cells in tumors

Adaptive immune cells are central orchestrators of antigen-specific responses, capable of mounting precise attacks against malignant cells while retaining long-term memory. Within the TME, T lymphocytes and B cells, as the two principal components of the adaptive immune system, exert distinct yet interconnected influences on tumor progression and therapeutic outcomes. Their degree of infiltration, functional status, and spatial distribution collectively shape whether the immune milieu supports tumor suppression or facilitates immune evasion. CTLs serve as the primary effectors of direct tumor cell elimination. Their activation relies on the recognition of tumor-derived peptides presented by MHC molecules on APCs, triggering cytolytic activity and cytokine release(51). CD4⊠ helper T cells (Th cells) further amplify these responses by delivering essential costimulatory signals and polarizing immunity through distinct cytokine programs(52).

Although historically underestimated in cancer immunology, B cells also contribute significantly to anti-tumor defense. They mediate antibody production, present antigens, and organize tertiary lymphoid structures (TLS). These immune aggregates facilitate high-affinity antibody generation and promote T cell priming, often reflecting an active and coordinated anti-tumor response(53). Yet, B cells may also adopt regulatory or immunosuppressive phenotypes, underscoring their functional heterogeneity within tumors. Recognizing both the protective and tolerogenic roles of adaptive immune cells is essential for the rational design of immunotherapies. Important information on immune escape mechanisms and treatment resistance will be revealed by a more thorough description of their molecular characteristics and interactions within the TME, ultimately guiding the development of more precise and durable therapeutic strategies.

T Cells

T cells serve as the central effectors of adaptive immunity,

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playing a crucial role in tumor recognition and elimination. Antigen-specific TCRs, which identify tumor-derived peptides displayed by MHC class I or II molecules on antigen-presenting cells or tumor cells, mediate their function. When cytotoxic CD8 T cells identify peptide–MHC I complexes, they release granzymes and perforin to carry out specific immune responses, which causes tumor cell death(54). CD4⊠ helper T cells support this process through cytokine secretion, enhancing the activation, persistence, and functionality of CD8⊠ T cells and other immune populations(55). Many tumors, however, evade immunity by downregulating or losing MHC I expression, thereby impairing CD8⊠ T cell recognition and enabling uncontrolled tumor growth. For instance, colorectal cancer cells promote CD8⊠ T cell exhaustion via the TSH/TSHR signaling pathway, leading to functional inhibition and elevated PD-1 expression. In such contexts, CD4⊠ T cells and NK cells may partially compensate by recognizing tumor antigens through alternative mechanisms, but overall anti-tumor efficacy is frequently compromised(56). TILs, particularly CD8⊠ T cells, are widely regarded as favorable prognostic markers across multiple cancer types, including melanoma and colorectal cancer(57). Nonetheless, chronic antigen exposure and persistent immunosuppressive signaling within the TME often induce T cell exhaustion. T cells that are exhausted exhibit decreased cytokine production, poor effector function, and increased expression of inhibitory receptors as TIM-3, LAG-3, and PD-1, ultimately limiting effective anti-tumor immunity.

B Cells

Historically known for their function in humoral immunity, B cells have become crucial TME modulators of anti-tumor responses. These cells detect tumor-associated antigens via surface immunoglobulin receptors and, upon activation, differentiate into antibody-producing plasma cells or memory B cells. Through antigen presentation, cytokine secretion, and antibody production, B cells contribute both to direct tumor control and to the coordination of broader immune responses. Unlike cytotoxic T lymphocytes, which rely on MHC I-mediated recognition, B cells can respond to soluble or surface-bound antigens independent of MHC restriction. T cell activation is facilitated by B cells' internalization and processing of tumor antigens after antigen contact, which is then presented to CD4 T helper cells on MHC class II molecules. B cells serve as expert antigen-presenting cells in this role, boosting T cell-mediated immunity.

Through complement activation or ADCC, B cell-derived antibodies mediate tumor cell killing, further amplifying anti-tumor actions. TIBs and TLSs within the TME are frequently associated with improved prognosis in cancers such as melanoma and renal cell carcinoma(58). As localized immunological hubs, TLSs facilitate class switching, somatic hypermutation, and B cell maturation, all of which increase the generation of high-affinity antibodies. Their presence generally corresponds with greater CD8⊠ T cell infiltration and higher responsiveness to immune checkpoint drugs. Despite these protective roles, B cells can also exert immunosuppressive effects. In tumors of the digestive system, including esophageal, liver, gastric, and pancreatic cancers, specific B cell subsets facilitate tumor progression by influencing proliferation, differentiation, and migration(59). Certain tumors can even exploit bone marrow B precursor cells, converting them into macrophage-like cells with immunosuppressive functions, thereby promoting metastasis.

Advances in cancer immunotherapy

Over the past two decades, cancer immunotherapy has reshaped oncology by offering strategies that harness the immune system to recognize and eliminate malignant cells. In contrast to traditional therapies that use radiation or cytotoxic drugs to directly target cancers, immunotherapy modulates immune responses to restore or enhance tumor-specific immunity. This paradigm shift reflects a deeper understanding of immune cell biology, tumor immune evasion, and the complex interactions within the TME.

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Checkpoint blockade therapy, which disrupts inhibitory pathways such as PD-1/PD-L1 and CTLA-4, has shown remarkable efficacy in malignancies including melanoma and renal cell carcinoma. By reinvigorating exhausted T cells, even in individuals with severe illness, these substances can provide long-lasting effects. Nevertheless, clinical benefit varies, as intrinsic or acquired resistance remains a major challenge. This has prompted efforts to identify predictive biomarkers and develop combinatorial approaches that enhance response rates and circumvent immune escape.

Adoptive cell therapies, including CAR-T cells and TIL therapies, offer additional promise. These approaches involve in vitro modification of patient-derived immune cells to improve specificity and cytotoxic potential prior to reinfusion. While antigen heterogeneity, TME-mediated suppression, and poor trafficking limit the effectiveness of CAR-T treatments in solid tumors, they have shown unparalleled success in hematologic malignancies. Concurrently, therapeutic cancer vaccines and oncolytic viruses are being explored to generate de novo immune responses against tumor antigens, broadening antigen recognition and promoting long-term immune surveillance.

Future progress in immunotherapy relies on an integrative understanding of dynamic interactions between immune cells and tumor tissues. Advances in single-cell profiling, spatial transcriptomics, and systems immunology are accelerating the dissection of these interactions, enabling the design of personalized immunotherapeutic strategies.

Immune checkpoint inhibitors (ICIs)

By reviving anti-tumor T cell activity, ICIs have transformed the therapy of several cancers. These substances focus on inhibitory mechanisms that cancers use to avoid immune surveillance, most notably the PD-1/PD-L1 axis and CTLA-4. Under physiological conditions, these checkpoints prevent autoimmunity and maintain immune homeostasis. Within the TME, however, persistent antigen exposure and chronic inflammation upregulate these inhibitory signals, leading to T cell exhaustion and impaired cytotoxicity(60).

Monoclonal antibodies blocking PD-1 or PD-L1 can reinvigorate exhausted CD8⊠ T cells, restoring proliferative capacity and cytokine production. This strategy has demonstrated substantial clinical benefit in more cancers. CTLA-4 blockade, in contrast, enhances T cell priming by promoting co-stimulatory signaling during antigen presentation. CTLA-4 inhibitors, such as ipilimumab, have been evaluated in esophageal cancer(61). Combined PD-1 and CTLA-4 inhibition produces synergistic effects, particularly in melanoma and microsatellite instability-high (MSI-H) tumors. In MSI-H/dMMR colorectal cancer, ICIs improve T cell recognition and elimination of malignant cells(62). By contrast, patients with pMMR/MSS tumors, especially stage IV colorectal cancer, exhibit low response rates to monotherapy, prompting investigation into combinatorial strategies to overcome this limitation. Despite their transformative potential, ICIs are not universally effective. A substantial proportion of patients display primary resistance or develop immune escape mechanisms over time, underscoring the need for predictive biomarkers and novel combination approaches to optimize clinical outcomes.

Adoptive cell therapy (ACT)

Autologous or allogeneic immune cells with increased anti-tumor potential are isolated, expanded in vitro, and then reinfused as part of the highly customized immunotherapeutic technique known as ACT. Unlike immune checkpoint blockade, which aims to restore endogenous immune function, ACT directly delivers tumor-reactive lymphocytes into patients, often following genetic or functional modification. This strategy has demonstrated remarkable clinical efficacy, particularly in hematologic malignancies, and is increasingly investigated in solid tumors(63).

Among ACT modalities, CAR-T cell therapy has gained the most attention. Instead of requiring antigen presentation via MHC I, CAR-T cells are designed to generate synthetic receptors that identify tumor-associated antigens in an MHC-independent way, which is frequently downregulated in many cancers(64). This characteristic provides a distinct advantage in tumors that evade immune detection through MHC I loss. While CD19-directed CAR-T therapy has transformed the treatment of B cell malignancies by causing long-lasting remissions in diffuse large B-cell lymphoma and relapsed or refractory acute lymphoblastic leukemia, CAR-T therapies that target antigens like GPC3 have demonstrated promise in hepatocellular carcinoma(65).

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Another ACT tactic is TIL treatment, which uses resected tumor materials to stimulate the growth of naturally existing tumor-specific T lymphocytes. These cells, often enriched for neoantigen-specific TCRs, mediate potent anti-tumor responses upon reinfusion following lymphodepletion. TIL therapy has produced durable responses in metastatic melanoma and is under evaluation for other solid tumor types(66). Integrating ACT with additional immunomodulatory agents may further enhance therapeutic efficacy and extend clinical benefit to patients with otherwise refractory cancers.

Cancer vaccine development

By exposing TAAs or TSAs to an immunogenic environment, cancer vaccines aim to activate the host immune system to identify and destroy tumor cells. Unlike prophylactic vaccines targeting infectious agents, therapeutic cancer vaccines aim to activate pre-existing immune cells or induce de novo responses against established malignancies. This strategy offers the potential for precise and durable tumor control, particularly when combined with other immunomodulatory therapies. Early generations of cancer vaccines targeted shared TAAs such as MUC1, HER2, or PSA; however, limited immunogenicity and susceptibility to immune tolerance restricted their clinical efficacy. The discovery of patient-specific neoantigens—non-self peptides resulting from somatic mutations—has been made possible by developments in next-generation sequencing and bioinformatics. These neoantigens are less prone to central tolerance, rendering them highly attractive for personalized vaccine platforms(67).

Several delivery methods have been created to improve T cell activation and antigen presentation, including peptide-based, DNA/RNA-based, DC-based, and viral vector-based vaccines. Among these, mRNA vaccines have gained prominence due to favorable safety, rapid manufacturing, and the ability to elicit both CD4⊠ and CD8⊠ T cell responses. Individualized neoantigen mRNA vaccines have demonstrated immunogenicity and early signs of clinical benefit in melanoma and pancreatic cancer trials(68, 69). DC vaccines, exemplified by sipuleucel-T for metastatic prostate cancer, employ in vitro–loaded autologous DCs to prime patient T cells(70). Although survival benefits have been modest, these approaches highlight the feasibility of cell-based vaccination. Strategies to enhance vaccine potency include co-delivery with adjuvants, induction of immunogenic cell death, and combination with checkpoint inhibitors to counteract tumor-induced tolerance. The dynamic and immunosuppressive nature of the TME remains a major barrier to efficacy. With ongoing technological advances, cancer vaccines are expected to become key components of personalized immunotherapy, providing tailored solutions for tumors with high mutational heterogeneity.

Combination therapy strategies

Owing to intrinsic tumor resistance mechanisms and the immunosuppressive TME, a substantial proportion of patients exhibit limited or transient responses to immunotherapy. Consequently, combination therapy strategies have emerged as a critical approach to enhance anti-tumor immunity, broaden patient benefit, and overcome resistance. One rational strategy involves combining ICIs with conventional treatments such as chemotherapy or radiotherapy. Chemotherapeutic agents can increase tumor antigen release and induce immunogenic cell death, thereby activating the immune system. For instance, in advanced non-small cell lung cancer, ICI combined with paclitaxel significantly prolongs PFS and OS, establishing a standard treatment option(71). For NSCLC patients with acquired resistance to EGFR-TKIs, immunotherapy combined with chemotherapy provides an additional therapeutic avenue. Radiotherapy not only induces DNA damage but also promotes the release of DAMPs, stimulating dendritic cell activation and T cell recruitment. In locally advanced rectal cancer, radiotherapy combined with ICIs achieves high pCR rates, including in microsatellite stable tumors(72); in muscle-invasive bladder cancer, this combination aims to preserve bladder function while reducing surgical intervention(73).

Combining ICIs with targeted therapies, such as tyrosine kinase inhibitors or angiogenesis inhibitors, represents another promising approach. These agents can normalize tumor vasculature, alleviate hypoxia, and restrict the growth of myeloid-derived suppressor cells or regulatory T cells in the TME. For example, anti-VEGF therapy combined with PD-1 blockade demonstrates superior efficacy over monotherapy in hepatocellular carcinoma(74). Integrative

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strategies involving cancer vaccines or oncolytic viruses with ICIs are under active investigation, as they can expand the T cell repertoire and enhance tumor-specific immunity, particularly in tumors with low neoantigen burden. Additionally, adoptive cell therapies, including CAR-T cells or TILs, are being combined with cytokines, immune agonists, or checkpoint inhibitors to improve persistence, trafficking, and resistance to immunosuppression. In head and neck squamous cell carcinoma, neoantigen vaccines combined with ACT and ICIs are undergoing clinical trials to overcome immunotherapy resistance(75). Tailored combination regimens are expected to convert transient immune responses into durable clinical benefit across diverse tumor types.

Application of single-cell sequencing (scRNA-seq) and spatial omics in TME research

Recent developments in spatial transcriptomics and scRNA-seq have revolutionized our knowledge of the TME. scRNA-seq has uncovered extensive heterogeneity among tumor-infiltrating immune cells, including distinct T cell subsets, macrophages, dendritic cells, and myeloid-derived suppressor cells(76). These studies have identified novel regulatory circuits and immunosuppressive pathways that contribute to therapeutic resistance. For instance, exhausted T cell subsets expressing different checkpoint receptors are linked to heterogeneous responses to PD-1 blockade.

Spatial omics complements single-cell analyses by preserving tissue architecture, enabling contextual interpretation of transcriptional programs. Techniques such as spatial transcriptomics, imaging mass cytometry, and multiplexed ion beam imaging allow visualization of spatially defined immune niches, tertiary lymphoid structures, and tumor-stroma interfaces. These approaches have revealed spatially restricted immunosuppressive gradients and proximity-dependent cellular interactions that modulate immune infiltration and effector function(77).

Finding treatment targets and prognostic biomarkers is made easier by combining single-cell and geographical data to create a systems-level perspective of the TME(78). This combined approach informs rational immunotherapy design, guides the development of optimized combination strategies, and supports the advancement of personalized cancer treatment.

Conclusion

In summary, cancer genesis, progression, and treatment results are influenced by the complex interactions between immune cells and the TME. Innate and adaptive immune populations exhibit context-dependent functions, with cytotoxic effectors mediating tumor control while regulatory subsets facilitate immune evasion. Immunotherapeutic interventions, including checkpoint blockade, adoptive cell transfer, and cancer vaccines, have harnessed these mechanisms to restore anti-tumor immunity, yet heterogeneous responses and resistance remain major challenges. Unprecedented variability and spatial organization within the TME have been revealed by developments in single-cell and spatial omics technology, providing mechanistic insights into immune suppression and therapy failure. Integrating these high-dimensional approaches with rationally designed combination therapies holds the potential to overcome resistance, refine patient stratification, and guide personalized interventions. A deeper mechanistic understanding of immune–tumor interactions will be essential for the development of next-generation immunotherapies capable of achieving durable clinical benefit across diverse malignancies.

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