TUMOR MICROENVIRONMENT: EMERGING INSIGHTS INTO CANCER PROGRESSION AND THERAPEUTIC TARGETS - A NARRATIVE REVIEW

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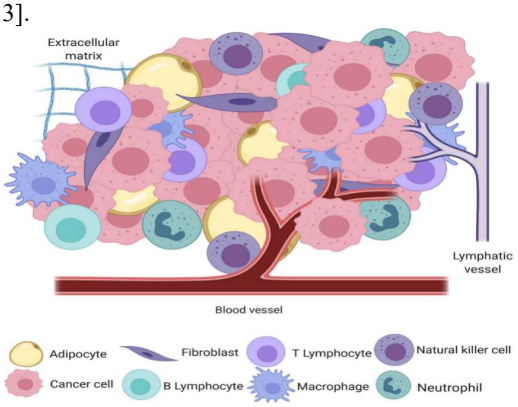
ABSTRACT
The tumor microenvironment (TME) is increasingly recognized as a dynamic and biologically active ecosystem that profoundly influences cancer initiation, progression, metastasis, immune escape, and therapeutic resistance. Rather than functioning as an isolated mass of malignant cells, a tumor consists of complex interactions among cancer cells, immune cells, cancer-associated fibroblasts, endothelial cells, pericytes, extracellular matrix components, soluble mediators, and metabolic factors. These interactions create spatially and temporally heterogeneous niches that can either restrain or promote malignant progression. Tumor-associated macrophages, regulatory T cells, myeloid-derived suppressor cells, dysfunctional dendritic cells, and exhausted T lymphocytes are major contributors to immunosuppression, whereas cancer-associated fibroblasts and extracellular matrix remodeling facilitate invasion, angiogenesis, and treatment resistance. Hypoxia and abnormal tumor vasculature further promote aggressive phenotypes through hypoxia-inducible factors and vascular endothelial growth factor-dependent pathways. The development of immune checkpoint inhibitors targeting programmed cell death protein 1, programmed death-ligand 1, and cytotoxic T-lymphocyte-associated protein 4 has demonstrated that therapeutic manipulation of the TME can produce durable clinical responses. Nevertheless, primary and acquired resistance remain major challenges. Recent advances include combination checkpoint blockade, vascular normalization, targeting of cancer-associated fibroblasts and tumor-associated macrophages, bispecific antibodies, adoptive cellular therapies, personalized cancer vaccines, metabolic interventions, and spatially resolved molecular profiling. This narrative review summarizes the major cellular and non-cellular components of the TME, tumor–immune interactions, angiogenesis and stromal responses, immune checkpoint pathways, clinical implications, recent therapeutic advances, and future opportunities for TME-directed precision oncology. A deeper understanding of the evolving and heterogeneous nature of the TME is essential for developing rational combination strategies capable of converting immunologically resistant tumors into therapeutically responsive states.

Keywords: Tumor microenvironment; cancer progression; tumor immunity; cancer-associated fibroblasts; tumor-associated macrophages; angiogenesis; immune checkpoints; immunotherapy; therapeutic resistance; precision oncology.
How to cite this article: Singla D, Singhal S, Sharma S. Tumor microenvironment: emerging insights into cancer progression and therapeutic targets - a narrative review. Int J Drug Deliv Technol. 2026;16(73s): 424-446. DOI: 10.25258/ijddt.16.73s.48

INTRODUCTION

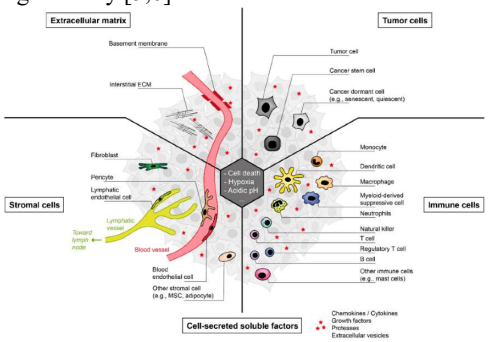
Cancer is a multifactorial and biologically heterogeneous disease that remains one of the leading causes of morbidity and mortality worldwide. Although genetic mutations, epigenetic alterations, and dysregulated intracellular signaling are fundamental drivers of malignant transformation, increasing evidence indicates that tumor progression is not governed solely by intrinsic abnormalities of cancer cells. Instead, cancer develops within a highly organized and continuously evolving tissue ecosystem known as the **tumor microenvironment (TME)**. The TME consists of malignant cells interacting with a diverse population of non-malignant stromal and immune cells, extracellular matrix (ECM), blood and lymphatic vessels, soluble mediators, extracellular vesicles, and metabolic components. These interactions establish a dynamic communication network that profoundly influences tumor initiation, growth, invasion, metastasis, immune escape, and therapeutic responsiveness [1–

3].



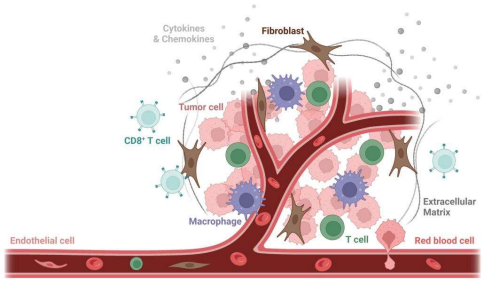
Rather than serving as a passive scaffold, the TME actively shapes cancer biology through reciprocal signaling between tumor cells and surrounding host tissues. Cancer-associated fibroblasts (CAFs), endothelial cells, pericytes, tumor-associated macrophages, dendritic cells, neutrophils, natural killer cells, regulatory T cells, and myeloid-derived suppressor cells collectively regulate extracellular matrix remodeling, inflammatory responses, angiogenesis, and immune surveillance. Simultaneously, tumor cells modify the surrounding environment by secreting cytokines, chemokines, growth factors, matrix-remodeling enzymes, and extracellular vesicles that promote stromal activation and facilitate malignant progression. Consequently, the TME has emerged as a critical determinant of both disease aggressiveness and clinical outcome [2,4].

One of the defining characteristics of the TME is its remarkable spatial and temporal heterogeneity. Distinct regions within the same tumor may exhibit substantial differences in immune-cell infiltration, vascular density, stromal composition, oxygen availability, nutrient supply, extracellular acidity, and metabolic activity. Hypoxia, a hallmark of most solid tumors, activates hypoxia-inducible signaling pathways that promote angiogenesis, metabolic reprogramming, epithelial–mesenchymal transition, invasion, and resistance to chemotherapy, radiotherapy, and immunotherapy. Continuous remodeling of the extracellular matrix further alters tissue stiffness and cellular migration, creating physical as well as biochemical barriers that influence tumor dissemination and therapeutic drug delivery [5,6].



The tumor immune microenvironment (TIME), a specialized functional component of the TME, has gained unprecedented attention with the rapid development of cancer immunotherapy. Immune checkpoint inhibitors targeting programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) have revolutionized the management of several malignancies by restoring antitumor immune responses. Nevertheless, only a subset of patients achieves durable clinical benefit because the immunosuppressive TME frequently promotes T-cell exhaustion, impaired antigen presentation, abnormal vascularization, metabolic competition, and recruitment of suppressive immune populations. These mechanisms collectively contribute to both primary and acquired resistance to immunotherapy, highlighting the need for combination strategies that simultaneously target tumor cells and their surrounding ecosystem [7–9].

Current oncology has therefore shifted from a tumor-centric paradigm toward an ecosystem-based model in which the TME is recognized as both a prognostic biomarker and a therapeutic



target. Advances in spatial transcriptomics, single-cell sequencing, multiplex imaging, and artificial intelligence-assisted tissue profiling have substantially improved our understanding of cellular interactions within the TME, enabling the identification of novel therapeutic targets and predictive biomarkers. Contemporary therapeutic approaches increasingly aim to normalize tumor vasculature, remodel stromal architecture, reverse immune suppression, and reprogram metabolic pathways in order to enhance treatment efficacy. This narrative review summarizes the current understanding of the cellular and molecular components of the tumor microenvironment, tumor–immune interactions, angiogenesis, stromal remodeling, immune checkpoint pathways, and emerging TME-directed therapeutic strategies that are reshaping precision oncology [10].

METHODOLOGY

This narrative review was prepared through a structured literature search of major biomedical databases and scientific resources, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Relevant peer-reviewed articles published predominantly between 2015 and 2026

were considered, while earlier landmark publications were included when necessary to provide historical or mechanistic context.

Search terms were used individually and in combination, including “tumor microenvironment,” “tumor immune microenvironment,” “cancer-associated fibroblasts,” “tumor-associated macrophages,” “myeloid-derived suppressor cells,” “tumor angiogenesis,” “extracellular matrix,” “immune checkpoint inhibitors,” “PD-1,” “PD-L1,” “CTLA-4,” “immunotherapy resistance,” “hypoxia,” “metabolic reprogramming,” “spatial transcriptomics,” and “TME therapeutic targets.”

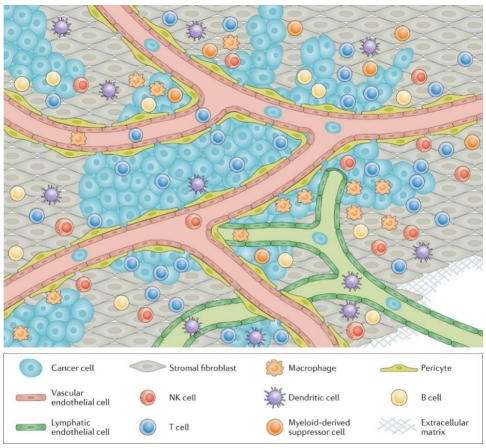
Priority was given to high-quality narrative and systematic reviews, landmark mechanistic studies, translational investigations, and clinically relevant publications concerning the biological and therapeutic importance of the TME. Studies were included when they addressed the cellular or non-cellular composition of the TME, mechanisms of cancer progression and immune escape, angiogenic and stromal responses, therapeutic resistance, biomarkers, or emerging TME-directed treatment strategies. Articles with limited relevance to the predefined scope were excluded.

Because this was a narrative rather than systematic review, formal meta-analysis, quantitative evidence synthesis, and risk-of-bias assessment were not performed. The selected literature was synthesized thematically to provide an integrated overview of established concepts and emerging developments.

LITERATURE REVIEW

Concept and Biological Organization of the Tumor Microenvironment

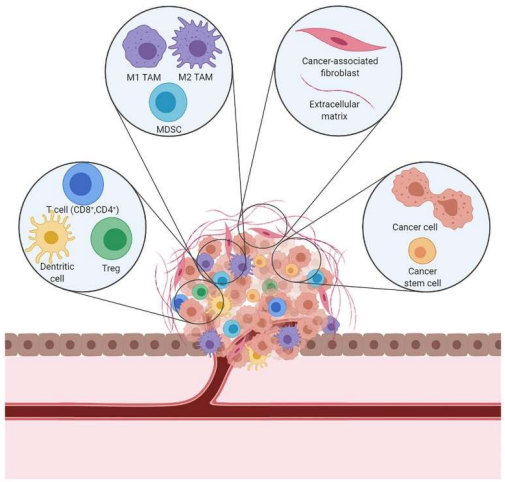
The tumor microenvironment (TME) is now recognized as a highly organized and dynamic biological ecosystem rather than a passive structural framework surrounding malignant cells. It comprises a heterogeneous network of cancer cells, immune cells, stromal cells, endothelial cells, pericytes, extracellular matrix (ECM), soluble mediators, extracellular vesicles, metabolites, and biomechanical components that continuously communicate through direct cell-to-cell contact and complex molecular signaling pathways. These reciprocal interactions regulate virtually every stage of tumorigenesis, including malignant transformation, tumor growth, angiogenesis, invasion, metastasis, immune modulation, and therapeutic response. Importantly, the TME evolves throughout disease progression, adapting to changes in tumor biology and selective pressures imposed by anticancer therapies, thereby contributing to tumor plasticity and treatment resistance [11–13].



Malignant cells are the primary architects of the TME. Through the secretion of cytokines, chemokines, growth factors, matrix metalloproteinases (MMPs), and extracellular vesicles such as exosomes, tumor cells actively remodel their surrounding environment to create conditions favorable for survival and expansion. Cytokines including transforming growth factor-β (TGF-β), interleukin-6 (IL-6), interleukin-10 (IL-10), and vascular endothelial growth factor (VEGF) stimulate angiogenesis, suppress antitumor immunity, and recruit stromal and inflammatory cells that further reinforce tumor progression. Likewise, extracellular vesicles transport proteins, nucleic acids, lipids, and microRNAs that modify the phenotype of neighboring stromal and immune cells, promote extracellular matrix remodeling, facilitate pre-metastatic niche formation, and contribute to therapeutic resistance. Consequently, the TME should be regarded as a continuously evolving communication network in which tumor cells actively educate surrounding tissues to support malignant behavior [11,14].

The biological organization of the TME is characterized by remarkable spatial, temporal, and functional heterogeneity. Considerable variability exists not only among different cancer types but also among patients with the same malignancy and even within separate regions of an individual tumor. Differences in stromal density, immune-cell composition, vascular architecture, extracellular matrix organization, oxygen availability, nutrient gradients, pH, and metabolic activity generate distinct intratumoral niches with unique biological properties. Hypoxic regions frequently exhibit increased stabilization of hypoxia-inducible factors (HIFs), enhanced glycolytic metabolism, angiogenic signaling, epithelial–mesenchymal transition, and resistance to chemotherapy, radiotherapy, and immunotherapy. Conversely, relatively well-vascularized tumor regions may demonstrate improved immune-cell infiltration and greater sensitivity to therapeutic interventions. This intratumoral heterogeneity represents a major obstacle to precision oncology because individual

tumor regions may respond differently to the same treatment strategy [12,15].



Among the various components of the TME, the tumor immune microenvironment (TIME) has emerged as a particularly important determinant of clinical outcome. Based on the pattern of immune-cell infiltration, tumors are broadly categorized into three major immune phenotypes: immune-inflamed, immune-excluded, and immune-desert. Immune-inflamed ("hot") tumors are characterized by abundant infiltration of activated $CD8^+$ cytotoxic T lymphocytes, dendritic cells, natural killer cells, and interferon-γ-associated inflammatory signaling. These tumors often exhibit increased expression of immune checkpoint molecules such as PD-1 and PD-L1 and generally demonstrate superior responsiveness to immune checkpoint inhibitors. Nevertheless, persistent antigen stimulation within these tumors may eventually induce T-cell exhaustion, necessitating combination therapeutic approaches that restore immune function while simultaneously overcoming additional suppressive mechanisms [16,17].

In contrast, immune-excluded tumors contain substantial immune-cell populations that accumulate predominantly within the stromal compartment or at the invasive tumor margin but fail to penetrate the malignant cell nests. Multiple biological mechanisms contribute to this phenomenon, including dense extracellular matrix deposition, activation of cancer-associated fibroblasts, abnormal vascular architecture, increased interstitial pressure, and immunosuppressive cytokines such as TGF-β. These stromal and vascular barriers physically and functionally prevent effective contact between cytotoxic lymphocytes and tumor cells, thereby limiting the efficacy of immunotherapy despite the presence of immune cells. Therapeutic strategies targeting stromal remodeling, vascular normalization, or TGF-β signaling are therefore being actively investigated to convert immune-excluded tumors into immune-responsive phenotypes [18].

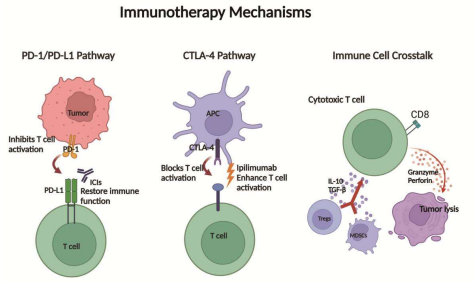
Immune-desert ("cold") tumors represent the most immunologically inactive phenotype and are characterized by minimal T-cell infiltration, poor antigen presentation, defective dendritic-cell activation, low tumor immunogenicity, and profound immune ignorance. These tumors frequently display limited responsiveness to immune checkpoint blockade because effective antitumor immune responses are absent from the outset. Current research focuses on converting immune-desert tumors into immune-inflamed lesions through therapeutic vaccination, oncolytic viruses, adoptive cellular therapies, epigenetic modulation, and combination immunotherapy approaches. Increasing evidence indicates that successful cancer treatment depends not merely on the presence of immune cells but also on their spatial localization, functional activation, metabolic fitness, interaction with stromal components, and exposure to inhibitory checkpoint pathways. Therefore, understanding the biological organization of the TME has become fundamental for developing personalized therapeutic strategies and improving long-term clinical outcomes in oncology [19,20].

Major Components of the Tumor Microenvironment

Malignant Cells

Malignant cells are the principal drivers of tumor initiation and progression and function as the central architects of the tumor microenvironment (TME). Rather than existing in isolation, cancer cells continuously interact with surrounding stromal, immune, and vascular components through a highly coordinated network of molecular signals. Owing to genomic instability, epigenetic alterations, and remarkable phenotypic plasticity, malignant cells acquire the capacity to adapt to diverse environmental conditions while simultaneously reshaping the surrounding tissue to support their own survival. They secrete a wide spectrum of biologically active molecules, including vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), colony-stimulating factors (CSFs), interleukins, chemokines, matrix metalloproteinases (MMPs), and extracellular vesicles. These mediators stimulate angiogenesis, recruit immunosuppressive cells, activate fibroblasts, remodel the extracellular matrix, and establish a pro-tumorigenic niche that facilitates local invasion and distant metastasis. Furthermore, tumor-derived exosomes transport proteins, lipids, messenger RNA, microRNA, and other regulatory molecules that influence neighboring stromal cells and prepare distant organs for metastatic colonization [21,22].

Cancer cells also develop sophisticated mechanisms to evade immune surveillance and resist therapeutic interventions. Downregulation or loss of major histocompatibility complex (MHC) class I molecules reduces antigen presentation and limits recognition by cytotoxic T lymphocytes. Simultaneously, increased expression of immune checkpoint ligands, particularly programmed death-ligand 1 (PD-L1), suppresses T-cell activation and promotes immune tolerance. Tumor cells further alter their metabolic environment through enhanced glycolysis, lactate accumulation, amino acid depletion, and adenosine production, creating conditions that impair immune-cell function. In addition, epithelial–mesenchymal transition (EMT) enables malignant cells to acquire migratory and invasive characteristics while enhancing stem-like properties and resistance to chemotherapy, radiotherapy, and immunotherapy. These adaptive changes illustrate the remarkable ability of cancer cells to evolve under continuous immune and therapeutic pressure, making them highly resilient components of the TME [22,23].



Immune Cells

The immune compartment of the TME is composed of a highly diverse population of innate and adaptive immune cells whose collective activities determine whether the tumor is eliminated or allowed to progress. Cytotoxic $CD8^+$ T lymphocytes represent the primary effectors of adaptive antitumor immunity by recognizing tumor-associated antigens presented on MHC class I molecules and inducing apoptosis through perforin, granzyme, and Fas–Fas ligand pathways. $CD4^+$ helper T cells coordinate immune responses by producing cytokines that support cytotoxic T-cell activation, B-cell maturation, and macrophage polarization. Natural killer (NK) cells provide an additional layer of immune surveillance by directly eliminating transformed cells that have lost MHC class I expression, whereas dendritic cells function as professional antigen-presenting cells that initiate and regulate adaptive immune responses through efficient T-cell priming [24].

Despite these protective mechanisms, tumors frequently establish an immunosuppressive environment dominated by regulatory immune populations. Regulatory T cells (Tregs), tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), tolerogenic dendritic cells, and certain neutrophil subsets suppress effective antitumor immunity through multiple complementary mechanisms. These include secretion of immunosuppressive cytokines such as interleukin-10 and TGF-β, expression of inhibitory immune checkpoint molecules, depletion of essential amino acids, generation of reactive oxygen species, and inhibition of dendritic-cell maturation. Tumor-associated macrophages frequently adopt an M2-like phenotype that promotes angiogenesis, extracellular matrix remodeling, tissue repair, and metastatic dissemination rather than tumor elimination. Consequently, the balance between immune activation and immune suppression within the TME is a critical determinant of disease progression, prognosis, and responsiveness to immunotherapeutic strategies. Recent advances in single-cell sequencing have further demonstrated that immune-cell phenotypes exist along a dynamic spectrum rather than as fixed populations, highlighting the complexity of immune regulation within tumors [25,26].

Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) constitute one of the most abundant and functionally diverse stromal populations in the TME of solid malignancies. Unlike normal fibroblasts, CAFs exhibit persistent activation and arise from multiple cellular origins, including resident fibroblasts, mesenchymal stem cells, adipocytes, endothelial cells undergoing endothelial-to-mesenchymal transition, and pericytes. Their phenotypic heterogeneity reflects continuous adaptation to tumor-derived signals, resulting in distinct CAF subsets with specialized biological functions. Activated CAFs synthesize large quantities of extracellular matrix proteins, growth factors, cytokines, chemokines, and proteolytic enzymes that collectively remodel the tumor stroma and influence cancer progression [27].

CAFs exert profound effects on tumor biology by secreting mediators such as TGF-β, interleukin-6, CXCL12, hepatocyte growth factor (HGF), fibroblast growth factors (FGFs), and vascular endothelial growth factor. These molecules stimulate cancer-cell proliferation, epithelial–mesenchymal transition, invasion, angiogenesis, stemness, metabolic adaptation, and resistance to systemic therapy. Simultaneously, CAF-mediated extracellular matrix deposition increases tissue stiffness and interstitial pressure, thereby restricting vascular perfusion, limiting drug penetration, and preventing efficient infiltration of cytotoxic immune cells. Nevertheless, recent studies have demonstrated that CAFs are not universally tumor-promoting. Distinct fibroblast subsets may exert tumor-restraining or immune-supportive functions by maintaining tissue architecture or facilitating antitumor immune responses. Consequently,

current therapeutic research emphasizes selective targeting or functional reprogramming of pathogenic CAF populations rather than indiscriminate fibroblast depletion, which may inadvertently accelerate tumor progression in certain settings [27,28].

Endothelial Cells and Pericytes

Tumor-associated endothelial cells and pericytes play fundamental roles in establishing the abnormal vascular architecture that characterizes most solid malignancies. Unlike normal blood vessels, tumor vasculature develops rapidly under persistent angiogenic stimulation and is structurally disorganized, excessively permeable, tortuous, and poorly perfused. Endothelial cells exhibit abnormal junctional integrity, while incomplete or irregular pericyte coverage compromises vascular stability and maturation. These abnormalities generate heterogeneous blood flow, increased interstitial fluid pressure, and inefficient oxygen and nutrient delivery throughout the tumor mass. Consequently, extensive regions of hypoxia develop, promoting further angiogenesis, metabolic adaptation, epithelial–mesenchymal transition, and therapeutic resistance [29].

Beyond their vascular functions, endothelial cells actively regulate immune-cell trafficking within the TME. Altered expression of adhesion molecules, chemokines, and endothelial checkpoint regulators influences leukocyte recruitment and migration across the vascular wall. Dysfunctional tumor vessels often create an endothelial barrier that limits infiltration of cytotoxic lymphocytes while preferentially facilitating the accumulation of immunosuppressive myeloid cells. This phenomenon contributes significantly to resistance against immune checkpoint blockade and other immunotherapeutic strategies. Restoration of vascular integrity through vascular normalization has therefore emerged as a promising therapeutic approach capable of improving tissue oxygenation, enhancing immune-cell infiltration, and increasing the effectiveness of systemic anticancer therapies [29,30].

Extracellular Matrix

The extracellular matrix (ECM) is a highly organized three-dimensional scaffold composed primarily of collagen, fibronectin, laminins, elastin, hyaluronan, proteoglycans, and glycoproteins. Beyond providing structural support, the ECM functions as a dynamic signaling platform that regulates cellular adhesion, migration, proliferation, differentiation, and survival. Continuous interactions between tumor cells, fibroblasts, endothelial cells, and immune cells modify the composition and mechanical properties of the ECM throughout tumor progression. Increased collagen deposition, abnormal cross-linking, and altered matrix organization contribute to progressive tissue stiffening, which activates mechanotransduction pathways involving integrins, focal adhesion kinase (FAK), and Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ), thereby enhancing tumor growth and metastatic potential [28,30].

Matrix remodeling is largely mediated by matrix metalloproteinases and other proteolytic enzymes that degrade structural barriers and facilitate cancer-cell invasion into surrounding tissues. Simultaneously, dense ECM architecture compresses blood vessels, impairs oxygen diffusion, restricts immune-cell migration, and reduces penetration of therapeutic agents. Thus, the ECM is increasingly recognized as an active participant in tumor progression rather than an inert structural component. Therapeutic strategies directed toward ECM remodeling, collagen normalization, and mechanotransductionsignaling are currently under active investigation as complementary approaches to conventional anticancer therapy [28,30].

Soluble Mediators and Extracellular Vesicles

Communication within the TME is largely orchestrated by an extensive network of soluble mediators and extracellular vesicles that enable coordinated interactions among malignant, stromal, vascular, and immune cells. Cytokines, chemokines, growth factors, hormones, metabolites, lipid mediators, and damage-associated molecular patterns regulate cell recruitment, activation, differentiation, and survival. Simultaneously, extracellular vesicles—including exosomes and microvesicles—serve as highly efficient carriers of proteins, messenger RNA, microRNA, long non-coding RNA, lipids, metabolites, and even DNA fragments. These vesicles facilitate local communication within the primary tumor while also mediating long-distance signaling that prepares distant organs for metastatic colonization [21,22].

Tumor-derived extracellular vesicles promote angiogenesis, extracellular matrix remodeling, immune suppression, metabolic reprogramming, and resistance to chemotherapy and immunotherapy. Likewise, cytokine and chemokine networks exhibit considerable biological complexity because individual mediators may exert either tumor-promoting or tumor-suppressive effects depending on the cellular context, receptor expression, and disease stage. This intricate communication network enables continuous adaptation of the TME and represents an attractive target for novel therapeutic interventions aimed at disrupting tumor-supportive signaling pathways.

Tumor–Immune Cell Interactions

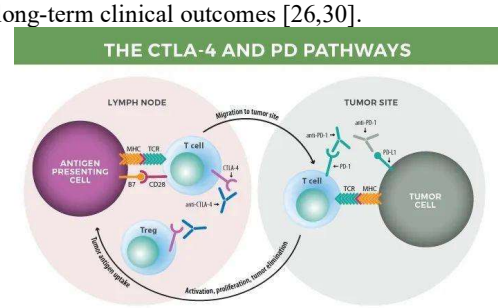
The interaction between cancer cells and the immune system is highly dynamic and evolves throughout the natural history of malignancy. The immune system continuously surveys tissues to identify and eliminate transformed cells, a process

known as immune surveillance. However, tumors possess remarkable evolutionary capacity and gradually acquire mechanisms that enable survival despite persistent immune pressure. This reciprocal relationship is described by the concept of cancer immunoediting, which encompasses three sequential phases: elimination, equilibrium, and escape. During the elimination phase, innate and adaptive immune cells cooperate to recognize and destroy emerging malignant cells. If complete eradication is unsuccessful, surviving tumor cells enter an equilibrium phase characterized by prolonged immune-mediated selection. Ultimately, genetically and phenotypically adapted tumor clones develop immune-evasive mechanisms that permit uncontrolled growth during the escape phase. Cancer immunoediting therefore explains how immune surveillance simultaneously suppresses tumor development while inadvertently selecting more aggressive and immune-resistant cancer cell populations [23,24].

Cytotoxic T Lymphocytes

$CD8^+$ cytotoxic T lymphocytes (CTLs) represent the principal effector cells responsible for adaptive antitumor immunity. Activation begins when dendritic cells capture tumor-associated antigens and present antigenic peptides via major histocompatibility complex (MHC) class I molecules to naïve $CD8^+$ T cells within secondary lymphoid organs. Following activation and clonal expansion, CTLs migrate to the tumor site, where they recognize malignant cells expressing the corresponding antigen–MHC complex. Tumor-cell destruction occurs through several complementary mechanisms, including release of perforin and granzymes, activation of Fas–Fas ligand-mediated apoptosis, and secretion of interferon-γ and tumor necrosis factor-α, which collectively inhibit tumor proliferation and recruit additional immune effector cells. High intratumoral infiltration of functional $CD8^+$ T cells has consistently been associated with favorable prognosis and improved responses to immunotherapy across multiple cancer types [24,25].

Despite their potent cytotoxic capacity, persistent antigen exposure within the immunosuppressive TME frequently induces **T-cell exhaustion**, a dysfunctional differentiation state characterized by progressive loss of proliferative capacity, reduced cytokine secretion, impaired cytotoxicity, altered metabolic fitness, and sustained expression of multiple inhibitory receptors including programmed cell death protein-1 (PD-1), lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin-domain-containing protein-3 (TIM-3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4). Exhausted T cells also undergo extensive transcriptional and epigenetic reprogramming that limits complete functional recovery. Consequently, reversing T-cell exhaustion has become a major objective of modern cancer immunotherapy. Immune checkpoint inhibitors, therapeutic vaccines, adoptive T-cell therapies, cytokine modulation, and metabolic reprogramming strategies are increasingly being combined to restore durable antitumor immunity and improve long-term clinical outcomes [26,30].



Regulatory T Cells

Regulatory T cells (Tregs) are a specialized subset of $CD4^+$ T lymphocytes characterized by the expression of the transcription factor forkhead box P3 (FOXP3), which is essential for maintaining peripheral immune tolerance and preventing autoimmune disease. Under physiological conditions, Tregs suppress excessive immune activation and preserve tissue homeostasis. However, within the tumor microenvironment (TME), these cells are frequently co-opted by malignant tissues to inhibit protective antitumor immunity. Tumor-derived chemokines such as CCL17, CCL22, and CCL28 promote the selective recruitment of Tregs into the tumor bed, where they accumulate in close proximity to effector T cells and antigen-presenting cells. Once established, Tregs generate a profoundly immunosuppressive environment that enables tumor cells to evade immune surveillance and continue proliferating [31].

The immunosuppressive activity of Tregs is mediated through multiple complementary mechanisms. These cells secrete inhibitory cytokines including interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and interleukin-35, all of which suppress the activation and proliferation of cytotoxic $CD8^+$ T lymphocytes, natural killer (NK) cells, and dendritic cells. Tregs also compete metabolically for interleukin-2, depriving effector T cells of a critical growth factor necessary for sustained immune responses. In addition, expression of inhibitory receptors such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), and programmed death-1 (PD-1) further dampens antigen presentation and T-cell activation. High densities of intratumoral Tregs have been associated with poor prognosis in numerous malignancies, including ovarian, pancreatic, hepatocellular, and gastric cancers, although their

prognostic significance varies among different tumor types and anatomical locations. Consequently, selective modulation of Treg function rather than complete depletion has emerged as a promising strategy for improving the efficacy of cancer immunotherapy while minimizing the risk of autoimmune toxicity [31,32].

Tumor-Associated Macrophages

Macrophages represent one of the most abundant immune-cell populations within the TME and exhibit extraordinary phenotypic and functional plasticity. Traditionally, macrophages have been classified into classically activated M1 macrophages, which possess pro-inflammatory and antitumor properties, and alternatively activated M2 macrophages, which promote tissue repair and immune suppression. Although this M1/M2 classification provides a useful conceptual framework, advances in single-cell transcriptomics have demonstrated that tumor-associated macrophages (TAMs) exist along a dynamic continuum of activation states rather than as two discrete phenotypes. Their functional characteristics are determined by continuous interactions with tumor cells, stromal components, cytokines, metabolic signals, and extracellular matrix molecules within the TME [33].

In many solid tumors, TAMs acquire predominantly tumor-promoting functions that facilitate cancer progression through multiple interconnected mechanisms. They secrete vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), interleukin-10, colony-stimulating factors, matrix metalloproteinases, and numerous chemokines that collectively stimulate angiogenesis, extracellular matrix remodeling, invasion, epithelial–mesenchymal transition, and metastatic dissemination. TAMs further suppress adaptive immunity by inhibiting cytotoxic T-cell activation, recruiting regulatory T cells, expressing immune checkpoint ligands, and producing immunosuppressive metabolites. Increasing evidence indicates that macrophages also contribute substantially to resistance against immune checkpoint inhibitors, chemotherapy, radiotherapy, and targeted therapies. Accordingly, novel therapeutic strategies are focusing on inhibition of monocyte recruitment, blockade of colony-stimulating factor-1 receptor (CSF1R) signaling, depletion of selected macrophage populations, enhancement of macrophage-mediated phagocytosis, and functional reprogramming toward pro-inflammatory antitumor phenotypes capable of restoring effective immune surveillance [33,34].

Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) constitute a heterogeneous population of immature myeloid cells that expand substantially during chronic inflammation and malignancy. Under normal physiological conditions, immature myeloid cells differentiate into mature macrophages, dendritic cells, and granulocytes. In cancer, however, persistent inflammatory signals interrupt normal differentiation, leading to the accumulation of immature cells with potent immunosuppressive activity. MDSCs are broadly classified into monocytic and polymorphonuclear subsets, each employing distinct yet overlapping mechanisms to suppress antitumor immunity [35].

Within the TME, MDSCs inhibit T-cell proliferation and cytotoxic function through depletion of essential amino acids such as arginine and cysteine, production of arginase-1, inducible nitric oxide synthase, reactive oxygen species, nitric oxide, prostaglandin E_2, and immunosuppressive cytokines. They also promote expansion of regulatory T cells, impair natural killer cell activity, inhibit dendritic-cell maturation, and facilitate tumor angiogenesis and metastatic dissemination. Elevated circulating or intratumoral MDSC levels have consistently been associated with advanced disease stage, poor clinical prognosis, and diminished responsiveness to immune checkpoint blockade across multiple malignancies. Consequently, therapeutic strategies aimed at reducing MDSC recruitment, inducing their differentiation into mature myeloid cells, inhibiting their suppressive functions, or selectively eliminating these cells are currently being investigated in combination with immunotherapy, chemotherapy, and targeted treatments [35,36].

Natural Killer Cells and Dendritic Cells

Natural killer (NK) cells are innate lymphoid cells that provide rapid antitumor cytotoxicity without requiring prior antigen sensitization. They recognize transformed cells through a balance between activating and inhibitory surface receptors and are particularly effective against tumor cells exhibiting reduced major histocompatibility complex (MHC) class I expression, a common mechanism of immune escape from cytotoxic T lymphocytes. Activated NK cells eliminate malignant cells through perforin- and granzyme-mediated cytotoxicity, death receptor signaling, and secretion of interferon-γ and tumor necrosis factor-α, which further stimulate adaptive immune responses. However, multiple components of the TME—including hypoxia, transforming growth factor-β, prostaglandin E_2, adenosine accumulation, suppressive myeloid cells, and metabolic stress—substantially impair NK-cell maturation, migration, cytokine production, and cytotoxic activity. Restoring NK-cell function has therefore become an important objective of contemporary cancer immunotherapy through adoptive NK-cell transfer, cytokine stimulation, bispecific antibodies, and

engineered chimeric antigen receptor (CAR)-NK cell therapies [37].

Dendritic cells (DCs) serve as the critical interface between innate and adaptive immunity by capturing tumor-associated antigens, processing them, and presenting antigenic peptides to naïve T lymphocytes within secondary lymphoid organs. Efficient dendritic-cell maturation is essential for initiating robust cytotoxic T-cell responses capable of eliminating malignant cells. Unfortunately, the TME frequently disrupts dendritic-cell differentiation through immunosuppressive cytokines, vascular endothelial growth factor, metabolic competition, and chronic inflammatory signaling. Dysfunctional dendritic cells display impaired antigen presentation, reduced co-stimulatory molecule expression, defective migration to lymphoid tissues, and inadequate T-cell priming, thereby contributing to the development of immunologically "cold" tumors. Consequently, therapeutic strategies aimed at enhancing dendritic-cell maturation—including dendritic-cell vaccines, Toll-like receptor agonists, cytokine therapy, and combination immunotherapy—have gained considerable interest as approaches for improving durable antitumor immune responses [38].

Mechanisms of Immune Evasion

Successful tumor progression depends largely on the ability of malignant cells to evade immune-mediated destruction. Rather than relying on a single escape mechanism, cancers typically employ multiple complementary strategies that evolve continuously during disease progression. These mechanisms interact synergistically within the TME, creating an environment that suppresses immune surveillance while promoting tumor survival and metastatic dissemination. The complexity of immune evasion explains why many patients exhibit limited responses to therapies targeting only one immunological pathway and highlights the need for rational combination treatment strategies [39].

One of the earliest mechanisms of immune escape involves the loss, mutation, or reduced expression of tumor-associated antigens, making malignant cells less recognizable to cytotoxic lymphocytes. Simultaneously, defects in antigen-processing machinery—including alterations in transporter associated with antigen processing (TAP) proteins and proteasomal components—impair presentation of tumor-derived peptides through major histocompatibility complex (MHC) class I molecules. Downregulation or complete loss of MHC class I expression further prevents efficient recognition by $CD8^+$ T cells. In parallel, many tumors markedly increase expression of immune checkpoint ligands such as programmed death-ligand 1 (PD-L1), which suppress T-cell activation and promote immune tolerance through engagement of inhibitory receptors on lymphocytes [39,40].

Immune suppression is further amplified through recruitment of regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells, all of which inhibit effective cytotoxic immune responses. Tumor-derived cytokines—including transforming growth factor-β, interleukin-10, vascular endothelial growth factor, and colony-stimulating factors—establish an anti-inflammatory milieu that limits dendritic-cell maturation and promotes immune exhaustion. Simultaneously, metabolic alterations such as glucose depletion, lactate accumulation, adenosine production, amino acid deprivation, and hypoxia impair the metabolic fitness of infiltrating immune cells. Dense stromal architecture, excessive extracellular matrix deposition, and abnormal tumor vasculature create additional physical barriers that prevent efficient lymphocyte infiltration into malignant tissues. Chronic antigen exposure eventually induces T-cell exhaustion characterized by sustained expression of inhibitory receptors including PD-1, TIM-3, LAG-3, TIGIT, and CTLA-4. Because these mechanisms frequently coexist within individual tumors, contemporary therapeutic strategies increasingly combine immune checkpoint inhibition with stromal remodeling, antiangiogenic therapy, metabolic modulation, cytokine targeting, and cellular immunotherapy to achieve more durable antitumor responses [39,40].

Angiogenesis and the Tumor Microenvironment

Angiogenesis is a fundamental biological process that enables sustained tumor growth beyond the diffusion limit of oxygen and nutrients. As malignant tissues expand rapidly, existing blood vessels become insufficient to meet increasing metabolic demands, leading to the development of regional hypoxia. Reduced oxygen tension stabilizes hypoxia-inducible factors (HIFs), particularly HIF-1α and HIF-2α, which function as master transcriptional regulators of cellular adaptation to hypoxia. Activation of these transcription factors induces expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), angiopoietins, and numerous additional proangiogenic mediators that stimulate endothelial-cell proliferation, migration, and formation of new blood vessels. Consequently, angiogenesis becomes a hallmark of tumor progression and an essential prerequisite for continued cancer expansion and metastatic dissemination [31,40].

Unlike the highly organized vasculature of normal tissues, tumor blood vessels are structurally and functionally abnormal. Newly formed vessels are typically tortuous, dilated, irregularly branched, excessively permeable, and poorly supported by pericytes and basement membrane components.

These abnormalities generate heterogeneous blood flow, elevated interstitial fluid pressure, impaired oxygen delivery, and inefficient transport of nutrients and therapeutic agents. As a result, large regions of persistent hypoxia develop within tumors, creating powerful selective pressures that favor survival of aggressive cancer-cell clones capable of adapting to metabolically hostile conditions. Hypoxia also promotes epithelial–mesenchymal transition, maintenance of cancer stem-cell populations, genomic instability, metabolic reprogramming toward glycolysis, immune suppression, and resistance to chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Therefore, hypoxia not only reflects inadequate vascular function but also actively contributes to malignant progression and poor clinical outcomes [32,33].

Beyond its role in vascular development, VEGF exerts profound immunological effects within the TME. Excessive VEGF signaling inhibits dendritic-cell maturation, suppresses antigen presentation, promotes expansion of regulatory T cells and myeloid-derived suppressor cells, and contributes to formation of an abnormal endothelial barrier that restricts infiltration of cytotoxic lymphocytes into tumor tissue. These observations provide a strong biological rationale for combining antiangiogenic agents with immune checkpoint inhibitors, thereby simultaneously improving vascular function and restoring antitumor immunity. Clinical studies have demonstrated encouraging outcomes with such combination strategies in several malignancies, including renal cell carcinoma, hepatocellular carcinoma, non-small cell lung cancer, and endometrial carcinoma [34].

An emerging concept in modern oncology is vascular normalization, which differs fundamentally from the traditional goal of completely eliminating tumor blood vessels. Appropriately dosed antiangiogenic therapy can transiently remodel abnormal tumor vasculature, improve vessel maturity, enhance pericyte coverage, reduce vascular permeability, lower interstitial fluid pressure, and restore more efficient tissue perfusion. These changes improve oxygenation, facilitate immune-cell trafficking, enhance delivery of cytotoxic drugs, and increase the effectiveness of radiotherapy and immunotherapy. Consequently, vascular normalization is increasingly recognized as an important therapeutic strategy for overcoming multiple barriers imposed by the tumor microenvironment and improving the efficacy of multimodal cancer treatment [35].

Stromal Response and Cancer Progression

The tumor stroma is no longer regarded as a passive structural framework surrounding malignant cells but rather as a biologically active and highly dynamic component of the tumor microenvironment (TME). It comprises cancer-associated fibroblasts (CAFs), extracellular matrix (ECM), endothelial cells, pericytes, immune cells, adipocytes, mesenchymal stem cells, and numerous soluble mediators that interact continuously with cancer cells. These reciprocal interactions regulate tumor growth, angiogenesis, immune modulation, invasion, and metastatic dissemination. Stromal cells respond to signals released by malignant cells, while simultaneously secreting cytokines, chemokines, growth factors, and extracellular vesicles that reshape tumorbehavior. Consequently, tumor progression reflects the coordinated activity of malignant cells and their surrounding stromal ecosystem rather than the biological properties of cancer cells alone [41].

Fibrosis and Desmoplasia

One of the defining pathological features of several solid malignancies, particularly pancreatic ductal adenocarcinoma, cholangiocarcinoma, breast carcinoma, and certain colorectal cancers, is the development of **desmoplasia**, a dense fibrotic stromal reaction characterized by excessive extracellular matrix deposition and persistent fibroblast activation. Cancer-associated fibroblasts produce abundant collagen, fibronectin, hyaluronan, laminins, and proteoglycans that progressively increase stromal density and tissue rigidity. Excessive fibrosis elevates interstitial fluid pressure, compresses intratumoral blood vessels, impairs oxygen diffusion, restricts penetration of anticancer drugs, and creates physical barriers that limit infiltration of cytotoxic immune cells. Moreover, the fibrotic stroma serves as a reservoir for cytokines and growth factors that further promote malignant progression. Although desmoplasia has traditionally been considered uniformly tumor-promoting, recent evidence indicates that certain stromal elements may also restrain tumor expansion, emphasizing the need for selective stromal modulation rather than indiscriminate stromal depletion [42].

Matrix Remodeling

The extracellular matrix undergoes continuous remodeling throughout tumor progression through the coordinated activity of matrix metalloproteinases (MMPs), cathepsins, lysyl oxidases, and other proteolytic enzymes produced by tumor cells, fibroblasts, macrophages, and endothelial cells. Matrix degradation facilitates local invasion by removing structural barriers and creating migration pathways for malignant cells. However, ECM remodeling extends far beyond simple tissue destruction. Proteolytic cleavage generates biologically active matrix fragments, referred to as matrikines, that regulate angiogenesis, inflammation, immune-cell recruitment, and cell survival. Simultaneously, changes in matrix composition alter integrin-mediated signaling pathways that influence cellular

proliferation, differentiation, migration, and resistance to therapy. Therefore, ECM remodeling represents a highly regulated biological process that profoundly influences both tumor progression and therapeutic response [43].

Mechanical Signaling

The progressive accumulation and cross-linking of extracellular matrix proteins substantially increase tissue stiffness within the TME. Mechanical alterations are sensed by integrins and associated mechanoreceptors, initiating intracellular signaling cascades involving focal adhesion kinase (FAK), Src family kinases, Rho GTPases, and the transcriptional co-activators Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). Activation of these mechanotransduction pathways promotes cancer-cell proliferation, epithelial–mesenchymal transition, stem-cell maintenance, metabolic adaptation, invasion, metastatic competence, and therapeutic resistance. Mechanical signaling also influences endothelial-cell behavior, immune-cell trafficking, and fibroblast activation, illustrating that physical properties of the tumor stroma are integral regulators of cancer biology. Consequently, targeting mechanotransduction pathways has emerged as a promising therapeutic strategy in solid tumors characterized by excessive stromal stiffness [44].

Stromal–Immune Crosstalk

An increasingly recognized feature of the TME is the intimate communication between stromal and immune compartments. Cancer-associated fibroblasts actively shape immune-cell recruitment and function through secretion of transforming growth factor-β (TGF-β), CXCL12, interleukin-6, colony-stimulating factors, and numerous additional mediators. These signals recruit regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages while simultaneously restricting infiltration of cytotoxic T lymphocytes into tumor nests. Dense extracellular matrix deposition further reinforces immune exclusion by creating physical barriers that limit immune-cell migration. Consequently, stromal biology represents a critical mechanistic link between tissue architecture and immune dysfunction. Current therapeutic strategies increasingly focus on simultaneously targeting stromal remodeling and immune suppression to improve responses to immunotherapy and overcome treatment resistance [41,45].

Metabolic Reprogramming of the TME

Metabolic reprogramming is a defining hallmark of the tumor microenvironment and reflects the intense metabolic demands of rapidly proliferating cancer cells. To sustain uncontrolled growth, malignant cells consume large quantities of glucose, amino acids, lipids, and oxygen while generating substantial amounts of lactate and other metabolic by-products. This metabolic competition profoundly alters the biochemical composition of the TME, producing hypoxia, extracellular acidosis, oxidative stress, nutrient deprivation, and altered redox balance. Unlike normal tissues, tumors display remarkable metabolic plasticity, enabling cancer cells to switch between glycolysis, oxidative phosphorylation, fatty acid oxidation, and glutamine metabolism according to environmental conditions. These adaptive responses not only support tumor survival but also profoundly influence the function of surrounding stromal and immune cells [46].

One of the most prominent metabolic features of the TME is enhanced aerobic glycolysis, commonly referred to as the Warburg effect, which results in excessive lactate accumulation and extracellular acidification. Elevated lactate concentrations suppress proliferation and cytotoxic activity of $CD8^+$ T lymphocytes and natural killer cells while promoting differentiation of regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells toward immunosuppressive phenotypes. Simultaneously, depletion of glucose limits the metabolic fitness of activated immune cells, reducing cytokine production and impairing antitumor responses. Additional immunometabolic pathways involving adenosine signaling, indoleamine 2,3-dioxygenase (IDO)-mediated tryptophan metabolism, arginine depletion, glutamine utilization, cholesterol metabolism, and lipid accumulation further contribute to immune dysfunction and therapeutic resistance. These metabolic alterations establish an environment that favors malignant survival while suppressing effective immune surveillance [47].

Because metabolic abnormalities influence both cancer cells and immune cells, targeting tumor metabolism has emerged as an attractive therapeutic strategy. Current approaches include inhibition of glycolysis, glutaminase, fatty acid synthesis, adenosine receptors, IDO signaling, oxidative phosphorylation, and lactate transporters. However, achieving therapeutic selectivity remains challenging because many metabolic pathways are essential for the function of activated immune cells as well as malignant cells. Future therapeutic development therefore requires a comprehensive understanding of tumor-specific metabolic vulnerabilities together with strategies that preserve or enhance antitumor immune function while selectively disrupting cancer-cell metabolism [46,47].

Immune Checkpoint Pathways

Immune checkpoint pathways are essential physiological mechanisms that maintain immune homeostasis by limiting excessive immune activation and preventing autoimmune tissue injury. Under normal conditions, these inhibitory pathways terminate immune responses following

pathogen elimination and preserve peripheral tolerance. Malignant cells, however, exploit these regulatory mechanisms to suppress antitumor immunity and escape immune-mediated destruction. Persistent antigen exposure within the TME leads to sustained expression of inhibitory receptors on T lymphocytes, resulting in progressive functional exhaustion and impaired cytotoxicity. The development of immune checkpoint inhibitors has fundamentally transformed cancer treatment by restoring immune-cell function, yet substantial biological complexity remains because multiple inhibitory pathways often coexist within individual tumors [48].

CTLA-4

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is one of the earliest immune checkpoint molecules involved in regulating T-cell activation. CTLA-4 is expressed predominantly on activated T cells and regulatory T cells, where it competes with the co-stimulatory receptor CD28 for binding to CD80 and CD86 expressed on antigen-presenting cells. Because CTLA-4 binds these ligands with considerably higher affinity than CD28, it effectively suppresses co-stimulatory signaling required for complete T-cell activation. Blockade of CTLA-4 enhances early T-cell priming within secondary lymphoid organs, expands the repertoire of tumor-reactive lymphocytes, and may reduce suppressive activity of intratumoral regulatory T cells. Clinical use of CTLA-4 inhibitors has demonstrated durable responses in selected malignancies, particularly metastatic melanoma, although treatment is associated with a relatively high incidence of immune-related adverse events due to generalized immune activation [48].

PD-1/PD-L1 Pathway

The programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway represents the most extensively studied immune checkpoint in contemporary oncology. PD-1 is expressed on activated T cells, B cells, natural killer cells, and other immune populations following prolonged antigen stimulation. Binding of PD-1 to its ligands PD-L1 or PD-L2 inhibits T-cell receptor signaling, reduces cytokine production, impairs proliferation, and promotes functional exhaustion. PD-L1 expression occurs not only on malignant cells but also on endothelial cells, macrophages, dendritic cells, fibroblasts, and other stromal components within the TME. Expression may result from constitutive oncogenic signaling or adaptive induction by inflammatory cytokines, particularly interferon-γ. Therapeutic antibodies targeting PD-1 or PD-L1 have demonstrated remarkable clinical efficacy across melanoma, non-small-cell lung cancer, renal-cell carcinoma, urothelial carcinoma, hepatocellular carcinoma, head and neck squamous-cell carcinoma, gastrointestinal malignancies, and several additional tumor types, establishing checkpoint inhibition as a cornerstone of modern precision oncology [49].

Emerging Checkpoints

Although blockade of CTLA-4 and PD-1/PD-L1 has revolutionized cancer treatment, many patients fail to achieve durable responses because additional inhibitory pathways continue to suppress immune function. Several emerging checkpoint molecules—including lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin-domain-containing protein-3 (TIM-3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), V-domain Ig suppressor of T-cell activation (VISTA), B- and T-lymphocyte attenuator (BTLA), and CD96—have attracted considerable research interest. These receptors regulate distinct aspects of immune-cell activation, differentiation, and exhaustion and often function cooperatively with PD-1 signaling. LAG-3-targeted therapy has already entered clinical practice in selected settings, while numerous additional checkpoint inhibitors are currently undergoing clinical evaluation. Future immunotherapeutic strategies are expected to rely increasingly on biomarker-guided combination regimens tailored to the dominant immune-evasion mechanisms present within individual tumors rather than indiscriminate blockade of multiple inhibitory receptors [50].

Mechanisms of Resistance to Immunotherapy

Despite remarkable advances in immune checkpoint inhibition, durable clinical benefit remains limited to a subset of patients, highlighting the complexity of resistance mechanisms within the TME. Resistance may be classified broadly as primary (intrinsic) resistance, in which tumors fail to respond from the outset, or acquired (secondary) resistance, which develops following an initial period of therapeutic response. These forms of resistance arise through diverse biological mechanisms involving tumor cells, stromal components, immune populations, metabolic pathways, and host-related factors. Importantly, resistance should not be viewed as a single biological entity but rather as a heterogeneous spectrum of adaptive processes that vary among patients, tumor types, and stages of disease progression [48–50].

Primary resistance commonly results from insufficient tumor antigenicity, defective antigen-processing machinery, reduced major histocompatibility complex expression, absence of effective T-cell infiltration, constitutive oncogenic signaling pathways, dense stromal exclusion, profound immunosuppression, or unfavorable metabolic conditions within the TME. Conversely, acquired resistance may emerge through loss of target antigens, defects in interferon signaling, alterations in antigen presentation, expansion of suppressive myeloid populations, activation of

alternative immune checkpoint pathways, progressive T-cell dysfunction, metabolic adaptation, epigenetic reprogramming, and continued clonal evolution of resistant tumor-cell populations. Because multiple resistance mechanisms frequently coexist within individual tumors, future precision oncology will increasingly depend upon comprehensive molecular and immune profiling to identify patient-specific vulnerabilities and guide rational combination therapies capable of simultaneously targeting several complementary pathways. Such personalized therapeutic strategies are expected to play a central role in overcoming immunotherapy resistance and improving long-term clinical outcomes.

Clinical Significance of the Tumor Microenvironment

The tumor microenvironment (TME) has emerged as one of the most clinically relevant aspects of modern oncology because it influences cancer diagnosis, prognosis, therapeutic response, and long-term patient outcomes. Rather than serving merely as a structural framework, the TME reflects the biological interactions occurring between malignant cells, immune populations, stromal elements, vascular components, and metabolic mediators throughout disease progression. Advances in molecular pathology, digital pathology, spatial transcriptomics, multiplex imaging, and single-cell sequencing have demonstrated that the composition and functional state of the TME often predict clinical behavior more accurately than conventional histopathological characteristics alone. Consequently, assessment of the TME is increasingly incorporated into translational research and precision oncology, where it provides valuable information for risk stratification and individualized treatment planning [51].

One of the most extensively studied clinical features of the TME is the density, composition, and spatial distribution of tumor-infiltrating immune cells. High infiltration of functional $CD8^+$ cytotoxic T lymphocytes generally correlates with favorable prognosis in many solid malignancies because it reflects the presence of an active antitumor immune response. Conversely, tumors enriched with regulatory T cells, tumor-associated macrophages, or myeloid-derived suppressor cells often exhibit aggressive biological behavior and poorer clinical outcomes. Importantly, the prognostic significance of immune-cell infiltration depends not only on the number of immune cells but also on their functional phenotype, localization within the tumor, activation status, and interactions with stromal components. Modern approaches such as the Immunoscore and spatial immune profiling therefore provide more comprehensive prognostic information than simple quantification of immune-cell density alone [51].

Among currently available predictive biomarkers, programmed death-ligand 1 (PD-L1) expression remains the most widely used for selecting patients who may benefit from immune checkpoint inhibitors. Nevertheless, PD-L1 expression possesses several important limitations. Considerable spatial heterogeneity may exist between different regions of the same tumor, while temporal variability can occur following chemotherapy, radiotherapy, targeted therapy, or immunotherapy. Furthermore, differences among commercially available immunohistochemical assays, scoring algorithms, antibody clones, and positivity thresholds contribute to variability in clinical interpretation. Most importantly, PD-L1 expression alone lacks perfect predictive accuracy because some PD-L1-negative tumors respond favorably to immunotherapy, whereas many PD-L1-positive tumors fail to achieve durable benefit. These observations emphasize that therapeutic responsiveness is determined by the integrated biology of the entire TME rather than by a single molecular marker [52].

Consequently, increasing attention has shifted toward multimodal biomarker development that integrates multiple biological layers. Tumor mutational burden (TMB) provides an estimate of neoantigen generation and has demonstrated predictive value in selected malignancies. Microsatellite instability (MSI) and mismatch repair deficiency (dMMR) identify tumors with high mutational loads that frequently respond well to immune checkpoint inhibition. Gene-expression signatures reflecting interferon signaling, T-cell activation, inflammatory pathways, and stromal remodeling further improve biological characterization of individual tumors. Additional clinically relevant biomarkers include circulating immune-cell populations, soluble cytokines, angiogenic signatures, T-cell receptor repertoire diversity, microbiome-associated factors, circulating tumor DNA, extracellular vesicle profiles, and spatial cellular organization determined through advanced imaging technologies. Future precision oncology is therefore expected to rely on integrated biomarker platforms that combine genomic, transcriptomic, proteomic, metabolomic, immunologic, and spatial information to guide personalized therapeutic decision-making and improve patient outcomes [51,52].

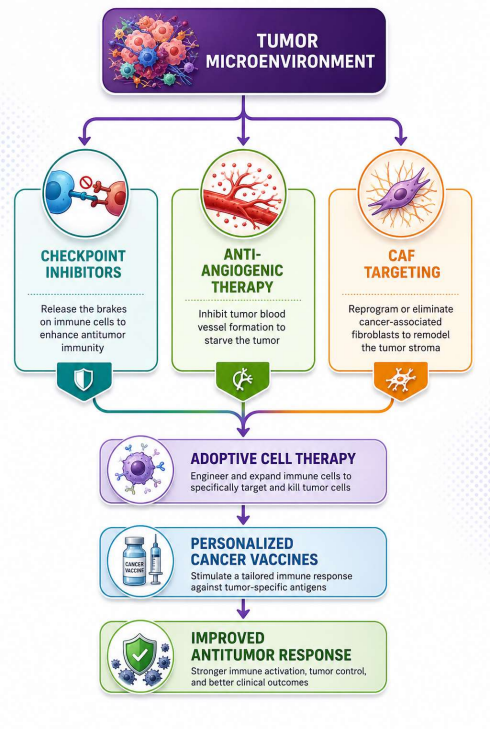
Recent Advances in Management

Combination Immune Checkpoint Blockade

The remarkable success of immune checkpoint inhibitors has transformed the treatment of numerous malignancies; however, durable clinical responses remain limited to a subset of patients. One major explanation is that tumors frequently

activate multiple inhibitory immune pathways simultaneously, allowing immune escape despite blockade of a single checkpoint. Combination immune checkpoint therapy has therefore emerged as a rational strategy to enhance antitumor immunity by targeting complementary regulatory mechanisms. The combination of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibition and programmed cell death protein-1 (PD-1) blockade enhances both early T-cell priming within lymphoid organs and restoration of exhausted effector T cells within the tumor microenvironment. Clinical studies have demonstrated superior response rates and prolonged survival with combined checkpoint inhibition in selected malignancies, including melanoma, renal cell carcinoma, hepatocellular carcinoma, and microsatellite instability-high colorectal cancer. Nevertheless, these benefits are accompanied by increased immune-related adverse events affecting the skin, gastrointestinal tract, liver, endocrine organs, and lungs, necessitating careful patient selection and toxicity management [53].

Recent therapeutic development has expanded beyond CTLA-4 and PD-1 to include additional inhibitory receptors such as lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin-domain-containing protein-3 (TIM-3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), and V-domain Ig suppressor of T-cell activation (VISTA). Among these, LAG-3-directed therapy has already demonstrated encouraging clinical efficacy in selected settings when combined with PD-1 inhibition. Future combination strategies are expected to rely increasingly on biomarker-guided selection of complementary checkpoint inhibitors according to the dominant immune-evasion pathways operating within individual tumors. Such personalized approaches aim to maximize therapeutic efficacy while minimizing unnecessary immune-related toxicity [53].



Combining Immunotherapy with Antiangiogenic Therapy

The biological relationship between angiogenesis and immune suppression has provided a strong rationale for combining antiangiogenic agents with immune checkpoint inhibitors. Excessive vascular endothelial growth factor (VEGF) signaling contributes not only to abnormal blood-vessel formation but also to impaired dendritic-cell maturation, expansion of regulatory T cells and myeloid-derived suppressor cells, endothelial immune barriers, and reduced infiltration of cytotoxic lymphocytes. Antiangiogenic therapy administered at appropriate doses may partially normalize tumor vasculature, improve tissue perfusion, reduce hypoxia, facilitate immune-cell trafficking, and enhance delivery of systemic therapies. These vascular changes create a more favorable immune environment that complements checkpoint blockade and promotes durable antitumor responses [54].

Clinical experience has demonstrated substantial benefit from VEGF/VEGFR-directed combinations in several malignancies, including renal cell carcinoma, hepatocellular carcinoma, endometrial carcinoma, and non-small-cell lung cancer. The success of these regimens illustrates the importance of simultaneously targeting malignant cells and the supporting tumor microenvironment rather than focusing exclusively on either component. Ongoing clinical trials continue to evaluate optimal sequencing, dosing schedules, and biomarker-guided patient selection for these combination strategies [54].

Targeting Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) have become attractive therapeutic targets because of their central role in extracellular matrix remodeling, immune suppression, angiogenesis, and therapeutic resistance. Current investigational strategies include inhibition of fibroblast activation protein (FAP), blockade of CAF-derived cytokines and chemokines, suppression of transforming growth factor-β signaling, disruption of stromal communication pathways, extracellular matrix remodeling, and functional reprogramming of tumor-promoting fibroblast populations. These approaches seek to reduce stromal barriers, improve immune-cell infiltration, and enhance penetration of anticancer drugs into dense tumor tissues [55].

However, growing evidence indicates that CAFs comprise multiple biologically distinct subpopulations with both tumor-promoting and tumor-restraining functions. Consequently, indiscriminate elimination of all fibroblasts may produce unintended adverse effects, including accelerated tumor progression in certain settings. Future therapeutic development therefore emphasizes precise molecular characterization of CAF subsets and selective targeting of pathogenic populations while preserving fibroblast populations that contribute to tissue homeostasis or antitumor immunity. Integration of single-cell sequencing and spatial transcriptomics is expected to play a major role in identifying these therapeutically relevant fibroblast subtypes [55].

Targeting Tumor-Associated Macrophages

Tumor-associated macrophages (TAMs) are increasingly recognized as key regulators of immune suppression, angiogenesis, extracellular matrix remodeling, and metastatic dissemination. Therapeutic strategies targeting macrophages have therefore expanded considerably over recent years. Current approaches include inhibition of monocyte recruitment through chemokine pathway blockade, suppression of colony-stimulating factor-1 receptor (CSF1R) signaling, interference with macrophage survival pathways, enhancement of macrophage-mediated phagocytosis through CD47–SIRPα blockade, and pharmacological reprogramming of immunosuppressive macrophages toward pro-inflammatory antitumor phenotypes. Rather than eliminating all macrophages, contemporary therapeutic strategies aim to restore physiological immune surveillance by modifying macrophage function while preserving their essential roles in tissue repair and host defense. Combination therapies integrating macrophage-directed treatment with immune checkpoint inhibition, chemotherapy, or targeted therapy are currently under active clinical investigation and represent an important frontier in precision immuno-oncology [53,55].

Bispecific Antibodies and T-Cell Engagers

Bispecific antibodies represent one of the most promising advances in cancer immunotherapy because they simultaneously bind a tumor-associated antigen and an immune-cell target, most commonly CD3 expressed on T lymphocytes. By physically bringing cytotoxic T cells into close proximity with malignant cells, these agents promote rapid and highly specific tumor-cell killing independent of conventional antigen presentation. Bispecific T-cell engagers have demonstrated remarkable efficacy in hematological malignancies, particularly acute lymphoblastic leukemia and certain B-cell lymphomas, and their application in solid tumors is expanding rapidly. Novel bispecific formats targeting HER2, EGFR, PSMA, CEA, DLL3, and other tumor-associated antigens are currently undergoing clinical evaluation.

Despite encouraging therapeutic activity, several challenges remain. Cytokine-release syndrome, immune effector cell-associated toxicities, antigen heterogeneity, on-target off-tumor effects, and adaptive immune escape continue to limit broader clinical application. Furthermore, the immunosuppressive nature of the solid-tumor microenvironment—including hypoxia, stromal barriers, metabolic competition, and inhibitory immune checkpoints—may reduce the effectiveness of T-cell engager therapies. Current research therefore focuses on optimizing antibody engineering, improving tumor specificity, reducing toxicity, and combining bispecific antibodies with checkpoint inhibitors or other immunomodulatory agents to enhance durable clinical responses [53].

Adoptive Cellular Therapy

Adoptive cellular therapy has become one of the most transformative developments in modern cancer treatment. Chimeric antigen receptor T-cell (CAR-T) therapy has produced unprecedented clinical responses in several hematological malignancies, including acute lymphoblastic leukemia, diffuse large B-cell lymphoma, mantle-cell lymphoma, and multiple myeloma. CAR-T cells are genetically engineered to recognize tumor-associated antigens independently of major histocompatibility complex presentation, thereby overcoming several conventional mechanisms of immune escape. However, translating this success to solid tumors has proven substantially more challenging because of antigen heterogeneity, poor cellular trafficking, dense stromal barriers, hypoxia, metabolic deprivation, and profound immunosuppression within the tumor microenvironment.

To overcome these limitations, numerous next-generation cellular therapies are currently under development. These include armored CAR-T cells capable of secreting cytokines or checkpoint inhibitors, tumor-infiltrating lymphocyte (TIL) therapy, T-cell receptor (TCR)-engineered lymphocytes targeting intracellular tumor antigens,

chimeric antigen receptor natural killer (CAR-NK) cells with improved safety profiles, macrophage-based cellular therapies, and gene-edited immune cells generated using CRISPR-based technologies. Combination approaches integrating adoptive cellular therapy with immune checkpoint inhibitors, antiangiogenic agents, stromal-targeting therapies, or metabolic modulators are expected to enhance persistence, trafficking, and antitumor efficacy within hostile solid-tumor microenvironments. These advances are paving the way toward highly personalized cellular immunotherapy capable of addressing the complex biological challenges posed by the TME [54,55].

Personalized Cancer Vaccines

The rapid evolution of next-generation sequencing, bioinformatics, and artificial intelligence has transformed the development of personalized cancer vaccines. Unlike conventional cancer vaccines that target shared tumor-associated antigens, personalized neoantigen vaccines are designed using the unique somatic mutations identified within an individual patient's tumor. Computational algorithms predict which mutated peptides are most likely to bind major histocompatibility complex (MHC) molecules and stimulate effective T-cell responses. These patient-specific neoantigens are subsequently incorporated into messenger RNA (mRNA), peptide, DNA, or dendritic-cell-based vaccine platforms with the objective of generating highly selective and durable antitumor immunity. Because neoantigens are absent from normal tissues, they offer the advantage of minimizing central immune tolerance while reducing the risk of off-target toxicity. Recent clinical studies have demonstrated encouraging immunogenicity and durable T-cell responses in melanoma, pancreatic cancer, glioblastoma, and several other solid malignancies, supporting the growing role of individualized vaccine strategies in precision oncology [56].

Despite these advances, the immunosuppressive tumor microenvironment (TME) remains a major barrier to vaccine efficacy. Activated vaccine-induced T cells must overcome inhibitory checkpoint signaling, regulatory immune populations, abnormal vasculature, stromal exclusion, and metabolic suppression before they can eliminate malignant cells effectively. Consequently, personalized cancer vaccines are increasingly being evaluated in combination with immune checkpoint inhibitors, cytokine-based therapies, oncolytic viruses, radiotherapy, and targeted therapies capable of modifying the TME. Future vaccine development is expected to integrate genomic sequencing, spatial immune profiling, and real-time monitoring of immune responses to optimize antigen selection and improve long-term therapeutic efficacy [56].

Targeting Hypoxia and Tumor Metabolism

Hypoxia and metabolic reprogramming represent fundamental characteristics of the TME and have therefore emerged as attractive therapeutic targets. Persistent oxygen deprivation stabilizes hypoxia-inducible factors (HIFs), particularly HIF-1α and HIF-2α, leading to transcriptional activation of genes involved in angiogenesis, glycolysis, epithelial–mesenchymal transition, immune suppression, and metastatic dissemination. Simultaneously, malignant cells undergo extensive metabolic adaptation by increasing glucose uptake, glutamine utilization, lipid metabolism, and lactate production, enabling continued proliferation under hostile environmental conditions. These metabolic alterations also suppress antitumor immune responses by depriving immune cells of essential nutrients and generating immunosuppressive metabolites [57].

Current therapeutic strategies aim to interfere with these adaptive pathways through inhibition of HIF signaling, glycolytic enzymes, lactate transporters, adenosine receptors, glutaminase, indoleamine 2,3-dioxygenase (IDO), arginine metabolism, and lipid metabolic pathways. However, selective targeting remains a significant challenge because activated immune cells often depend on many of the same metabolic pathways required by cancer cells. Consequently, future therapeutic development focuses on identifying metabolic vulnerabilities unique to malignant cells while simultaneously preserving or enhancing immune-cell function. Rational integration of metabolic therapy with immunotherapy, antiangiogenic treatment, and cellular therapy may further improve clinical outcomes by simultaneously disrupting multiple mechanisms of tumor adaptation [57].

Nanotechnology and TME-Responsive Drug Delivery

Nanotechnology has emerged as an innovative platform for improving the precision and efficacy of anticancer therapy by exploiting the unique biological characteristics of the TME. Nanoparticle-based drug delivery systems are capable of enhancing drug accumulation within tumors through the enhanced permeability and retention effect while protecting therapeutic agents from premature degradation during systemic circulation. Various nanocarriers—including liposomes, polymeric nanoparticles, dendrimers, inorganic nanoparticles, lipid nanoparticles, and biomimetic vesicles—have been engineered to deliver chemotherapeutic agents, nucleic acids, proteins, immune modulators, and gene-editing systems directly to malignant tissues with improved pharmacokinetic profiles and reduced systemic toxicity [58].

An important recent development is the design of TME-responsive nanoplatforms capable of releasing therapeutic payloads selectively in response to local environmental stimuli. These

systems exploit acidic extracellular pH, hypoxia, elevated reactive oxygen species, matrix-degrading enzymes, redox imbalance, or altered metabolic conditions to trigger controlled drug release specifically within the tumor. Such precision-targeted delivery minimizes damage to healthy tissues while maximizing local therapeutic concentration. In addition, multifunctional nanoparticles are being developed to simultaneously deliver combinations of chemotherapy, immune checkpoint inhibitors, cytokines, messenger RNA, small interfering RNA, CRISPR-based gene-editing systems, and imaging agents. These integrated approaches hold considerable promise for overcoming multiple barriers imposed by the TME and enhancing the effectiveness of combination cancer therapy [58].

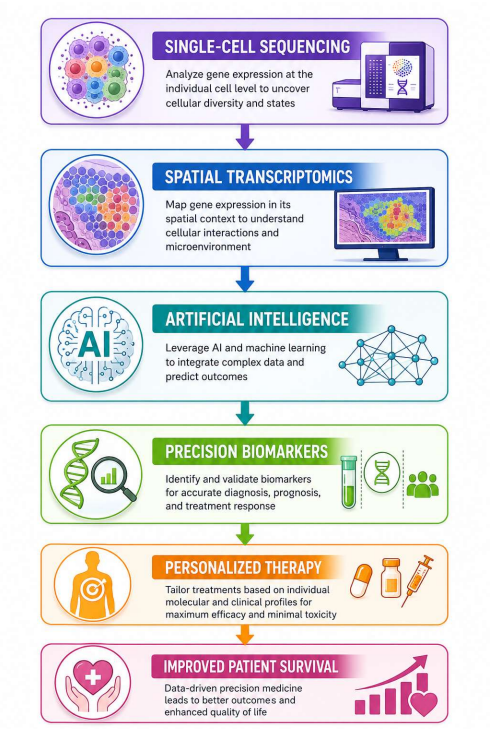
Single-Cell and Spatial Technologies

The development of single-cell and spatial analytical technologies has fundamentally transformed understanding of the TME by revealing previously unrecognized cellular diversity and functional complexity. Single-cell RNA sequencing (scRNA-seq) enables transcriptomic characterization of thousands of individual cells simultaneously, allowing identification of rare immune populations, stromal subsets, malignant cell states, and developmental trajectories that cannot be detected using conventional bulk sequencing. These technologies have demonstrated that tumors consist of numerous dynamically interacting cellular populations rather than homogeneous groups of malignant cells, thereby providing unprecedented insight into mechanisms of tumor progression, immune evasion, and therapeutic resistance [59].

Spatial transcriptomics, multiplex immunofluorescence, imaging mass cytometry, digital pathology, and other spatially resolved technologies complement single-cell sequencing by preserving the anatomical organization of tissues while simultaneously measuring gene and protein expression. These approaches enable investigators to analyze cellular neighborhoods, immune niches, stromal architecture, vascular organization, and direct cell-to-cell interactions within intact tumor specimens. Increasing evidence indicates that the spatial arrangement of cells may influence therapeutic response as strongly as cellular composition itself. Integration of single-cell sequencing with spatial profiling therefore provides a more comprehensive understanding of tumor biology and is expected to accelerate biomarker discovery, improve prediction of treatment response, and facilitate development of highly individualized therapeutic strategies [59].

Future Directions

The future of tumor microenvironment research lies in recognizing cancer as a continuously evolving multicellular ecosystem rather than a disease driven solely by malignant cells. Rapid advances in molecular biology, computational science, artificial intelligence, and systems medicine are enabling increasingly comprehensive characterization of interactions among tumor cells, immune populations, stromal elements, vascular networks, and metabolic pathways. These technological developments are expected to transform precision oncology by supporting individualized therapeutic strategies based on the dominant biological mechanisms operating within each patient's tumor rather than relying exclusively on tumor histology or genetic alterations [60].



Precision TME Profiling

Future precision oncology will increasingly integrate multidimensional biological information to characterize the TME at unprecedented resolution. Comprehensive profiling may combine genomic, transcriptomic, epigenomic, proteomic, metabolomic, microbiome, immune, stromal, vascular, and spatial datasets to identify the principal mechanisms responsible for tumor progression, metastasis, or therapeutic resistance in individual patients. Such integrated molecular profiling has the potential to guide personalized treatment selection, predict therapeutic benefit, and identify novel targets for combination therapy. As analytical technologies become more accessible, precision TME profiling is expected to become an integral component of routine clinical oncology.

Dynamic Biomarkers

One of the major limitations of current oncology is reliance on a single tissue biopsy obtained at one

point during disease progression. Because the TME undergoes continuous biological evolution in response to tumor growth and therapeutic intervention, static biomarkers frequently fail to capture clinically relevant changes. Future biomarker development is therefore expected to emphasize dynamic monitoring through liquid biopsy, circulating tumor DNA, extracellular vesicles, circulating immune-cell populations, molecular imaging, serial tissue sampling, and real-time assessment of immune activity. Continuous monitoring may allow earlier detection of emerging resistance mechanisms, therapeutic response, and disease recurrence, thereby supporting adaptive treatment strategies throughout the course of cancer management.

Spatially Guided Oncology

Emerging evidence suggests that the spatial organization of cancer cells, immune populations, fibroblasts, endothelial cells, and extracellular matrix components may be as clinically important as their absolute abundance. Spatial biomarkers describing cellular neighborhoods, immune exclusion patterns, vascular architecture, and stromal organization are likely to improve prediction of metastatic risk, therapeutic response, and long-term survival. Future oncology practice may therefore integrate spatial pathology with conventional molecular diagnostics to provide a more comprehensive understanding of tumor biology and support individualized clinical decision-making.

Reprogramming Rather Than Depletion

Many components of the TME perform both protective physiological functions and tumor-promoting activities. Consequently, indiscriminate elimination of entire cellular populations may disrupt normal tissue homeostasis while producing unintended adverse effects. Future therapeutic strategies are increasingly expected to emphasize functional reprogramming rather than complete depletion. Examples include converting immunosuppressive macrophages into pro-inflammatory antitumor phenotypes, normalizing abnormal tumor vasculature instead of destroying blood vessels, restoring dendritic-cell function, reversing T-cell exhaustion, and selectively targeting pathogenic subsets of cancer-associated fibroblasts while preserving fibroblast populations that maintain normal tissue integrity. Such approaches aim to restore physiological immune surveillance while minimizing treatment-associated toxicity.

Rational Combination Therapy

Because tumor progression results from the coordinated activity of multiple interconnected biological pathways, combination therapy will remain a central principle of future cancer treatment. Rational combinations should be selected according to the dominant mechanisms operating within each patient's TME rather than empirical therapeutic pairing. Promising examples include immune checkpoint blockade combined with vascular normalization, immunotherapy integrated with cancer-associated fibroblast targeting, adoptive cellular therapy combined with stromal remodeling, personalized cancer vaccines administered alongside checkpoint inhibitors, metabolic therapy integrated with immunotherapy, and radiotherapy combined with immune modulation. The major challenge will be identifying the optimal therapeutic combination for individual patients while minimizing overlapping toxicities and maintaining long-term treatment efficacy.

Artificial Intelligence and Systems Oncology

Artificial intelligence (AI), machine learning, and systems biology are expected to play increasingly important roles in future oncology by integrating complex multidimensional datasets generated from genomic sequencing, transcriptomics, proteomics, metabolomics, digital pathology, radiomics, and spatial biology. Advanced computational models can identify subtle biological patterns that may not be apparent through conventional statistical analyses, enabling improved prediction of therapeutic response, resistance mechanisms, disease recurrence, and patient survival. AI-assisted pathology and multi-omics integration may also facilitate automated patient stratification and support real-time clinical decision-making, thereby advancing the implementation of precision medicine in routine oncology practice.

Targeting the Premetastatic Niche

Metastasis remains the principal cause of cancer-related mortality, and increasing evidence indicates that primary tumors actively prepare distant organs before metastatic cells arrive. Through circulating cytokines, chemokines, growth factors, extracellular vesicles, and immune-cell reprogramming, primary tumors establish a premetastatic niche that promotes future colonization by disseminated tumor cells. This permissive microenvironment is characterized by extracellular matrix remodeling, vascular alterations, recruitment of bone marrow-derived cells, immune suppression, and metabolic adaptation. Preventing formation of the premetastatic niche therefore represents a promising therapeutic strategy for reducing metastatic recurrence and improving long-term survival. Future research aimed at interrupting these early systemic interactions may provide opportunities for metastasis prevention before clinically detectable secondary tumors develop.

DISCUSSION

The concept of the tumor microenvironment (TME) has transformed contemporary cancer biology by shifting the focus from a tumor cell-centered perspective to a systems-based

understanding of cancer as a complex and evolving multicellular ecosystem. Earlier models primarily attributed tumor progression to the accumulation of genetic mutations within malignant cells; however, accumulating evidence demonstrates that cancer development is equally dependent on continuous interactions among malignant cells, immune populations, stromal cells, vascular components, extracellular matrix (ECM), and metabolic regulators. These bidirectional interactions determine tumor initiation, local invasion, metastatic dissemination, therapeutic response, and clinical outcome. Consequently, successful cancer treatment increasingly requires simultaneous targeting of both tumor-intrinsic molecular alterations and the surrounding microenvironment that supports malignant progression [61].

The findings summarized in this review are consistent with the observations reported by Hanahan, who proposed that the hallmarks of cancer continue to evolve through dynamic interactions between malignant cells and the host microenvironment rather than through isolated genetic events alone. Hanahan emphasized that immune modulation, stromal remodeling, metabolic adaptation, and inflammatory signaling collectively represent enabling characteristics that sustain tumor progression. Similarly, Joyce and Fearon described the TME as an integrated biological network in which reciprocal communication between tumor cells and host tissues determines disease evolution and therapeutic responsiveness. These observations reinforce the current understanding that malignant behavior cannot be explained solely by the genomic characteristics of cancer cells but must instead be interpreted within the broader biological context of the tumor ecosystem [61,62].

One of the most important concepts emerging from recent studies is the remarkable functional heterogeneity of TME components. Immune cells, fibroblasts, endothelial cells, macrophages, neutrophils, cytokines, and extracellular matrix proteins cannot be categorized simply as either tumor-promoting or tumor-suppressive. Instead, their biological activities are highly dependent on cellular differentiation state, anatomical location, metabolic conditions, disease stage, and exposure to therapy. This conclusion agrees with the work of Hinshaw and Shevde, who demonstrated that the TME exhibits continuous functional plasticity throughout tumor progression, allowing individual cellular populations to adopt distinct phenotypes in response to environmental stimuli. Likewise, Baghban and colleagues reported that stromal and immune cells continuously undergo phenotypic reprogramming under the influence of tumor-derived cytokines, growth factors, and extracellular vesicles, thereby contributing to marked intratumoral heterogeneity [63,64].

The functional diversity of cancer-associated fibroblasts (CAFs) represents one of the clearest examples of this biological complexity. Earlier therapeutic strategies focused on eliminating stromal fibroblasts with the assumption that all CAF populations promoted tumor growth. However, subsequent investigations have revealed substantial heterogeneity among fibroblast subpopulations, with certain subsets exhibiting tumor-restraining functions while others actively promote angiogenesis, immune suppression, extracellular matrix remodeling, and metastatic dissemination. This review therefore supports the conclusions of Öhlund et al., who identified distinct inflammatory and myofibroblastic CAF subsets with divergent biological functions in pancreatic cancer. Similarly, Kalluri emphasized that therapeutic success will depend on selectively targeting pathogenic fibroblast populations while preserving stromal components that maintain tissue integrity and support antitumor immunity. These findings explain why indiscriminate stromal depletion has frequently produced disappointing clinical outcomes and underscore the importance of stromal reprogramming rather than complete elimination [65,66].

The present review also highlights the pivotal role of tumor-associated macrophages (TAMs) in orchestrating immune suppression and therapeutic resistance. Rather than existing exclusively as classically activated (M1) or alternatively activated (M2) macrophages, contemporary evidence indicates that TAMs comprise multiple transcriptionally distinct populations occupying a continuous spectrum of activation states. These cells regulate angiogenesis, extracellular matrix remodeling, immune checkpoint expression, metastatic dissemination, and resistance to systemic therapy. This interpretation closely parallels the findings of Cassetta and Pollard, who demonstrated that macrophage phenotypes are dynamically shaped by local environmental signals and that functional reprogramming may represent a more effective therapeutic strategy than macrophage depletion. Comparable observations have also been reported by Mantovani and colleagues, who described macrophages as central regulators of cancer-related inflammation and immune escape. Together, these studies support the concept that modulation of macrophage function is likely to become an important component of future combination immunotherapy [67].

The relationship between angiogenesis and antitumor immunity represents another major theme emerging from recent research. Abnormal tumor vasculature contributes not only to inadequate oxygenation and impaired drug delivery but also to immune exclusion by limiting lymphocyte trafficking into malignant tissues. Persistent hypoxia promotes stabilization of

hypoxia-inducible factors, enhances epithelial–mesenchymal transition, stimulates angiogenesis, and favors expansion of immunosuppressive cell populations. These observations are consistent with the vascular normalization hypothesis proposed by Jain, who demonstrated that appropriately dosed antiangiogenic therapy can transiently restore vascular function, reduce hypoxia, improve immune-cell infiltration, and enhance the efficacy of chemotherapy, radiotherapy, and immune checkpoint inhibitors. Likewise, Huang and colleagues reported that vascular normalization provides a biological foundation for combining antiangiogenic agents with immunotherapy to achieve synergistic antitumor effects. These studies strongly support the growing clinical adoption of integrated antiangiogenic–immunotherapeutic strategies [68].

Another important development discussed in this review is the transition from static to dynamic characterization of the TME. Conventional histopathological assessment based on a single pretreatment biopsy provides only a limited snapshot of an ecosystem that undergoes continuous biological evolution during disease progression and therapeutic intervention. Treatment pressure may rapidly alter immune-cell composition, checkpoint molecule expression, stromal organization, metabolic pathways, and clonal architecture. This concept closely aligns with observations reported by Wagner and colleagues using single-cell technologies, which demonstrated remarkable temporal changes in immune and stromal populations during treatment. Similarly, Satpathy et al. emphasized that integration of longitudinal tissue sampling with single-cell and spatial multi-omics technologies provides a far more comprehensive understanding of treatment response than conventional bulk tissue analysis. These findings suggest that future precision oncology should increasingly incorporate serial monitoring of the TME through liquid biopsy, spatial transcriptomics, circulating biomarkers, and molecular imaging to guide adaptive therapeutic decision-making [69].

Despite substantial scientific progress, important challenges continue to limit successful clinical translation of TME-directed therapies. Many molecular pathways targeted within the TME also perform essential physiological functions in normal tissues, increasing the risk of systemic toxicity and immune-related adverse events. Furthermore, currently available predictive biomarkers—including PD-L1 expression, tumor mutational burden, and microsatellite instability—demonstrate only moderate predictive accuracy because they fail to capture the full biological complexity of the TME. Experimental findings generated in animal models or simplified in vitro systems may also differ significantly from observations in human malignancies owing to differences in immune composition, stromal organization, and metabolic regulation. In addition, rational combination therapy requires careful consideration of treatment sequencing, dosage optimization, toxicity management, economic feasibility, and patient selection. These challenges have also been emphasized by Hegde and Chen, who argued that overcoming resistance to cancer immunotherapy requires integrated understanding of the tumor ecosystem rather than isolated targeting of individual signaling pathways [70].

Overall, the available evidence indicates that the tumor microenvironment represents one of the most promising therapeutic frontiers in modern oncology. Rather than attempting indiscriminate elimination of individual cellular populations, future strategies are likely to emphasize selective modulation, normalization, and functional reprogramming of the tumor ecosystem. Advances in single-cell sequencing, spatial biology, artificial intelligence, systems immunology, and precision medicine are expected to accelerate the identification of patient-specific therapeutic vulnerabilities and facilitate biologically rational combination therapies. Such integrated approaches have the potential to improve therapeutic efficacy, overcome resistance, reduce treatment-related toxicity, and ultimately enhance long-term survival across a broad spectrum of human malignancies.

CONCLUSION

The tumor microenvironment is a central determinant of cancer progression, metastasis, immune escape, and therapeutic response. Its major components—including immune cells, cancer-associated fibroblasts, endothelial cells, extracellular matrix, soluble mediators, and metabolic factors—form interconnected networks that can support malignant survival and adaptation.

Tumor–immune interactions are particularly important because cancer cells exploit physiological regulatory mechanisms to suppress antitumor immunity. Immune checkpoint blockade has demonstrated the therapeutic potential of reversing this suppression, but resistance remains common because of the broader complexity of the TME.

Angiogenesis, hypoxia, stromal remodeling, immunosuppressive myeloid populations, T-cell exhaustion, and metabolic competition represent important therapeutic targets. Recent advances in checkpoint combinations, antiangiogenic–immunotherapy combinations, bispecific antibodies, adoptive cellular therapy, cancer vaccines, macrophage and fibroblast targeting, metabolic interventions, and TME-responsive drug delivery are expanding the therapeutic landscape.

Future progress will depend on recognizing the TME as a heterogeneous and evolving ecosystem. Single-cell analysis, spatial profiling, multi-omics

integration, artificial intelligence, and dynamic biomarker assessment are expected to support increasingly personalized therapeutic strategies. Rather than targeting isolated molecular pathways, future cancer therapy is likely to focus on rationally remodeling the entire tumor ecosystem to restore effective immunity, improve drug delivery, prevent metastatic progression, and overcome treatment resistance.

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