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TGF- β Signaling in Cancer Immunity: Immune Suppression, Stromal Remodeling, and Therapeutic Targeting

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Abstract

Transforming growth factor- β (TGF- β) is a pleiotropic cytokine with context-dependent roles in cancer. TGF- β signaling regulates cell proliferation, immune responses, extracellular matrix remodeling, and tissue homeostasis through SMAD-dependent and noncanonical pathways. Although TGF- β functions as a tumor suppressor during early tumorigenesis by limiting epithelial proliferation and preserving tissue integrity, advanced tumors frequently exploit this pathway to promote immune evasion, stromal remodeling, and metastatic progression. Increasing evidence identifies TGF- β as a central regulator of the tumor microenvironment (TME), where it suppresses cytotoxic lymphocyte activity, expands immunosuppressive myeloid populations, and activates stromal programs that exclude effector T cells from tumor nests. Through these coordinated mechanisms, TGF- β establishes an immunosuppressive milieu that contributes to resistance to immune checkpoint blockade and other immunotherapies. In this review, we summarize current understanding of how TGF- β shapes tumor immunity through its effects on T cells, natural killer cells, myeloid-derived suppressor cells, tumor-associated macrophages, and cancer-associated fibroblasts. We also discuss emerging therapeutic strategies targeting the TGF- β pathway, including receptor kinase inhibitors, ligand traps, and bifunctional molecules that simultaneously inhibit TGF- β and immune checkpoints. While early clinical studies have demonstrated promising immunomodulatory activity, recent trials highlight the challenges of targeting a pathway that also regulates normal tissue homeostasis. Improved mechanistic insights and biomarker-driven patient stratification will be essential for maximizing the therapeutic potential of TGF- β inhibition in cancer immunotherapy. Collectively, these findings position TGF- β signaling as a central axis linking tumor

cells, stromal remodeling, immunosuppression, and therapeutic resistance across diverse solid and hematologic malignancies.

Keywords: TGF- β signaling; tumor microenvironment; cancer immunotherapy; immune checkpoint blockade; PD-1 pathway; stromal exclusion.

1. Introduction

1.1 Foundations and Emerging Strategies in Cancer Immunotherapy

Cancer immunotherapy has transformed treatment by harnessing the immune system to eliminate malignant cells. Although immune surveillance can detect abnormal cells, tumors evolve mechanisms to evade detection. Immunotherapy aims to overcome these barriers and enhance antitumor responses. A major advance has been the use of immune checkpoint inhibitors (ICIs), which target inhibitory pathways such as PD-1/PD-L1 and CTLA-4. While these pathways normally maintain immune tolerance, tumors exploit them to suppress T-cell activity. Blocking these checkpoints restores immune function and enables stronger antitumor responses. ICIs have shown success in melanoma, non-small cell lung cancer, and Hodgkin lymphoma, with some patients achieving durable remission. However, responses remain variable, and resistance often arises from tumor heterogeneity, low immunogenicity, and an immunosuppressive tumor microenvironment (TME). Combination strategies integrating ICIs with chemotherapy, radiation, or targeted therapies are therefore being explored to enhance efficacy (1, 2). Adoptive cell therapy (ACT) is another key strategy that involves engineering or expanding immune cells to target cancer. Chimeric antigen receptor (CAR) T-cell therapy, in which T cells are modified to recognize tumor-associated antigens, has demonstrated remarkable efficacy in hematologic malignancies, leading to FDA-approved therapies such as tisagenlecleucel and axicabtagene ciloleucel. However, application to solid tumors remains limited by immunosuppressive TMEs, poor infiltration, and antigen heterogeneity. To overcome these barriers, next-generation CAR-T approaches aim to improve persistence, safety, and efficacy, often in combination with cytokines, oncolytic viruses, or ICIs. Additional ACT modalities, including tumor-infiltrating lymphocyte (TIL) therapy and natural killer (NK) cell therapy, are also under investigation, offering alternative strategies to enhance antitumor immunity (3, 4).

Despite these advances, major challenges remain. Clinical responses vary widely and depend on factors such as tumor mutational burden, immune infiltration, and TME composition. Identifying predictive biomarkers, including PD-L1 expression and tumor mutational burden, is essential for patient selection. Immune-related adverse events (irAEs) caused by systemic immune activation also require careful monitoring. Future strategies will increasingly rely on personalized approaches integrating tumor genomics and immune profiling. Emerging technologies such as single-cell sequencing, CRISPR-based editing, and artificial intelligence are expected to enable more precise therapies. Combining immunotherapy with targeted, radiologic, or metabolic approaches may further overcome resistance and improve outcomes (5, 6).

Cancer immunotherapy is now entering a phase of diversification and personalization (7, 8). Beyond ICIs and CAR-T therapies, emerging strategies show promising clinical and translational progress (9, 10). Bispecific antibodies enable simultaneous targeting of immune checkpoints and tumor antigens, while next-generation PD-1-based constructs aim to enhance specificity and reduce toxicity (11, 12). Personalized neoantigen vaccines, particularly those leveraging sequencing and computational epitope prediction, are gaining traction. Early trials, including mRNA-based platforms, have demonstrated

encouraging immunogenicity and recurrence-free survival in melanoma and other solid tumors (13, 14). T cell receptor-engineered T-cell (TCR-T) therapies expand ACT by targeting intracellular antigens, and mRNA-based vaccines offer a flexible and rapidly deployable platform (15, 16). Nonetheless, resistance remains common in solid tumors characterized by immune exclusion and stromal barriers, with increasing evidence implicating TGF- β signaling as a key driver of immunosuppressive microenvironments and therapeutic resistance.

1.2 Role of TGF- β in Cancer Biology

TGF- β is a multifunctional cytokine that has a complex, context-dependent role in cancer biology. In modern tumor biology, TGF- β signaling is increasingly recognized as a master regulator of tumor-microenvironment interactions that integrate immune suppression, stromal activation, and metastatic progression. In normal cells and early-stage tumors, TGF- β acts as a tumor suppressor. It regulates essential processes, including proliferation, differentiation, apoptosis, and tissue homeostasis. TGF- β primarily exerts its tumor-suppressive effects through the canonical Smad-dependent signaling pathway, which induces cell cycle arrest by upregulating cyclin-dependent kinase inhibitors like p21 and p15. Additionally, TGF- β promotes genomic stability and reduces inflammation, supporting its protective role in early carcinogenesis. However, as tumors advance, they often develop resistance to TGF- β 's growth-inhibitory effects. This change is frequently triggered by mutations in TGF- β receptors or downstream signaling components. Alterations in the TME can also enhance TGF- β 's pro-tumorigenic functions (17, 18). Figure 1 illustrates the TGF- β axis. As summarized in Figure 1, canonical and noncanonical TGF- β signaling converge on transcriptional programs regulating immune suppression and stromal remodeling

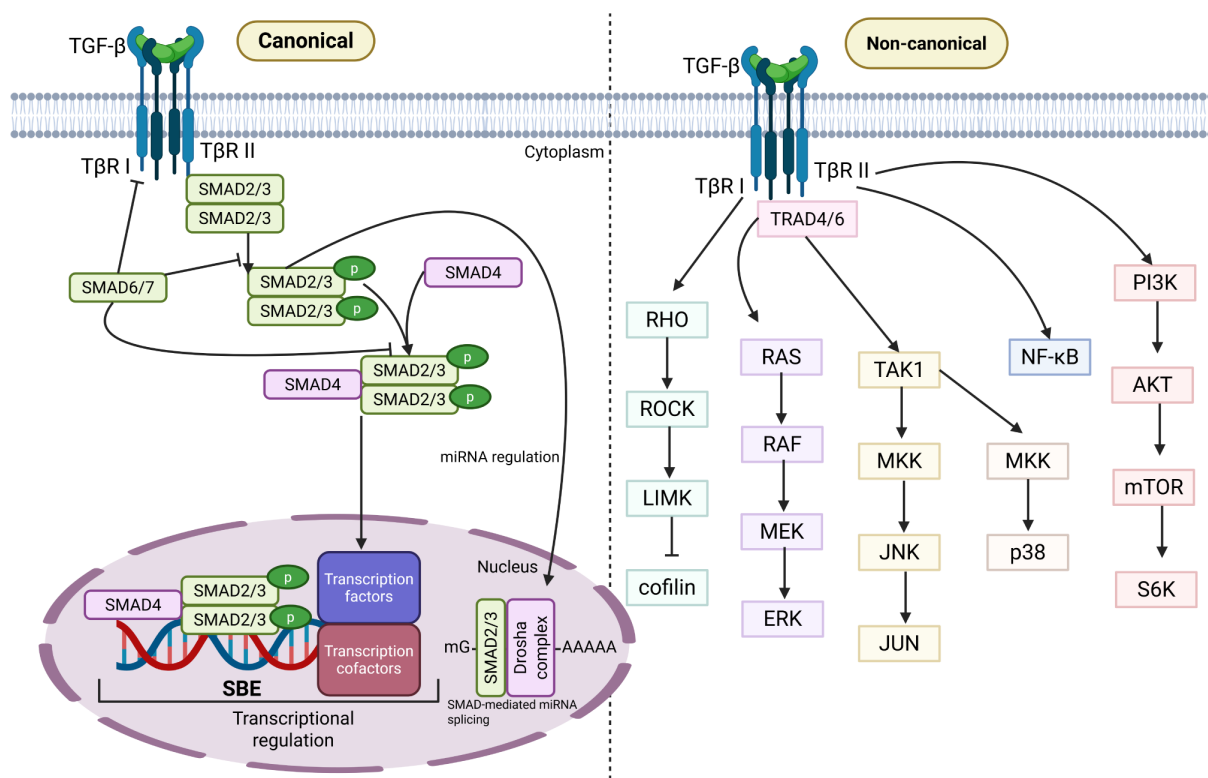


Figure 1: Overview of canonical and noncanonical TGF- β signaling pathways. TGF- β signaling is initiated by binding of TGF- β to T β RII, which recruits and activates T β RI. In the canonical pathway, activated T β RI phosphorylates SMAD2 and SMAD3, which form complexes with SMAD4 and translocate to the nucleus to regulate gene transcription and miRNA processing. In the noncanonical pathway, TGF- β activates alternative signaling cascades, including RAS/ERK, PI3K/AKT,

JNK, p38 MAPK, NF- κ B, and Rho pathways. TGF- β signaling also interacts with other pathways, including Wnt, Hedgehog, interferon, TNF, and Notch signaling (19).

In advanced cancers, TGF- β becomes a powerful driver of tumor growth and spread. It promotes epithelial-mesenchymal transition (EMT), a process that enables cancer cells to become invasive, thereby aiding their spread to distant parts of the body. TGF- β also helps create an immunosuppressive TME by recruiting and activating regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), which work together to weaken anti-tumor immune responses. Additionally, TGF- β promotes new blood vessel formation by increasing VEGF and other angiogenic factors, thereby supporting tumor growth and survival. It also modifies the extracellular matrix (ECM), forming a fibrous, stiff tissue that promotes tumor cell invasion and increases tumor resistance to treatment.

Despite the promising therapeutic potential of targeting TGF- β signaling, clinical development has been challenging because the pathway plays complex roles in tissue homeostasis and tumor suppression. Several types of TGF- β inhibitors, including receptor kinase inhibitors, ligand traps, and neutralizing antibodies, have been studied in preclinical and clinical research (20). One of the most advanced clinical approaches involved bintrafusp alfa (M7824), a bifunctional fusion protein made of a PD-L1-blocking antibody fused to the extracellular domain of TGF- β receptor II, which acts as a TGF- β “trap”. Early-phase studies within the INTR@PID clinical trial program indicated potential antitumor activity across various tumor types (21, 22). However, later phase III trials, including the INTR@PID Lung 037 study in NSCLC, failed to show improved clinical outcomes compared to standard PD-1/PD-L1 blockade, leading to the discontinuation of further development in this area (23, 24). These results emphasize the complexity of targeting TGF- β signaling in cancer therapy and highlight the need for better patient selection and more precise strategies to regulate TGF- β activity within the TME (25, 26). The dual role of TGF- β as both a tumor suppressor in early tumor development and a promoter of metastasis and immune evasion in advanced cancers makes therapeutic targeting even more challenging. Therefore, future approaches will likely require context-dependent modulation of TGF- β signaling, especially when combined with ICI, while carefully balancing effectiveness with toxicity and resistance mechanisms.

1.3 Rationale for Studying TGF- β in Immunotherapy and TME Remodeling

The rationale for studying TGF- β in cancer immunotherapy and TME remodeling is its critical role as a master regulator of immune suppression and stromal dynamics, which are essential barriers to effective anti-tumor immunity. TGF- β is a pleiotropic cytokine that has significant effects on both immune and non-immune cells within the TME, creating an immunosuppressive and pro-tumor environment. In the immune system, TGF- β inhibits the activity of cytotoxic T cells and NK cells, which are vital for identifying and destroying cancer cells. It also promotes the growth and function of Tregs and MDSCs, further weakening anti-tumor immune responses. Additionally, TGF- β impairs the maturation and antigen-presenting capacity of dendritic cells (DCs), disrupting the initiation of adaptive immunity. These immunosuppressive effects are enhanced by TGF- β 's ability to induce immune checkpoint molecules such as PD-1 and CTLA-4, which make immune cells less responsive to tumor antigens. As a result, TGF- β contributes to the failure of ICIs in many patients, particularly those with TGF- β -rich tumors. Therefore, targeting TGF- β signaling has emerged as a promising strategy to overcome immune evasion and improve immunotherapy responses, particularly when combined with ICB (27, 28).

Beyond its immunosuppressive functions, TGF- β plays a key role in remodeling the TME to support tumor growth and spread. It activates cancer-associated fibroblasts (CAFs), which release ECM

components and growth factors that boost tumor development, invasion, and resistance to therapy. TGF- β also triggers EMT, a process that increases the migratory and invasive abilities of cancer cells, helping them spread to other areas. Additionally, TGF- β promotes new blood vessel formation by increasing pro-angiogenic factors, such as VEGF, thereby securing a robust blood supply for tumor expansion. The fibrotic, rigid stroma created by TGF- β not only blocks immune cell entry but also creates a low-oxygen, nutrient-poor environment that further weakens immune function. These dual roles of TGF- β , in immune suppression and stromal remodeling, make it a crucial target for therapy. Inhibiting TGF- β signaling could potentially reverse immune suppression and normalize the TME, increasing the success of immunotherapies and other cancer treatments. Preclinical studies and early clinical trials indicate that TGF- β inhibitors can enhance immune cell infiltration, reduce fibrosis, and be well tolerated when combined with ICIs, supporting further research (29).

TGF- β is a versatile cytokine that functions as a tumor suppressor in early-stage cancers but promotes tumor growth, metastasis, and immune evasion in later stages. The research seeks to understand how TGF- β contributes to the creation of an immunosuppressive TME by regulating immune cell activity, inducing EMT, and promoting fibrosis and angiogenesis. By exploring the mechanisms by which TGF- β signaling affects immune evasion and stromal interactions, the study aims to identify therapeutic strategies targeting TGF- β signaling to improve the effectiveness of immunotherapy, such as ICI, and to overcome treatment resistance. Collectively, these mechanisms support a framework in which TGF- β functions as a central coordinator of immune suppression, stromal remodeling, and metastatic plasticity within the tumor ecosystem.

2. TGF- β Signaling Pathway

TGF- β signaling in cancer operates through multiple interconnected regulatory layers, including ligand activation, receptor signaling, SMAD-mediated transcriptional programs, and extensive crosstalk with metabolic and oncogenic signaling pathways.

2.1 Overview of TGF- β Signaling

TGF- β 1, hereafter referred to as TGF- β , is the most extensively studied member of the TGF- β subfamily within the larger TGF- β superfamily of structurally and functionally related cytokines (30). This superfamily also includes TGF- β 2, TGF- β 3, activins, nodal, inhibins, Müllerian-inhibiting substance, growth and differentiation factors, and bone morphogenetic proteins (BMPs). TGF- β was first identified in the early 1980s as a secreted factor that, when combined with TGF- β or epidermal growth factor (EGF), promoted the growth of normal rat kidney cells in soft agar. Significant progress has been made in understanding this multifunctional cytokine. The TGF- β gene encodes a 390-amino-acid prepropeptide. The precursor is processed by furin proteases into an amino-terminal fragment and a carboxy-terminal fragment of 112 amino acids, which together form the mature, bioactive TGF- β (31). The amino-terminal segment, known as the latency-associated peptide (LAP), remains noncovalently attached to the mature TGF- β (32). The latent form of TGF- β is activated by specific proteases that cleave LAP or by mechanical forces exerted by cell-surface integrins, leading to the release of mature, active TGF- β (33, 34). The bioactive TGF- β is a disulfide-bond-linked dimeric protein that binds to cell-surface receptors and has an apparent molecular weight of 25 kDa (35).

Pro-TGF- β is produced as a latent complex within the ECM, including a signal peptide in its extensive N-terminal region, called the LAP, and a mature cytokine in the C-terminal segment (36–38). The large latent complex comprises LAP, mature TGF- β , and latent TGF- β -binding proteins, primarily LTBP1, LTBP3, and LTBP4. Activation of latent TGF- β is promoted by proteins and enzymes such as

thrombospondin 1, glycoprotein A repetitions predominant protein, integrins, and other TGF- β -binding proteins, which form disulfide-linked dimers and homodimers. Once activated, TGF- β interacts with the T β R complex or other cytokines to regulate biological responses via the SMAD and/or non-SMAD signaling pathways (39, 40). The SMAD family serves as a key group of intracellular mediators in TGF- β superfamily signaling. It includes five receptor-regulated SMADs (R-SMADs), SMAD1, SMAD2, SMAD3, SMAD5, and SMAD9 (also known as SMAD8); the common mediator SMAD (Co-SMAD), SMAD4, which forms transcriptionally active complexes with activated R-SMADs; and two inhibitory SMADs (I-SMADs), SMAD6 and SMAD7, which negatively regulate SMAD activation and signaling. Besides ligand-activated receptors, several proteins influence receptor-activated SMAD activity. The regulation of SMAD-mediated transcription and target-gene selection involves many adaptor proteins located in both the cytoplasm and the nucleus. Active SMAD complexes work with other proteins to accurately identify target genes and produce responses suited to specific cellular contexts. The TGF- β /SMAD signaling pathways are intricate, context-dependent, and vital for maintaining tissue homeostasis in adults and supporting proper immune system function (41).

TGF- β family signaling occurs when the mature polypeptide forms a disulfide-linked dimer, which acts as a ligand for cell-surface receptors. TGF- β signaling is initiated at the cell surface when TGF- β binds to the type II TGF- β receptor (T β RII). Ligand binding promotes the formation of a heteromeric receptor complex in which the constitutively active T β RII phosphorylates serine and threonine residues within the juxtamembrane GS domain of the type I receptor (T β RI), leading to activation of the T β RI kinase and the propagation of downstream signaling cascades (42). Additionally, TGF- β binding to the cell-surface receptor complex activates both Smad- and non-Smad-mediated signaling pathways. While TGF- β or activin binds to their respective receptor complexes, activating Smad2 and Smad3, BMP binding activates Smad1 and Smad5 (43). Once activated by TGF- β 1, Smad2 and Smad3 are phosphorylated and form a complex through Smad signaling. This process involves receptors internalized via clathrin-coated pits, whose activity is regulated, ultimately driving the transcription of TGF- β /Smad target genes (44).

2.2 Regulation of TGF- β Signaling in Cancer

Beyond tumor-intrinsic signaling, TGF- β also regulates stromal and immune interactions within the tumor microenvironment, contributing to ECM remodeling and immune exclusion that limit the efficacy of immunotherapy (27).

2.2.1 Epigenetic and Transcriptional Regulation

Several studies have shown that TGF- β signaling is precisely regulated at the transcriptional and chromatin levels. During TGF- β -induced EMT in colorectal cancer (CRC), S100A8 and the transcription factor USF2 are increased. USF2 binds to the S100A8 promoter and enhances its transcription, which promotes EMT, invasion, and motility. Higher tumor cell S100A8 levels are associated with lower overall survival, and USF2 expression is positively associated with S100A8 in tumor cells but negatively associated with S100A8 in stromal cells (45). Post-translational modification of SMAD proteins adds another layer of regulation. PRMT5 methylates SMAD4 at R361 after TGF- β 1 stimulation, aiding in SMAD complex formation and its movement into the nucleus. Mutating SMAD4 R361 prevents TGF- β 1-induced EMT and metastasis in CRC, and increased PRMT5 levels or SMAD4 R361 methylation are connected to poorer clinical outcomes (46). Likewise, lysine-specific demethylase 4C (KDM4C) enhances TGF- β 2 transcription by reducing H3K9me3 levels at its promoter, thereby activating Smad/ATM/Chk2 signaling and leading to radioresistance in lung cancer.

The deubiquitinase USP9X stabilizes KDM4C, and its reduction disturbs TGF- β 2/Smad signaling and radioresistance, highlighting an epigenetic-post-translational regulatory axis (47).

2.2.2 Immune Microenvironment Regulation

TGF- β signaling is also heavily influenced by interactions between immune cells within the tumor microenvironment. Chemotherapy-induced neutrophil extracellular traps promote chemoresistance in breast cancer lung metastasis. NET-associated integrin- α v β 1 sequesters latent TGF- β , while matrix metalloproteinase 9 activates TGF- β , thereby inducing EMT and resistance (48). In squamous cell carcinoma models, tumor-initiating cells use NRF2-mediated antioxidant activity to induce IL-33 release. IL-33 supports Fc ϵ RI α + macrophage development, which then delivers paracrine TGF- β signals that enhance TIC invasiveness and drug resistance, creating a feed-forward loop (49). In chronic inflammation models, PD-1^{high} macrophages show immunoregulatory features and higher expression of TGF- β receptors. TGF- β 1 directly induces PD-1 expression via a SMAD3-STAT3 complex at the *Pdcd1* promoter, thereby strengthening immunosuppression (50). Additionally, integrin α v β 8 selectively activates latent TGF- β , and blocking it disrupts immunosuppressive T cell development, offering potential for therapy (51).

2.2.3 Metabolic and Post-Translational Modifications

Metabolic rewiring and glycosylation changes further refine the output of TGF- β signaling. MORC2 undergoes O-GlcNAcylation at T556 by OGT, a modification increased by TGF- β 1 through stabilizing GFAT, the rate-limiting enzyme of the hexosamine biosynthetic pathway. O-GlcNAcylated MORC2 activates transcription of CTGF and SNAIL, promoting breast cancer invasion and metastasis. Higher levels of OGT, MORC2, SNAIL, and CTGF are associated with a poorer prognosis (52). These findings show how metabolic inputs interact with TGF- β signaling to influence transcriptional outputs that drive tumor progression.

2.2.4 Crosstalk with Other Signaling Pathways

TGF- β signaling also interacts extensively with non-canonical pathways and regulatory RNA networks. CircPTEN1, often downregulated in CRC, binds the MH2 domain of Smad4 and disrupts Smad2/3 interaction, suppressing Smad complex formation and downstream EMT gene expression. eIF4A3 inhibits circPTEN1 cyclization, revealing RNA-mediated modulation of TGF- β signaling (53). CCDC113 is positively linked to TGF- β signaling activity in CRC, and the TGF- β inhibitor galunisertib (LY2157299) reverses CCDC113-driven proliferation and migration in vitro and in vivo (54). DACT1, activated by TGF- β , forms phase-separated cytoplasmic condensates that inhibit Wnt signaling by sequestering casein kinase 2, illustrating crosstalk between TGF- β and Wnt pathways (55).

Collectively, these studies illustrate that TGF- β signaling in cancer is governed by multilayer regulatory modules that encompass transcriptional, epigenetic, immune, metabolic, and signaling crosstalk. Figure 2 highlights the integrated regulatory landscape of TGF- β in cancer progression. This multilayer regulatory architecture explains how TGF- β signaling can simultaneously control tumor cell behavior, immune responses, and stromal dynamics during cancer progression. Figure 2 highlights the multilayer regulatory architecture that links epigenetic regulation, immune signaling, and metabolic rewiring to TGF- β -driven tumor progression.

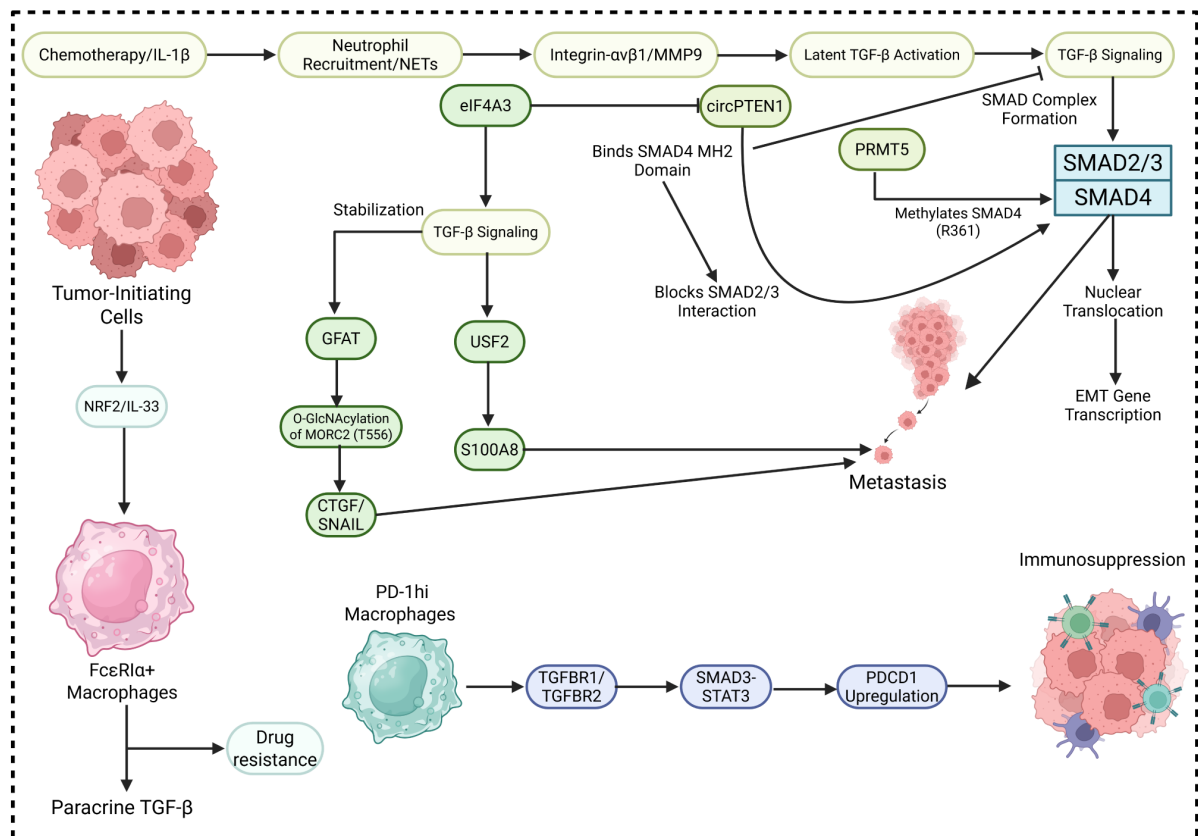


Figure 2: Multilayer regulation of TGF- β signaling during tumor progression. TGF- β signaling is regulated through interconnected transcriptional, epigenetic, metabolic, immune, and signaling networks within the tumor microenvironment. Epigenetic regulators, including PRMT5, KDM4C, and USP9X, modulate SMAD signaling and transcriptional activity, whereas metabolic pathways, such as O-GlcNAcylation, influence TGF- β -driven EMT and metastasis. Crosstalk with Wnt, PI3K/AKT, MAPK, and inflammatory signaling pathways further shapes tumor progression and therapeutic resistance. Interactions with immune cells, extracellular matrix remodeling, and stromal activation collectively promote immune suppression, invasion, metastasis, and resistance to immunotherapy.

3. TGF- β in the Tumor Microenvironment

TGF- β is a central regulator of tumor immune escape and stromal remodeling. Within tumors, TGF- β signaling functions as a central ecosystem regulator that coordinates immune suppression, stromal architecture, and ECM remodeling. These processes collectively suppress cytotoxic immune responses, promote immunoregulatory cell populations, and create structural barriers that prevent effective infiltration of immune cells into tumors. Through these mechanisms, TGF- β signaling contributes to immune exclusion and resistance to immunotherapies, particularly immune checkpoint blockade.

3.1 Lymphoid Suppression

TGF- β is a central regulator of immune suppression in cancer and exhibits a context-dependent dual role during tumor progression. TGF- β suppresses the activation, proliferation, and effector functions of cytotoxic CD8⁺ T cells while promoting the differentiation and expansion of Tregs, thereby dampening antitumor T-cell responses and promoting the expression of inhibitory checkpoint molecules such as PD-1. TGF- β also inhibits NK cell cytotoxicity and cytokine production, including IFN- γ . In addition, TGF- β disrupts dendritic cell maturation and antigen-presenting capacity, limiting effective T-cell priming and promoting tolerogenic DC phenotypes that support Treg expansion.

Beyond lymphoid regulation, TGF- β also promotes the expansion of immunosuppressive myeloid populations, including MDSCs and M2-like TAMs. TGF- β can also inhibit B-cell proliferation and antibody production while promoting regulatory B-cell populations. These effects are mediated primarily through SMAD-dependent transcriptional programs but also involve non-canonical signaling pathways, including PI3K/AKT and MAPK, which further modulate immune checkpoint signaling in tumor and immune cells. Consequently, targeting TGF- β signaling has emerged as a promising strategy to restore antitumor immunity, particularly through combination approaches with immune checkpoint blockade.

Disabling the endogenous TGF- β receptor II (TGFB2) in CAR T cells using CRISPR/Cas9 technology enhances their effectiveness by decreasing Treg conversion, preventing exhaustion, and improving tumor eradication in both cell-line-derived and patient-derived xenograft solid tumor models, while also promoting memory subset development (56). cGAMP produced by tumors activates the STING pathway in $\gamma\delta$ T cells during the early stages of tumor development, encouraging IFN- γ production and tumor surveillance. However, as the tumor progresses, TGF- β downregulates STING, thereby triggering immunosuppression. Combining TGF- β inhibition with STING agonists boosts the antitumor activity of $\gamma\delta$ T cells (57). The organization of CAF populations in breast cancer forms distinct clusters, including EMILIN1, a TGF- β inhibitor elevated in IFN γ -iCAFs, which significantly impacts TGF- β immunosuppression, increases CD8 $^{+}$ T-cell infiltration, and associates with improved patient outcomes (58). CAFs stimulate CXCL13 production in CD4 $^{+}$ and CD8 $^{+}$ T cells through TGF- β signaling, while limiting IL-2 availability, leading to a T helper peripheral cell phenotype and Treg proliferation; TGF- β inhibition prevents these effects (59). Treg cells expressing $\alpha\text{v}\beta 8$ integrin (Itg $\beta 8$) are essential activators of TGF β within the tumor microenvironment, aiding immune evasion; targeting Itg $\beta 8$ improves CD8 $^{+}$ T cell effector function and tumor control, with anti-Itg $\beta 8$ antibodies showing therapeutic potential in cancer patients (60).

Malignant breast cancer cells spread active T β R2 via tumor-derived extracellular vesicles (TEVs), thereby promoting EMT, metastasis, and CD8 $^{+}$ T cell fatigue. Circulating T β R2 $^{+}$ EVs may also serve as potential biomarkers for tumor progression and patient survival (61). The inhibition of SATB1 by TGF- β promotes Tfh cell development, thereby enhancing Tfh: B cell interactions and the formation of tertiary lymphoid structures (TLS) in tumors. These structures reduce tumor growth in a CD4 $^{+}$ T cell- and CXCL13-dependent manner, with Tfh cell transfer showing anticancer effects (62). TGF-beta promotes regulatory T cell expansion and suppresses cytotoxic CD8 $^{+}$ T cell function, contributing to immune evasion and poor clinical outcomes. Inhibition of TGF-beta signaling enhances the efficacy of adoptive cell therapies by improving T cell proliferation, effector function, and resistance to exhaustion within the tumor microenvironment. TGF-beta-driven stromal remodeling and extracellular matrix signaling contribute to immune exclusion by limiting T cell infiltration and promoting an immunosuppressive tumor microenvironment.

Expanding V γ 9V δ 2 T cells in the presence of TGF- β 1 and IL-2 ($\gamma\delta$ (T2) cells) increases their yield, viability, cytolytic activity, cytokine secretion, and antitumor efficacy in leukemia and solid tumor models. This effect is further enhanced by cancer cell sensitization and supported by a beneficial $\gamma\delta$ (T2) signature in acute myeloid leukemia (AML) (63). The expression of integrin α V on cancer cells activates latent TGF- β , which modifies the TME and reduces the effectiveness of anti-PD-1/PD-L1 therapy; lower α V levels are associated with better progression-free survival, higher CD8 $^{+}$ CD103 $^{+}$ T cell density, and improved differentiation of resident memory T cells via TGF- β signaling (64). Analysis of PBMCs from 32 patients revealed that strong immune responses to the TGF- β -derived epitope TGF- β -15 at therapy start were associated with longer progression-free and overall survival, and this link

remained significant after adjusting for other factors. Patients showing strong or weak TGF- β -specific responses had similar responses to viral antigens. T cells specific to TGF- β from a clinical responder demonstrated targeted reactivity and destruction of autologous regulatory immune cells. Repeated in vitro stimulations with the TGF- β -15 epitope, mimicking vaccination, enhanced the immune response to TGF- β -15 (65).

TGF- β is a crucial regulator of NK cell biology and plays an important role in suppressing NK-cell-mediated antitumor immunity within the TME (66). In tumors, elevated TGF- β levels inhibit NK-cell cytotoxicity by downregulating activating receptors and reducing cytokine production, such as IFN- γ . In the tumor microenvironment, TGF- β is often overexpressed and suppresses NK cell function by downregulating activating receptors (e.g., NKG2D and NKp30), impairing cytotoxicity, and inhibiting cytokine production. This immunosuppressive effect allows cancer cells to evade immune surveillance. Targeting TGF- β signaling has emerged as a therapeutic strategy to restore NK cell activity, enhance antitumor immunity, and improve outcomes in cancer immunotherapy. TGF- β diminishes human NK cell efficacy by decreasing tumor cell lysis and altering perforin localization. It reduces the surface expression of activating receptors such as 2DS4 and NKp44 by depleting DAP12, an essential protein for receptor stability and activation. TGF- β stimulates miR-183, which inhibits DAP12 expression, as shown by luciferase assays and miR-183 manipulation in NK cells (67). In patients with gastric cancer, NK cell cytotoxicity, serum levels of IL-10 and TGF- β 1, and *Helicobacter pylori* infection status were assessed. The study included 42 gastric cancer patients (14 in stages I-II and 28 in stages III-IV) and 20 healthy controls. In early-stage patients, 71.4% exhibited normal NK cytotoxicity and IL-10 levels, but 68% of advanced-stage patients showed decreased NK cytotoxicity and elevated IL-10 levels. Increased TGF- β 1 levels were observed in most patients, regardless of disease stage or NK activity. *H. pylori* infection was not linked to NK cytotoxicity, IL-10, or TGF- β 1 levels. Gastric adenocarcinoma cells produced IL-10 and TGF- β 1 in vitro; however, their supernatants did not affect NK cell cytotoxicity (67).

IL-18 exhibits anticancer properties in CRC through pathways that activate NK cells. Although IL-18 alone did not induce apoptosis in HCT116 cells, it increased NK cell-mediated apoptosis and suppressed proliferation in coculture. IL-18 boosts NK cell-mediated antitumor activity in CRC models. This effect is linked to modulation of the miR-574-3p regulatory axis, which targets components of the TGF- β 1 pathway (68). A novel technique for engineering NK cells for adoptive transfer was developed using nanogels with dual functions: (i) reducing TGF- β -mediated immunosuppression in the TME, and (ii) enhancing NK cell anti-tumor effectiveness. The nanogels encapsulate galunisertib, a TGF- β receptor antagonist, and are coated with 25 kDa branched polyethylenimine (bPEI), which activates NK cells. In TGF- β -enriched culture media, nanogel-treated NK cells showed increased motility, degranulation, and cytotoxicity compared to untreated NK cells. In vivo, NK cells treated with nanogels exhibited significantly improved efficacy against PC-3 xenografts compared with NK cells primed only with bPEI (69). NK cells in bladder tumors exhibited reduced Fc γ RIIIa/CD16 expression, which is vital for antibody-dependent cellular cytotoxicity (ADCC), along with heightened TGF- β signaling, both of which are associated with immunosuppression and tissue residency. TGF- β downregulated CD16 and promoted a tissue-resident NK cell phenotype in vitro, a process reversed by TGF- β R inhibition, thereby restoring ADCC activity. In a humanized murine bladder cancer model, blocking TGF- β increased ADCC compared with antibody therapy alone (70).

3.2 Myeloid Suppression

TGF- β -mediated immune suppression also extends to myeloid populations, particularly dendritic cells, myeloid-derived suppressor cells, and macrophages, thereby weakening antigen presentation, promoting the expansion of suppressive myeloid cells, and reinforcing tumor-promoting inflammation.

DC-based antitumor vaccines are a promising strategy in cancer immunotherapy. However, initial clinical trials have shown disappointing results, possibly due to immunosuppressive factors such as TGF- β released by tumors. This study showed that TGF- β significantly reduces the effectiveness of DC/tumor fusion vaccines. Murine colon cancer cell lines that either secrete TGF- β (CT26-TGF- β) or do not (CT26-neo) were created using retroviral vectors. The DC/CT26-TGF- β fusion cells failed to induce strong T cell proliferation *in vitro*, mainly because TGF- β suppressed T cell responsiveness rather than impairing DC function. Animals vaccinated with DC/CT26-TGF- β fusion cells had lower tumor-specific cytotoxic T lymphocyte (CTL) activity and significantly reduced survival after tumor challenge compared to those vaccinated with DC/CT26-neo hybrids. *Ex vivo* exposure of DCs to TGF- β did not weaken vaccine efficacy, highlighting TGF- β 's direct effect on T cell-mediated immunity. HCC cells with RIG-I knockdown showed increased expression of stem cell markers, higher secretion of molecules that inhibit DC generation *in vitro*, and induced a tumor-infiltrating DC (TIDC) phenotype characterized by reduced DC marker expression in tumors of nude mice. Both DCs and TIDCs exhibited a diminished mixed lymphocyte response, indicating immunotolerance resulting from RIG-I depletion. RIG-I-deficient HCC cells released more TGF- β 1 compared to controls, and tumors derived from these cells had higher TGF- β 1 levels. The suppression of DC production and MLR by conditioned media from RIG-I-deficient HCC cells was reversed by an anti-TGF- β 1 antibody. In RIG-I-deficient HCC spheres, TGF- β 1-induced phosphorylation of Smad2 and Akt was increased, but knocking down the AKT gene eliminated the additional phosphorylation of Smad2. Akt and p-Akt co-immunoprecipitated with Smad2 in the cytoplasm of RIG-I-deficient spheres, and TGF- β treatment further increased their co-immunoprecipitation (71).

CD4⁺ CD25⁺ Tregs are a crucial immunosuppressive subset that plays a major role in cancer development by inhibiting the effector functions of CD4⁺ and CD8⁺ T lymphocytes. However, their ability to regulate DC activity during tumor growth remains unclear. The suppressive effect of CD4⁺ CD25⁺ Tregs from mice with BCR-ABL⁺ leukemia was tested on bone marrow-derived dendritic cells. Results showed that CD4⁺ CD25⁺ FoxP3⁺ Tregs from tumor-bearing mice reduced DC function by decreasing NF- κ B activation. This suppression led to reduced expression of co-stimulatory molecules (CD80, CD86, CD40) and decreased production of TNF- α , IL-12, and CCL5/RANTES by DCs. The suppression was mediated by TGF- β and IL-10, which activated the Smad signaling pathway and stimulated STAT3 transcription factor activity (72). In a canine tumor model, IL-6 produced by TILs attenuated the TGF- β -induced reduction in MHC expression and T-cell activation. TGF- β inhibited the development and activity of monocyte-derived DCs, but IL-6 restored the expression of DC surface markers (MHC II, CD1a, CD40, CD80, CD83, CD86) and supported DC-associated T-cell activation. IL-6 also inhibited nuclear translocation of the TGF- β signaling proteins Smad2/3, even when Smad7 was overexpressed (73).

In cancers with low immunogenicity, such as mesothelioma, DC dysfunction hampers effective anticancer T-cell responses, primarily due to the acidic TME. Acidosis in mesothelioma boosts TGF- β 2 release, leading to lipid droplet formation and metabolic changes in dendritic cells, which reduces their immunostimulatory capacity. DCs exposed to this acidic environment exhibit diminished migratory capacity and reduced T-cell activation, thereby reducing the effectiveness of anticancer vaccines. Blocking TGF- β 2 signaling and diacylglycerol O-acyltransferase (DGAT), a key enzyme in

triglyceride formation, significantly restores DC function and enhances the anticancer immune response (74).

Overexpression of elements of the TGF- β pathway in pancreatic ductal adenocarcinoma (PDAC) suppresses immune responses. In vitro, higher DC levels increased CD8⁺ cytotoxic T cell (Tc) and IFN- γ production, while reducing CD4⁺ helper T cell (Th) and IL-10 levels. Blocking TGF- β further boosted IFN- γ and reduced T cell death. In a mouse PDAC model, combining an anti-TGF- β antibody with DC vaccination greatly improved survival compared to single treatments, demonstrating the success of this combined approach in strengthening anti-tumor immunity (75). NK cell activity decreases after DC immunization. In vitro, DCs suppress NK cells without direct contact, and this suppression depends on increased STAT3 phosphorylation (pSTAT3) in DCs. Inhibiting STAT3 phosphorylation in DCs limits NK cell suppression, boosting LT α and IL-12 production while reducing TGF- β release. Adding recombinant LT α or IL-12 to DC-NK cell cocultures restores NK cell activity, and neutralizing TGF- β enhances DC production of LT α and IL-12. DCs matured with R848, poly I: C, and IFN- γ display lower pSTAT3 levels, higher LT α and IL-12 levels, and do not inhibit NK cells compared to LPS-matured DCs. These findings highlight that LT α , IL-12, and TGF- β are crucial in NK cell-DC interactions (76).

TGF- β plays a critical role in the expansion, activation, and immunosuppressive functions of MDSCs, a diverse group of immature myeloid cells that build up in cancer, chronic infections, and inflammatory conditions. TGF- β signaling promotes the differentiation and recruitment of MDSCs to tumor sites, where they suppress antitumor immunity by inhibiting T cell and NK cell functions through mechanisms including arginase-1, inducible nitric oxide synthase (iNOS), and the production of reactive oxygen species (ROS). Furthermore, TGF- β increases the expression of immune checkpoint molecules, such as PD-L1, on MDSCs, thereby helping tumors evade the immune system. By creating an immunosuppressive tumor microenvironment, TGF- β -driven MDSC activity weakens the effectiveness of immunotherapies, making TGF- β an important therapeutic target to reduce MDSC-mediated immune suppression and improve cancer treatment outcomes. The simultaneous inhibition of CXCR1/2, TGF- β , and PD-L1 signaling reduces mesenchymal features in breast and lung cancer models, increases epithelial E-cadherin levels, decreases the number of immunosuppressive granulocytic MDSCs, enhances T-cell infiltration and activation, and significantly improves antitumor responses (77). TGF- β did not affect the numbers of MDSCs or DCs in the original pancreatic tumors but decreased the proportion of MDSCs and DCs in liver metastases. The percentage of TAMs with higher PD-L1 expression increased significantly, without altering the overall proportion of TAMs in primary or metastatic tumors. Analysis of the TCGA PDAC database revealed a strong association between TAM PD-L1 gene expression and *tgfb1* and *tgfb1* gene expression (78). NK cells, key players in innate immunity, are essential for antitumor responses; however, their function is greatly impaired in hosts with tumors, especially in the liver and spleen. This impairment is linked to the proliferation of MDSCs, which suppress NK cell cytotoxicity, NKG2D expression, and IFN- γ production both in vitro and in vivo. The membrane-bound TGF- β 1 on MDSCs is identified as the main factor enabling this suppression. Reducing MDSCs, rather than regulatory T cells, restores NK cell function in orthotopic liver cancer models, highlighting MDSCs as a major reason for NK cell dysfunction in tumor-bearing hosts (79).

TGF- β plays a dual role in regulating macrophage function in cancer, contributing to both tumor growth and immune suppression. In the tumor microenvironment, TGF- β promotes macrophage polarization toward an M2-like TAM phenotype, characterized by increased expression of immunosuppressive markers, including PD-L1, arginase-1, and IL-10. These TAMs inhibit antitumor immunity by

suppressing T-cell and NK-cell activity, promoting angiogenesis, and supporting tumor invasion and metastasis (80). Additionally, TGF- β enhances macrophage recruitment and survival in tumors, thereby further strengthening its protumoral effects. However, TGF- β also reduces macrophages' antitumor potential by suppressing their phagocytic activity and proinflammatory responses. Targeting TGF- β signaling in macrophages has become a promising approach to reprogram TAMs toward an M1-like, antitumor phenotype, thereby enhancing immune-mediated tumor clearance and improving cancer therapies.

The expression levels of TGF- β 1, TGF- β 2, BMP4, and BMP7 were markedly higher in macrophages co-cultured with cancer cells than in those cultured in isolation. Macrophages enhanced invasion rates and the expression of invasion-related genes in both AGS and Hs-746T gastric cancer cell lines, but the expression patterns differed between the cell lines. Inhibition of TGF- β R1 and BMPR1 markedly decreased the invasion rate and the expression of invasion-related genes in AGS cells co-cultured with macrophages. RAD18 expression is markedly increased in individuals with advanced T-stage triple-negative breast cancer (TNBC) and is inversely associated with prognosis. RAD18 facilitates a stem-cell-like phenotype in triple-negative breast cancer via the Hippo/YAP pathway, enhancing tumor growth. TGF- β , a cytokine byproduct, promotes an M2-like TAM phenotype, whereas TAM-derived TGF- β reciprocally activates RAD18 in TNBC, thereby augmenting tumor stemness and establishing a positive feedback loop. Inhibition of YAP or TGF- β interrupts this cycle, diminishing cancer stemness and proliferation. In nude mice, RAD18 enhances subcutaneous tumor proliferation and attracts M2-type TAMs. Macrophage-conditioned media (M ϕ CM) activated ERK/TGF- β 1 signaling, thereby augmenting cancer stem cells (CSCs) and EMT in MCF7 cells and mammospheres. The MEK inhibitor PD98059, which obstructs TGF- β 1 production, and SB431542, which inhibits TGF- β 1 signaling, restored these effects. The CSC population comprised both hybrid (ALDH1+) and mesenchymal (CD44+ CD24-) phenotypes. The hybrid epithelial/mesenchymal (E/M) state was validated at the single-cell level by elevated expression of claudin-1 (epithelial) and vimentin (mesenchymal). Nevertheless, this hybrid state did not confer a growth advantage in SCID mice, and examination of CSC and EMT markers before and during tumor development revealed a reversal of these markers in recovered tumor cells. The elimination of M ϕ CM and the neutralization of TNF- α , IL-6, and IL-1 β in M ϕ CM eliminated ERK phosphorylation, TGF- β signaling, and CSC enrichment, suggesting that persistent signaling is necessary to sustain these phenotypes. Bioinformatics analysis and immunohistochemical labeling demonstrated a robust association between tumor glycolysis, M2 TAM infiltration, and prognosis in bladder cancer patients. In vitro studies have shown that bladder cancer cells modify M2 TAMs via lactate, prompting TGF- β release via the HIF-1 α signaling pathway. In vitro and in vivo investigations have demonstrated that M2 TAMs augment glycolysis in bladder cancer cells via TGF- β -mediated activation of the Smad2/3 signaling pathway. M2 TAMs also enhanced CSC characteristics and facilitated EMT in bladder cancer cells. M2 TAMs significantly elevated PD-L1 mRNA m6A methylation via enhancing METTL3 expression in bladder cancer cells through the TGF- β /Smad2/3 pathway in the TME.

3.3 Stromal Immune Exclusion

TGF- β signaling drives the activation and differentiation of fibroblasts into CAFs, which promote tumor progression and remodeling of the tumor microenvironment. Importantly, CAF-derived TGF- β can form stromal barriers that exclude cytotoxic T cells from tumor nests and reduce the effectiveness of ICB. Activated CAFs secrete ECM proteins, growth factors, and cytokines that boost tumor cell proliferation, invasion, and metastasis. TGF- β also helps CAFs suppress antitumor immunity by attracting immunosuppressive cells, such as Tregs and MDSCs, and by producing immune-inhibitory

factors. Furthermore, TGF- β signaling in CAFs can induce EMT in cancer cells, thereby promoting metastasis. However, TGF- β 's role in CAFs depends on the context, as it can also have tumor-suppressive effects in early-stage cancers by preventing fibroblast activation. Targeting TGF- β signaling in CAFs has become a promising approach to break down the tumor-supporting stroma and improve cancer treatment outcomes.

SPHK1 is highly expressed in the tumor stroma of high-grade serous ovarian cancer (HGSC) and plays a vital role in CAFs differentiation and tumor-promoting functions. Knockout or pharmacological inhibition of SPHK1 in ovarian fibroblasts reduces TGF- β -induced expression of CAF markers and impairs their ability to promote ovarian cancer cell migration and invasion in co-culture models. SPHK1 enhances TGF- β signaling by transactivating S1P receptors (S1PR2 and S1PR3), thereby activating p38 MAPK. In vivo data confirm the critical role of stromal SPHK1 in carcinogenesis, showing significantly reduced tumor growth and metastasis in SPHK1-knockout mice (81). FOXF2 modulates TGF- β /SMAD signaling by transrepressing TGF- β -related genes in BLBC cells. FOXF2-deficient BLBC cells exhibit a myofibroblast/CAF-like phenotype, promoting visceral metastasis through increased autocrine and paracrine TGF- β signaling, which boosts aggressiveness in neighboring cells. TGF-beta inhibits FOXF2 expression by upregulating miR-182-5p, establishing reciprocal regulatory loops that amplify TGF-beta signaling and promote metastatic progression in basal-like breast cancer. Loss of FOXF2 further reinforces this circuit, enhancing tumor dissemination. More broadly, TGF-beta signaling drives metastasis through transcriptional and post-transcriptional programs that regulate invasion and cellular plasticity (82).

The dual roles of TGF-beta signaling as both a tumor suppressor and promoter complicate its therapeutic targeting. In preclinical models, blockade of TGF-beta signaling enhances the efficacy of immune checkpoint inhibition by remodeling the tumor microenvironment, reducing immunosuppression, and restoring antitumor immune activity. Table 1 summarizes TGF-beta's role in regulating components of the tumor microenvironment and immune cell function.

Table 1: Cell-Type-Specific Effects of TGF- β in the Tumor Microenvironment.

Functional category	Cell type	Effect of TGF- β	Biological consequence	Reference
Lymphoid immune suppression	NK cells	Elevated TGF- β suppresses NK cytotoxicity and cytokine production in the tumor microenvironment.	Impaired innate immune surveillance and tumor progression.	(83)
Lymphoid immune suppression	CD8+ T cells	TGF- β maintains stem-like PD-1+TCF-1+ CD8 T cells while promoting terminal exhaustion.	Reduced cytotoxic T-cell activity and immune dysfunction.	(84)
Lymphoid immune suppression	T cells	CCR4-mediated recruitment of Tregs contributes to TGF- β -dependent immunosuppression in tumors. VEGF and TGF- β cooperate to promote Treg expansion and suppress effector T-cell responses.	Enhanced tumor immune evasion. Reduced responsiveness to immunotherapy.	(85, 86)
Lymphoid immune suppression	T and NK cells	Bifunctional inhibitors targeting TGF- β signaling can restore NK and CD8+ T-cell activity.	Enhanced antitumor immune responses.	(87)
Myeloid immune suppression	MDSCs	TGF- β promotes immunosuppressive MDSC activity through mTOR/HIF-1 α signaling.	Suppression of T-cell responses and therapy resistance.	(88)

Myeloid immune suppression	MDSCs	Tumor-derived TGF- β enhances M-MDSC immunosuppressive activity and IL-10 production.	Expansion of immunosuppressive myeloid populations.	(89)
Myeloid immune suppression	Macrophages	Hypoxia-induced signaling promotes M2 macrophage polarization and increased TGF- β production. TGF- β -mediated macrophage polarization supports tumor metastasis and immune evasion.	Tumor invasion and immune suppression. Increased metastatic potential.	(90)
Stromal immune exclusion	Cancer-associated fibroblasts	TGF- β activates stromal fibroblast programs that remodel ECM and exclude cytotoxic T cells from tumor nests.	Immune exclusion and resistance to immune checkpoint blockade.	(28)
Stromal immune exclusion	Cancer-associated fibroblasts	Neutralization of TGF- β enhances chemotherapy and checkpoint blockade by promoting inflammatory CAF programs. Tumor-derived TGF- β activates myofibroblastic CAFs that promote EMT and tumor progression.	Improved immunotherapy response. Increased invasion and metastasis.	(91)

3.4 TGF- β -Mediated Immune Evasion

TGF- β is a well-established master regulator of tumor immune evasion, supported by extensive preclinical and translational evidence. Mechanistically, TGF- β suppresses the effector functions of cytotoxic CD8⁺ T cells and NK cells, promotes the expansion of Tregs and MDSCs, inhibits DC maturation and class I expression, and reduces tumor immunogenicity by downregulating MHC class I expression. Additionally, stromal TGF- β signaling has been shown to drive immune exclusion programs that prevent T-cell infiltration into tumors, thereby contributing to resistance to ICB (28). These coordinated effects collectively establish an immunosuppressive TME and contribute to resistance to immune checkpoint blockade. Consistent with this, pan-cancer analyses have identified a TGF- β -driven ECM transcriptional program associated with poor prognosis, immunosuppressive fibroblast activation, and reduced responsiveness to PD-1 blockade, outperforming several previously proposed biomarkers (92). TGF- β enhances the expression of the transcriptional coactivator MRTF-A in non-small-cell lung cancer (NSCLC) cells, where MRTF-A associates with NF- κ B/p65 rather than SRF. This relationship enables NF- κ B/p65 to bind the PD-L1 promoter, thereby promoting PD-L1 transcription and expression, which fosters immune evasion in NSCLC cells. This process depends on activation of the TGF- β signaling pathway. In vivo, findings indicate that inhibiting MRTF-A significantly reduces lung tumor proliferation in syngraft models and increases infiltration of NK and T cells into the tumor. These findings underscore the importance of the TGF- β /MRTF-A/NF- κ B pathway in facilitating PD-L1-mediated immune evasion and propose MRTF-A as a potential therapeutic target in NSCLC (93). Integrin inhibition, particularly with GLPG-0187, enhances cancer cell susceptibility to immune cell-mediated destruction by potentially interfering with TGF- β -induced PD-L1 overexpression, suggesting that integrin inhibitors may improve immunotherapy by modulating immune checkpoint expression.

Ubiquitin-specific peptidase 8 (USP8) has been identified as a potent metastasis-promoting deubiquitinase in aggressive breast carcinomas. USP8 promotes cancer stemness and activates the TGF- β /SMAD signaling pathway. It directly deubiquitinates and stabilizes the T β RII, increasing its presence on the plasma membrane and in tumor-derived extracellular vesicles (TEVs). Elevated USP8 activity was observed in individuals resistant to neoadjuvant chemotherapy. USP8 facilitates TGF- β /SMAD-mediated EMT, invasion, and metastasis in cancer cells. Additionally, USP8 expression enables T β RII+

circulating extracellular vesicles (crEVs) to induce T cell exhaustion and confer resistance to chemoimmunotherapy. Pharmacological inhibition of USP8 reduces TGF- β /SMAD signaling, decreases T β RII stability, and lowers T β RII+ crEV levels, thereby preventing CD8+ T cell exhaustion and restoring anti-tumor immunity (94). The recurrence of glioblastoma multiforme (GBM) is driven by therapy-resistant glioblastoma stem cells (GSCs). Although GSCs can be lysed by healthy allogeneic NK cells in vitro, tumor-infiltrating NK cells in GBM patients display a distinct phenotype and diminished lytic capacity compared to peripheral blood NK cells. This immune evasion is mediated through direct cell-to-cell interactions between GSCs and NK cells, facilitated by α v integrin-dependent TGF- β activation. In GSC-engrafted mouse models, combining allogeneic NK cells with integrin or TGF- β signaling inhibitors, or using TGFBR2 gene-edited NK cells, reduced NK cell dysfunction and suppressed tumor growth, highlighting potential therapeutic strategies to counteract GSC-mediated immune evasion (95).

Bintrafusp alfa (BA), a bifunctional fusion protein that concurrently suppresses TGF- β and PD-L1 and synergistically boosts radiotherapy, resulting in improved survival in several therapy-resistant mouse tumor models with insufficient immune infiltration. The combination of BA and radiotherapy (RT) (BART) enhances TILs, reprograms the tumor microenvironment, and reduces RT-induced fibrosis, thereby restoring tumor immunity and regressing spontaneous lung metastases. The benefits of BART are somewhat offset by a reduction in cytotoxic CD8+ T cells. Importantly, BA's targeting of the TGF- β trap in PD-L1+ endothelial cells and the M2/lipofibroblast-like cell population alleviates late-stage radiation-induced lung fibrosis. MDSCs and Tregs are key players in immunosuppressive networks that allow tumors to evade immune responses. Although the mechanisms behind their expansion and interaction remain unclear, tumor-induced granulocytic MDSCs (gr-MDSCs) inhibit conventional T cells and, unexpectedly, suppress the TGF- β 1-driven formation of CD4+ CD25+ FoxP3+ induced Tregs (iTregs). Moreover, gr-MDSCs hinder the growth of natural Tregs (nTregs) while leaving FoxP3 expression unchanged. The suppression of iTreg differentiation by gr-MDSCs occurs early in the polarization process, relies on ROS and indoleamine 2,3-dioxygenase (IDO), and is independent of arginase 1, iNOS, NO, cystine/cysteine depletion, PD-1/PD-L1 signaling, or COX-2 (96). Table 2 illustrates the role of TGF- β in immune evasion in cancer. Through its coordinated effects on lymphoid cells, myeloid populations, and stromal elements, TGF- β establishes a TME that promotes immune evasion and limits the efficacy of immunotherapies.

Table 2: The role of TGF- β in cancer immune evasion.

Functional category	Target cell population	Mechanism mediated by TGF- β	Consequence for tumor immunity	Reference
Lymphoid immune suppression	CD4+ T cells	TGF- β promotes regulatory T-cell differentiation and suppresses effector CD4+ T-cell responses.	Expansion of immunosuppressive Tregs.	(97)
Lymphoid immune suppression	CD8+ regulatory T cells	TGF- β induces suppressive CD8+ Tregs via p38 MAPK signaling.	Enhanced immune suppression in tumors.	(98)
Lymphoid immune suppression	T cells	Hypoxia-induced TGF- β signaling promotes Foxp3 expression and Treg expansion.	Establishment of immunosuppressive tumor microenvironment.	(99)
Myeloid immune suppression	MDSCs	TGF- β signaling promotes MDSC expansion and immunosuppressive activity.	Inhibition of antitumor T-cell and NK-cell responses.	(100)

NK-cell immune suppression	NK cells	Elevated TGF- β suppresses NK-cell activation and cytotoxic receptor expression.	Reduced innate immune surveillance.	(101)
NK-cell immune suppression	NK cells	Therapeutic blockade of TGF- β signaling restores NK-cell effector function in tumors.	Improved antitumor immunity.	(102)
Checkpoint regulation	T cells	TGF- β signaling enhances immune checkpoint pathways including PD-L1 regulation.	Reduced responsiveness to immunotherapy.	(103)

4. TGF- β in Cancer Immunotherapy

4.1 Challenges in TGF- β -Immunotherapy

TGF- β -mediated cancer immunotherapy presents a complex challenge because the cytokine has dual, context-dependent roles in tumor suppression and promotion. In early-stage cancers, TGF- β functions as a tumor suppressor by inhibiting cell proliferation, inducing apoptosis, and maintaining tissue homeostasis. However, in advanced cancers, TGF- β signaling often undergoes a functional switch, promoting tumor progression through mechanisms such as EMT, which increases cancer cell invasiveness and metastasis. Additionally, TGF- β helps cancer evade the immune system by suppressing the activity of cytotoxic T cells and NK cells while promoting the expansion of immunosuppressive cell populations, such as Tregs and MDSCs. This immunosuppressive microenvironment greatly limits the effectiveness of immunotherapies, including ICIs. The dual nature of TGF- β signaling complicates therapeutic targeting, as systemic inhibition may interfere with its tumor-suppressive functions in normal tissues or early lesions, potentially causing unintended effects such as autoimmune reactions or promoting early tumor development. Consequently, therapeutic strategies targeting TGF- β must balance suppression of tumor-promoting immune programs with preservation of the pathway's physiological roles in tissue homeostasis.

Another significant challenge in TGF- β -mediated cancer immunotherapy is the complexity of the TME, where TGF- β signaling intricately influences the behavior of stromal and immune cells. CAFs, often activated by TGF- β , play a key role in creating a fibrotic and immunosuppressive TME that promotes tumor growth and therapy resistance. TGF- β also guides the differentiation and activity of immunosuppressive cells, such as Tregs and MDSCs, which further reduce antitumor immune responses. Additionally, TGF- β signaling in tumor and stromal cells can induce the production of immune checkpoint molecules, such as PD-L1, thereby adding further resistance to ICB therapies. To address these issues, researchers are exploring strategies such as localized delivery of TGF- β inhibitors to reduce systemic toxicity, combination therapies that simultaneously target TGF- β and other immune pathways, and biomarkers to identify patients most likely to benefit from TGF- β inhibition. Despite these efforts, the wide-ranging effects of TGF- β and its key role in immune regulation require careful consideration to balance boosting antitumor immunity with minimizing side effects.

4.2 Strategies to Target TGF- β in Immunotherapy

Therapeutic strategies targeting TGF- β signaling are rapidly evolving and include approaches that remodel the tumor microenvironment, combine TGF- β inhibition with immune activation pathways, or employ targeted delivery systems to enhance therapeutic specificity. The following sections summarize representative experimental and translational strategies illustrating how TGF- β blockade can enhance antitumor immunity and overcome resistance to current treatments.

4.2.1 Tumor microenvironment remodeling and stromal targeting

Cancer arises from the dynamic interaction between malignant cells and host tissues. Current cancer treatments, including oncogene-targeted and immune checkpoint therapies, are effective but often lead to acquired resistance. An alternative approach aims to repair host tissue defects, such as aberrant vasculature, but targeting proangiogenic factors, such as VEGFA, has yielded only modest results. Studies suggest that blocking TGF- β signaling in CD4⁺ T cells changes the tumor environment and slows tumor growth. In a mouse model of breast cancer resistant to immune checkpoint or anti-VEGF therapy, turning off TGFBR2 in CD4⁺ T cells prevented tumor development. A bispecific receptor decoy called CD4 TGF- β Trap (4T-Trap) was created by fusing the TGF- β -neutralizing part of TGFBR2 with ibalizumab, a non-immunosuppressive CD4 antibody. Unlike a non-targeted TGF- β -Trap, the 4T-Trap specifically blocked TGF- β signaling in TH cells in lymph nodes near tumors, thereby reshaping tumor vasculature and, in the presence of the TH2 cytokine IL-4, leading to cancer cell death. Tumor hypoxia induced by 4T-Trap increased VEGFA levels, whereas VEGF inhibition enhanced cancer cell death and strengthened the anticancer effects of 4T-Trap (104).

Patients with metastatic CRC showed increased uptake rates of ⁶⁸Ga-FAPI, along with reduced tumor immunity and poorer prognosis. Inhibition of TGF- β R boosted tumor-infiltrating T cells and notably enhanced the sensitivity of metastatic CRC to KN046. ⁶⁸Ga-FAPI PET/CT imaging effectively tracked dynamic changes in CAFs and evaluated tumor response to the combination of TGF- β R inhibition and immunotherapy (105). The bispecific antibody Y332D maintained distinct binding affinities for TGF- β and VEGFA, effectively neutralizing their *in vitro* biological activities. Y332D reduced TGF- β -induced immunosuppression, activated TGF- β signaling, EMT, VEGF/VEGFR signaling, and HUVEC proliferation and tube formation. *In vivo* studies showed that Y332D was more effective than monotherapies targeting either anti-TGF- β or anti-VEGF in inhibiting tumor growth and metastasis. When combined with PD-1 blockade, Y332D elicited the most significant and sustained anticancer effects. This combination increased TIL density and function, thereby boosting antitumor immunity (106).

4.2.2 Dual checkpoint blockade and immune activation strategies

Some cancer patients exhibit resistance to radiation due to reduced DNA damage under hypoxic conditions and immune tolerance, aided by TGF- β 1 and membrane-associated PD-L1. Cytoplasm-distributed PD-L1 also promotes resistance by boosting DNA damage repair (DDR). Clinically used PD-L1 antibodies are ineffective against cytoplasm-localized PD-L1. A nanoadjuvant was developed to increase tumor sensitivity to radiation by targeting multiple mechanisms of resistance. The nanoadjuvant Tpp-Met@MnO₂@Alb blocks PD-L1 and TGF- β 1 through triphenylphosphine-derived metformin, activates the cGAS-STING pathway by releasing Mn²⁺ from MnO₂, and boosts dsDNA by reducing hypoxia and disrupting DDR. This approach improves radiation efficacy, reducing both local and distant tumors, including lung metastases, while promoting long-lasting antitumor immunity with minimal side effects (107).

The bispecific antibody YM101 selectively interacts with TGF- β and PD-L1. *In vitro* studies showed that YM101 effectively blocks the biological effects of TGF- β and the PD-1/PD-L1 pathway, including activation of Smad signaling, promotion of epithelial-mesenchymal transition, and immunosuppression simultaneously. *In vivo* tests demonstrated that YM101 had enhanced anti-tumor efficacy compared to monotherapies targeting TGF- β and PD-L1. Mechanistically, YM101 converted tumors into "hot tumors" by increasing TILs and dendritic cells, raising the M1/M2 macrophage ratio, and boosting T-

cell cytokine production. The stabilization of the tumor immune microenvironment and the strengthened anti-tumor immune response likely contributed to the significant anti-tumor activity of YM101 (108).

Mn²⁺ activates the STING pathway and promotes the development of human and murine DCs. Findings from a one-way mixed lymphocyte reaction showed that Mn²⁺ enhances YM101-induced T cell activation. In many syngeneic mouse tumor models, the combination of Mn²⁺ and YM101 treatment demonstrated sustained anticancer effects and extended the lifespan of tumor-bearing animals. Compared with YM101 monotherapy and Mn²⁺ combined with anti-PD-L1 therapy, the Mn²⁺-YM101 combination showed enhanced antitumor efficacy and broader tumor inhibition. This combination mechanistically influenced several aspects of antitumor immunity, helping to convert immune-excluded or immune-desert tumors into immune-inflamed cancers. Examination of the TME revealed that Mn²⁺ combined with YM101 stimulated both innate and adaptive immunity, enhanced cancer antigen presentation, and increased TIL density and activity. Stabilizing the TME and reviving antitumor immune responses contributed to the increased effectiveness of the combined treatment (109).

Chimeric mRNAs expressing single-chain IL-12 linked to single-chain fragment variable (scFv) antibodies targeting TGF- β and CD137 (4-1BB) have been created. Several TGF- β -neutralizing agents and CD137 agonists are currently in early-phase clinical trials. Bispecific tandem scFv antibodies (taFvs) were produced from the monoclonal antibodies (mAbs) 1D11 and 1D8 to enable TGF- β and CD137 binding. Transfection with mRNAs encoding these chimeric constructs resulted in the production of functional proteins that targeted their respective molecules. Intratumoral injections of these mRNAs in murine cancer models (CT26, MC38, and B16OVA) demonstrated significant therapeutic effects after multiple administrations. The success depended on the infiltration of CD8⁺ T lymphocytes that recognize tumor antigens within the cancer tissue (110).

4.2.3 Nanotechnology-based and local delivery approaches

Pancreatic cancer, an extremely deadly disease, shows minimal response to conventional treatments. Irreversible electroporation (IRE) has emerged as a promising ablative therapy for pancreatic cancer. Combining IRE with immunotherapies, including anti-programmed death 1 (α PD1) ICI, has yielded encouraging results in both preclinical and clinical studies. However, tumor recurrence remains a significant challenge. Research shows that IRE causes notable neutrophil infiltration into pancreatic tumors. Immunosuppressive factors, especially TGF- β , transform these neutrophils into a tumor-promoting phenotype. Using glutathione-responsive, degradable mesoporous silica nanoparticles loaded with SB525334, a TGF- β 1 receptor antagonist, to directly block TGF- β activity in the TME can reprogram neutrophils into an anti-cancer phenotype. This enhances the response to combined IRE and α PD1 treatment in pancreatic cancer and helps establish long-term antitumor memory. The therapy's benefits are also linked to increased infiltration of CD8⁺ cytotoxic T cells, reduced numbers of regulatory T cells, and improved maturation of antigen-presenting DCs (111).

The next-generation, non-nucleoside STING agonist MSA-2 enhances the maturation and antigen-presenting functions of murine DCs. In a unidirectional mixed lymphocyte response experiment, MSA-2, together with YM101, boosted the activation of naïve T cells. Additionally, MSA-2 triggered classical macrophage activation while having minimal effect on alternative activation. In vivo studies showed that MSA-2 increased the expression of several proinflammatory cytokines and chemokines in the TME. The combination of MSA-2 and YM101 significantly slowed tumor growth in immune-

excluded and immune-desert models, demonstrating improved anticancer effectiveness compared to single treatments. Flow cytometry, bulk RNA-seq, and single-cell RNA-seq analyses revealed that the combination therapy simultaneously boosted innate and adaptive immunity, supported antigen presentation, promoted T cell migration and chemotaxis, and increased the number and activity of TILs (112).

Mice received intraperitoneal injections of a combination of Toll-like receptor 9 (TLR9) agonist CpG ODN and TGF- β 2 antisense oligodeoxynucleotide TIO3 every other day for a total of four doses, starting 24 hours after LLC cell inoculation. The combination altered the TME, boosting and activating CD8⁺ T cells and NK cells while significantly reducing TGF- β 2 levels. This treatment notably suppressed tumor growth, increased survival, and protected tumor-free animals from tumor re-challenge. Both CpG ODN and TIO3 were essential; replacing CpG ODN with the TLR9 inhibitor CCT ODN abolished the anticancer effect, and neither CpG ODN nor TIO3 alone yielded strong results. The effect was likely due to DCs' activation at the tumor site (113).

Immunologically excluded tumors (IETs) have limited response to current immunotherapies due to both intrinsic and adaptive immune resistance. This study shows that blocking TGF- β receptor 1 reduces tumor fibrosis, which improves the recruitment of tumor-infiltrating T cells. A nanovesicle was engineered for targeted delivery of the TGF- β inhibitor LY2157299 (LY) and the photosensitizer pyropheophorbide a (PPa) to the tumor. The LY-loaded nanovesicles decrease tumor fibrosis, thereby enhancing T lymphocyte infiltration within the tumor. Additionally, PPa chelated with gadolinium ions enables triple-modal imaging-guided photodynamic therapy through fluorescence, photoacoustic, and magnetic resonance imaging. This approach induces immunogenic tumor cell death and boosts antitumor immunity in preclinical cancer models using female mice (114).

A nanodrug (NCG) was developed containing the TGF- β receptor inhibitor galunisertib (Gal) and the sonosensitizer chlorin e6 (Ce6), designed to turn cold tumors into hot ones to boost ICB therapy. When administered to the tumor, NCG produced ROS upon ultrasonic irradiation, leading to tumor immunogenic cell death and the release of immunostimulatory signals, including calreticulin and HMGB1. This increased tumor immunogenicity and stimulated innate T-cell responses. Additionally, NCG responded to the acidic TME by releasing Gal, thereby inhibiting Smad2/3 phosphorylation and reducing immunosuppressive signaling. This hindered the development of MDSCs, promoted M1-like polarization of TAMs, and weakened the immunosuppressive barrier of tumor-associated fibroblasts, thereby boosting effector T cell infiltration. These changes counteracted the immunosuppressive TME and improved the efficacy of anti-PD-L1 antibodies (115).

4.2.4 Translational and clinical insights

In lung cancer patients receiving anti-PD-1/PD-L1 antibodies, inadequate lymphocyte recovery was associated with reduced progression-free survival, increased accumulation of regulatory Tregs, and lower CD8⁺ T cell counts in peripheral blood. Similar abnormalities in CD8⁺ T cells and Tregs were observed in tumors and peripheral immune organs of mice showing poor lymphocyte recovery after chemotherapy. These mice did not respond to anti-PD-1 antibodies but remained sensitive to the anti-PD-L1/TGF- β R fusion protein (SHR-1701). Consistent with these results, SHR-1701, unlike anti-PD-1 antibodies, significantly boosted IFN- γ production and Ki-67 expression in peripheral CD8⁺ T cells from patients with impaired lymphocyte recovery (116).

Co-incorporated CaCO₃/PDA nanoparticles containing curcumin (CUR) and ropivacaine (Ropi) (CaPNMCUR+Ropi) are shown to enhance tumor immunotherapy and reduce cancer-related pain. The

therapeutic effectiveness and mechanisms were studied both *in vitro* and *in vivo*. The results indicate that CaPNMCUR+Ropi is degradation-sensitive to the tumor microenvironment, enabling the rapid release of calcium ions, Ropi, and CUR. Excess intracellular calcium causes tumor cell death, while Ropi alleviates the temporary discomfort following tumor injection. At the same time, CUR decreases levels of immunosuppressive factors (TGF- β) and inflammatory mediators (IL-6, IL-1 β , and TNF- α) within the TME, thereby boosting immune responses and reducing inflammatory pain in cancer-bearing mice. Additionally, lower TGF- β levels lead to reduced expression of transient receptor potential vanilloid 1 (TRPV1), decreasing hyperalgesia and providing extended pain relief (117).

In a syngeneic HGSC model generated from mouse ID8 cells with IFN γ -inducible PD-L1 expression, BA treatment significantly reduced ascites formation and tumor burden. BA therapies lowered TGF- β and VEGF levels in ascites and shifted the tumor immune microenvironment (TIME) toward a cytotoxic phenotype compared to controls. In the BR5 HGSC syngeneic model, BA treatments increased tumor-infiltrating CD8 $^{+}$ T cells showing effector memory and cytotoxic markers, alongside cytolytic NK cells. Prolonged BA therapy in the BR5 model resulted in approximately 50% of animals being cured, and these mice developed resistance to tumor rechallenge. The BA-treated mice also showed higher numbers of peritoneal T-effector memory cells and NK cells compared to the control group (118).

A genetically engineered mouse model (GEMM), "KPN," resembling the human 'CMS4'-like subtype, was used to study therapeutic regulation of immune responses in metastatic colorectal cancer (mCRC). TGF- β 1 released by KPN organoids was shown to promote cancer cell proliferation and suppress splenocyte activation *in vitro*. TGF- β 1 inhibited the activation of naïve T cells but not that of pre-activated T cells, demonstrating differential effects across immune cell types. *In vivo*, blocking TGF- β in KPN tumors resulted in increased infiltration of T cells, monocytes, and monocytic intermediates, while reducing neutrophils and epithelial cells. Simultaneous suppression of TGF- β and PD-L1 signaling significantly boosted cytotoxic CD8 $^{+}$ T cells, heightened innate immune responses, and triggered interferon-related gene signatures. However, concurrent activation of cancer-associated metabolic genes was linked to limited control of tumor growth and progression despite the combination therapy (119).

Collectively, these studies indicate that TGF- β -directed therapeutic strategies are moving beyond simple pathway inhibition toward more integrated approaches that reshape the tumor microenvironment, enhance immune infiltration, improve antigen presentation, and overcome resistance to checkpoint blockade. Across different tumor contexts, the most effective strategies appear to be those that combine TGF- β inhibition with complementary modalities, including PD-1/PD-L1 blockade, STING activation, anti-fibrotic remodeling, or targeted nanoparticle-based delivery.

5. TGF- β and Immune Checkpoints

TGF-beta plays a complex role in regulating immune checkpoints in cancer, aiding immune evasion and tumor growth. It can increase the levels of immune checkpoint molecules such as PD-1, CTLA-4, TIM-3, LAG-3, and TIGIT on T cells, thereby reducing their ability to attack tumors and leading to T cell exhaustion. Moreover, TGF-beta boosts the suppressive functions of Tregs and MDSCs, further weakening the immune response. By creating an immunosuppressive tumor environment, TGF-beta helps cancer cells evade immune detection. Targeting TGF-beta signaling, combined with ICI, is increasingly recognized as a promising approach to restore anti-tumor immunity and improve cancer treatment outcomes. The study also examined how the Kirsten rat sarcoma viral oncogene homolog (KRAS) mutant, which is common in non-small cell lung cancer (NSCLC) and linked to poor prognosis

and reduced survival, influences PD-L1 expression. PD-L1 levels were significantly higher in KRAS mutant cell lines, especially in NCI-H441 cells with the KRAS G12V mutation. Overexpressing KRAS G12V increased PD-L1 mRNA and protein levels, while inhibiting KRAS G12V lowered PD-L1 expression (120). Similarly, elevated PD-L1 was found in tissues with KRAS mutations and in tumor-derived CD4⁺ and CD8⁺ T cells in a tumor xenograft model using B-NDG mice. KRAS G12V was shown to boost PD-L1 expression by promoting EMT, as confirmed in both laboratory and animal studies. Pembrolizumab also improved anti-tumor effects and reduced tumor growth in NSCLC with KRAS G12V (119). PD-L1 mRNA levels were strongly associated with Human Papilloma Virus (HPV) 16/18 E6 oncoprotein and EGFR mutations in 223 surgically resected NSCLC patients. The prognostic significance of PD-L1 was especially notable in patients with high PD-L1/E6-positive and high PD-L1/EGFR-mutant tumors. The increase in PD-L1 transcription driven by E6 or mutant EGFR mainly occurs through the ERK-C/EBP β -TLR4-NF- κ B pathway. PD-L1 also promoted colony formation, growth in soft agar, and invasive cell behaviors. Additionally, PD-L1 upregulated BAG-1 expression, resulting in lower TGF- β 1 levels. The reduction in TGF- β 1 and SMAD4 induced by TGF- β 1 was controlled by the p53/microRNA-224 (miR-224) pathway. Decreases in TGF- β 1 and SMAD4 were identified as key factors in PD-L1-driven cell invasion (121).

Primary liver cancer (PLC) ranks among the most common malignancies worldwide, with HCC constituting over 90% of PLC cases. The HCC microenvironment is crucial to HCC development and progression, making immunotherapy targeting this environment an effective treatment approach. T lymphocytes play an essential role in the HCC microenvironment, with programmed cell death 1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) being the main immunosuppressive molecules on T cells. TGF- β 1 is known to inhibit T cell immune activity and promote tumor growth. However, few studies have explored TGF- β 1's potential to increase the expression of PD-1 and CTLA-4 on T cells. This research shows that TGF- β 1 enhances the expression of PD-1 and CTLA-4 on T lymphocytes, thus reducing their ability to kill HCC cells in both laboratory and animal models. TGF- β 1 also promotes T lymphocyte apoptosis caused by HCC cells. The process by which TGF- β 1 induces overexpression of PD-1 and CTLA-4 on T cells might involve the calcineurin-nuclear factor of activated T cells 1 (CaN/NFATc1) pathway (122). The combination of tranilast and doxil significantly decreased ECM components while increasing intratumoral blood vessel width and pericyte coverage, indicating normalization of the TME. These changes improved tumor blood flow and oxygen levels, leading to greater treatment effectiveness, evidenced by a notable reduction in tumor size. Tranilast supported normalization of the tumor immune landscape by boosting T cell infiltration and increasing the T cell-to-immunosuppressive cancer-associated fibroblast ratio. Moreover, combining tranilast with doxil nanomedicine notably increased the number of immunostimulatory M1 macrophages in tumor tissue and enhanced the effectiveness of ICI, particularly anti-PD-1 and anti-CTLA-4 antibodies (123).

JG-1, a potent and selective small-molecule ROR γ t agonist, was used to assess the therapeutic potential and mechanism of targeting ROR γ t in tumor immunity. JG-1 enhances Th17 cell development while suppressing Treg cell differentiation. It significantly reduces tumor growth across various syngeneic models and synergizes with the CTLA-4 antibody. In tumors, JG-1 not only promotes Th17 cell differentiation and increases the expression of C-C Motif Chemokine Receptor 6 (CCR6) and Chemokine (C-C motif) ligand 20 (CCL20) but also inhibits TGF- β 1 expression and decreases Treg cell differentiation and infiltration (124). Tim-3 expression was markedly elevated in both peripheral blood monocytes and TAMs in individuals with HCC. Increased Tim-3 expression in monocytes/TAMs was significantly linked to higher tumor grade and lower survival rates in HCC patients. Similarly, HCC-conditioned media or TGF- β increased Tim-3 expression and promoted alternative macrophage activation. Furthermore, blocking Tim-3 in macrophages significantly reduced their alternative

activation and limited HCC cell proliferation both in vitro and in vivo. Inhibiting interleukin-6 (IL-6) counteracted the effects of Tim-3 on HCC cell proliferation in vitro (125).

A better understanding of cancer immunology has explained why tumors often come back after initial successful treatment. A delicate balance exists between the immune system's ability to control tumor growth and the various resistance mechanisms that tumors develop to evade or block the host's immune response. These resistance mechanisms include, but are not limited to, (i) the adaptive expression of inhibitory checkpoint molecules in response to a proinflammatory environment and (ii) the growth of CSCs, a small group of tumor cells with the ability to self-renew that help the tumor resist treatment and cause metastasis after long periods of remission. Many drugs have been developed to prevent T-cell depletion or disrupt the interaction between CSCs and the tumor-promoting environment. A combination of three therapies, an mRNA-based vaccine to trigger antigen-specific T-cell responses, monoclonal antibodies targeting inhibitory checkpoint molecules (PD-1, TIM-3, LAG-3), and antibodies against IL-6 and TGF- β , has shown improved treatment results in subcutaneous TC-1 tumors and significantly increased survival in treated mice (126).

6. Clinical studies

Targeting TGF- β in cancer immunotherapy has progressed from initial preclinical reasoning to include multiple early- and late-phase clinical trials. To clarify the concept, current clinical studies can be grouped into four main categories: (i) bispecific and fusion proteins, (ii) monoclonal antibodies and receptor/ligand antagonists, (iii) safety and toxicity assessments, and (iv) companion diagnostics and heterogeneity markers.

6.1 Bispecific and Fusion Proteins Targeting TGF- β and Immune Checkpoints

Dual inhibition of TGF- β and PD-1/PD-L1 is among the most clinically advanced strategies. The bifunctional fusion protein combining a TGF- β trap (extracellular domain of TGF- β RII) with an anti-PD-L1 antibody Bintrafusp alfa, has been tested in multiple tumor types. In a phase I study in advanced CRC (NCT02517398), the objective response rate (ORR) was modest (3.1%) (127), indicating limited activity in heavily pretreated microsatellite-stable CRC. However, in other tumor types, including checkpoint inhibitor-naïve populations, ORRs up to 30% have been reported (128). Circulating TGF- β levels were rapidly suppressed (>97%) after treatment initiation (129), indicating pharmacodynamic target engagement. SHR-1701, another anti-PD-L1/TGF- β fusion protein, showed an ORR of 20% in gastric cancer, with manageable toxicity (130). Notably, patients with PD-L1 CPS ≥ 1 or elevated pSMAD2 scores exhibited numerically better responses, suggesting potential for biomarker-guided stratification. These bispecific agents are currently in early- to mid-stage clinical development and represent the approaches closest to translational readiness. However, response rates vary by tumor type, underscoring the need for molecular selection strategies.

6.2 Antibodies and Receptor/Ligand Antagonists

Targeting specific TGF- β ligands or receptors remains an active area of research. NIS793, evaluated both alone and with spartalizumab, showed manageable toxicity and confirmed target engagement via biomarkers (131). Partial responses were seen in MSS-CRC and renal cell carcinoma. Gene-expression studies revealed decreased TGF- β signatures and increased immune-related markers, supporting a mechanistic rationale for combination therapy. PF-06952229, a TGF- β receptor inhibitor, demonstrated dose-dependent pharmacokinetics and modulated pSMAD2/3 signaling in peripheral monocytes (132). One long-lasting partial response (31 months) occurred in prostate cancer. Galunisertib has undergone early human trials and combination studies (133). These trials focus on dose optimization and defining

therapeutic windows rather than on achieving high response rates, placing these agents in the early translational stages. Compared with bispecific approaches, monospecific inhibitors may require rational combination strategies or sequential use with ICB to achieve greater efficacy.

6.3 Clinical Safety and Toxicity Monitoring

Given TGF- β 's role in tissue homeostasis, cardiovascular monitoring and pharmacokinetic assessment are essential. In first-in-human studies of galunisertib, comprehensive cardiac monitoring, including echocardiography, Doppler imaging, BNP, troponin I, and hs-CRP, showed no clinically significant cardiovascular toxicity. Similarly, galunisertib trials reported no dose-limiting cardiovascular events (134). Radiation-induced lung toxicity (RILT) studies identified IL-8 and TGF- β 1 dynamics as predictive markers of grade ≥ 2 RILT, and their combination with mean lung dose improved predictive accuracy. These findings highlight the importance of toxicity stratification and cytokine-based monitoring in combination therapies.

6.4 Companion Diagnostics and Tumor Heterogeneity Markers

Emerging evidence supports biomarker-driven stratification. In SHR-1701 trials, PD-L1 CPS and pSMAD2 histoscores were linked to improved ORR. CAF-specific TGFBR2 expression was associated with better recurrence-free survival in breast cancer and may serve as a stromal stratification marker. Biomarker analyses in bintrafusp-treated NSCLC patients identified associations among baseline immune analytes, TAM polarization states, and clinical outcomes (135). These findings indicate that future clinical development should include dynamic biomarkers.

7. Discussion

TGF- β signaling represents one of the most paradoxical yet promising pathways in cancer biology. Its tumor-suppressive role during early tumorigenesis contrasts sharply with its pro-metastatic, immunosuppressive, and stromal-remodeling functions in advanced cancers. This duality continues to pose a major translational challenge: selectively disrupting tumor-promoting TGF- β activity while preserving its essential roles in tissue homeostasis and immune regulation. Over the next five years, progress in this field will likely be driven by four key developments. First, precise stratification of TGF- β -active tumors will be essential for clinical success. Rather than universal pathway inhibition, patient selection based on TGF- β -responsive transcriptional signatures, such as stromal activation programs, pSMAD2/3 signaling, or C-ECM signatures, and tumor immune phenotypes will help define therapeutic windows. Biomarker-guided enrollment in clinical trials is therefore expected to improve response rates while minimizing unnecessary exposure.

Second, strategies that achieve tumor-restricted or spatially confined blockade are likely to replace systemic inhibition. As summarized in Table 1, TGF- β drives tumor immune evasion through three interconnected mechanisms: suppression of cytotoxic lymphoid responses, expansion of immunosuppressive myeloid populations, and activation of stromal programs that exclude effector T cells from tumors. These coordinated effects highlight why targeting this pathway may enhance the effectiveness of cancer immunotherapy. Approaches such as bispecific fusion proteins, integrin-targeted activation blockers, and microenvironment-specific delivery platforms aim to localize TGF- β neutralization within the tumor microenvironment, thereby improving the therapeutic index and reducing systemic toxicity.

Third, rational combination and sequential therapeutic strategies are likely to evolve beyond simple pairing with ICI. Emerging evidence suggests that TGF- β blockade may be most effective when timed

to coincide with radiotherapy-induced antigen release, ACT expansion, or metabolic modulation of the tumor microenvironment. Optimizing the timing of these interventions may therefore be as important as selecting the appropriate therapeutic agent.

Fourth, advances in single-cell multi-omics, spatial transcriptomics, and AI-driven predictive modeling are expected to deepen our understanding of TGF- β -dependent cellular states, including the heterogeneity of MDSCs, fibroblasts, and exhausted T-cell subsets. These technologies will enable more precise monitoring of pathway activity and support adaptive therapeutic strategies.

Despite encouraging early-phase clinical studies, several critical questions remain: which tumor contexts are truly dependent on TGF- β signaling? How can resistance to dual PD-1/TGF- β blockade be predicted and overcome? And can intermittent or conditional inhibition maintain safety without compromising therapeutic efficacy? Addressing these questions will determine whether TGF- β targeting becomes a mainstream strategy in cancer immunotherapy or remains limited to specific tumor contexts. In summary, the future of TGF- β -based cancer immunotherapy will depend on precision modulation rather than broad suppression. Biomarker-guided patient selection, tumor-specific delivery strategies, and rational therapeutic combinations are likely to drive the next generation of clinical advances. Understanding TGF- β as a central organizer of tumor immune ecosystems provides a conceptual framework for developing next-generation immunotherapies that simultaneously target tumor cells, stromal components, and immune regulatory pathways.

TGF- β signaling should not be viewed solely as an immunosuppressive cytokine pathway, but rather as a systems-level regulator that integrates stromal remodeling, immune exclusion, metabolic adaptation, and metastatic plasticity within the tumor ecosystem.

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