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The Dual Role of Transforming Growth Factor-Beta (TGF-β) Signaling: Balancing Cellular Senescence and Tumor Progression for Precision Therapeutics

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ABSTRACT

Transforming growth factor-β (TGF-β) signaling plays a complex and dual role in regulating cellular senescence and tumor progression. In normal tissues, TGF-β acts as a tumor suppressor by regulating the cell cycle, inducing apoptosis, and maintaining the integrity of the extracellular matrix (ECM). These functions collectively restrict tumor initiation and support tissue homeostasis. However, in the tumor microenvironment, sustained TGF-β signaling frequently switches to a tumor-promoting role, driving tumor cell proliferation, metastatic dissemination, immune evasion, and therapy resistance. This review aims to clarify the dual role of TGF-β signaling in cellular senescence and tumor progression. It focuses on the molecular mechanisms that drive its transition between tumor suppression and tumor promotion in various biological contexts. We analyze the key determinants governing this functional switch, including tumor type, cellular environment, and signaling crosstalk. Furthermore, we critically evaluate the clinical challenges of therapeutic TGF-β targeting. We highlight emerging strategies to therapeutically modulate TGF-β signaling, focusing on precision medicine approaches that reconcile its tumor-suppressive and oncogenic functions. By providing a comprehensive understanding of TGF-β's dual role, this review offers new insights that may guide personalized cancer therapies and optimize treatment strategies for improved clinical outcomes.

Keywords: Transforming Growth Factor Beta; Cellular Senescence; Neoplasms; Signal Transduction; Precision Medicine; Immune Evasion

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INTRODUCTION

Transforming growth factor-β (TGF-β) signaling is a highly conserved pathway critical in various biological processes. TGF-β and its downstream signaling molecules such as Smad proteins play a significant role in regulating cell proliferation, differentiation, apoptosis, migration, and extracellular matrix (ECM) remodeling (1). Under normal physiological conditions, this pathway maintains tissue homeostasis, supports wound healing, and modulates immune responses (2, 3). Specifically, TGF-β signaling contributes to cellular senescence by regulating the senescence-associated secretory phenotype (SASP) and inhibiting aberrant cell proliferation, thereby preserving tissue health and function (4).

Given its pivotal role in cellular homeostasis, TGF-β has emerged as a promising therapeutic target in cancer. However, its context- and stage-dependent effects pose substantial challenges. While TGF-β acts as a tumor suppressor during early carcinogenesis,, it transforms into a potent driver of tumor progression, metastasis, and therapy resistance in advanced disease (5-7).

This functional dichotomy underscores the need for precision medicine approaches that can contextually modulate TGF-β signaling to achieve therapeutic benefit (8).

Emerging evidence suggests that TGF-β signaling is dynamically regulated by various factors, including tumor type, stage, and microenvironmental cues. In particular, the functional switch of this signaling cascade under different physiological or pathological conditions depends on upstream and downstream regulatory networks, ligand concentrations, and target cell responses. For example, in some tumors, TGF-β signaling may support the tumor microenvironment by promoting fibrosis or immunosuppression, while in other contexts, it may inhibit tumor dissemination by enhancing immune-mediated tumor clearance (6). The core challenge in precision therapy lies in tailoring TGF-β signaling activity to the specific molecular and pathological conditions of individual patients, achieving effective tumor control while preserving its normal physiological functions.

This article focuses on the dual role of TGF-β signaling in cellular senescence and tumor progression. It systematically analyzes its functional changes under different physiological and pathological conditions. By summarizing the mechanisms through which TGF-β regulates the tumor microenvironment and tumor evolution, we explore advancements and challenges in precision therapeutic strategies targeting this pathway, particularly the potential and limitations of inhibitors and agonists in clinical applications. Future research directions, such as more precise drug development strategies, optimal timing of interventions, and combination therapies, are also suggested. These insights not only enhance our understanding of the complexity of TGF-β signaling, but also serve as crucial references for the development of more effective and personalized cancer treatments.

1.1. Tumor-Suppressive Role of TGF-β in Normal Tissues

TGF-β plays a crucial tumor-suppressive role in normal tissues by regulating cell proliferation, ECM composition, and senescence-related mechanisms to maintain tissue homeostasis and prevent tumor initiation and progression (Fig. 1). In normal cells and tissues, the functions of TGF-β are tightly controlled, ensuring its role as an inhibitory factor in cell cycle regulation, apoptosis, senescence, and immune modulation.

A. Regulation of the Cell Cycle:

TGF-β signaling suppresses aberrant cell proliferation through the classical Smad-dependent pathway (9). When TGF-β receptors are activated, downstream Smad2/3 proteins are phosphorylated and combine with Smad4 to form a functional complex. This complex then translocates to the nucleus and triggers the expression of essential cell cycle inhibitors, such as p15^INK4B^, p16^INK4A^, and p21 (5).

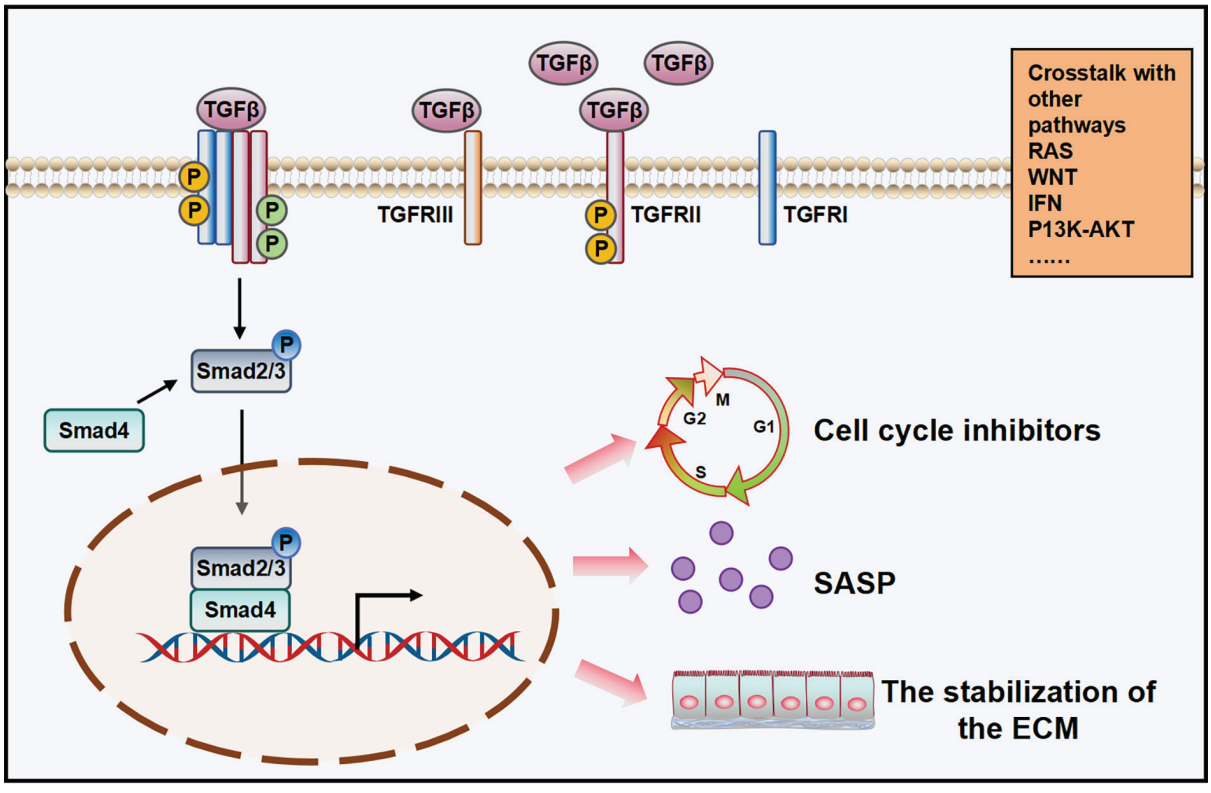

Fig. 1. The Inhibitory Role of TGF-β Signaling in Cellular Senescence. This schematic illustrates the inhibitory role of TGF-β signaling in cellular senescence. The TGF-β ligand binds to TGF-β receptor II (TGFβRII), which then recruits and activates TGF-β receptor I (TGFβRI) through phosphorylation. This activation leads to the phosphorylation of Smad2/3, which then form a complex with Smad4 and translocate into the nucleus. In the nucleus, the Smad complex regulates the expression of cell cycle inhibitors and cell cycle arrest. Additionally, TGF-β signaling induces the senescence-associated secretory phenotype (SASP), which contributes to immune surveillance and cellular homeostasis, and promotes the stabilization of the extracellular matrix (ECM) to maintain tissue integrity. The pathway also interacts with other key signaling cascades, such as RAS, WNT, IFN, and PI3K-AKT, highlighting its regulatory complexity.

These inhibitors suppress cyclin-dependent kinases (CDKs), thereby halting cell cycle progression and reducing abnormal cell proliferation (10). Additionally, TGF-β promotes cellular senescence by promoting SASP, which enhances immune-mediated clearance of damaged cells through factors such as IL-6, IL-8, and MMPs which recruit immune cells to eliminate senescent or compromised cells (11). Furthermore, TGF-β reinforces senescence by upregulating the same cell cycle inhibitors, maintaining tissue homeostasis and preventing tumor initiation (12).

In summary, TGF-β signaling in normal tissues has strong tumor-suppressive effects by inhibiting cell cycle progression, enhancing immune surveillance, and maintaining structural integrity. This underscores its crucial role in preventing cancer development.
B. the Extracellular Matrix (ECM) Stability:

The ECM is essential for maintaining tissue architecture and suppressing cancer by restricting tumor cell dissemination (13). TGF-β plays a crucial role in maintaining ECM homeostasis by promoting the synthesis of structural proteins, notably collagen types I and III and fibronectin, which enhance tissue strength and integrity (14). At the same time, TGF-β upregulates tissue inhibitors of metalloproteinases (TIMPs) to inhibit matrix metalloproteinase (MMP) activity, which can degrade the ECM and promote metastasis (15). Additionally, TGF-β modulates cell-ECM signaling by regulating fibronectin and glycosaminoglycan production, strengthening cellular adhesion and structural stability (16).

In summary, TGF-β safeguards the integrity of the ECM through coordinated regulation of its components and enzymes. It effectively acts as a structural barrier against tumor progression.

C. Anti-Tumor Effects Associated with Senescence:

Cellular senescence prevents uncontrolled proliferation by enforcing irreversible cell cycle arrest and is tightly regulated by TGF-β. This cytokine amplifies SASP, promoting immune-mediated clearance of abnormal cells through increasing the secretion of IL-6, IL-8, and MMPs (17, 18). Furthermore, TGF-β activates immune cells by inducing cytokines like TNF-α, IL-1β, IFN-γ, and IL-12, thereby enhancing cytotoxic responses of $CD8^+$ T cells and NK cells (19). In aging or premalignant tissues, TGF-β reinforces senescence through upregulation of p15^INK4B^ and p21, and promotes apoptosis in damaged cells, —a mechanism observed in early colorectal or pancreatic lesions (4). Additionally, TGF-β-stimulated fibroblasts enhance ECM production, creatinganti-invasive barriers in cancers like early-stage breast cancer (20).

In conclusion, TGF-β not only drives cellular senescence but also enhance immune surveillance and ECM remodeling, positioning it as a central player in early tumor suppression.

1.2. Tumor-Promoting Role of TGF-β in the Tumor Microenvironment

While TGF-β acts as a potent tumor suppressor in normal tissues, its role undergoes a paradoxical shift within the tumor microenvironment (TME), particularly during advanced cancer stages. In this pathological setting, TGF-β signaling becomes reprogrammed, transitioning from canonical Smad-dependent tumor suppression to Smad-independent pathways that drive oncogenic processes.. This functional switch critically enables multiple hallmarks of cancer progression, including enhanced invasion, immune evasion, therapy resistance, and angiogenesis (Fig. 2).

A. Functional Reprogramming of Signaling:

Within the TME, TGF-β drives tumor cell invasiveness and metastatic potential by inducing EMT (21). This process is orchestrated through both Smad-dependent and -independent pathways, leading to characteristic molecular changes: downregulation of epithelial markers (e.g., E-cadherin) and upregulation of mesenchymal markers (e.g., N-cadherin, vimentin, and fibronectin) (22). Additionally, TGF-β promotes ECM degradation through induction of MMPs, enabling tumor cells to breach tissue barriers and establish distant metastasis (23). Collectively, these mechanisms represent critical drivers of advanced tumor progression.

B. Immune Suppression:

TGF-β significantly contributes to the establishment of an immunosuppressive microenvironment that enables tumors to evade immune surveillance. It drives the polarization of tumor-associated macrophages (TAMs) into an M2-like phenotype and activates cancer-associated fibroblasts (CAFs). Both cell types subsequently secrete immunosuppressive cytokines like IL-10 and TGF-β itself (24-26). These cells not only suppress T and NK cell activity but also remodel the ECM to promote angiogenesis and invasion. However, these effects are negligible or absent in early tumor stages, underscoring that TGF-β–mediated immunosuppression is predominantly a late-stage, tumor-promoting mechanism.

C. Promoting Drug Resistance and Angiogenesis:

TGF-β maintain cancer stem cell (CSC) properties by upregulating key stemness markers (CD44, ALDH1), enhancing resistance to chemotherapy and radiotherapy (27, 28). Additionally, it activates anti-apoptotic genes and drug efflux mechanisms including P-glycoprotein (29, 30), directly compromising treatment efficacy. Moreover, TGF-β drives neovascularization by inducing VEGF and bFGF expression in endothelial and stromal cells (31). These pro-resistance and pro-angiogenic effects further highlight the shift in TGF-β signaling from an early tumor-suppressive role to a late tumor-promoting function.

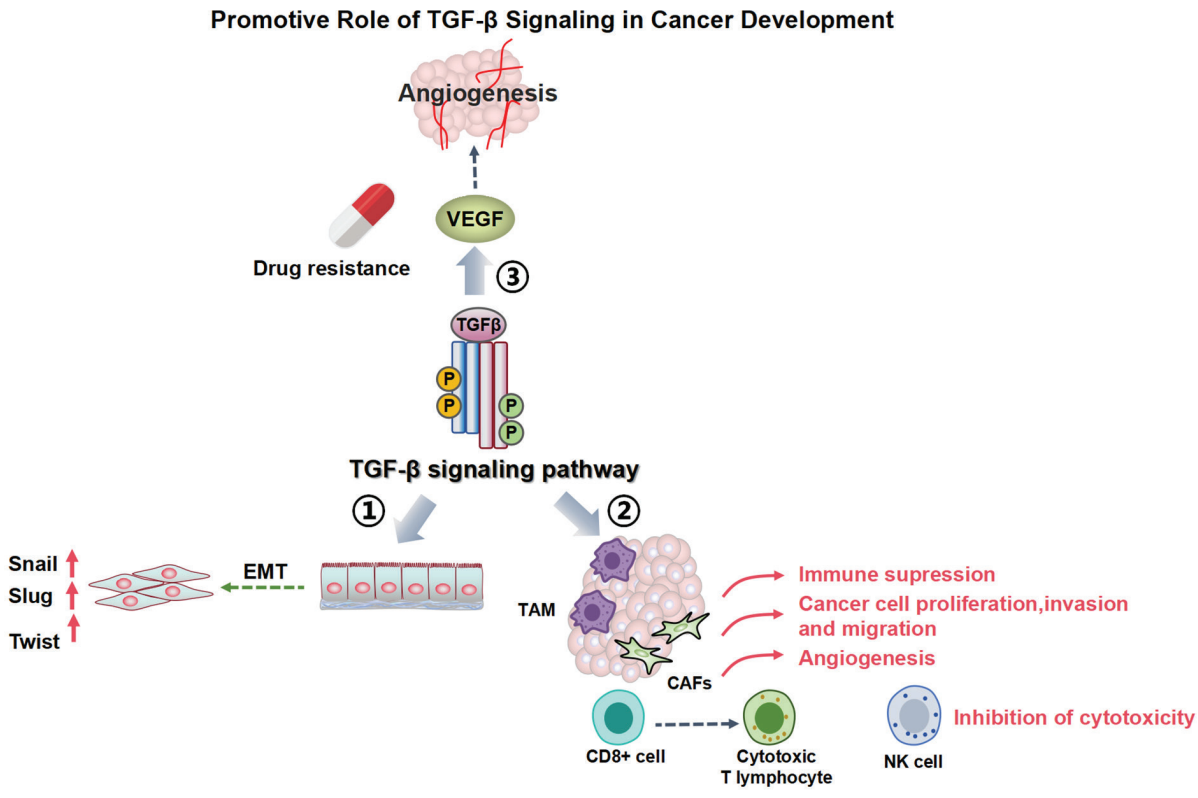

Fig. 2. The Promotive Role of TGF-β Signaling in Cancer Development. This diagram illustrates the tumor-promoting effects of TGF-β signaling in cancer progression. (1)TGF-β induces epithelial-mesenchymal transition (EMT) by upregulating transcription factors such as Snail, Slug, and Twist, which enhance cancer cell invasion and migration. (2) TGF-β contributes to immune suppression by modulating tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), and other immunosuppressive cells, inhibiting the activity of cytotoxic T lymphocytes (CD8+ T cells) and natural killer (NK) cells. This immune- suppressive environment promotes cancer cell proliferation, migration, and angiogenesis. (3) TGF-β signaling promotes angiogenesis by inducing VEGF production and enhances drug resistance by maintaining cancer stem cell properties and influencing the tumor microenvironment. Together, these mechanisms highlight the central role of TGF-β in fostering tumor progression and therapeutic resistance.

In summary, TGF-β drives tumor progression in the TME by promoting EMT, immune evasion, CSC maintenance, therapy resistance, and angiogenesis. These oncogenic effects contrast sharply with its early tumor-suppressive functions, which dominates during early-stage tumorigenesis.

1.3. Dynamic Transition of the Dual Role

TGF-β signaling plays a dual role in cancer progression, initially serving as a tumor suppressor in early-stage disease, but later shifting to a tumor promoter in advanced stages. This transition is tightly controlled by factors like signaling intensity, duration of pathway activation, and changing characteristics of the TME (7, 32, 33). Understanding this shift is crucial for differentiating the context-dependent functions of TGF-β and for guiding stage-specific therapeutic approaches.

A. Signal Intensity and Activation Thresholds:

During early tumor-suppressive phase, moderate TGF-β activation occurs primarily through Smad-dependent pathways. This leads to upregulation of tumor suppressor genes such as p15^INK4B^ and p21, and repression of oncogenic drivers like MYC, inducing cell cycle arrest and apoptosis, critical mechanisms for restraining initial tumor development (32, 33). However, in the advanced tumor-promoting phase, elevated TGF-β levels from autocrine signaling or stromal sources surpass a functional threshold that activates non-Smad pathways, PI3K/AKT or MAPK (34). In this context, TGF-β

promotes EMT, migration, and invasion. Notably, in late-stage colorectal cancer, SMAD4 mutations or KRAS activation redirect TGF-β signaling toward oncogenic outcomes (35).

Collectively, low signal intensity supports tumor suppression, while high levels of TGF-β reprogram the pathway to promote malignancy.

B. Temporal Dynamics and Chronic Activation

Acute activation of TGF-β in normal and early-stage tumor cells tends to strengthen tumor-suppressive mechanisms, such as apoptosis and cell cycle arrest. For instance, in pancreatic cancer, early-stage TGF-β inhibits tumor initiation by upregulating CDK inhibitors and suppressing proliferation (36). However, chronic exposure to high levels of TGF-β, often seen in advanced cancers, leads to pathway desensitization or changes in downstream signaling cascades. This prolonged activation leads to the expression of EMT transcription factors, like Snail and Twist, which promote phenotypic plasticity and increase metastatic potential. Furthermore, in pancreatic cancer, TGF-β interacts with cancer-associated fibroblasts (CAFs), to induce collagen deposition and remodel the ECM, while TAMs secrete pro-metastatic cytokines (37).

Taken together, transient TGF-β activation mediates tumor suppression during early carcinogenesis, whereas chronic TGF-β signaling reprograms cellular behavior to drive malignant progression.

C. Microenvironmental Influences

TME plays a crucial role in mediating the dual effects of TGF-β. In early-stage colorectal cancer, the interaction between TGF-β and surrounding fibroblasts results in the deposition of ECM components, enhancing tissue stability and inhibiting tumor invasion (38). However, in advanced stages of cancer, the TME undergoes significant changes characterized by ECM remodeling, hypoxia, and the infiltration of immunosuppressive cell. These changes amplify the tumor-promoting effects of TGF-β. Hypoxic conditions in the TME, for example, trigger the production of VEGF downstream of TGF-β. This leads to accelerated angiogenesis and metastatic spread (39). Additionally, alterations in matrix stiffness and increased availability of TGF-β ligand further drive signaling towards invasive phenotypes.

In conclusion, the function of TGF-β is redefined by the surrounding stroma, with the shift from suppressive to promoting largely shaped by the evolving TME.

2. Therapeutic Strategies for Modulating TGF-β Signaling

The dual role of the TGF-β signaling pathway complicates its g targeting in cancer therapy. Clinical strategies aim to inhibit its tumor-promoting effects while retaining its tumor-suppressive functions. Advances in understanding this pathway have led to the development of targeted therapies such as small-molecule inhibitors, monoclonal antibodies, and nucleic acid-based drugs (Fig. 3). Additionally, researchers are exploring biomarkers to assess TGF-β signaling activity and personalized therapeutic strategies opening new avenues for cancer treatment.

2.1. Progress in Single-Target Inhibitors

Targeted therapies against TGF-β signaling primarily focus on inhibiting TGF-β receptors or downstream signaling molecules (40). Below are the main categories of targeted inhibitors and their advancements in cancer therapy:

A. Small-Molecule Inhibitors:

Galunisertib, also known as LY2157299, is a small-molecule inhibitor that targets TGF-β receptor I (TGF-βRI) (41). By inhibiting the kinase activity of TGF-βRI, it blocks TGF-β signal transduction, reducing TGF-β-mediated tumor-promoting effects. Clinical studies of Galunisertib in pancreatic and breast cancers have demonstrated its ability to slow tumor growth and enhance the efficacy of chemotherapy when used in combination regimens (42-44).

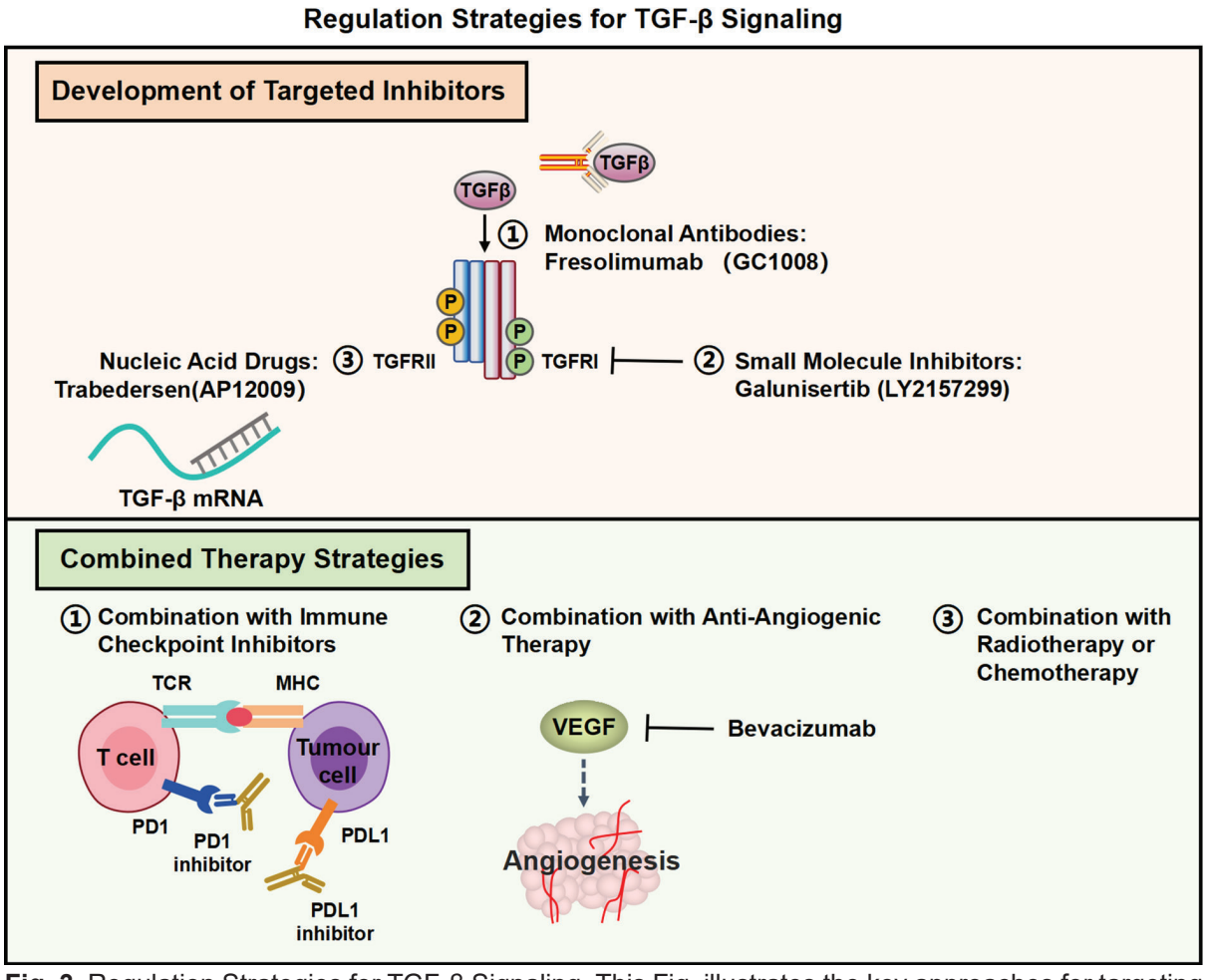

Fig. 3. Regulation Strategies for TGF-β Signaling. This Fig. illustrates the key approaches for targeting TGF-β signaling in cancer therapy. The strategies are categorized into two main groups: A) Development of Targeted Inhibitors: (1) Monoclonal antibodies: Fresolimumab (GC1008) blocks TGF-β ligand activity by inhibiting its interaction with receptors. (2) Small molecule inhibitors: Galunisertib (LY2157299) inhibits TGF-β receptor I (TGFβRI) kinase activity, thereby disrupting downstream signaling. (3) Nucleic acid drugs: Trabedersen (AP12009) specifically targets TGF-β mRNA to suppress TGF-β2 expression. B) Combined Therapy Strategies: (1) Combination with immune checkpoint inhibitors: TGF-β inhibitors are paired with PD-1/PD-L1 inhibitors to enhance T-cell-mediated tumor immune responses by alleviating the immunosuppressive tumor microenvironment. (2) Combination with anti-angiogenic therapy: TGF-β inhibitors combined with bevacizumab (anti-VEGF monoclonal antibody) reduce angiogenesis and enhance therapeutic efficacy by targeting both TGF-β and VEGF signaling. (3) Combination with radiotherapy or chemotherapy: TGF-β inhibitors improve tumor sensitivity to conventional therapies by mitigating drug resistance and enhancing cell death mechanisms. These strategies aim to optimize treatment efficacy by modulating the dual roles of TGF-β signaling in tumor progression and the tumor microenvironment.

For example, in clinical trials for pancreatic cancer, Galunisertib combined with the chemotherapeutic agent gemcitabine has shown potential survival benefits (45). However, despite its initial efficacy in clinical trials, the effectiveness of Galunisertib is influenced by the complexity of the TGF-β signaling pathway and the tumor microenvironment. Further research is required to refine its use in personalized treatment strategies.

B. Monoclonal Antibodies:

Fresolimumab is a monoclonal antibody that targets TGF-β, blocking its activity and alleviating immunosuppression in the tumor microenvironment (46). By preventing TGF-β from binding to its receptors, Fresolimumab reverses the immunosuppressive effects of

TGF-β on the immune system, restoring immune cell activation and potentiating cancer immunotherapy (47). Clinical studies have shown that Fresolimumab has antitumor effects in certain cancer types, such as colorectal and lung cancers. Notably, when combined with immune checkpoint inhibitors (e.g., PD-1 inhibitors), Fresolimumab's ability to alleviate immunosuppression enhances antitumor immunity.

C. Nucleic Acid-Based Drugs:

Trabedersen, also known as AP12009, is an antisense oligonucleotide (ASO) that specifically binds to TGF-β2 mRNA, suppressing its translation and modulating downstream TGF-β signaling (48). Studies have shown that Trabedersen reduce TGF-β2 bioavailability, improve the tumor microenvironment, and suppress tumor growth. The drug has shown promise in clinical trials for pancreatic cancer and glioblastoma, particularly in inhibiting tumor angiogenesis and improving the tumor immune environment (49, 50). While ongoing clinical trials continue to evaluate its therapeutic potential, Trabedersen demonstrates strong potential as a targeted therapeutic agent against TGF-β2, especially when combined with other anticancer therapies.

In summary, these single-target strategies are most effective in advanced-stage tumors where TGF-β promotes invasion, immune evasion, and therapy resistance. However, their application requires careful consideration of tumor stage, as these inhibitors may inadvertently disrupt TGF-β's tumor-suppressive functions during earlier phases of carcinogenesis.

2.2. Biomarkers and Personalized Therapy

TGF-β signaling plays a dual role in cancer, acting as a tumor suppressor in early stages and as a tumor promoter in advanced stages. Accurately distinguishing between these phases is crucial to guide therapeutic decisions and avoid inappropriate use of TGF-β inhibitors. Biomarkers that reflect the functional state of this signaling cascade are critical tools for determining the tumor microenvironment and tailoring treatments accordingly.

Key biomarkers, such as EMT-related factors, SASP cytokines, and TGF-β signaling intensity, are particularly valuable. For example, E-cadherin expression is usually linked to epithelial integrity and a tumor-suppressive environment, whereas elevated levels of N-cadherin and vimentin indicate EMT activation and heightened metastatic potential (22). In clinical studies, patients with high EMT scores have demonstrated improved responses to TGF-β inhibitors, particularly when used in conjunction with checkpoint inhibitors such as PD-1/PD-L1 blockers (41). SASP cytokines, such as IL-6 and IL-8, also act as dynamic markers of TGF-β's immunomodulatory phase. Elevated levels may suggest immune suppression and inflammatory remodeling, helping clinicians consider TGF-β blockade alongside immunotherapy (11). Furthermore, Smad2/3 phosphorylation and exosomal TGF-β can serve as real-time indicators of signaling activity and have been associated with resistance and a poor prognosis (51).

Beyond static measurements, biomarkers are now utilized to categorize patients before initiating treatment. For example, increased Smad2/3 activity has been employed to prospectively identify pancreatic cancer patients suitable for Galunisertib-based regimens, leading to enhanced responses to chemotherapy (52). In other cases, tumors displaying elevated levels of both TGF-β and VEGF have shown improvement with dual inhibition approaches that combine anti-angiogenic and anti-TGF-β agents (53). Additionally, the advancement of liquid biopsy technologies has expanded the usefulness of biomarkers by allowing non-invasive, real-time tracking of treatment responses. Circulating tumor DNA (ctDNA), exosomal TGF-β, and EMT markers can be measured over time to track changes in resistance or sensitivity to therapy (54). In future, the combination of artificial intelligence (AI) and big data analysis

is anticipated to improve the utilization of these biomarkers. By analyzing large-scale patient datasets, machine learning algorithms can predict therapeutic responses to TGF-β inhibitors, pinpoint populations at high-risk, and discover new therapeutic combinations. These advancements will enable more accurate biomarker-based decision-making, ultimately improving treatment effectiveness and reducing side effects.

In conclusion, the application of biomarkers such as EMT-related factors, SASP cytokines, and TGF-β signaling activity enables clinicians to accurately assess the status of this pathway and customize therapies accordingly. This personalized approach ensures that TGF-β inhibitors are used appropriately in the tumor-promoting phase while preserving their protective roles in the tumor-suppressive phase, ultimately improving patient outcomes and advancing cancer treatment strategies.

3. Potential and Challenges of Combination Therapy

As our understanding of the role of TGF-β signaling in tumor biology deepens, research has increasingly explored combining TGF-β inhibitors with other therapeutic approaches. Single-agent TGF-β-targeted therapies often fail to achieve optimal efficacy, especially in the complex tumor microenvironment. Combination therapy strategies, which involve integrating drugs or treatments with different mechanisms of action, aim to improve therapeutic outcomes while overcoming the limitations of monotherapy (Fig. 3). Below are some promising combination strategies and their associated challenges.

3.1 Combination with Immunotherapy

Immunotherapy has emerged as a cornerstone of modern cancer treatment, driven with the remarkable success of immune checkpoint inhibitors (e.g., PD-1/PD-L1 or CTLA-4 inhibitors) in achieving significant therapeutic efficacy (55). However, despite the success of immune checkpoint inhibitors in certain cancers, many patients remain unresponsive due to the immunosuppressive tumor microenvironment. A key mediator of this immunosuppression is TGF-β signaling which promotes the recruitment and activity of immunosuppressive cells within the tumor microenvironment and suppresses the antitumor immunity (56, 57). Therefore, combining TGF-β inhibitors with immune checkpoint inhibitors represents a highly promising strategy to enhance the effectiveness of immunotherapy.

TGF-β signaling suppresses antitumor immune responses by driving the accumulation of immunosuppressive cells, such as TAMs and cancer-associated fibroblasts (CAFs), while simultaneously impairing T-cell function (25). TGF-β not only directly suppresses T-cell activity but also promotes immune tolerance, weakening the persistence of antitumor immune responses (58, 59). In this context, combining TGF-β inhibitors can effectively reverse the immunosuppressive state of the tumor microenvironment and synergize with immune checkpoint inhibitors such as PD-1/PD-L1 or CTLA-4 inhibitors, potentially overcoming resistance and amplifying therapeutic efficacy. Specifically, the combination of TGF-β inhibitors and PD-1/PD-L1 blockade has shown remarkable synergy in significantly enhancing T cell-mediated tumor recognition and destruction. For example, in clinical studies on non-small cell lung cancer (NSCLC), adding TGF-β inhibitors to PD-L1 blockade (e.g., nivolumab) has demonstrated superior antitumor effects compared to PD-L1 inhibitors alone (60). This enhanced efficacy stems from the ability of TGF-β inhibitors to reduce immunosuppressive cells in the tumor microenvironment, reinvigorate tumor-specific T cell function, and increase tumor cell exposure to the immune system, thereby enhancing the sensitivity to immune checkpoint inhibitors.

Additionally, combining TGF-β inhibitors with CTLA-4 inhibitors shows clinical promise. CTLA-4 inhibitors enhance T-cell antitumor responses by releasing the negative

feedback inhibition on T cells. However, TGF-β's immunosuppressive effects persist within the tumor microenvironment, which limits the efficacy of CTLA-4 inhibitors (61). Combining TGF-β inhibitors further eliminates this immunosuppression, enabling better T-cell activation and improved therapeutic outcomes with CTLA-4 inhibitors.

In summary, combination immunotherapy improves the immune microenvironment by inhibiting TGF-β signaling, thereby enhancing the efficacy of immune checkpoint inhibitors. It also offers new opportunities for personalized treatment across different types of cancer. While challenges remain, such as patient stratification and the intricate biology of TGF-β signaling, the future of combination immunotherapy is highly promising and may represent a pivotal direction for advancing cancer treatment.

3.2 Combination with Anti-Angiogenic Therapy

Tumor growth and metastasis depend not only on the proliferative capacity of tumor cells but also on the formation of new blood vessels to meet the increasing oxygen and nutrient demands. Angiogenesis is a key process in the tumor microenvironment, where tumors secrete various angiogenic factors (e.g., VEGF) to promote blood vessel formation, ensuring the supply of nutrients and blood flow (62). Anti-angiogenic therapy has therefore become an important cancer treatment strategy designed to disrupt this vascular support system. By blocking key angiogenic signals, these treatments effectively weaken the tumor's blood supply and limit its growth and metastasis. Bevacizumab, an anti-VEGF monoclonal antibody, is widely used in treating various types of cancer. By blocking the interaction between VEGF and its receptor, Bevacizumab effectively inhibits tumor angiogenesis, and slows tumor progression (63, 64). However, anti-angiogenic therapy alone often encounters challenges such as limited efficacy and resistance, leading researchers to investigate its combination with other treatments, particularly TGF-β signaling inhibitors.

Anti-angiogenic therapy effectively suppresses tumor vascularization and slows tumor growth by inhibiting the VEGF pathway (65). However, its therapeutic potential is constrained by the multifaceted biology of the tumor microenvironment. . Tumor-associated vasculature not only serve as conduits for nutrient supply, but also as pathways for tumor cell invasion and metastasis. Furthermore, tumor vasculature often exhibits abnormal and disorganized structures, leading to inadequate blood flow and oxygen supply. This hypoxic and high-pressure tumor microenvironment, in turn, promotes resistance to anti-angiogenic therapy (66, 67). Consequently, while suppressing angiogenesis through anti-angiogenic therapy alone may offer short-term benefits, it aften fails to provide long-term inhibition of tumor growth and metastasis.

TGF-β signaling plays a crucial role in the tumor microenvironment, not only promoting tumor cell invasion and metastasis but also significantly contributing to tumor angiogenesis. TGF-β stimulates CAFs and other stromal cells to secrete VEGF and other angiogenic factors, enhancing the formation and stabilization of tumor vasculature (68). Additionally, TGF-β alters the composition of ECM, promoting interactions between tumor cells and blood vessels, further facilitating angiogenesis (69). Thus, TGF-β signaling is closely linked to tumor cell proliferation, microenvironment construction, immune evasion, and regulation of angiogenesis.

Combining TGF-β inhibitors with Bevacizumab offers a synergistic approach to optimizing therapeutic outcomes by targeting multiple pathways in tumor progression (70). In the tumor-suppressive phase, TGF-β signaling plays a protective role by maintaining vascular integrity and immune surveillance (71). During this phase, inhibiting TGF-β might disrupt these protective functions, making Bevacizumab monotherapy preferable to suppress VEGF-driven angiogenesis without

compromising TGF-β's tumor-suppressive functions. In contrast, during the tumor-promoting phase, TGF-β signaling drives VEGF production, extracellular matrix remodeling, and immune evasion, all of which support tumor progression (72). Currently, research on the combined application of Bevacizumab and TGF-β inhibitors is still in the early stages, with limited literature available. Challenges that need to be addressed include the precise selection of appropriate patient populations, optimization dosing for combination therapy, and consideration of potential toxicity and side effects.

In summary, combining TGF-β inhibitors with anti-angiogenic therapy represents a promising direction in cancer treatment. By targeting TGF-β and VEGF signaling pathways simultaneously, this approach suppresses tumor growth, invasion, and metastasis on multiple levels while reprograms the immunosuppressive tumor microenvironment. This combination offers a novel strategy to enhance therapeutic efficacy and reduce resistance to treatment. However, further clinical studies are needed to assess the safety, long-term effects, and optimization of these therapeutic strategies.

3.3. Combination with Chemotherapy and Radiotherapy

Chemotherapy and radiotherapy, as traditional methods of cancer treatment are still crucial in managing different types of cancers. However, the effectiveness of chemotherapy and radiotherapy alone is often limited by tumor cell resistance and alterations in the tumor microenvironment. TGF-β plays a critical role in tumor cell resistance, especially by maintaining CSC properties that boost the resistance of tumor cells to chemotherapy and radiotherapy. Studies have demonstrated that TGF-β, by activating its downstream Smad signaling pathway, promotes CSC characteristics, thereby making tumor cells more resistant to conventional treatments (29).

Thus, combining TGF-β inhibitors with chemotherapy or radiotherapy may overcome treatment resistance by enhancing tumor sensitivity. The Lucarini team conducted a study investigating the effects of combining TGF-β inhibitors with chemotherapy drugs, specifically mitoxantrone, in preclinical neuroblastoma models. They demonstrated that this combination not only enhanced the cytotoxic effects of mitoxantrone but also significantly remodeled the tumor immune microenvironment (73). Additionally, the combination of TGF-β inhibitors with radiotherapy is believed to improve outcomes by enhancing tumor blood flow, reducing immunosuppressive cells in the tumor microenvironment, and increasing tumor cell proliferation and apoptosis which in turn boost the effects of radiotherapy. Supporting this notion, a study titled "TGFβ Is a Master Regulator of Radiation Therapy-Induced Antitumor Immunity" (2015) (74) demonstrated that TGF-β inhibition enhances immune responses induced by radiotherapy. The study highlighted that blocking TGF-β signaling improved CD8+ T cell activation and reduced regulatory T cell (Treg) accumulation, thereby amplifying the antitumor immunity initiated by radiotherapy. These mechanistic insights provide a compelling rationale for combining TGF-β inhibitors with radiotherapy to improve cancer treatment outcomes.

However, combination strategies involving chemotherapy and radiotherapy face challenges, including potential side effects of TGF-β inhibitors, such as immune reactions and tissue damage. Additionally, overcoming tumor heterogeneity and resistance poses a difficulty. Developing more precise therapeutic approaches that incorporate the molecular characteristics and immune status of patients may be key to enhancing treatment efficacy and addressing these challenges.

4. Current Challenges and Future Perspectives

4.1. Current Challenges

The dual role of TGF-β signaling in cancer therapy poses significant regulatory

challenges. In normal tissues, TGF-β usually shows tumor-suppressive effects by inducing cell cycle arrest, inhibiting cell proliferation, and maintaining tissue homeostasis, which limits tumor initiation. However, in the tumor microenvironment, TGF-β promotes tumor cell proliferation, metastasis, and immune evasion, thereby accelerating tumor progression. Effectively balancing its dual roles, tumor-suppressive in normal tissues and tumor-promoting in malignancy, remains a central challenge in cancer therapy. Simply inhibiting TGF-β signaling may compromise its tumor-suppressive effects in normal tissues, while excessive activation of this pathway could promote tumor progression. Current targeted therapies have not yet achieved precise modulation of TGF-β's dual roles, leading to limited treatment efficacy.

Another major challenge is the development of tumor resistance (29). Tumor cells can activate compensatory signaling pathways to circumvent TGF-β inhibition, thereby escaping therapeutic effects. For instance, tumor cells can upregulate pathways such as Wnt, Notch, and PI3K/Akt to counteract TGF-β inhibition, allowing for continued proliferation and migration (75). This resistance mechanism diminishes the effectiveness of single-agent TGF-β-targeted therapies over time, especially in later stages of treatment when resistance often result in significant decline in therapeutic efficacy. Addressing tumor resistance to TGF-β inhibitors requires a deeper understanding of its complex molecular mechanisms and the development of novel combination therapies to overcome such resistance.

Additionally, TGF-β plays essential roles in immune regulation and tissue repair (76). Systemic inhibition of TGF-β signaling carries substantial risks, including immune dysfunction and impaired wound healing.. TGF-β is crucial for immune tolerance and fibrosis, consequently, disrupting TGF-β signaling may lead to loss of immune homeostasis or tissue damage. Avoiding these side effects while preserving the physiological functions of TGF-β and effectively suppressing its tumor-promoting effects remains a central challenge in therapeutic development.

4.2. Future Research Directions

Future research in TGF-β signaling must address the fundamental challenge of achieving context-dependent modulation. This is crucial because TGF-β plays a tumor-suppressive role in early-stage cancer, but a tumor-promoting function in advanced disease. Therefore, intervention strategies must be adapted to the stage of the disease [33]. The design of inhibitors must take into account signal strength, timing, and microenvironmental context to prevent unwanted suppression of physiological TGF-β activity.

One promising strategy focuses on advanced drug delivery systems with spatiotemporal control. For instance, pro-drugs that become activated in hypoxic or fibrotic tumor microenvironments can selectively release TGF-β inhibitors within tumor microenvironments, dramatically reducing off-target effects (52). Similarly, nanoparticle-based formulations and stimuli-responsive hydrogels have been shown to improve the localization of TGF-β inhibitors while minimizing systemic toxicity (77). These technologies may significantly enhance therapeutic precision and safety.

The integration of AI and multi-omics big data is revolutionizing TGF-β drug development. Machine learning algorithms can identify druggable sites within Smad-dependent and independent pathways, predict structural modifications that improve selectivity, and stratify patients based on integrated genomic, transcriptomic, and proteomic profiles. For example, deep learning approaches have been utilized to discover resistance mechanisms involving TGF-β signaling pathways, suggesting potential for predicting resistance to TGF-β inhibitors in the future (78).

Patient stratification will remain a key component of successful TGF-β-based therapy. Individuals showing high Smad phosphorylation or EMT marker expression

may respond well to TGF-β blockade, whereas those in tumor-suppressive phases may need alternative treatment approaches. Liquid biopsy platforms that measure exosomal TGF-β, circulating tumor DNA (ctDNA), or SASP-related cytokines, offer real-time feedback for adjusting therapy. This dynamic profiling allowing for flexible treatment modifications as the disease progresses.

Combination therapies represent a promising direction in cancer treatment. Inhibiting TGF-β alone may not be enough in resistant tumors, but when combined with immune checkpoint inhibitors, anti-angiogenic agents, or chemotherapy, synergistic effects has been observed in preclinical and early clinical trials. AI-based pharmacological modeling is currently being utilized to predict the optimal timing and sequencing of drug combinations, ultimately improving the chance of a durable response.

Moreover, AI-powered imaging analysis can non-invasively track changes in tumor vascularization, stromal remodeling, or immune infiltration following TGF-β-targeted therapies (79). The integration of clinical trial datasets, electronic health records, and real-world outcomes into predictive AI frameworks will further optimize patient management and treatment personalization.

In summary, future breakthroughs in TGF-β therapy will depend on a convergence of targeted drug design, spatiotemporal delivery, biomarker-driven stratification, and AI-assisted decision-making. This multidimensional approach will enable fine-tuned, stage-specific interventions that preserve TGF-β's physiologic function while selectively inhibiting its oncogenic effects, ultimately advancing precision oncology.

CONCLUSION

The dual role of TGF-β signaling in cancer has significant biological implications. In normal tissues, TGF-β exhibits tumor-suppressive effects by regulating the cell cycle and maintaining tissue homeostasis, thereby limiting tumor initiation. Conversely, in the tumor microenvironment, TGF-β promotes tumor progression by stimulating cell proliferation, facilitating metastasis, and inducing resistance. Precisely regulating TGF-β signaling to balance its tumor-suppressive and tumor-promoting functions remains a major challenge in cancer therapy.

With advances in targeted agents and immunotherapy, strategies for the precise regulation of TGF-β signaling have shown tremendous potential. By dynamically modulating the intensity and duration of this signaling cascade and developing multi-pathway combination therapies, tumor growth can be more effectively controlled, and resistance mechanisms can be mitigated. Furthermore, technological innovations, particularly the application of AI and big data in biomarker screening and efficacy prediction, will provide more precise guidance for personalized therapy.

Future research should further explore the intricate mechanisms of TGF-β signaling and develop more precise therapeutic methods to achieve optimal efficacy in different clinical contexts. This will open up new avenues for personalized cancer treatment and help enhance patient survival rates and quality of life.

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AUTHORS' CONTRIBUTION

JHL and MYH contributions to conception and design; TZ, JW and JHL been involved in drafting the manuscript and revising it critically for important intellectual content; TZ, JW and XXL made substantial contributions to acquisition of data; MYH and XXL analysis and interpretation of data; and all authors given final approval of the version to be published.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Heldin CH, Moustakas A. Role of Smads in TGFbeta signaling. Cell Tissue Res. 2012 Jan;347(1):21-36. PubMed PMID: 21643690. Epub 20110604.
2. Morikawa M, Derynck R, Miyazono K. TGF-beta and the TGF-beta Family: Context-Dependent Roles in Cell and Tissue Physiology. Cold Spring Harb Perspect Biol. 2016 May 2;8(5). PubMed PMID: 27141051. Pubmed Central PMCID: PMC4852809. Epub 20160502.
3. Deng Z, Fan T, Xiao C, Tian H, Zheng Y, Li C, et al. TGF-beta signaling in health, disease, and therapeutics. Signal Transduct Target Ther. 2024 Mar 22;9(1):61. PubMed PMID: 38514615. Pubmed Central PMCID: PMC10958066. Epub 20240322.
4. Tominaga K, Suzuki HI. TGF-beta Signaling in Cellular Senescence and Aging-Related Pathology. Int J Mol Sci. 2019 Oct 10;20(20). PubMed PMID: 31658594. Pubmed Central PMCID: PMC6834140. Epub 20191010.
5. Aashaq S, Batool A, Mir SA, Beigh MA, Andrabi KI, Shah ZA. TGF-beta signaling: A recap of SMAD-independent and SMAD-dependent pathways. J Cell Physiol. 2022 Jan;237(1):59-85. PubMed PMID: 34286853. Epub 20210719.
6. Giarratana AO, Prendergast CM, Salvatore MM, Capaccione KM. TGF-beta signaling: critical nexus of fibrogenesis and cancer. J Transl Med. 2024 Jun 26;22(1):594. PubMed PMID: 38926762. Pubmed Central PMCID: PMC11201862. Epub 20240626.
7. Gu S, Feng XH. TGF-beta signaling in cancer. Acta Biochim Biophys Sin (Shanghai). 2018 Oct 1;50(10):941-9. PubMed PMID: 30165534.
8. Goulet CR, Pouliot F. TGFbeta Signaling in the Tumor Microenvironment. Adv Exp Med Biol. 2021;1270:89-105. PubMed PMID: 33123995.
9. Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature. 2003 Oct 9;425(6958):577-84. PubMed PMID: 14534577.
10. Canepa ET, Scassa ME, Ceruti JM, Marazita MC, Carcagno AL, Sirkin PF, et al. INK4 proteins, a family of mammalian CDK inhibitors with novel biological functions. IUBMB Life. 2007 Jul;59(7):419-26. PubMed PMID: 17654117.
11. Ortiz-Montero P, Londono-Vallejo A, Vernot JP. Senescence-associated IL-6 and IL-8 cytokines induce a self- and cross-reinforced senescence/inflammatory milieu strengthening tumorigenic capabilities in the MCF-7 breast cancer cell line. Cell Commun Signal. 2017 May 4;15(1):17. PubMed PMID: 28472950. Pubmed Central PMCID: PMC5418812. Epub 20170504.
12. Salama R, Sadaie M, Hoare M, Narita M. Cellular senescence and its effector programs. Genes Dev. 2014 Jan 15;28(2):99-114. PubMed PMID: 24449267. Pubmed Central PMCID: PMC3909793.
13. Huang J, Zhang L, Wan D, Zhou L, Zheng S, Lin S, et al. Extracellular matrix and its therapeutic potential for cancer treatment. Signal Transduct Target Ther. 2021 Apr 23;6(1):153. PubMed PMID: 33888679. Pubmed Central PMCID: PMC8062524. Epub 20210423.
14. Vallee A, Lecarpentier Y. TGF-beta in fibrosis by acting as a conductor for contractile properties of myofibroblasts. Cell Biosci. 2019;9:98. PubMed PMID: 31827764. Pubmed Central PMCID: PMC6902440. Epub 20191209.
15. Gomes LR, Terra LF, Wailemann RA, Labriola L, Sogayar MC. TGF-beta1 modulates the homeostasis between MMPs and MMP inhibitors through p38 MAPK and ERK1/2 in highly invasive breast cancer cells. BMC Cancer. 2012 Jan 19;12:26. PubMed PMID: 22260435. Pubmed Central PMCID: PMC3277461. Epub 20120119.
16. Théret N, Feret J, Hodgkinson A, Boutillier P, Vignet P, Radulescu O. Integrative Models for TGF-β Signaling and Extracellular Matrix. In: Ricard-Blum S, editor. Extracellular Matrix Omics. Cham: Springer International Publishing; 2020. p. 209-25.
17. Han X, Lei Q, Xie J, Liu H, Li J, Zhang X, et al. Potential Regulators of the Senescence-Associated Secretory Phenotype During Senescence and Aging. J Gerontol A Biol Sci Med Sci. 2022 Nov 21;77(11):2207-18. PubMed PMID: 35524726.
18. Frasca D. The Senescence-Associated Secretory Phenotype: Induction, Regulation, Function and Therapeutic Interventions to Counteract the Negative Effects. In: Bueno V, editor. Cellular and Molecular Aspects of Ageing. Cham: Springer Nature Switzerland; 2024. p. 123-38.
19. Dahmani A, Delisle JS. TGF-beta in T Cell Biology: Implications for Cancer Immunotherapy. Cancers (Basel). 2018 Jun 11;10(6). PubMed PMID: 29891791. Pubmed Central PMCID: PMC6025055. Epub 20180611.
20. Franco-Valls H, Tusquets-Uxo E, Sala L, Val M, Pena R, Iaconcig A, et al. Formation of an invasion-permissive matrix requires TGFbeta/SNAIL1-regulated alternative splicing of fibronectin. Breast Cancer Res. 2023 Nov 14;25(1):143. PubMed PMID: 37964360. Pubmed

Central PMCID: PMC10647173. Epub 20231114.
21. Hao Y, Baker D, Ten Dijke P. TGF-beta-Mediated Epithelial-Mesenchymal Transition and Cancer Metastasis. Int J Mol Sci. 2019 Jun 5;20(11). PubMed PMID: 31195692. Pubmed Central PMCID: PMC6600375. Epub 20190605.
22. Loh CY, Chai JY, Tang TF, Wong WF, Sethi G, Shanmugam MK, et al. The E-Cadherin and N-Cadherin Switch in Epithelial-to-Mesenchymal Transition: Signaling, Therapeutic Implications, and Challenges. Cells. 2019 Sep 20;8(10). PubMed PMID: 31547193. Pubmed Central PMCID: PMC6830116. Epub 20190920.
23. Biray Avci C, Goker Bagca B, Nikanfar M, Takanlou LS, Takanlou MS, Nourazarian A. Tumor microenvironment and cancer metastasis: molecular mechanisms and therapeutic implications. Front Pharmacol. 2024;15:1442888. PubMed PMID: 39600368. Pubmed Central PMCID: PMC11588459. Epub 20241112.
24. Ma C, He D, Tian P, Wang Y, He Y, Wu Q, et al. miR-182 targeting reprograms tumor-associated macrophages and limits breast cancer progression. Proc Natl Acad Sci U S A. 2022 Feb 8;119(6). PubMed PMID: 35105806. Pubmed Central PMCID: PMC8833194.
25. Mao X, Xu J, Wang W, Liang C, Hua J, Liu J, et al. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. Mol Cancer. 2021 Oct 11;20(1):131. PubMed PMID: 34635121. Pubmed Central PMCID: PMC8504100. Epub 20211011.
26. Xiao Y, Wang Z, Gu M, Wei P, Wang X, Li W. Cancer-associated fibroblasts: heterogeneity and their role in the tumor immune response. Clin Exp Med. 2024 Jun 12;24(1):126. PubMed PMID: 38864912. Pubmed Central PMCID: PMC11169017. Epub 20240612.
27. Liu Q, Guo Z, Li G, Zhang Y, Liu X, Li B, et al. Cancer stem cells and their niche in cancer progression and therapy. Cancer Cell Int. 2023 Dec 1;23(1):305. PubMed PMID: 38041196. Pubmed Central PMCID: PMC10693166. Epub 20231201.
28. Zeng Z, Fu M, Hu Y, Wei Y, Wei X, Luo M. Regulation and signaling pathways in cancer stem cells: implications for targeted therapy for cancer. Mol Cancer. 2023 Oct 18;22(1):172. PubMed PMID: 37853437. Pubmed Central PMCID: PMC10583419. Epub 20231018.
29. Zhang M, Zhang YY, Chen Y, Wang J, Wang Q, Lu H. TGF-beta Signaling and Resistance to Cancer Therapy. Front Cell Dev Biol. 2021;9:786728. PubMed PMID: 34917620. Pubmed Central PMCID: PMC8669610. Epub 20211130.
30. Kong J, Qiu Y, Li Y, Zhang H, Wang W. TGF-beta1 elevates P-gp and BCRP in hepatocellular carcinoma through HOTAIR/miR-145 axis. Biopharm Drug Dispos. 2019 Feb;40(2):70-80. PubMed PMID: 30698830. Epub 20190218.
31. Jiang X, Wang J, Deng X, Xiong F, Zhang S, Gong Z, et al. The role of microenvironment in tumor angiogenesis. J Exp Clin Cancer Res. 2020 Sep 30;39(1):204. PubMed PMID: 32993787. Pubmed Central PMCID: PMC7526376. Epub 20200930.
32. Baba AB, Rah B, Bhat GR, Mushtaq I, Parveen S, Hassan R, et al. Transforming Growth Factor-Beta (TGF-beta) Signaling in Cancer-A Betrayal Within. Front Pharmacol. 2022;13:791272. PubMed PMID: 35295334. Pubmed Central PMCID: PMC8918694. Epub 20220228.
33. Batlle E, Massague J. Transforming Growth Factor-beta Signaling in Immunity and Cancer. Immunity. 2019 Apr 16;50(4):924-40. PubMed PMID: 30995507. Pubmed Central PMCID: PMC7507121.
34. Luo W, Shi Q, Han M, Zhang Z, Reiter RJ, Ashrafizadeh M, et al. TGF-beta-driven EMT in cancer progression and drug resistance. Cytokine Growth Factor Rev. 2025 May 15. PubMed PMID: 40436672. Epub 20250515.
35. Koveitypour Z, Panahi F, Vakilian M, Peymani M, Seyed Forootan F, Nasr Esfahani MH, et al. Signaling pathways involved in colorectal cancer progression. Cell Biosci. 2019;9:97. PubMed PMID: 31827763. Pubmed Central PMCID: PMC6889432. Epub 20191202.
36. Shen W, Tao GQ, Zhang Y, Cai B, Sun J, Tian ZQ. TGF-beta in pancreatic cancer initiation and progression: two sides of the same coin. Cell Biosci. 2017;7:39. PubMed PMID: 28794854. Pubmed Central PMCID: PMC5545849. Epub 20170807.
37. Chang CH, Pauklin S. ROS and TGFbeta: from pancreatic tumour growth to metastasis. J Exp Clin Cancer Res. 2021 May 3;40(1):152. PubMed PMID: 33941245. Pubmed Central PMCID: PMC8091747. Epub 20210503.
38. Le CC, Bennasroune A, Langlois B, Salesse S, Boulagnon-Rombi C, Morjani H, et al. Functional Interplay Between Collagen Network and Cell Behavior Within Tumor Microenvironment in Colorectal Cancer. Front Oncol. 2020;10:527. PubMed PMID: 32426274. Pubmed Central PMCID: PMC7204546. Epub 20200430.
39. Luo Q, Hu Z, Zhao H, Fan Y, Tu X, Wang Y, et al. The role of TGF-beta in the tumor microenvironment of pancreatic cancer. Genes Dis. 2023 Jul;10(4):1513-24. PubMed PMID: 37397548. Pubmed Central PMCID: PMC10311106. Epub 20221119.
40. Peng D, Fu M, Wang M, Wei Y, Wei X. Targeting TGF-beta signal transduction for fibrosis

and cancer therapy. Mol Cancer. 2022 Apr 23;21(1):104. PubMed PMID: 35461253. Pubmed Central PMCID: PMC9033932. Epub 20220423.
41. Holmgaard RB, Schaer DA, Li Y, Castaneda SP, Murphy MY, Xu X, et al. Targeting the TGFbeta pathway with galunisertib, a TGFbetaRI small molecule inhibitor, promotes anti-tumor immunity leading to durable, complete responses, as monotherapy and in combination with checkpoint blockade. J Immunother Cancer. 2018 Jun 4;6(1):47. PubMed PMID: 29866156. Pubmed Central PMCID: PMC5987416. Epub 20180604.
42. Melisi D, Oh DY, Hollebecque A, Calvo E, Varghese A, Borazanci E, et al. Safety and activity of the TGFbeta receptor I kinase inhibitor galunisertib plus the anti-PD-L1 antibody durvalumab in metastatic pancreatic cancer. J Immunother Cancer. 2021 Mar;9(3). PubMed PMID: 33688022. Pubmed Central PMCID: PMC7944986.
43. Kumar U, Hu Y, Masrour N, Castellanos-Uribe M, Harrod A, May ST, et al. MicroRNA-495/TGF-beta/FOXC1 axis regulates multidrug resistance in metaplastic breast cancer cells. Biochem Pharmacol. 2021 Oct;192:114692. PubMed PMID: 34298004. Epub 20210721.
44. Herbertz S, Sawyer JS, Stauber AJ, Gueorguieva I, Driscoll KE, Estrem ST, et al. Clinical development of galunisertib (LY2157299 monohydrate), a small molecule inhibitor of transforming growth factor-beta signaling pathway. Drug Des Devel Ther. 2015;9:4479-99. PubMed PMID: 26309397. Pubmed Central PMCID: PMC4539082. Epub 20150810.
45. Ikeda M, Takahashi H, Kondo S, Lahn MMF, Ogasawara K, Benhadji KA, et al. Phase 1b study of galunisertib in combination with gemcitabine in Japanese patients with metastatic or locally advanced pancreatic cancer. Cancer Chemother Pharmacol. 2017 Jun;79(6):1169-77. PubMed PMID: 28451833. Epub 20170427.
46. Chopra A. (89)Zr-Labeled fresolimumab (human anti-transforming growth factor-beta monoclonal antibody). Molecular Imaging and Contrast Agent Database (MICAD). Bethesda (MD)2004.
47. Morris JC, Tan AR, Olencki TE, Shapiro GI, Dezube BJ, Reiss M, et al. Phase I study of GC1008 (fresolimumab): a human anti-transforming growth factor-beta (TGFbeta) monoclonal antibody in patients with advanced malignant melanoma or renal cell carcinoma. PLoS One. 2014;9(3):e90353. PubMed PMID: 24618589. Pubmed Central PMCID: PMC3949712. Epub 20140311.
48. Rothhammer-Hampl T, Jaschinski F, Bäuerlein V, Haarstrich C, Heinrichs H, Schneider A. Abstract 2362: Targeted suppression of TGF-beta2 by trabedersen (AP 12009) in an orthotopic xenograft melanoma mouse model. Cancer Research. 2012;72(8_Supplement):2362-.
49. Schlingensiepen KH, Jaschinski F, Lang SA, Moser C, Geissler EK, Schlitt HJ, et al. Transforming growth factor-beta 2 gene silencing with trabedersen (AP 12009) in pancreatic cancer. Cancer Sci. 2011 Jun;102(6):1193-200. PubMed PMID: 21366804. Epub 20110330.
50. Bogdahn U, Hau P, Stockhammer G, Venkataramana NK, Mahapatra AK, Suri A, et al. Targeted therapy for high-grade glioma with the TGF-beta2 inhibitor trabedersen: results of a randomized and controlled phase IIb study. Neuro Oncol. 2011 Jan;13(1):132-42. PubMed PMID: 20980335. Pubmed Central PMCID: PMC3018908. Epub 20101027.
51. Liang J, Zhou Y, Zhang N, Wang D, Cheng X, Li K, et al. The phosphorylation of the Smad2/3 linker region by nemo-like kinase regulates TGF-beta signaling. J Biol Chem. 2021 Jan-Jun;296:100512. PubMed PMID: 33676893. Pubmed Central PMCID: PMC8047224. Epub 20210304.
52. di Miceli N, Baioni C, Barbieri L, Danielli D, Sala E, Salvioni L, et al. TGF-beta Signaling Loop in Pancreatic Ductal Adenocarcinoma Activates Fibroblasts and Increases Tumor Cell Aggressiveness. Cancers (Basel). 2024 Nov 1;16(21). PubMed PMID: 39518142. Pubmed Central PMCID: PMC11545076. Epub 20241101.
53. Kim NH, Lee J, Kim SH, Kang SH, Bae S, Yu CH, et al. ALK5/VEGFR2 dual inhibitor TU2218 alone or in combination with immune checkpoint inhibitors enhances immune-mediated antitumor effects. Cancer Immunol Immunother. 2024 Aug 6;73(10):190. PubMed PMID: 39105882. Pubmed Central PMCID: PMC11303640. Epub 20240806.
54. Ge Q, Zhang ZY, Li SN, Ma JQ, Zhao Z. Liquid biopsy: Comprehensive overview of circulating tumor DNA (Review). Oncol Lett. 2024 Nov;28(5):548. PubMed PMID: 39319213. Pubmed Central PMCID: PMC11420644. Epub 20240913.
55. Wang Y, Zhang H, Liu C, Wang Z, Wu W, Zhang N, et al. Immune checkpoint modulators in cancer immunotherapy: recent advances and emerging concepts. J Hematol Oncol. 2022 Aug 17;15(1):111. PubMed PMID: 35978433. Pubmed Central PMCID: PMC9386972. Epub 20220817.
56. Singh S, Gouri V, Samant M. TGF-beta in correlation with tumor progression, immunosuppression and targeted therapy in colorectal cancer. Med Oncol. 2023 Oct 19;40(11):335. PubMed PMID: 37855975. Epub 20231019.
57. Busse A, Keilholz U. Role of TGF-beta in

melanoma. Curr Pharm Biotechnol. 2011 Dec;12(12):2165-75. PubMed PMID: 21619542.
58. Tauriello DVF, Sancho E, Batlle E. Overcoming TGFbeta-mediated immune evasion in cancer. Nat Rev Cancer. 2022 Jan;22(1):25-44. PubMed PMID: 34671117. Epub 20211020.
59. Chen B, Mu C, Zhang Z, He X, Liu X. The Love-Hate Relationship Between TGF-beta Signaling and the Immune System During Development and Tumorigenesis. Front Immunol. 2022;13:891268. PubMed PMID: 35720407. Pubmed Central PMCID: PMC9204485. Epub 20220526.
60. Nadal E, Saleh M, Aix SP, Ochoa-de-Olza M, Patel SP, Antonia S, et al. A phase Ib/II study of galunisertib in combination with nivolumab in solid tumors and non-small cell lung cancer. BMC Cancer. 2023 Jul 28;23(1):708. PubMed PMID: 37507657. Pubmed Central PMCID: PMC10386782. Epub 20230728.
61. Park K, Veena MS, Shin DS. Key Players of the Immunosuppressive Tumor Microenvironment and Emerging Therapeutic Strategies. Front Cell Dev Biol. 2022;10:830208. PubMed PMID: 35345849. Pubmed Central PMCID: PMC8957227. Epub 20220308.
62. Geindreau M, Ghiringhelli F, Bruchard M. Vascular Endothelial Growth Factor, a Key Modulator of the Anti-Tumor Immune Response. Int J Mol Sci. 2021 May 4;22(9). PubMed PMID: 34064508. Pubmed Central PMCID: PMC8124522. Epub 20210504.
63. Li W, Zhou C, Yu L, Hou Z, Liu H, Kong L, et al. Tumor-derived lactate promotes resistance to bevacizumab treatment by facilitating autophagy enhancer protein RUBCNL expression through histone H3 lysine 18 lactylation (H3K18la) in colorectal cancer. Autophagy. 2024 Jan;20(1):114-30. PubMed PMID: 37615625. Pubmed Central PMCID: PMC10761097. Epub 20230829.
64. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, et al. Bevacizumab (Avastin(R)) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020 Jun;86:102017. PubMed PMID: 32335505. Epub 20200326.
65. Lopes-Coelho F, Martins F, Pereira SA, Serpa J. Anti-Angiogenic Therapy: Current Challenges and Future Perspectives. Int J Mol Sci. 2021 Apr 5;22(7). PubMed PMID: 33916438. Pubmed Central PMCID: PMC8038573. Epub 20210405.
66. Matuszewska K, Pereira M, Petrik D, Lawler J, Petrik J. Normalizing Tumor Vasculature to Reduce Hypoxia, Enhance Perfusion, and Optimize Therapy Uptake. Cancers (Basel). 2021 Sep 3;13(17). PubMed PMID: 34503254. Pubmed Central PMCID: PMC8431369. Epub 20210903.
67. Montemagno C, Pages G. Resistance to Anti-angiogenic Therapies: A Mechanism Depending on the Time of Exposure to the Drugs. Front Cell Dev Biol. 2020;8:584. PubMed PMID: 32775327. Pubmed Central PMCID: PMC7381352. Epub 20200707.
68. Guo T, Xu J. Cancer-associated fibroblasts: a versatile mediator in tumor progression, metastasis, and targeted therapy. Cancer Metastasis Rev. 2024 Sep;43(3):1095-116. PubMed PMID: 38602594. Pubmed Central PMCID: PMC11300527. Epub 20240411.
69. Viloria-Petit A, Richard A, Zours S, Jarad M, Coomber BL. Role of Transforming Growth Factor Beta Family in Angiogenesis. In: Mehta JL, Mathur P, Dhalla NS, editors. Biochemical Basis and Therapeutic Implications of Angiogenesis. Cham: Springer International Publishing; 2017. p. 75-103.
70. Li L, Wen Q, Ding R. Therapeutic targeting of VEGF and/or TGF-beta to enhance anti-PD-(L)1 therapy: The evidence from clinical trials. Front Oncol. 2022;12:905520. PubMed PMID: 35957885. Pubmed Central PMCID: PMC9360509. Epub 20220726.
71. Villar VH, Suboticki T, Dikic D, Mitrovic-Ajtic O, Simon F, Santibanez JF. Transforming Growth Factor-beta1 in Cancer Immunology: Opportunities for Immunotherapy. Adv Exp Med Biol. 2023;1408:309-28. PubMed PMID: 37093435.
72. Chung JY, Chan MK, Li JS, Chan AS, Tang PC, Leung KT, et al. TGF-beta Signaling: From Tissue Fibrosis to Tumor Microenvironment. Int J Mol Sci. 2021 Jul 15;22(14). PubMed PMID: 34299192. Pubmed Central PMCID: PMC8303588. Epub 20210715.
73. Lucarini V, Melaiu O, D'Amico S, Pastorino F, Tempora P, Scarsella M, et al. Combined mitoxantrone and anti-TGFbeta treatment with PD-1 blockade enhances antitumor immunity by remodelling the tumor immune landscape in neuroblastoma. J Exp Clin Cancer Res. 2022 Nov 17;41(1):326. PubMed PMID: 36397148. Pubmed Central PMCID: PMC9670422. Epub 20221117.
74. Vanpouille-Box C, Diamond JM, Pilones KA, Zavadil J, Babb JS, Formenti SC, et al. TGFbeta Is a Master Regulator of Radiation Therapy-Induced Antitumor Immunity. Cancer Res. 2015 Jun 1;75(11):2232-42. PubMed PMID: 25858148. Pubmed Central PMCID: PMC4522159. Epub 20150409.
75. Panda M, Biswal BK. Cell signaling and cancer: a mechanistic insight into drug resistance. Mol Biol Rep. 2019 Oct;46(5):5645-59. PubMed PMID: 31280421. Epub 20190706.
76. Tie Y, Tang F, Peng D, Zhang Y, Shi H. TGF-beta signal transduction: biology, function and

therapy for diseases. Mol Biomed. 2022 Dec 19;3(1):45. PubMed PMID: 36534225. Pubmed Central PMCID: PMC9761655. Epub 20221219.

77. Yen YT, Zhang Z, Chen A, Qiu Y, Liu Q, Wang Q, et al. Enzymatically responsive nanocarriers targeting PD-1 and TGF-beta pathways reverse immunotherapeutic resistance and elicit robust therapeutic efficacy. J Nanobiotechnology. 2025 Feb 19;23(1):124. PubMed PMID: 39972327. Pubmed Central PMCID: PMC11841268. Epub 20250219.
78. Lee SM, Han Y, Cho KH. Deep learning untangles the resistance mechanism of p53 reactivator in lung cancer cells. iScience. 2023 Dec 15;26(12):108377. PubMed PMID: 38034356. Pubmed Central PMCID: PMC10682260. Epub 20231101.
79. Feng S, Yin X, Shen Y. Artificial intelligence-powered precision: Unveiling the tumor microenvironment for a new frontier in personalized cancer therapy. Intelligent Medicine. 2025.