TGF-β1 in cancer: From tumour suppressor to promoter, molecular mechanisms, and precision therapeutic strategies (Review)

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Abstract. Transforming growth factor-β1 (TGF-β1) plays a dual role in cancer progression, acting as both a tumour suppressor and a tumour promoter, with complex and stage-dependent mechanisms of action. This article systematically reviews the molecular switching mechanism of TGF-β1 from a tumour suppressor to a tumour promoter and its systemic regulatory network in the tumour microenvironment. In the process through which TGF-β1 regulates cancer progression, its signalling pathways promote tumour invasion, metastasis and chemotherapy resistance through SMAD mutation, receptor expression downregulation, epithelial-mesenchymal transition activation, immune escape, non-SMAD pathway activation and remodelling of the tumour microenvironment. Although TGF-β1-targeting therapies such as antibodies, kinase inhibitors and antisense oligonucleotides face limitations in terms of efficacy and toxicity, combination immunotherapy (such as anti-PD-1 therapy) has the potential to enhance antitumour responses. Future precision intervention needs to integrate the dimension of time to distinguish between early tumour suppression and late tumour promotion windows, the dimension of spatiality and cell type to analyse the signal heterogeneity between primary and metastatic lesions, the dimension of signalling networks to selectively inhibit SMAD and non-SMAD pathways, and the dimension of technology, such as using single-cell sequencing and organoid models to guide personalised treatment, thereby achieving effective regulation of the complex role of TGF-β1 in cancer progression.

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1. Introduction

Transforming growth factor-β1 (TGF-β1), a pleiotropic cytokine, has a dynamic biphasic effect on cancer development and progression. The mechanism underlying its early tumour suppression and late tumour promotion has become a key scientific issue in the field of tumour therapy (1). Under physiological conditions, TGF-β1 maintains epithelial homeostasis through the suppressor of mother against decapentaplegic (SMAD)-dependent pathway. However, during tumour progression, this pathway is often inactivated because of SMAD mutations, receptor expression downregulation or negative regulator overexpression, resulting in the loss of its tumour-suppressive function (2,3). With tumour progression, TGF-β1 signalling induces tumour-promoting reprogramming, which activates epithelial-mesenchymal transition (EMT), non-SMAD pathways (such as phosphatidylinositol PI3K/AKT and MAPK), and the tumour stem cell maintenance network, inhibiting the binding ability of alkB homolog 5 to the forkhead box A1 (FOXA1) coding sequence region and thereby driving metastatic phenotype formation and chemotherapy resistance (2-4).

More notably, TGF-β1 signalling establishes a 'vicious cycle' that promotes metastasis by reshaping the three-dimensional regulatory network of the tumour microenvironment, including activating cancer-associated fibroblasts (CAFs), promoting angiogenesis and constructing an immunosuppressive microenvironment such as expanding T-regulatory (Treg) cells and inhibiting cytotoxic T lymphocyte (CTL) function (1,5,6). Recent studies have particularly emphasised that TGF-β1 forms a coinhibitory loop with immune checkpoints such as programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1), providing a theoretical basis for combined blocking strategies (6-8). Although TGF-β1-targeting therapeutic strategies (such as antibodies and kinase inhibitors) face challenges, including heterogeneous efficacy and toxicity in clinical translation, it is anticipated that by accurately distinguishing tumour development stages, analysing signal network heterogeneity and developing combined immunotherapy regimens, the current bottleneck can be overcome (5,9,10). This review systematically summarises the multidimensional mechanisms of action of TGF-β1 related to cancer progression, aiming to provide a molecular basis for the development of adaptive treatment strategies, which has important clinical significance for improving the survival prognosis in patients with advanced cancer.

2. Physiological basis and early inactivation mechanism of the tumour suppressor TGF-β1

Core role of TGF-β1 in maintaining epithelial homeostasis and cell cycle regulation. As a pleiotropic cytokine, the physiological functions of TGF-β1 include maintaining epithelial-mesenchymal balance, cell cycle arrest, apoptosis induction and DNA damage repair. In healthy tissues, TGF-β1 activates cyclin-dependent kinase inhibitor 2B (p15INK4b, CDKN2B) and CDKN1A (p21CIP1) expression through the SMAD2/3-dependent pathway (11), inducing G1-phase arrest and inhibiting excessive cell proliferation. In addition, TGF-β1 maintains the epithelial phenotype and inhibits the EMT process by regulating E-cadherin expression (12).

In vitro experiments have further revealed that TGF-β1 inhibits the anchorage-independent growth of breast cancer epithelial cells by suppressing tumour protein 63 expression (13). Notably, TGF-β1 also participates in tissue microenvironment remodelling through noncanonical pathways [such as TGF-β-activated kinase 1 (TAK1)-MAPK]. Its anticancer effect is dose dependent, promoting growth inhibition at low concentrations while potentially inducing profibrotic responses at high concentrations (14).

Key inactivation nodes of the TGF-β1 signalling pathway in the tumour initiation stage: SMAD mutation and receptor expression downregulation. As tumours progress, inflammatory factors and gene mutations in the tumour microenvironment can lead to a shift in TGF-β1 signalling towards a tumour-promoting phenotype (15), as shown in Fig. 1 and Table I. In the early stages of tumour progression, the inactivation of TGF-β1 signalling mainly occurs through three mechanisms, including SMAD4 gene mutations or deletions (16,17), TGF-β receptor 2 (TGFβR2) promoter methylation (18-20) and signalling pathway bias.

These key bias nodes include: i) The Ras homolog gene family member A/Rho-associated coiled-coil containing protein kinase (RhoA/ROCK) pathway-it involves inhibiting cofilin through LIM domain kinase 1 phosphorylation, promoting actin remodelling and increasing the efficiency of pseudopodia formation by a factor of two (21); ii) Notch crosstalk-TGF-β1 upregulates and activates the Notch1 intracellular domain, synergistically enhancing matrix metallopeptidase 9 (MMP9) expression with Smad3 and increasing vascular density in breast cancer models (22); and iii) PD-L1 bidirectional regulation-PD-L1 can increase the transcription and expression of TGF-β1 in tumour cells and knockdown of PD-L1 expression can significantly inhibit TGF-β1-induced EMT, proliferation and migration (23).

3. Multidimensional driving mechanisms through which TGF-β1 promotes cancer reprogramming

Molecular switching for EMT activation and tumour invasion. With the accumulation of genomic instability and microenvironmental alterations, tumour cells escape their growth-inhibiting effects through acquired mutations (such as SMAD4 deletion) or epigenetic modifications (such as downregulation of the expression of TGF-β receptor II) to promote invasion and metastasis (24-27). The critical point of this functional transition is usually associated with the activation of the EMT program. TGF-β1 drives tumour cells to acquire migration and invasion characteristics by regulating the expression of core EMT-related transcription factors (such as Snail family transcriptional repressor, Twist family bHLH transcription factor and zinc finger E-box binding homeobox 1) (Table II). The EMT-promoting effect of TGF-β1 has been confirmed in various cancer models, and its mechanism involves FOXA1 and non-coding RNA regulation (2,28).

Changes in the expression of key EMT regulators are significantly associated with clinical metastasis risk. In a pancreatic cancer model, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) protein promotes fibroblast growth factor pathway activation by stabilising the conformation of TGFβR1, leading to cytoskeleton remodelling and enhanced motility. Knockdown of Pin1 expression weakens tumour cell migration (29). Platelet-derived TGF-β1 induces autophagy in hepatocellular carcinoma (HCC) cells through the AMP kinase/mammalian target of rapamycin (mTOR) axis, increasing the number of autophagosomes in an HCC orthotopic model and significantly increasing both invasion and metastasis rates (30). This synergistic effect of multiple pathways explains why inhibition of a single SMAD pathway often fails to completely block the metastatic effect of TGF-β1.

The metastatic mechanism of EMT involves multiple biological processes. Studies have shown that TGF-β1 significantly increases the proportion of tumour stem cells by regulating the Wnt/β-catenin pathway (31). In addition, TGF-β1 promotes collagen deposition and changes in amino acid metabolism through prolyl 4-hydroxylase subunit α3-mediated proline hydroxylation, increasing the cell migration speed by a factor of two (32). TGF-β1 can also remodel the microenvironment. TGF-β1 induces autophagy in CAFs and decreases the microenvironment pH through upregulation of monocarboxylate transporter 4 expression, thus promoting angiogenesis (33).

Table I. Key molecular differences of TGF-β1 in the tumor suppressor and tumor-promoting stages.

Functional stage	Dominant pathway	Effector molecules	Biological results
Tumor suppression	SMAD2/3	p21/CDKN1A	Phase G1 arrest
		BAX/BIM	Mitochondrial apoptosis
Tumor promotion	PI3K/AKT	mTOR	Metabolic reprogramming
	MAPK	MMP2/9	Invasion and metastasis

CDKN1A, cyclin-dependent kinase inhibitor 1A; BAX, BCL2-associated X protein; BIM, BCL2-like 11.

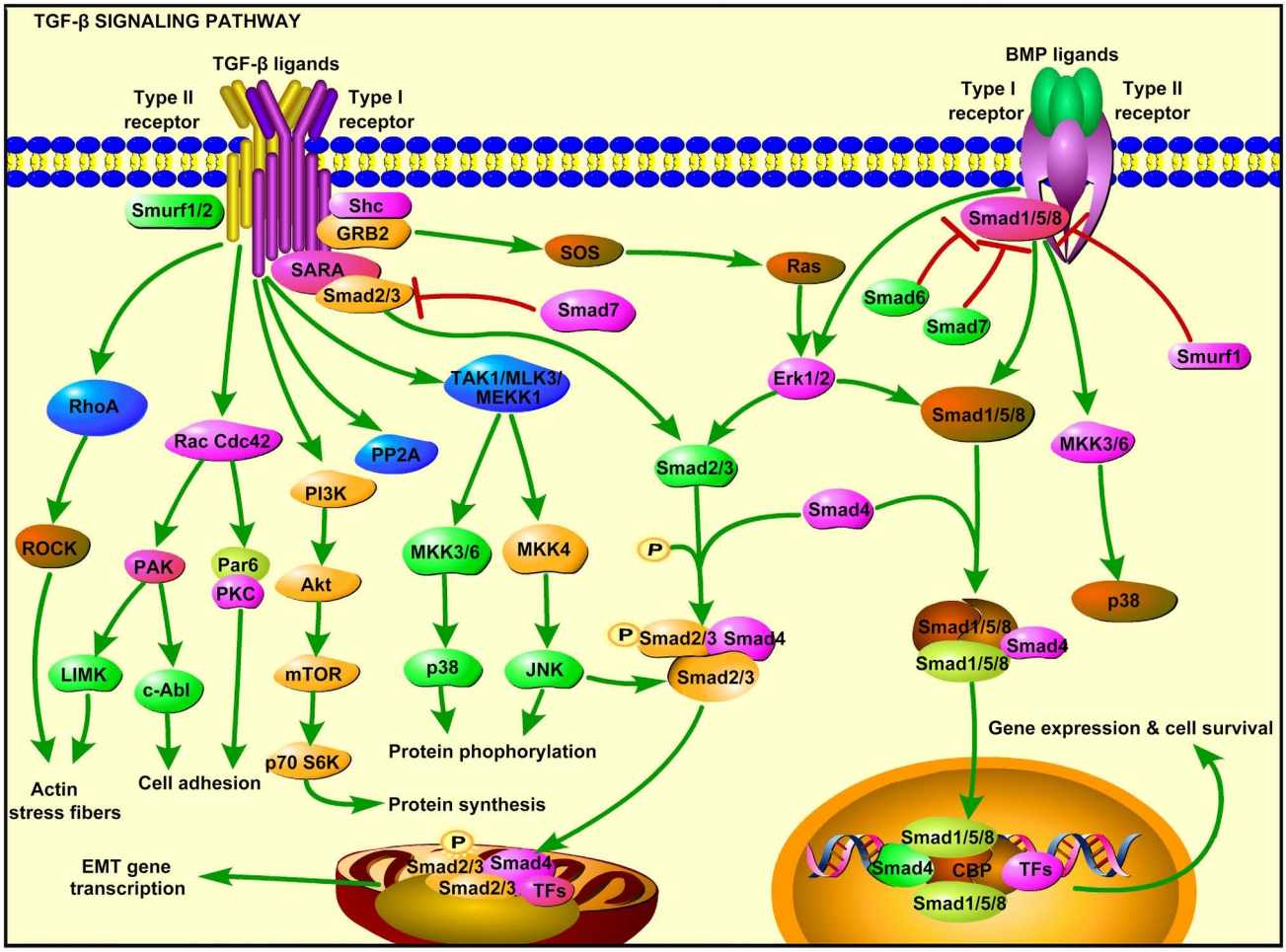

Figure 1. Schematic diagram of the mechanism of TGF-β signaling in EMT. TGF-β mainly regulates the expression of related transcription factors through SMAD and non-SMAD dependent signaling, thereby promoting the expression of related genes and cell functions. TGF-β, transforming growth factor-β; BMP, bone morphogenetic protein; EMT, epithelial-mesenchymal transition; Smad, small mothers against decapentaplegic; SARA, SMAD anchor for receptor activation; Smurf, smad ubiquitination regulatory factor; RhoA, ras homolog family member A; Rac, ras-related C3 botulinum toxin substrate; Cdc42, cell division cycle 42; ROCK, rho-associated coiled-coil containing protein kinase; PAK, p21-activated kinase; LIMK, LIM domain kinase; TAK1, TGF-β-activated kinase 1 (MAP3K7); MLK3, mixed lineage kinase 3; MEKK1, mitogen-activated protein kinase kinase kinase 1; MKK3/6, mitogen-activated protein kinase kinase 3/6; MKK4, mitogen-activated protein kinase kinase 4; Erk1/2, extracellular signal-regulated kinase 1/2; p38, p38 mitogen-activated protein kinase; JNK, c-jun n-terminal kinase; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; p70 S6K, p70 ribosomal protein s6 kinase; PP2A, protein phosphatase 2a; PKC, protein kinase C; c-Abl abelson murine leukemia viral oncogene homolog 1; Par6, partitioning defective 6 homolog; Shc, SH2 domain-containing transforming protein C; GRB2, growth factor receptor-bound protein 2; SOS, son of sevenless; Ras, rat sarcoma viral oncogene homolog; CBP, CREB-binding protein; TFs, transcription factors.

TGF-β1-mediated synergistic network for tumour stem cell maintenance and chemotherapy resistance. TGF-β1 maintains tumour stem cell characteristics through a dual mechanism. First, TGF-β1 directly activates SRY-box transcription factor 4 (SOX4) expression, and SOX4 overexpression in acute myeloid leukemia-resistant cell lines significantly increases chemotherapeutic drug tolerance (34). Second, by upregulating TGF-β1 autocrine secretion through C-terminal tensin-like protein, a positive feedback loop is formed in bladder cancer tissues, leading to a significant increase in the proportion of

Table II. Key molecular events of TGF-β1 functional transition.

Functional stage	Characteristic pathway	Effector molecules	Clinical relevance
Cancer suppression	SMAD2/3-p21	CDKN1A	Early tumor regression
Transitional period	PI3K/AKT-mTOR	HIF-1α	The sprout of resistance to treatment
Cancer promotion	SMAD4-independent	SNAIL/TWIST	Risk of distant metastasis

HIF, hypoxia-inducible factor; CDKN1A, cyclin-dependent kinase inhibitor 1A; SNAIL, snail family transcriptional repressor 1; TWIST, twist family BHLH transcription factor 1.

paclitaxel-resistant cells (35). A study on pancreatic cancer has shown that deficient expression of trefoil factor family 1 promotes EMT, significantly increasing the proportion of CD133+ cells (a tumour stem cell marker) and significantly decreasing the proportion of gemcitabine-sensitive cells (36).

This reprogramming of the stem cell microenvironment makes it difficult for traditional chemotherapy to eradicate tumour cells, suggesting that combining TGF-β pathway inhibitors may improve treatment efficacy. In patients with head and neck squamous cell carcinoma, SMAD4-mutant cells respond strongly to TGF-β1-induced stem cell marker expression (37), providing a molecular subtyping basis for precision treatment.

4. TGF-β1-mediated matrix interaction mechanism for remodelling the tumour microenvironment

Activation of CAFs and ECM remodelling. CAFs are the main effector cells of TGF-β1-mediated matrix remodelling. TGF-β1 drives CAF activation through SMAD-dependent and SMAD-independent pathways, thereby stimulating collagen crosslinking and fibronectin deposition to form a metastatic, sclerotic matrix. In a gallbladder cancer model, TGF-β1 upregulates FOXA1 expression through m6A modification, increasing the expression of α-smooth muscle actin (α-SMA) and fibronectin in CAFs (2). In types such as colon cancer, TGF-β1-induced CAFs can increase the collagen fibre diameter through Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signalling, resulting in the formation of a dense physical barrier. Treatment that neutralises TGF-β1 can promote the recruitment of antigen-specific CD8+ T cells into tumours (38,39). This fibrotic microenvironment activates latent TGF-β1 through integrin αvβ6, forming a positive feedback loop that maintains the concentration of active TGF-β1 at a high level (40). In a liver cancer model, the stabilising effect of TGFβ receptor-associated protein 1 (TGFβRAP1) on TGFβR1 enhances the contractility of CAFs, an effect that can be reversed by small interfering (si)RNA-mediated knockout of TGFβRAP1 (3). During the transformation of ductal carcinoma *in situ* to invasive carcinoma of the breast, TGF-β1 induces the loss of cadherin in myoepithelial cells via EMT and upregulates the expression of MMP-9 and IL-6 (41,42), significantly increasing the disruption of basement membrane integrity.

TGF-β1-dependent regulatory pathway of angiogenesis and lymphangiogenesis. Microenvironmental factors play important regulatory roles in the remodelling of TGF-β1 signalling. Under hypoxic conditions, the hypoxia-inducible factor 1α-microRNA (miR)145 axis promotes tumour angiogenesis by inhibiting TGFβ1-SMAD2/3-thrombospondin-1 signalling (43).

In mouse models, platelet-released TGF-β1 increases microvascular density and enhances vascular permeability (44). TGF-β1-induced endothelial-mesenchymal transition significantly enhances tumour angiogenesis (45), and a breast cancer mouse model showed increased microvascular density in the TGF-β1-treated group, accompanied by activation of the Notch pathway (22).

Lymphangiogenesis depends mainly on the upregulation of vascular endothelial growth factor C (VEGF-C) expression. As observed in a tube formation assay and a tumour xenograft mouse model, TGF-β1 induced high expression of VEGF-C by activating the Smad2/3 pathway, thereby significantly promoting lymphangiogenesis in a model of gastric cancer (46). Notably, transglutaminase 1 has been shown to participate in vascular basement membrane remodelling, and its inhibitors can significantly reduce the perivascular cell coverage of tumours, thereby enhancing the penetration of chemotherapeutic drugs (47).

5. TGF-β1 drives a synergistic inhibitory network for immune escape

A dual mechanism of Treg amplification and CTL function inhibition. TGF-β1 promotes the expansion and functional activation of Tregs through the SMAD2/3-dependent pathway. In a multiple myeloma model, Treg-derived TGF-β1 inhibited cyclic GMP-AMP synthase/stimulator of interferon genes signalling and promoted major histocompatibility complex class I (MHC I) molecule loss and PD-L1 expression upregulation (48). In a type 1 diabetes study, TGF-β1-regulated T-cell immunoreceptor with Ig and ITIM domains+ Tregs significantly inhibited the cytotoxicity of CD226+CD8+ T cells (49). In patients with colorectal cancer, the expression level of TGFBR2 in tumour-infiltrating Tregs was several times greater than that in peripheral blood, and its inhibitory activity was positively correlated with the concentration of TGF-β1 (50).

TGF-β1 can limit the ability of CD4+ (but not CD8+) anti-TGF-β chimeric antigen receptor (CAR) T-cells to partially inhibit tumour growth through the secretion of granzyme B and interferon (IFN)-γ. CD4+ T28zT2 T cells treated with TGF-β1 survived continuously in peripheral blood and tumours, maintained mitochondrial morphology and function,

and did not induce *in vivo* toxicity. These findings indicate that reprogramming the TGF-β signalling pathway using T28zT2 (anti-TGF-β CAR T cells) in CD4+ T cells is a promising strategy for eliminating solid tumours (51). This bidirectional regulation is achieved through a Smad3-dependent mechanism: TGF-β1 promotes Foxp3 expression by phosphorylating Smad3, while Smad3 knockout completely reverses the amplification effect of Tregs (52).

Molecular basis of myeloid-derived suppressor cell (MDSC) recruitment and TGF-β1. MDSCs are considered major tumour promoters and markers of cancer immune evasion mechanisms (53). TGF-β inhibits the activation and antitumour function of T lymphocytes, dendritic cells and natural killer (NK) cells while promoting the production of regulatory T cells and MDSCs, thereby inhibiting the antitumour activity of T cells (54). In patients with renal cell carcinoma, cellular homolog of Sloan-Kettering viral oncogene Ski (c-Ski) protein degradation is induced by TGF-β. The downregulation of TGF-β expression remodels the immunosuppressive tumour microenvironment by limiting tumour-infiltrating MDSCs, while c-Ski protein degradation is also inhibited (55). The long noncoding RNA Exo-AGAP2-AS1 from glioma cells regulates TGF-β1 expression in MDSCs through binding to miR-486-3p; thus, Exo-AGAP2-AS1 upregulation promotes glioblastoma multiforme cell growth and metastasis through MDSCs (56).

TGF-β1 activates the TGF-β1/2-Smad2/3 pathway by upregulating the expression of FAT atypical cadherin 1 (FAT1), promoting the recruitment of MDSCs to tumour foci and increasing the proportion of MDSCs. In glioma tumours, FAT1 expression is positively correlated with the expression of surrogate markers of MDSCs, including PD-L1, PD-L2 and IL-10 (57), suggesting that FAT1 may play a role in MDSC-mediated immunosuppression.

TGF-β1-mediated inhibition of NK-cell function. TGF-β1 exhibits dose-dependent inhibition of NK cells. In patients with metastatic melanoma, the use of anti-TGF-β1 antibodies restored the NK cell killing efficiency to baseline levels (58). These findings suggest that the relationship between high levels of TGF-β1 and NK cell inhibition in cancer patients is a major mechanism underlying tumour immune escape. This inhibitory mechanism involves the downregulation of the expression of the natural killer group 2D (NKG2D) ligands MHC class I polypeptide-related sequence A/B and PD-L1 via Smad4 by TGF-β1, thereby blocking NK cell activation signals (59).

The inhibition of NK cell function involves multiple mechanisms. For example, TGF-β1 induces receptor expression downregulation. After NK cells from patients with gastric cancer were treated with TGF-β1, the expression levels of NKp30, NKp46, NKG2D and DNAX accessory molecule-1 were significantly reduced (60). Second, during metabolic reprogramming, TGF-β1 significantly reduced mitochondrial oxidative phosphorylation efficiency through mTOR complex 1 inhibition (61,62). In response to cytokine dysregulation, IL-15-driven proliferation signalling is blocked by TGF-β1, and the proportion of cells undergoing cell cycle arrest in the G1 phase increases (63).

Table III. Effects of TGF-β1 on major immune cell subsets.

Immune cell type	Effect of TGF-β1	Key molecular mechanism
Tregs	Amplification	Smad3-Foxp3 axis
MDSCs	Recruitment	CCL2-CCR2
NK cells	Suppression	Smad4-NKG2D

Tregs, regulatory T cells; MDSCs, myeloid-derived suppressor cells; NK, natural killer; fox, forkhead box; CCL2, C-C motif chemokine ligand 2; NKG2D, NK group 2D.

As shown in Table III, the effects of TGF-β1 on major immune cell subsets significantly differed.

Construction of a coinhibitory loop between TGF-β1 and immune checkpoints such as PD-1, PD-L1 and butyrophilin subfamily 1 member A1 (BTN1A1). TGF-β1 forms a positive feedback loop with the PD-1/PD-L1 pathway. In chronic inflammation models, TGF-β1 upregulates PD-1 expression in macrophages via synergistic SMAD3/STAT3 signalling, and PD-1+ macrophages can secrete TGF-β1, resulting in the formation of an autocrine loop (64). In triple-negative breast cancer cells, TGF-βRII deficiency leads to a doubling of PD-L1 expression, while the proportion of lymphocyte activation gene 3+ T cells increases, resulting in resistance to immune checkpoint inhibitor (ICI) therapy (18,65).

Selective TGF-β1 inhibitors, such as compound 67, can block the EMT process and significantly reduce the number of metastatic lesions in an A549 lung cancer model (66). Tumour-activating prodrugs targeting TGFβR1, such as the LY2157299 precursor (galunisertib), are designed to selectively release the active drug within the tumour microenvironment, thereby minimising systemic exposure and reducing off-target toxicity. LY2157299 has been shown to decrease the incidence of cardiovascular events (67,68) by limiting systemic TGF-β pathway inhibition, which can otherwise lead to adverse effects. This targeted approach enhances the therapeutic window by balancing efficacy and safety.

In combination immunotherapy, TGF-β1 antibodies and PD-1 inhibitors can synergistically remodel the immune microenvironment. In patients with advanced colorectal cancer, the combination therapy group showed a significant increase in CD8+ T cell infiltration and a significant improvement in the objective response rate (69-71). These advances provide a precise intervention tool for understanding the dual role of TGF-β1.

BTN1A1 is a novel immune checkpoint mutually exclusive with PD-L1, and its inhibitory effect on T cell activation has been demonstrated both *in vitro* and *in vivo* (65). Increased expression of BTN1A1, a member of the butyrophilin subfamily, has been detected in BRAF-mutant tumours (72). Disruption of intact BTN1A1 protein expression leads to a large accumulation of Xanthine dehydrogenase in the cytoplasm, inducing the activation of acute-phase response genes and phosphorylated leukemia inhibitory factor genes downstream of STAT3 (73). Novel strategies have shown that simultaneous blockade of TGF-β1 and BTN1A1 can increase CD8+ T-cell

infiltration in the tumour microenvironment by a factor of two, which is superior to the effect of monotherapy (65).

These findings provide new insight into overcoming ICB resistance. In PD-1 resistance models, TREX1 inhibitors combined with anti-TGF-β1 antibodies can increase tumour regression rates (74,75).

6. Clinical translation bottlenecks and breakthrough paths for TGF-β1-targeted therapeutic strategies

Analysis of the limitations of monotherapy (antibodies and kinase inhibitors). TGF-β1, a key regulator of the tumour microenvironment, faces significant challenges related to targeted therapy. Although systemic inhibition of TGF-β1 can enhance antitumour immunity and limit the expansion, survival and function of CD4+ T cells (51) (Table IV), dose adjustments are often required because of cardiovascular toxicity and delayed wound healing events (58,76). A recent study showed that perfluorooctanoic acid induces pulmonary toxicity through the TGF-β1/Smad pathway (77). Therefore, an early phase Ib clinical trial of the use of TGF-β-targeted drugs such as PF-03446962 in combination with regorafenib for the treatment of metastatic colorectal cancer was terminated because of serious adverse events (78) (Table IV). PF-03446962 is a monoclonal antibody targeting activin receptor like kinase 1. However, a recent study showed that the combination of PF-03446962 and nivolumab has promising anti-cancer activity and safety in patients with advanced HCC (79).

The clinical response rate to TGF-β1 monotherapy is generally low, and its limitations also include the requirement that the kinase inhibitor galunisertib achieves a 50% inhibitory concentration of TGF-βRI in μmol (80).

However, the local delivery system of exosome-based TGF-β1 siRNA significantly improved the degree of fibrosis in the lung tissues of a fibrotic mouse model. siTGF-β1 effectively delivers specific siRNAs to the lungs, leading to TGF-β1 mRNA silencing and EMT pathway inhibition, thereby protecting lung tissue from fibrotic damage (81). Recent research has indicated that immunoliposomes can deliver siTGF-β1 to tumour cells (82), thereby improving a series of effects, such as poor stability, a short half-life and high toxicity of naked siRNA. In an A549 tumour-bearing nude mouse model, transfection with siTGF-β1 significantly reduced tumour growth and tumour volume (83). These findings suggest that targeting siTGF-β1 with immunoliposomes may be a novel strategy for cancer treatment.

In terms of selectively blocking downstream pathways, the TAK1 inhibitor takinib, while preserving Smad2/3 signalling, specifically inhibited the noncanonical NF-κB pathway, increasing the tumour growth inhibition rate in a melanoma model, but wound healing impairment was not observed. Compared with traditional inhibitors, this precise intervention significantly improves the therapeutic index, particularly when combined with ICIs (84-86). Consequently, future research is expected to overcome the historical challenges associated with TGF-β-targeted therapy.

Mechanistic basis through which TGF-β blockade enhances the anti-PD-1 response to combined immunotherapy. The TGF-β1 and PD-1 pathways exhibit bidirectional regulation. In colorectal and liver cancer models, TGF-β1 forms a complex at the PD-1 promoter via SMAD3/STAT3 cosignalling, significantly upregulating PD-1 expression in macrophages. PD-1+ T cells, in turn, increase the secretion of active TGF-β1 (64,87), creating a positive feedback loop of immunosuppression. Combined blockade can break this cycle. A study showed that the combined blockade of TGF-β and PD-1 activates GBM-infiltrating CD8+ T cells, which are characterised by upregulated TGFβRI expression (88). This finding is consistent with previous results from a phase 1b clinical trial in patients with relapsed/refractory multiple myeloma (89).

Mechanistic studies have shown that combination therapy enhances antitumour immunity through a triple effect (90,91), significantly reducing the proportion of Foxp3+ Tregs in tumours and decreasing immunosuppressive capacity (92,93). This combined effect can also remodel dendritic cell (DC) function, improve the antigen-presenting capacity of DCs and promote the expression of IFN-γ and granzyme b on CD8+ T cells and NK cells (94). Recent studies have shown that the intrinsic tumour cell function of PD-L1 drives immunosuppression and tumour progression through the PD-L1/JAK/STAT3/IL-6/MDSC axis (95) and that inhibiting the PD-L1 and TGF-β pathways has a synergistic effect on restoring CD4+ T-cell activity *in vitro* (96), thereby remodelling MDSC polarisation.

In a model of non-small cell lung cancer (97), anti-TGF-β1 antibody combined with anti-PD-1 antibody significantly inhibited the proliferation of recombinant epidermal growth factor receptor (EGFR)-mutant tumours in C57BL/6N mice through the EGFR-ERK1/2-p90RSK signalling pathway and was superior to monotherapy. This combination significantly increased CD8+ T-cell infiltration, thereby enhancing the antitumour function of CD8+ T cells. Single-cell RNA sequencing confirmed that the combination therapy group had a novel CD8+ T-cell subset, the proportion of which was positively associated with the clinical response (69,98).

7. The four-dimensional integrative direction of future precision intervention paradigms

The dimension of time: Dynamic targeting strategy to distinguish between early tumour suppression and late tumour promotion windows. The bidirectional regulatory nature of TGF-β1 signalling necessitates that intervention strategies must consider disease stage specificity. In early-stage tumours, TGF-β1 maintains genomic stability by activating p16INK4a (CDKN2A) and p21 wild-type p53-activated fragment 1/CDK-interacting protein 1 (p21WAF1/CIP1) (99,100), and targeted inhibition at this stage may lead to cumulative DNA damage. A study using a preclinical model has shown that in desmoglein-2 variant-induced arrhythmic cardiomyopathy, overactivation of the activating transcription factor 4/TGF-β1 pathway significantly promotes collagen deposition only in the later stages of fibrosis, whereas early inhibition of this pathway weakens the repair capacity of cardiomyocytes (101).

A pancreatic ductal adenocarcinoma liver metastasis model revealed that AVID200/BMS-986416-mediated depletion of TGF-β can reduce the formation of metastatic lesions when it is applied in the early stages of tumour development, but if treatment is initiated in the late stages, it accelerates

Table IV. Trials with TGF-β inhibitors.

Inhibitor or drug	Phase	Outcome	Trial number	(Refs.)
Glutamine	Phase I	Improving radiation sensitivity	NCT05856188	(91)
STP705	Phase I	Rare and transient adverse events, A favorable safety profile.	NCT05422378	(92)
PTX	RCT	Improvement in the ESA resistance index	NCT05708248	(93)
SAR4349459 (±cemiplimab)	Phase 1/1b	Approximately half of the patients experienced Grade 3 adverse events. Terminated due to low objective response and bleeding risk.	NCT03192345	(94,95)
PF-03446962	Phase 1b	No clinical activity, unacceptable toxicities.	REGAL-1	(96)
Bintrafusp alfa (+Regorafenib)	Phase I	Only 1 CMS4 patient exhibited a long response,	NCT02517398	(97)
	Phase Ib/II	No significant activity in MSI-H mCRC;	NCT03436563	(98)
	Phase II	The main adverse event was anemia.	NCT04246489 (without Regorafenib)	(69)
LY2109761	Preclinical	Inhibited tumourigenicity and liver metastasis of colon cancer.		(99)
Galunisertib (LY2157299)	Preclinical	Significantly improved eradication of liver metastases in mice,		(100,101)
(+Bemcentinib)	Preclinical	Reduced colony formation and migration capabilities.		
Sitagliptin	Preclinical	Inhibition of EMT and metastatic traits, Suppressed cell cycle.w		(102)

PTX, Pentoxifylline; ESA, erythropoiesis-stimulating agents; RCT, randomized controlled clinical trial; MSI-H, microsatellite instability-high; EMT, epithelial-mesenchymal transition; CMS4, consensus molecular subtype 4; mCRC, metastatic colorectal cancer.

CAF-mediated immune escape (reduced CD8+ T-cell infiltration) (103).

The dimensions of spatiality and cell type: Analysis of heterogeneity in TGF-β1 signalling in primary and metastatic lesions. Single-cell transcriptome analysis revealed that TGF-β1 is highly expressed in the tumour core (CD44+ stem cell-like cells) in primary head and neck squamous cell carcinoma lesions (103), whereas it is enriched in the peripheral matrix (α-SMA + CAFs) in metastatic lesions (104). Recent advances in radiomics, such as the use of minimum redundancy maximum relevance and recursive feature elimination algorithms, have enabled the non-invasive prediction of TGF-β1 spatial distribution within tumours. For instance, a CT radiomics model achieved an area under the curve (AUC) of 0.849 in predicting TGF-β1 expression patterns (105), highlighting its potential as a tool for precision oncology. This approach leverages quantitative imaging features to map TGF-β1 heterogeneity, which may inform targeted therapeutic strategies. In a liver metastasis model of colorectal cancer, Smad2/3 proteins are predominantly phosphorylated in cells from primary lesions, whereas metastatic lesions exhibit activation of the noncanonical TGF-β/cysteine-and-glycine-rich protein 2 axis. This difference may lead to a significant difference in the response rate to targeted therapy (106,107).

Spatial heterogeneity is also reflected in the immune microenvironment. TGF-β1 reduces CD8+ T-cell response efficiency by inhibiting IL-4 secretion from follicular helper T cells (108). Given the significant differences in TGF-β1 activity across different regions within the same tumour, this spatial heterogeneity directly leads to stratification of immunotherapy response rates (109,110). In breast cancer tissues, regions with high TGF-β1 activity have significantly lower CD8+ T-cell infiltration density and significantly higher PD-1 expression levels than regions with low TGF-β1 activity (111,112). By integrating single-cell transcriptomics and spatial transcriptomics data, researchers have mapped the

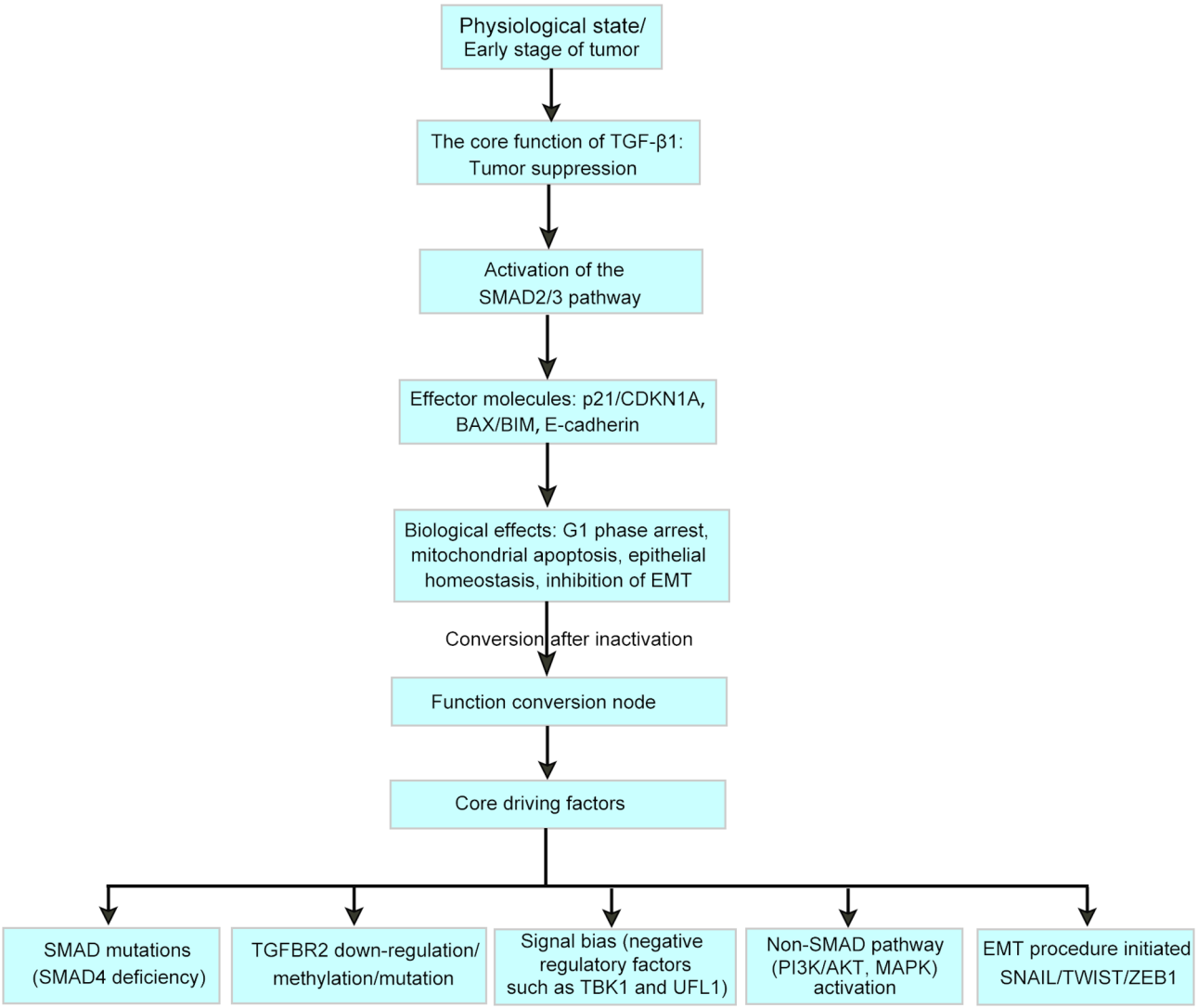

Figure 2. Diagram illustrating the dual role of TGF-β1 in cancer, transitioning from a tumor suppressor to a promoter during tumor progression. TGF-β1, transforming growth factor-β1; SMAD2/3, mothers against decapentaplegic homolog 2/3; SMAD4, mothers against decapentaplegic homolog 4; p21/CDKN1A, cyclin-dependent kinase inhibitor 1A; BAX, BCL2-associated X protein; BIM, BCL2-like 11; TGFBR2, TGF-β receptor 2; TBK1, TANK-binding kinase 1; UFL1, UFM1 specific ligase 1; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein kinase; SNAIL, snail family transcriptional repressor 1; TWIST1, twist family BHLH transcription factor 1; ZEB1, zinc finger e-box binding homeobox 1; EMT, epithelial-mesenchymal transition.

quantitative correlation between TGF-β1 signalling gradients and the degree of immunosuppression, providing new evidence for precise intervention (113).

Researchers have developed spatial epigenomic techniques for quantifying histone modifications, such as histone H3 lysine 27 trimethylation (H3K27me3), H3K4me3 and H3K27ac, on the basis of spatial transcriptomics (114). This remarkable approach can reveal key spatial regulatory elements controlling identity (i.e., spatial enhancer prediction) and advance epigenetic research into the spatial era.

Deterministic barcoding in tissue for spatial omics sequencing supports the simultaneous recording of spatially barcoded mRNA and analysis of proteins of interest (a set of 22 proteins) (115). The development of spatial multiomics has also provided integrated, spatial transcriptomics- and antibody-based proteomics analysis without the need for complex infrastructure (116). This platform was tested in mouse cerebral cortex samples and a significant correlation was observed between specific mRNA and protein expression.

The dimension of technology: Individualised intervention design guided by single-cell sequencing and organoid models. Patient-derived organoids (PDOs) combined with single-cell multiomics can enable the dynamic optimisation of treatment regimens (117). In a study using a colorectal cancer model, gene or drug targeting of TGF-βR1 enhanced NK cell-mediated PDO killing or activation (118). AVID200 is a TGF-β ligand-trapping agent and is reported to have a binding affinity 1,000 times greater than that of other trapping agents (102,119). Although studies on the effects of AVID200 on solid tumours are limited, in a phase I study (NCT03834662) of 19 patients with advanced or metastatic solid tumours, AVID200 monotherapy was well tolerated and effectively modulated TGF-β1/3 (120,121).

Compared with whole-cell RNA sequencing, single-cell RNA sequencing can capture intratumoural heterogeneity. Furthermore, cellular dynamic events can be studied using pseudotime trajectory analysis of single-cell RNA sequencing data (122). Currently, the Samsung Medical

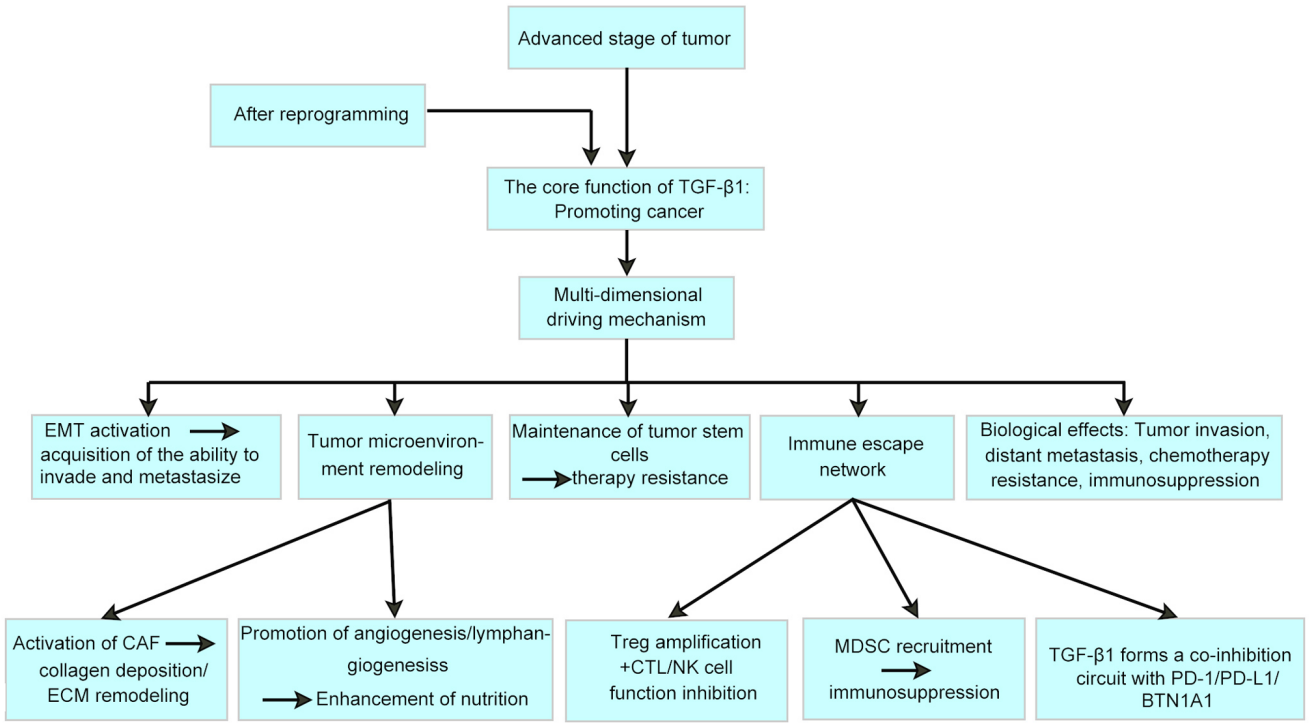

Figure 3. TGF-β1-mediated oncogenic signaling in advanced-stage tumors. Advanced stage of tumor: The pathological progression of cancer to a late phase, characterized by increased invasiveness and metastatic potential. After reprogramming: Epigenetic or cellular state changes that prime the tumor microenvironment for TGF-β1-driven oncogenic activity. The core function of TGF-β1: Promoting cancer-the central role of TGF-β1 in facilitating malignant progression, which is executed through a multi-dimensional network. Multi-dimensional driving mechanisms: This section represents the key biological pathways activated by TGF-β1, including EMT activation, tumor microenvironment remodeling, maintenance of tumor stem cells and immune escape network. Downstream effectors include activation of CAF, promoting angiogenesis/lymphangiogenesis, Treg amplification and MDSC recruitment. EMT, epithelial-mesenchymal transition; TGF-β1, transforming growth factor-β1; CAF, cancer-associated fibroblast; ECM, extracellular matrix; Treg, regulatory T cell; CTL, cytotoxic T lymphocyte; NK cell, natural killer cell; MDSC, myeloid-derived suppressor cell; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; BTN1A1, butyrophilin subfamily 1 member A1.

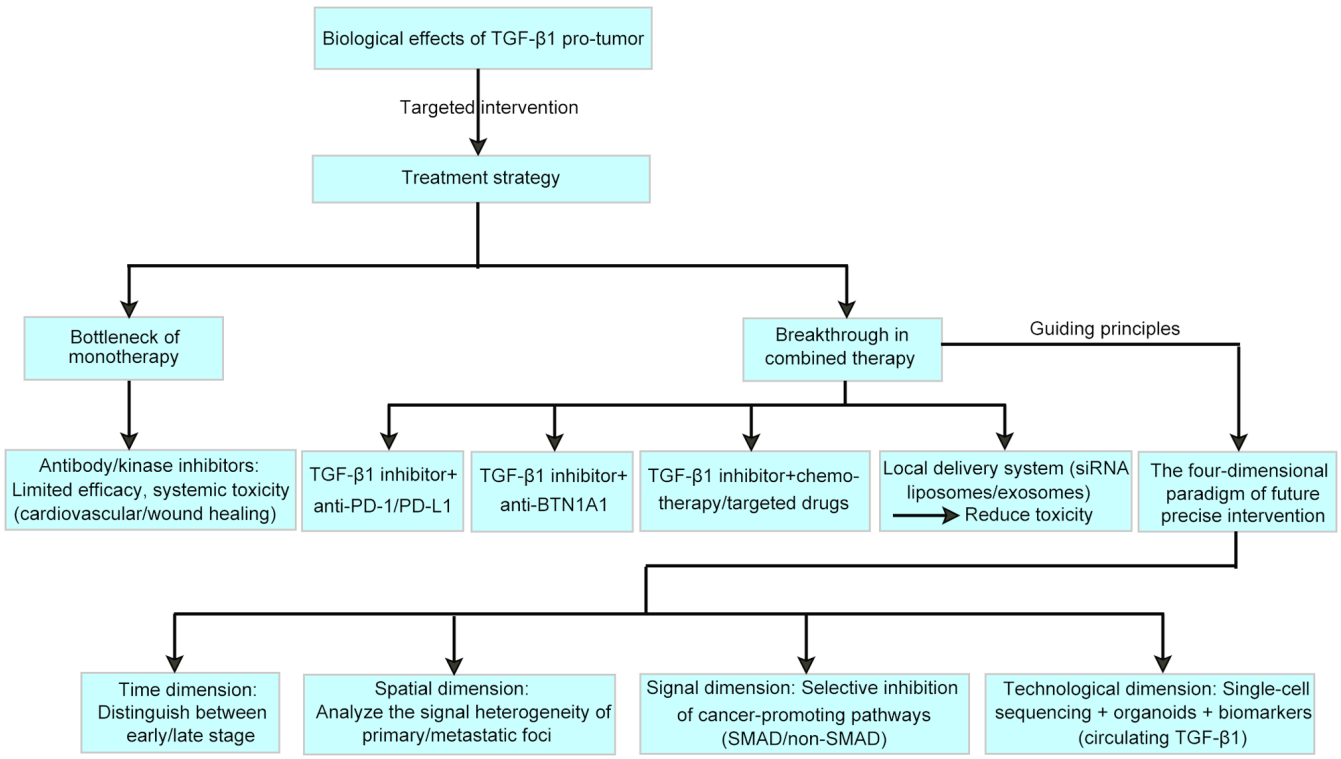

Figure 4. Therapeutic strategies targeting TGF-β1 in cancer. This diagram illustrates the framework for targeted intervention against the pro-tumor biological effects of TGF-β1, highlighting the limitations of monotherapy and the breakthroughs in combined therapy, guided by a four-dimensional paradigm for future precise intervention.

Center colorectal cancer single-cell RNA sequencing dataset can be used to identify important tumour epithelial cell subtypes (122). Through pseudotime trajectory analysis, researchers reported that TGFB1 and IL-1B may be effective ligands and transcription factors that regulate pseudotime-related gene expression. By constructing a LASSO Cox regression for 20 pseudotime genes, the 3-year survival rate of patients with colorectal cancer can be predicted with an AUC >0.7 (122).

Potential of circulating TGF-β1 as a biomarker for personalised treatment guidance. Current integrated technology pathways include diagnostic, therapeutic and monitoring stages. For example, epithelial cell adhesion molecule-based immunoisolation can be used to capture circulating tumour cells (CTCs) that undergo EMT after TGF-β1-induced stimulation (123,124). Spatial transcriptomics of a gastric cancer brain metastasis model revealed atypical vascular strategies supporting immune signatures. Tumours with high EMT and transcriptomic gene expression signatures consisting of catenin β1, secreted protein acidic and cysteine rich, ventral intermediate, SMAD3, SMAD4, TGFB1, TGFB2 and TGFB3 are more prone to blood vessel co-option than angiogenesis (125).

The role of DNA methylation driver genes (MDGs) in pancreatic cancer has been assessed by integrating epigenomic, transcriptomic and clinicopathological data. High signature risk-scores (126), a quantitative metrics derived from mathematical or bioinformatics models based on MDG signature, were found to be associated with poor histological grade and advanced TNM stage. The negative regulatory genes of the cancer-immunity cycle demonstrated that the immunosuppressive factors TGF-β1 and CD274 (PD-L1) were positively correlated with risk scores. These factors are negatively correlated with CD8+ lymphocytes but positively correlated with MDSCs (126).

8. Future perspectives

TGF-β1 plays a significant stage-dependent dual role in cancer development (127-131) and its functional transition is a key molecular event in tumour evolution (Figs. 2-4). For instance, under physiological or early-stage tumor conditions, TGF-β1 and the signaling pathways it mediates mainly exert anti-cancer effects through cell cycle arrest, promoting apoptosis and inhibiting EMT. However, once the functional transformation of its signaling pathway nodes occurs, it plays a significant role in promoting cancer (Fig. 2). In the advanced stage of tumors, TGF-β1 mainly promotes cancer progression by facilitating EMT activation, microenvironment remodeling, stem cell maintenance and immune tolerance (Fig. 3). The treatment targeting TGF-β1 shows a good anti-cancer effect, but the efficacy of monotherapy is limited due to severe adverse reactions. Therefore, the development of a combined treatment targeting TGF-β1 and a targeted drug delivery system brings a promising prospect (Fig. 4). Future precision interventions targeting TGF-β1 require the establishment of a four-dimensional integrated paradigm (Figs. 2-4). Temporally, distinguishing the critical windows of tumour-suppressive effects in early stages vs. tumour-promoting effects in advanced stages is essential when stage-adaptive targeting strategies are implemented. Spatially and across cell types, technologies such as spatial transcriptomics and radiomics should be employed to decipher signalling heterogeneity between primary and metastatic lesions, enabling precise locoregional intervention. At the signalling network level, the selective inhibition of cancer-promoting SMAD and non-SMAD pathways is necessary while avoiding the disruption of normal physiological functions. Technologically, leveraging single-cell sequencing, patient-derived organoid models and circulating TGF-β1 biomarkers will facilitate the design of personalised therapeutic regimens.

9. Conclusions

TGF-β1 exhibits a dual role in cancer progression, acting as both a tumour suppressor and promoter through stage-dependent mechanisms. Its signalling pathways drive tumour invasion, metastasis and therapy resistance via SMAD and non-SMAD pathways, EMT and immune evasion. Current TGF-β1-targeted therapies face challenges, but combination immunotherapy holds promise. Future precision strategies must integrate temporal, spatial, cellular and technological dimensions to selectively modulate TGF-β1's complex functions. Advancements in single-cell sequencing and organoid models will be critical for guiding personalised therapeutic interventions.

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Availability of data and materials

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Authors' contributions

CH wrote and revised the manuscript, including conception and design of the study and literature search/selection. Data authentication is not applicable. The author has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

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