CTGF: The remodeler of the tumor immune microenvironment (Review)

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Abstract. The tumor immune microenvironment (TIME) is the key determinant of limited efficacy and acquired resistance to cancer immunotherapy across human malignancies. In this context, connective tissue growth factor (CTGF) has been implicated in multiple TIME-related processes, including tumor-cell phenotypic regulation, extracellular matrix (ECM) remodeling, immune-cell modulation, and cytokine-network alterations. Collectively, this suggests that CTGF may participate in coordinated crosstalk among structural, signaling, and immune components of the TIME. Empirical evidence supports roles for CTGF in selected tumor and stromal settings. However, its broader contribution to coordinated TIME remodeling remains partly inferential and requires further experimental validation. Where present, such coordinated effects may impair antitumor immune recognition and promote tumor-cell survival within specific tumor microenvironmental settings. The present review summarizes the core mechanisms of CTGF-mediated TIME remodeling and outlines the translational potential of CTGF-targeted combination immunotherapies and key research priorities to advance its clinical translation.

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Abbreviations: AKT, protein kinase B (PKB); ATP, adenosine triphosphate; Bcl-xL, B-cell lymphoma-extra large; Bregs, regulatory B cells; CAF, cancer-associated fibroblasts; CCL18, C-C motif chemokine ligand 18; CCN, cellular communication network; CTGF, connective tissue growth factor, cellular communication network factor 2 (CCN2); CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; cIAP1, cellular inhibitor of apoptosis protein 1; CSC, cancer stem cell; CXCL1, C-X-C motif chemokine ligand 1; CXCL2, C-X-C motif chemokine ligand 2; CXCL5, C-X-C motif chemokine ligand 5; CXCL8, C-X-C motif chemokine ligand 8; CXCR1, C-X-C motif chemokine receptor 1; CXCR2, C-X-C motif chemokine receptor 2; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; ERK/MAPK, extracellular signal-regulated kinase/mitogen-activated protein kinase; EZH1, enhancer of zeste homolog 1; FGFR3, fibroblast growth factor receptor 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor 1-α; hsa-miR-27a-3p, Homo sapiens microRNA-27a-3p; IFN-γ, interferon-γ; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-12, interleukin-12; IL-35, interleukin-35; JNK, c-Jun N-terminal kinase; KDM3A, lysine demethylase 3A; M1, classically activated macrophage phenotype; M2, alternatively activated macrophage phenotype; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cell; MDSCs, myeloid-derived suppressor cells; MMP, matrix metalloproteinase; mtDNA, mitochondrial DNA; mtTFA, mitochondrial transcription factor A; N1, anti-tumor tumor-associated neutrophil phenotype; N2, pro-tumor tumor-associated neutrophil phenotype; NF-κB, nuclear factor-κB; NK, natural killer cell; Notch1, Notch receptor 1; OSCC, oral squamous cell carcinoma; p38 MAPK, p38 mitogen-activated protein kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphatidylinositol 3-kinase; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; ROS, reactive oxygen species; SDC1, syndecan-1; Snail1, Snail family transcriptional repressor 1; SRC, SRC proto-oncogene, non-receptor tyrosine kinase; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; TGF-β, transforming growth factor-β; Th17, T helper 17 cell; TIME, tumor immune microenvironment; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α; Twist1, twist family bHLH transcription factor 1; VEGF, vascular endothelial growth factor

Key words: connective tissue growth factor, tumor immune microenvironment, cancer-associated fibroblasts, epithelial-mesenchymal transition, extracellular matrix, immune evasion

Contents

1. Introduction

Currently, the incidence and mortality of malignant tumors continue to rise globally (1,2), imposing a substantial burden on the global healthcare systems (1,3). Immunity refers to a physiological surveillance mechanism whereby organisms distinguish self from non-self antigens, eliminate exogenous pathogens and aberrant cells, and maintain internal environmental homeostasis via immune responses. The immune microenvironment constitutes a dynamic regulatory network composed of immune cells, non-immune stromal cells, extracellular matrix, and soluble mediators. This network not only mediates canonical immune reactions but also orchestrates immune homeostasis through immunosuppressive cell populations and paracrine factors. Under physiological conditions, the immune microenvironment recognizes and eliminates nascent tumor cells. In tumor-bearing tissues, however, malignant cells upregulate immunosuppressive mediators, reprogram immune cell lineages and metabolic circuits, and remodel the local niche into a tumor immune microenvironment (TIME) characterized by functional dysfunction and dominant immune suppression. This transformation enables tumor cells to evade immune surveillance and clearance (4,5). The biological features of the TIME display substantial heterogeneity, and the regulatory functions of each constituent dynamically shift throughout disease progression. This highly complex microenvironment plays a pivotal role in shaping tumor therapeutic responses to immunotherapies.

Connective tissue growth factor (CTGF), also termed cellular communication network factor 2 (CCN2), is a core member of the cellular communication network (CCN) matricellular protein family. Mounting evidence implicates CTGF in the recruitment and phenotypic polarization of immune cells, including driving M1-to-M2 macrophage polarization (6,7). Moreover, CTGF drives fibroblast activation and extracellular matrix (ECM) remodeling, enabling these stromal populations to assemble physical tissue barriers (8,9). In addition, CTGF collaborates with regulatory cytokines, including interleukin (IL)-6 (10), IL-8 (11), tumor necrosis factor (TNF)-α (7), and transforming growth factor (TGF)-β (12), to collectively modulate the reprogramming of the immune microenvironment, facilitate tumor immune evasion, and contribute to the initiation and progression of malignant tumors. Thus, the pleiotropic effects of CTGF within the TIME establish CTGF as a central modulator of tumor immune escape and immunotherapy resistance. Several recent reviews have summarized CTGF/CCN2 from the perspectives of molecular structure, gene regulation, disease-associated signaling, drug discovery, broad therapeutic targeting, or cancer progression in specific tumor types (13-16). However, these studies have not systematically distinguished how CTGF may coordinate the structural, signaling, and immune dimensions of the tumor immune microenvironment. In particular, the potential links among CTGF-driven ECM remodeling, stromal stiffening, vascular aberrancy, cancer-associated fibroblast (CAF) activation, immune-cell spatial exclusion, cytokine-network remodeling, and immunotherapy resistance remain insufficiently integrated.

In the present review, the core signaling axes and intercellular crosstalk mechanisms governing CTGF-dependent TIME remodeling are systematically summarized, translatable therapeutic strategies and unresolved research gaps are elaborated, and the cell-type-specific molecular and cellular cascades through which CTGF synergistically promotes tumor immune evasion are dissected, with the aim of identifying novel combinatorial therapeutic targets to enhance the efficacy of cancer immunotherapies. Compared with previous CTGF/CCN2 reviews (13-16), the major incremental contribution of the present review is the construction of a TIME-centered 'structure-signal-immunity' framework. This framework organizes available evidence into four interconnected layers: Tumor-cell phenotypic remodeling, ECM and vascular remodeling, immune-cell functional reprogramming, and cytokine-network remodeling. By doing so, this review shifts the discussion of CTGF from a general profibrotic or tumor-promoting molecule toward a context-dependent regulatory node that may shape immune exclusion and therapeutic resistance within the TIME. The mechanisms that are experimentally supported, those that remain inferential, and those that should be prioritized for spatially resolved, tumor-type-specific, and immunotherapy-oriented validation are further highlighted.

2. CTGF regulates tumor cell phenotype in TIME

Tumor cells are central contributors to the formation and remodeling of the TIME. Tumor stem cells with stem-like properties contribute to tumor initiation, recurrence, and metastasis by secreting immunosuppressive factors, recruiting suppressive immune cells, and expressing immune checkpoint molecules, thereby limiting effector immune-cell infiltration and promoting an immunosuppressive TIME (17). As a multifunctional matricellular protein, CTGF is associated with malignant tumor-cell phenotypes in several settings (18) and may contribute to TIME remodeling during tumor progression (Fig. 1).

CTGF-mediated induction and maintenance of cancer stem cell (CSC) properties. CSCs, characterized by self-renewal capacity and therapeutic resistance, are considered major contributors to tumor recurrence and metastasis (19). In addition, CSCs highly express immune checkpoint molecules such as programmed death-ligand 1 (PD-L1) and actively secrete immunosuppressive factors, which directly inhibit T-cell function or mediate immune tolerance. Thus, CSCs participate in TIME shaping and act as a core driver of tumor immune evasion (20-23).

It has been demonstrated that CTGF binds to its receptor integrin αvβ3 to activate the downstream focal adhesion kinase-SRC proto-oncogene, non-receptor tyrosine

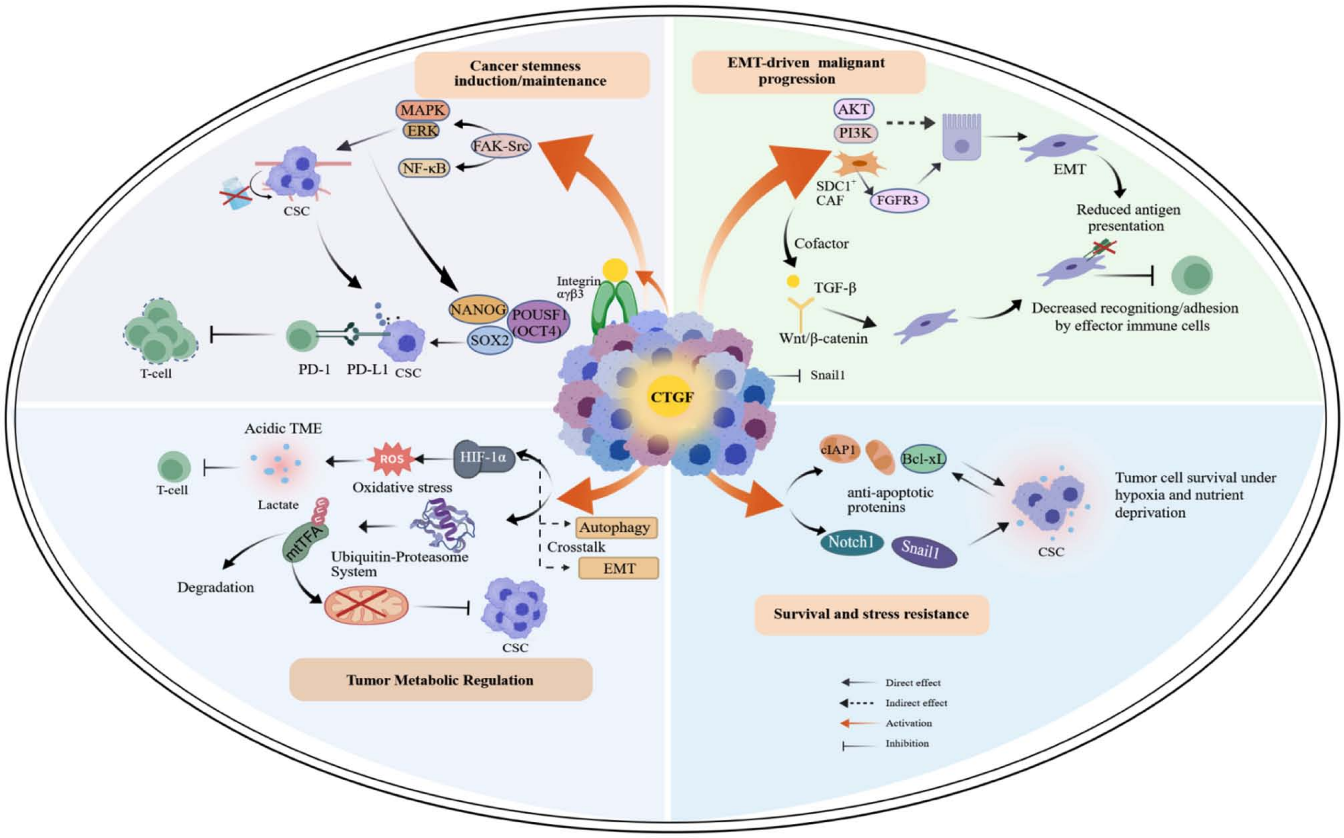

Figure 1. CTGF modulates tumor-cell phenotypes associated with CSC maintenance, EMT plasticity, metabolic reprogramming, and stress resistance, thereby contributing to an immunosuppressive TIME. CTGF regulates CSC properties through integrin αvβ3/FAK-Src-NF-κB and ERK/MAPK signaling; EMT through PI3K/AKT and CAF-derived CTGF-FGFR3 signaling; metabolism through two opposing regulatory axes: HIF-1α-driven glycolysis and mtTFA-mediated mitochondrial suppression; and cell survival through Bcl-xL, cIAP1, Notch1, and Snail1. CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; TIME, tumor immune microenvironment; ERK/MAPK, extracellular signal-regulated kinase/mitogen-activated protein kinase; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; HIF-1α, hypoxia-inducible factor-1α; mtTFA, mitochondrial transcription factor A; Notch1/Snail1, Notch homolog 1/Snail family transcriptional repressor 1; FAK, focal adhesion kinase; Src, SRC proto-oncogene, non-receptor tyrosine kinase; NF-κB, nuclear factor-κB; FGFR3, fibroblast growth factor receptor 3; OSCC, oral squamous cell carcinoma; Bcl-xL, B-cell lymphoma-extra large; cIAP1, cellular inhibitor of apoptosis protein 1; SOX2, SRY-box transcription factor 2; POUSF1, POU class 5 homeobox 1; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; CAF, cancer-associated fibroblast; SDC1, syndecan-1.

kinase (SRC)-nuclear factor-κB (NF-κB) and extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathways (14,20,21). CTGF may contribute to the upregulation of stemness-associated transcription factors, including Nanog homeobox, SRY-box transcription factor 2, and POU class 5 homeobox 1 (22), which may maintain CSC-like properties and enhance tumor invasive potential under specific microenvironmental conditions.

This mechanism is supported by functional *in vitro* pathway activation research (24). However, the extent to which CTGF directly maintains CSC stemness *in vivo* remains incompletely validated. Further clarification is needed to determine whether CTGF regulates CSC properties directly or through secondary changes in the TIME.

CTGF-driven epithelial-mesenchymal transition (EMT) mediates malignant progression of tumor cells. CTGF has been implicated in the regulation of EMT (25-27). However, most evidence is context-dependent and derived from pathway activation studies, rather than direct lineage-tracing or EMT-reversal experiments (28,29). Rather than acting as a uniformly pro-EMT factor, CTGF may modulate EMT through both tumor cell-intrinsic signaling and stromal paracrine mechanisms.

Indirect evidence suggests that CTGF may promote EMT through phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling. CTGF-mediated PI3K/AKT activation has been validated in retinal pigment epithelial cells (30). Although PI3K/AKT-dependent EMT has been widely reported, CTGF-specific causal induction of EMT across tumor types remains largely inferential (31-34). In addition, syndecan-1 $(SDC1)^+$ CAF-derived CTGF has been shown to activate fibroblast growth factor receptor 3 (FGFR3) signaling in tumor cells, thereby driving EMT progression (26). Following EMT, tumor cells have been reported to exhibit reduced antigen-presentation capacity and diminished recognition or adhesion by effector immune cells. These changes may enhance phenotypic plasticity and immune evasion potential, while altered secretory profiles may contribute to TIME remodeling (35).

Notably, emerging evidence indicates that CTGF may exert context-dependent or even opposing roles in EMT regulation. In epithelial ovarian cancer cells, CTGF expression was enriched in epithelial-like cells but was reduced or undetectable

in mesenchymal-like cells. CTGF knockout induced early EMT-associated changes, including Snail upregulation, cytoskeletal reorganization, ECM remodeling, increased cell stiffness, anoikis resistance, and enhanced invasiveness, while Twist1 remained inactive, suggesting a partial or intermediate epithelial-mesenchymal state rather than complete EMT transition (28). Consistently, recombinant CTGF partially reversed several CTGF-loss-associated phenotypes, supporting the notion that CTGF is required, at least in part, for maintaining epithelial architecture and restraining early mesenchymal transformation in this context (28). Therefore, CTGF may function as either a pro-EMT mediator or an epithelial phenotype maintainer depending on tumor type, cellular state, stromal context, and upstream signaling background. These divergent findings indicate that CTGF-related EMT regulation remains incompletely defined across malignancies. Such bidirectional and context-specific regulatory behavior may even lead to opposing phenotypes within the same tumor entity. To better illustrate the heterogeneity of CTGF functions across tumor types, key tumor-specific mechanisms covered in the present review are summarized in Table I.

CTGF-mediated metabolic reprogramming of tumor cells. CTGF contributes to oxidative stress and hypoxia-inducible factor-1α (HIF-1α) expression, thereby supporting a shift toward glycolysis-dominant (Warburg-like) metabolic reprogramming (18,36). Lactate accumulation resulting from this process contributes to an acidic TME and impaired immune-cell function (33)

Notably, CTGF may also suppress tumor metabolism in specific contexts. In oral squamous cell carcinoma (OSCC), CTGF was shown to decrease the extracellular acidification rate, oxygen consumption rate, ATP production and mitochondrial DNA copy number, and was demonstrated to promote ubiquitin-proteasome-mediated degradation of mitochondrial transcription factor A (mtTFA). Restoration of mtTFA rescued CTGF-suppressed glycolysis, oxidative phosphorylation, migration, and invasion. These findings suggest that CTGF may inhibit OSCC progression by disrupting mtTFA-dependent metabolic activity rather than promoting Warburg-like reprogramming (37).

Therefore, CTGF may exert context-dependent bidirectional effects on tumor metabolism. Its role depends not only on tumor type and microenvironmental context but also on whether CTGF preferentially activates HIF-1α-driven glycolytic programs or suppresses mitochondrial biogenesis via mtTFA degradation. The metabolic consequences of CTGF signaling, therefore, require tumor-type-specific validation. This bidirectional metabolic regulation further highlights the context-dependent activity of CTGF. Representative tumor-specific regulatory mechanisms covered in the present review are summarized in Table I.

CTGF-mediated enhancement of tumor cell survival and stress resistance. In the process of shaping the TIME, CTGF may contribute to tumor cell survival and stress resistance under adverse microenvironmental conditions. It contributes to the tumor cell survival by upregulating Bcl-xL and cellular inhibitor of apoptosis protein 1 (38), and by activating pro-survival signaling pathways such as Notch1 and Snail1. These pathways collectively enhance tumor-cell fitness under stress conditions, including hypoxia and nutrient deprivation (39,40). This CTGF-associated survival advantage may enable subsets of tumor cells to persist under hostile microenvironment conditions. Consequently, it may help sustain the immunosuppressive state of the TIME and contribute to tumor progression.

3. CTGF modulates ECM remodeling

ECM remodeling is a dynamic process that is characterized by alterations in the content, activity, assembly, and cross-linking of ECM components, which in turn induce changes in cellular signaling transduction (41). In tumors, this process is primarily manifested as ECM stiffening, CAF activation, and vascular abnormalities. CTGF is associated with and contributes to these processes. Collectively, CTGF may participate in the establishment of physical and mechanical barriers that sustain the TIME (8,40,42) (Fig. 2).

CTGF-mediated enhancement of extracellular matrix stiffening. ECM stiffening is predominantly driven by the excessive deposition and aberrant cross-linking of fibrous proteins such as collagen. CTGF promotes collagen deposition or cross-linking, thereby remodeling ECM architecture and increasing tissue stiffness, which provides structural support for tumor progression (43); furthermore, elevated CTGF expression is associated with, and in selected models contributes to, matrix metalloproteinase (MMP) induction. This process enables localized ECM degradation and may generate permissive tracks for tumor cell migration and invasion (44-46).

The interplay between collagen accumulation and matrix degradation creates a heterogeneous ECM landscape that facilitates tumor invasion. Increased ECM stiffness can also function as a physical barrier that restricts effector immune-cell infiltration, particularly $CD8^+$ T cells, into the tumor core. This represents a mechanobiological mode of immune suppression that is partially independent of canonical cytokine signaling (43,47). However, whether CTGF-driven ECM stiffening directly impairs immune-cell penetration in specific tumor contexts remains to be fully validated.

CTGF-mediated enhancement of CAF activation. CAFs are key effector cells that drive ECM remodeling and shape the TIME. CTGF contributes to CAF activation and ECM remodeling, thereby promoting the formation of dense matrix networks and reinforcing physical barriers within the TIME (9). This conclusion is supported by functional knockdown experiments in selected tumor models and correlative clinical observations (8,26). Current evidence supports this effect based on a combination of functional knockdown studies and correlative analyses (8,26,48). However, CTGF alone is unlikely to be sufficient to define lineage commitment or full functional reprogramming.

Activated CAFs can further secrete immunosuppressive mediators that impair $CD4^+$ and $CD8^+$ T-cell function, thereby attenuating antitumor immune responses at the cellular level (49). In gastric cancer, tumor cell-derived TGF-β1 was found to induce CTGF expression in CAFs

Table I. Context-dependent regulatory roles and molecular mechanisms of CTGF across distinct tumor types.

Tumor type	Core mechanism and signaling axis	Regulated biological functions	Evidence type and experimental design	(Refs.)
Epithelioid hemangioendothelioma	CTGF acts as an oncogenic transcriptional target of TAZ-CAMTA1, directly binds tointegrin αIIbβ3, and activates the Ras-MAPK signaling cascade	Maintains anchorage-independent proliferation, mediates cell malignant transformation and tumorigenic phenotype	*In vitro* molecular and cellular functional assays (gene knockdown, pathway activity detection, and drug inhibition assay)	(81)
Breast cancer (including triple-negative subtype)	i) TNBC: Extracellular CTGF binds to integrin αvβ3, activates the FAK/Src/ NFκB p65-Glut3 axis; ii) luminal subtype: CTGF activates the integrin αvβ3-ERK1/2 pathway, upregulates S100A4, Bcl-xL and cIAP1; and iii) stromal regulation: Cav1 deficiency activates the TGF-β pathway, upregulates CTGF, induces HIF-1α-dependent metabolic reprogramming.	i) Promotes TNBC cell proliferation, migration, invasion, adhesion and glycolytic metabolic reprogramming; ii) enhances breast cancer cell motility, induces EMT and chemoresistance to doxorubicin/ paclitaxel; and iii) drives CAF autophagy, glycolysis and senescence, metabolically promoting tumor growth	Clinical sample prognostic correlation analysis, *in vivo* tumorigenesis assay, *in vitro* cell functional assay, neutralizing antibody experiment, and gene overexpression/knockdown validation	(18,24, 36,38)
Colorectal cancer	CSF1R inhibitor activates the PI3K/AKT pathway, and promotes CTGF release; CTGF mediates CAF activation and inhibits T-cell infiltration and function (PI3K/AKT-CTGF-CAF activation axis)	Induces immunotherapy resistance; anti-CTGF combined with CSF1R inhibitor and immune checkpoint therapy achieves complete tumor regression	Imaging mass cytometry, *in vivo* animal model, and combination therapy validation experiment	(9)
Ovarian cancer	CTGF deficiency/inhibition triggers cytoskeleton remodeling, ECM reconstruction, and drives EMT initiation (CTGF deficiency-LAMC2-FAK-PI3K-Akt-Snail-partial EMT axis)	Induces partial EMT, gains anoikis resistance, tumorigenesis and migration capacity, and promotes ovarian cancer metastasis	*In vitro* cell functional assay, cell phenotype and ECM detection, and EMT phenotype validation	(28)
Oral squamous cell carcinoma	CTGF promotes mtTFA ubiquitination and proteasomal degradation, and downregulates mitochondrial function-related indicators (CTGF-mtTFA ubiquitin-proteasome-mitochondrial function axis)	Inhibits mitochondrial metabolism, suppresses tumor cell migration and invasion; and mtTFA overexpression reverses the pro-metastatic effect of CTGF	Immunoprecipitation, proteasome inhibitor experiment, overexpression rescue experiment, and mitochondrial functional assay	(37)
Glioma/glioblastoma multiforme	i) Cell proliferation/drug resistance: CTGF upregulates anti-apoptotic proteins Bcl-xL, Survivin, and Flip, and activates multiple oncogenic pathways; ii) immune regulation: GBM cell-derived EVs secrete hsa-miR-27a-3p, activate CTGF transcription via H3K27ac modification (hsa-miR-27a-3p/EZH1/KDM3A/CTGF axis); and iii) clinical correlation: CTGF is overexpressed in a MES-like glioma subpopulation, associated with SPP1-CD44 pathway activation	i) Promotes glioma cell proliferation, migration, *in vivo* tumor formation and temozolomide resistance; ii) induces M2 polarization of TAMs, constructs immunosuppressive TIME; and iii) associated with poor clinical prognosis and high-risk glioma subtypes	*In vitro* cell functional assay, *in vivo* nude mouse tumorigenesis assay, molecular interaction validation, multi-omics analysis, and clinical sample correlation analysis	(6,7, 39)
HCC	i) Metastasis regulation: CAF-derived EVs secrete CTGF, and CTGF activates the Notch1/Snail1 signaling pathway; ii) immune regulation: Mesenchymal-like HCC cells secrete CTGF, induce M2-TAM polarization, and form a	i) Promotes HCC cell proliferation, invasion and metastasis; ii) induces M2 polarization of TAMs, and constructs an immunosuppressive TIME; and	*In vitro* cell functional assay, clinical sample correlation analysis, *in vivo* xenograft model, and neutralizing antibody blocking experiment	(40,53, 76)

Table I. Continued.

Tumor type	Core mechanism and signaling axis	Regulated biological functions	Evidence type and experimental design	(Refs.)
	CTGF-M2-TAM-CCL18 positive feedback loop; and iii) stromal activation: HCC cell-derived CTGF activates HSCs, and forms an IL-6/STAT3 positive feedback loop	iii) activates HSCs, promotes liver fibrosis and HCC progression		
Osteosarcoma	i) Angiogenesis: CTGF activates the PLC/PKCδ pathway, upregulates Angpt2, and negatively regulates miR-543 (CTGF-PLC/PKCδ-Angpt2/miR-543 axis); and ii) metastasis: CTGF activates MEK/ERK pathway, downregulates miR-519d, upregulates MMP2/3 (CTGF-MEK/ERK-miR-519d-MMP2/3 axis)	i) Promotes tumor angiogenesis; and ii) enhances cell migration, invasion and *in vivo* lung metastasis; and CTGF expression is correlated with patient clinical stage and tumor metastasis	*In vivo*/*in vitro* angiogenesis assay, *in vitro* cell functional assay, *in vivo* lung metastasis model, and clinical sample correlation analysis	(42,44)
GC	i) Stromal CTGF induction: GC cell-derived TGF-β1 activates SRC kinase in CAFs, induces CTGF transcription via the ERK/Smad2/3 pathway GC-derived (TGF-β1 → SRC in CAFs → ERK/Smad2/3 → CTGF transcription axis); and ii) EMT induction: CAF-secreted CTGF acts on GC cells, inhibits epithelial markers E-cadherin/ZO-1, and disrupts intercellular adhesion	i) Induces CTGF secretion by CAFs, provides paracrine signals for GC cell EMT and migration; and ii) promotes GC cell EMT progression, and enhances migration and invasion capacities	Pathway inhibitor experiment, CAF-GC co-culture experiment, CTGF targeting inhibition experiment, and EMT marker detection	(8)
Pancreatic cancer (including colon/ bladder cancer subtype analysis)	i) Colon/pancreatic/bladder cancer: Transcription factor KLF6 activates CTGF expression in SDC1$^+$ CAFs, paracrine CTGF binds to FGFR3 receptor, and induces EMT (SDC1$^+$ CAF-KLF6-CTGF-FGFR3-EMT axis); and ii) pancreatic fibrosis: CTGF binds to α5β1 integrin on PSCs, activates the NF-κB pathway, induces pro-inflammatory cytokines IL-1β/IL-6, promotes PSC proliferation and collagen synthesis (CTGF-α5β1 integrin-NF-κB-IL-6/IL-1β axis)	i) Promotes tumor EMT, invasion and lymphatic metastasis, and associated with poor tumor prognosis; and ii) induces PSC activation, proliferation and collagen synthesis, mediates pancreatic fibrosis and chronic inflammation, indirectly promotes pancreatic cancer progression	Clinical sample correlation analysis, *in vivo* lymphatic metastasis model, *in vitro* cell functional assay, siRNA knockdown experiment, qPCR, and ChIP	(26,75)

CTGF, connective tissue growth factor; TAZ-CAMTA1, transcriptional coactivator with pdz-binding motif-calmodulin-binding transcription activator 1; αIIbβ3, integrin α IIb β3; Ras-MAPK, rat sarcoma viral oncogene homolog-mitogen-activated protein kinase; TNBC, triple-negative breast cancer; αvβ3, integrin α v β3; FAK/Src/NFκB p65-Glut3, focal adhesion kinase/SRC proto-oncogene, non-receptor tyrosine kinase/nuclear factor-κB/glucose transporter 3; ERK1/2, extracellular signal-regulated kinase 1/2; S100A4, s100 calcium-binding protein a4; Bcl-xL, B-cell lymphoma-extra large; cIAP1, cellular inhibitor of apoptosis protein 1; Cav1, caveolin-1; TGF-β, transforming growth factor-β; HIF-1α, hypoxia-inducible factor 1α; EMT, epithelial-mesenchymal transition; CAF, cancer-associated fibroblast; CSF1R, colony-stimulating factor 1 receptor; PI3K/AKT, phosphoinositide 3-kinase/protein kinase b; LAMC2, laminin subunit γ2; Snail, snail family transcriptional repressor; ECM, extracellular matrix; mtTFA, mitochondrial transcription factor a; GBM, glioblastoma multiforme; Flip, flice-like inhibitory protein; EVs, extracellular vesicles; hsa-miR-27a-3p, homo sapiens microRNA-27a-3p; H3K27ac, histone h3 lysine 27 acetylation; EZH1, enhancer of zeste homolog 1; KDM3A, lysine demethylase 3a; MES-like, mesenchymal-like; SPP1-CD44, secreted phosphoprotein 1-cluster of differentiation 44; HCC, hepatocellular carcinoma; Notch1/Snail1, notch receptor 1/snail family transcriptional repressor 1; TAM, tumor-associated macrophage; CCL18, C-C motif chemokine ligand 18; HSCs, hepatic stellate cells; IL-6/STAT3, interleukin 6/signal transducer and activator of transcription 3; PLC/PKCδ, phospholipase c/protein kinase Cδ; Angpt2, angiopoietin 2; miR-543, microRNA-543; MEK/ERK, mitogen-activated protein kinase kinase/extracellular signal-regulated kinase; miR-519d, microRNA-519d; MMP2/3, matrix metalloproteinases 2 and 3; GC, gastric cancer; TGF-β1, transforming growth factor β1; SRC, src proto-oncogene, non-receptor tyrosine kinase; Smad2/3, mothers against decapentaplegic homologs 2 and 3; ZO-1, zonula occludens-1; KLF6, krüppel-like factor 6; SDC1□, syndecan-1-positive; FGFR3, fibroblast growth factor receptor 3; α5β1, integrin α5β1; PSCs, pancreatic stellate cells; siRNA, small interfering PNA; qPCR, quantitative polymerase chain reaction; ChIP, chromatin immunoprecipitation.

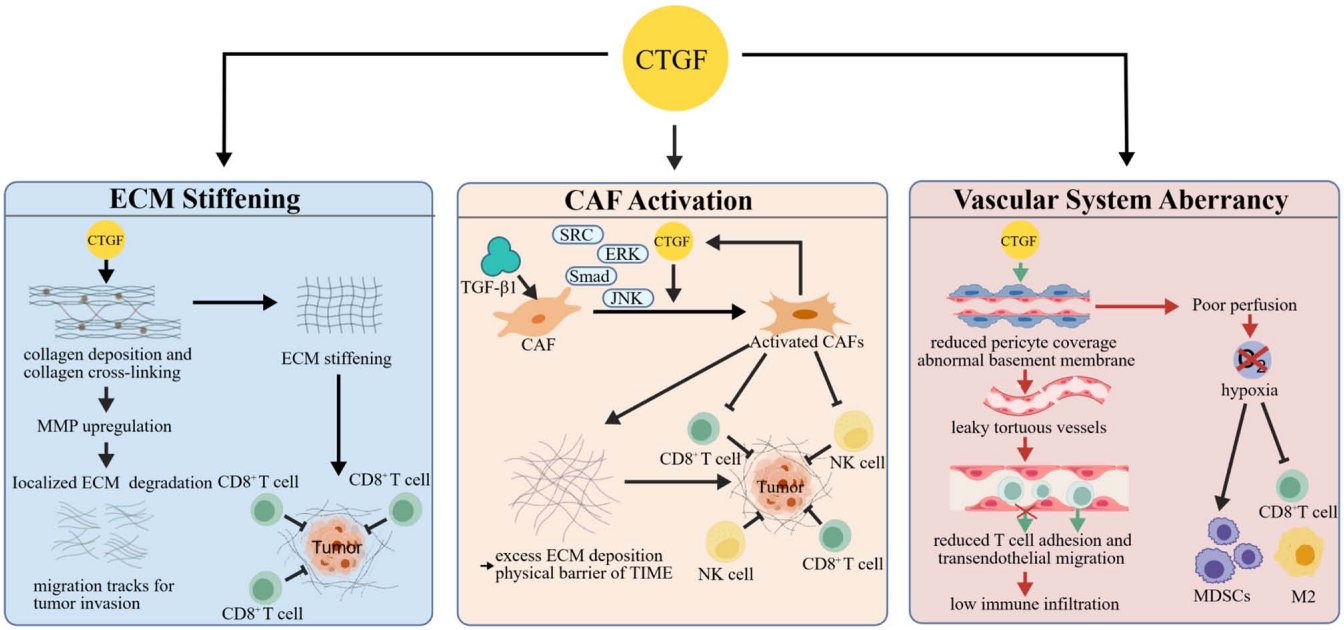

Figure 2. CTGF modulates ECM remodeling to establish physical and mechanical barriers in the tumor microenvironment. CTGF may promote ECM stiffening through collagen deposition, cross-linking, and MMP induction; activate CAFs through tumor-derived TGF-β1/SRC-dependent ERK/Smad/JNK signaling; and impair vascular integrity through reduced pericyte coverage and abnormal basement membrane formation. CTGF, connective tissue growth factor; ECM, extracellular matrix; MMP, matrix metalloproteinase; CAFs, cancer-associated fibroblasts; TGF-β1, transforming growth factor-β1; SRC, SRC proto-oncogene, non-receptor tyrosine kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; Smad, mothers against decapentaplegic; TIME, tumor immune microenvironment; NK, natural killer; MDSCs, myeloid-derived suppressor cells.

through SRC-dependent ERK/Smad/JNK signaling pathways. CTGF targeting has been shown to reduce CAF-mediated tumor cell migration and invasion in this context (8). Notably, a conserved SDC1$^+$ CAF subset associated with advanced tumor stage and poor prognosis drives tumor cell EMT, invasion, and lymphatic metastasis via Krüppel-like factor 6-regulated CTGF secretion and activation of tumor FGFR3 signaling, highlighting that CTGF and FGFR3 may serve as actionable stromal targets with anti-metastatic therapeutic implications across multiple malignancies (26).

Furthermore, an anti-CTGF/programmed cell death protein 1 (PD-1) bispecific antibody Y126S was shown to mediate suppression of CAF activation, reduction of collagen deposition, and downregulation of PD-L1 expression on CAFs by targeting CTGF in a pancreatic cancer model. This dual targeting strategy was found to enhance CD8$^+$ T-cell-mediated antitumor immunity and to improve the efficacy of PD-1 blockade (48). However, the functional heterogeneity of CTGF across CAF subsets remains incompletely characterized.

CTGF-mediated vascular system aberrancy. The vascular system is a highly organized tubular network responsible for oxygen and nutrient delivery and metabolic waste removal. As a functional unit embedded within the ECM, its structure and function are directly regulated by the physicochemical properties of the ECM. Accordingly, vascular abnormalities represent a key feature and functional consequence of ECM remodeling in tumors. As a critical factor involved in vascular homeostasis, dysregulated CTGF signaling is associated with reduced pericyte coverage and abnormal basement membrane formation, as shown in vascular modeling systems and tumor-associated vascular analyses. These alterations contribute to vascular destabilization and structural disorganization (50).

CTGF-associated vascular dysfunction may impair effector T-cell adhesion and transendothelial migration, resulting in reduced immune-cell infiltration into tumor tissues (51). In addition, CTGF-associated vascular abnormalities may compromise tissue perfusion, promote hypoxia, suppress T-cell cytotoxic function, and facilitate the recruitment of immunosuppressive cell populations. Collectively, these effects further reinforce the immunosuppressive and immune-excluded state of the TIME.

4. CTGF orchestrates immune cell remodeling

In the TIME, the functional state of immune cells is a key determinant of antitumor immune efficacy (52). As an important signaling molecule, CTGF may directly or indirectly modulate multiple immune cell populations and may promote their polarization toward pro-tumor phenotypes, thereby contributing to the establishment of a tumor-promoting TIME (Fig. 3).

Tumor-associated macrophages (TAMs). TAMs are broadly classified into M1 and M2 subsets, which exert antitumor and pro-tumor activities, respectively. CTGF may contribute to pro-tumorigenic M2 polarization in solid tumors. Correlative findings from clinical and omics analysis indicate that high CTGF expression is associated with increased infiltration of M2-type TAMs (6). In addition, functional research suggests that CTGF contributes to macrophage polarization signaling via the hsa-miR-27a-3p/enhancer of zeste homolog 1 (EZH1)/lysine demethylase 3A (KDM3A) axis (7). However, direct *in vivo*

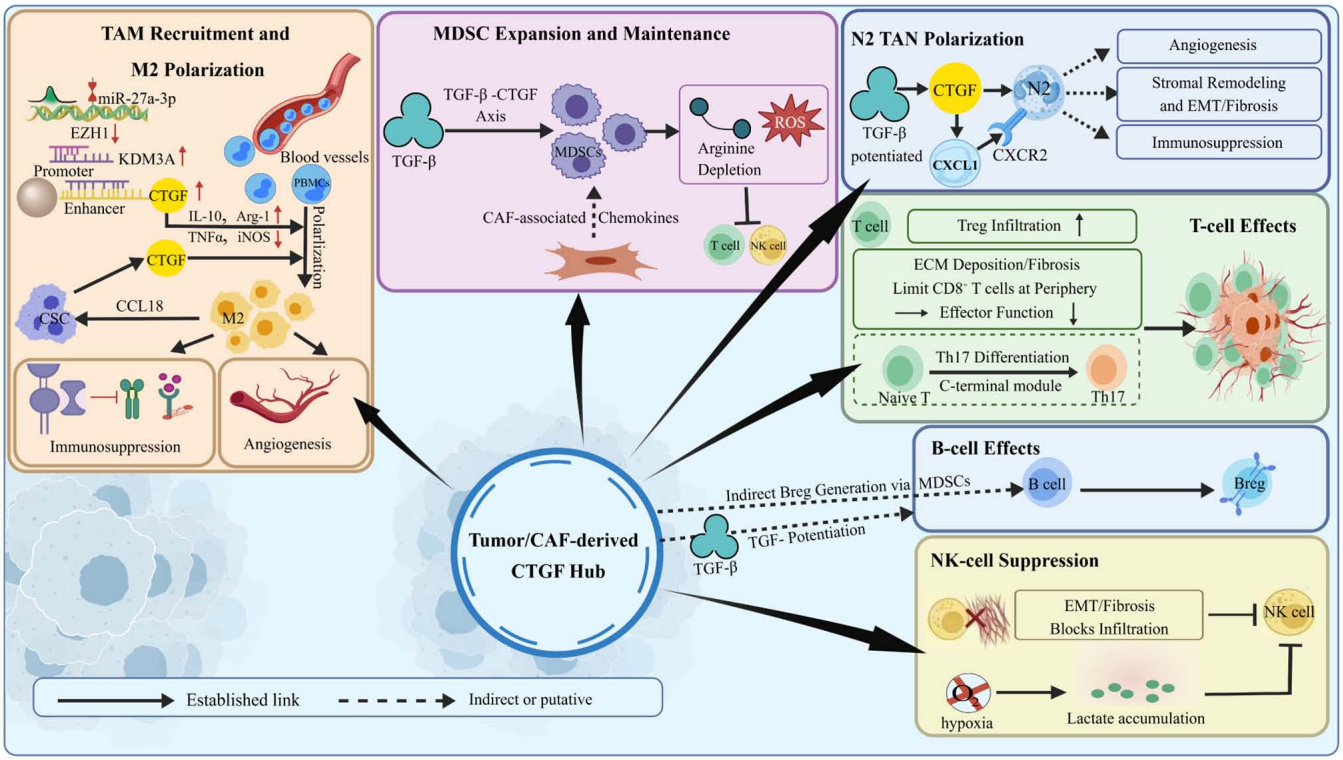

Figure 3. CTGF promotes M2-type TAM polarization via the miR-27a-3p/EZH1/KDM3A axis and forms a CTGF-M2 TAM-CCL18 positive feedback loop; potentiates TGF-β-dependent MDSC expansion, with MDSCs suppressing T and NK cell function through arginine depletion and ROS accumulation; amplifies TGF-β-induced N2 TAN polarization via upregulating CXCL1-CXCR2 chemokine signaling to mediate angiogenesis, stromal fibrosis and immune suppression; remodels T-cell responses by driving C-terminal module-dependent Th17 differentiation, boosting Treg infiltration, and restricting $CD8^+$ T-cell effector function via ECM physical barriers; indirectly induces Breg generation through MDSC intermediates; and inhibits NK cell antitumor activity via dual mechanisms: ECM/EMT-mediated infiltration blockage and hypoxia-lactate metabolic dysfunction. Solid lines represent established regulatory links; dashed lines represent indirect or putative regulatory axes. CTGF, connective tissue growth factor; TAM, tumor-associated macrophage; miR-, microRNA; EZH1, enhancer of zeste homolog 1; KDM3A, lysine demethylase 3A; CCL18, C-C motif chemokine ligand 18; TGF-β, transforming growth factor-β; MDSC, myeloid-derived suppressor cell; NK, natural killer; ROS, reactive oxygen species; TAN, tumor-associated neutrophil; CXCL1, C-X-C motif chemokine ligand 1; CXCR2, C-X-C motif chemokine receptor 2; Th17, T helper 17 cell; Treg, regulatory T cell; ECM, extracellular matrix; Breg, regulatory B cell; IL-10, interleukin 10; Arg-1, Arginase-1; TNF-α, tumor necrosis factor-α; iNOS, inducible nitric oxide synthase; PBMCs, peripheral blood mononuclear cells; CAF, cancer-associated fibroblast.

causal validation across tumor types remains limited. In hepatocellular carcinoma (HCC), experimental evidence demonstrates that CTGF derived from mesenchymal-like tumor cells promotes M2 macrophage polarization. These M2-like TAMs further enhance tumor progression by secreting C-C motif chemokine ligand 18 (CCL18), forming a CTGF-M2 TAM-CCL18 positive feedback loop (53). Whether this regulatory axis is broadly conserved across solid tumors remains unclear.

Myeloid-derived suppressor cells (MDSCs). MDSCs, as key immunosuppressive cells, inhibit the functions of T cells and natural killer (NK) cells by depleting arginine and generating reactive oxygen species (ROS), thereby mediating tumor immune evasion (54,55). As a critical downstream molecule of the TGF-β signaling pathway, CTGF may potentiate TGF-β-driven MDSC expansion and functional maintenance (14,56). However, this mechanism is mainly supported by pathway-level evidence and indirect inference rather than direct CTGF-MDSC functional or depletion studies. High CTGF expression is associated with increased secretion of MDSC-recruiting chemokines derived from CAFs and with MDSC accumulation in the TIME (57), suggesting a correlative link between CTGF-enriched stromal environments and MDSC infiltration rather than a fully established causal relationship. Current evidence is largely limited to correlative findings, and it remains unclear whether MDSCs and $CTGF^+$ CAFs are spatially and functionally coupled within the TIME. The subtype-specific regulatory effects of CTGF on polymorphonuclear MDSCs and monocytic MDSCs, including their proliferation, apoptosis, metabolic programs, and suppressive effector molecule expression, remain largely undefined.

Tumor-associated neutrophils (TANs). TANs predominantly exhibit the pro-tumor N2-like phenotype in the TME, contributing to angiogenesis, stromal remodeling, and immunosuppression (58). CTGF may contribute to the establishment of a pro-tumor TAN niche by reinforcing TGF-β-associated stromal remodeling and neutrophil-recruiting inflammatory programs. However, current evidence remains largely indirect, based on TGF-β-dependent TAN polarization models and CTGF-associated stromal signatures, rather than direct experimental validation of CTGF in TAN lineage commitment. TGF-β is a key regulator of TAN functional polarization, promoting pro-tumor N2-like pro-tumor phenotypes, whereas TGF-β blockade can reprogram TANs toward an antitumor N1-like state (59,60). As a downstream effector and functional amplifier of TGF-β signaling, CTGF contributes

to CAF activation, collagen deposition, ECM remodeling, and tissue fibrosis (14). These stromal alterations may collectively facilitate the recruitment and functional polarization of N2-like TANs, which are associated with angiogenesis, matrix remodeling, chronic inflammation, immune suppression, and tumor progression (61).

In addition to stromal remodeling, CTGF may regulate TAN infiltration through chemokine-mediated neutrophil recruitment. TAN trafficking is largely controlled by neutrophil-attracting C-X-C motif chemokine receptor (CXCR)2 ligands, including C-X-C motif chemokine ligand (CXCL)1, CXCL2, CXCL5, and CXCL8/IL-8 (61). Evidence from inflammatory stromal models suggests that CTGF contributes to CXCL1 induction, indicating that CTGF-rich stromal environments may enhance neutrophil recruitment and sustain a pro-tumor TAN-enriched niche (62). Collectively, CTGF may contribute to tumor progression by a TGF-β/ECM-chemokine axis that supports TAN recruitment, N2 polarization, angiogenesis, matrix remodeling, and immunosuppression.

T cells. Research in chronic inflammatory disorders, such as kidney disease, have demonstrated that CTGF and its C-terminal module mediate human $CD4^+$ T-cell polarization by driving the differentiation of proinflammatory Th17 polarization and local inflammatory responses (63). Although this mechanism was characterized in non-neoplastic inflammatory settings, given that the tumor microenvironment, such as in pancreatic cancer, shares key features with chronic inflammatory tissues, including persistent protease activity that drives ECM remodeling and tumor progression (64), it is plausible that the proinflammatory effects of CTGF fragments observed in inflammatory contexts may also contribute to shaping the T-cell landscape in cancer. In addition, CTGF contributes to CAF activation and ECM deposition, which may physically restrict infiltration of $CD8^+$ T cells into tumor cores and impair effector function (9). CTGF expression was also shown to be positively correlated with regulatory T-cell infiltration in the TIME (6). These findings suggest that CTGF may promote immunosuppressive T-cell polarization while simultaneously limiting effector T-cell infiltration and activity through stromal remodeling. However, the precise molecular mechanisms underlying CTGF-induced T-cell dysfunction remain incompletely understood. Its potential role in regulating T-cell exhaustion, metabolic reprogramming, and spatial distribution within tumors remains to be elucidated.

B cells. B cells exert dual functions in the tumor immune microenvironment, exerting both antitumor effects and immunosuppressive functions through differentiation into regulatory B cells (Bregs) (65,66). Direct evidence for CTGF-mediated regulation of B cells remains limited. However, studies in hematologic malignancies have indicated that high CTGF expression is associated with poor prognosis in precursor B-cell leukemia (67,68). In solid tumors, CTGF-associated fibrotic and inflammatory microenvironments may promote the accumulation of MDSCs and other immunosuppressive cell populations, and MDSCs may contribute to Breg generation (69). This suggests that CTGF may indirectly regulate B-cell immunosuppressive programs through an MDSC-dependent axis.

NK cells. NK cells represent the first-line effector population in antitumor immunity (70). CTGF may suppress NK-cell function primarily through indirect mechanisms. Structurally, CTGF-driven EMT and ECM remodeling may restrict NK-cell infiltration into the tumor parenchyma. Metabolically, CTGF-mediated hypoxia and lactic acid accumulation may further impair NK-cell effector functions (36,71).

5. CTGF shapes cytokine network remodeling

The immunosuppressive state of the TIME is closely associated with aberrations in the cytokine signaling network. By regulating multiple key cytokines, CTGF may reshape the cytokine landscape and thereby contribute to the establishment and maintenance of the TIME (Fig. 4).

CTGF-mediated regulation of direct cytokines. Direct cytokines within the TIME mainly include TGF-β, VEGF, IL-6, IL-35, IL-1β, IL-12, TNF-α, and interferon (IFN)-γ. In tumors characterized by prominent fibrosis, such as breast cancer, CTGF and TGF-β are frequently co-localized and highly expressed (12). This co-activation can synergistically amplify profibrotic signaling, promoting CAF activation and ECM deposition (8,14), enhancing MDSC expansion and functional maintenance (14), and increasing oxidative stress (36,69,72). Accordingly, CTGF may function as a downstream effector or transcriptional target of TGF-β signaling in fibrotic and metabolically stressed tumor contexts (14,18,36,56). In these settings, CTGF can further amplify TGF-β-driven stromal and immunosuppressive programs by reinforcing CAF activation, ECM deposition, and MDSC accumulation (8,14,56). However, CTGF may also act as a relatively independent paracrine regulator when produced by specific stromal or tumor-cell subsets, such as $SDC1^+$ CAFs or mesenchymal-like HCC cells (31,53). This may contribute to spatial segregation between tumor cells and immune effector cells, thereby impairing immune-cell function and promoting tumor progression (73).

In acute myeloid leukemia, CTGF was shown to mediate enhanced tumor angiogenic capacity through the CTGF-VEGFA axis. This axis promotes aberrant angiogenesis and suppresses endothelial adhesion molecule expression, thereby restricting T-cell adhesion and infiltration. Collectively, these effects further consolidate an immunosuppressive TIME and support tumor progression and metastasis (74). CTGF activates and upregulates the expression of IL-1β and IL-6 by activating the NF-κB signaling pathway, thereby triggering STAT3 activation, exacerbating local inflammation (10,75), and driving inflammation-cancer transformation (76). In addition, the miR-27a-3p/EZH1/KDM3A/CTGF axis was also shown to contribute to TNF-α downregulation *in vivo* (7). Reduced TNF-α may facilitate M2 macrophage polarization, weaken antitumor immunity, and ultimately promote tumor progression (7). However, most evidence is derived from pathway activation studies (7,10,74,75) rather than direct cytokine perturbation experiments that isolate CTGF as a primary upstream regulator. Therefore, the cytokine regulatory network governed by CTGF remains to be further validated in tumor-specific experimental models.

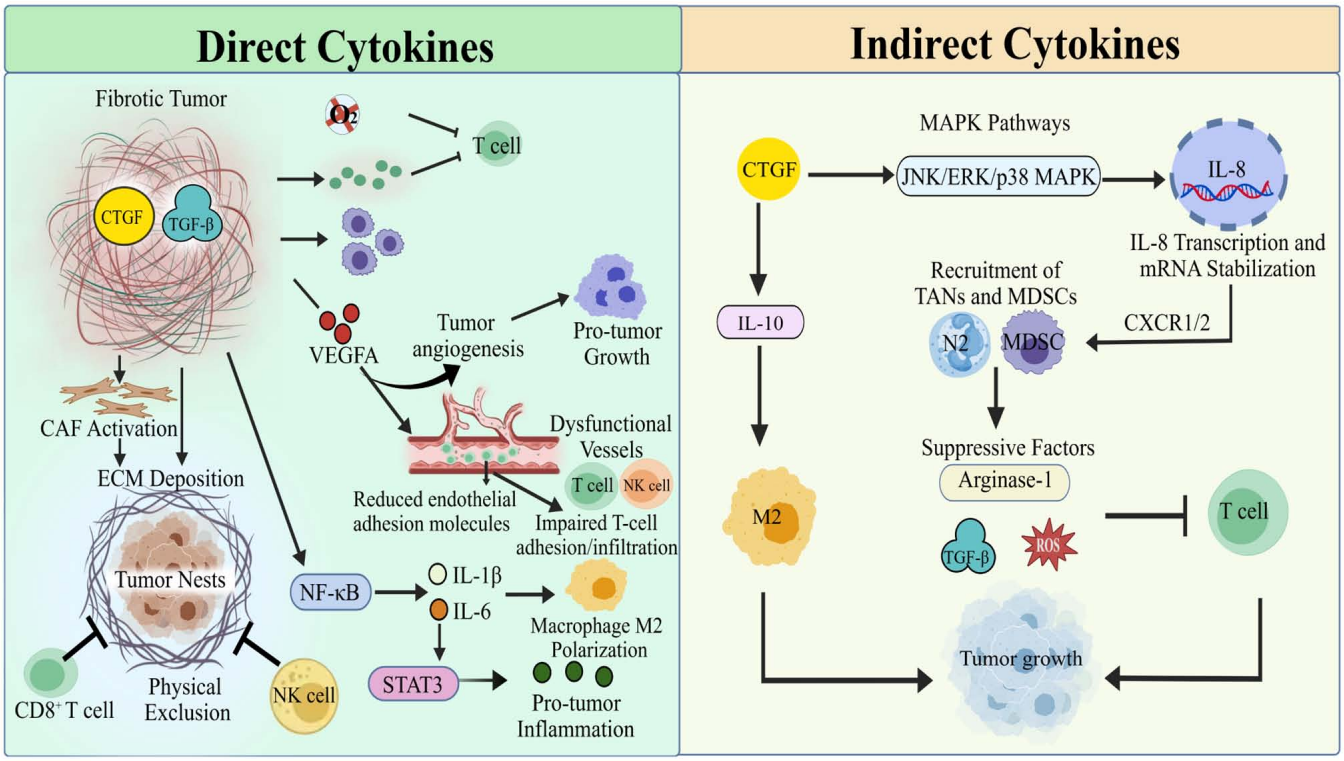

Figure 4. CTGF remodels the TIME cytokine network via two distinct regulatory branches: Direct cytokine modulation and indirect chemokine/cytokine cascades. In fibrotic tumors, CTGF synergizes with TGF-β to drive CAF activation, ECM deposition and physical immune exclusion of $CD8^+$ T cells and NK cells; CTGF upregulates VEGFA to induce dysfunctional angiogenesis and limit T-cell endothelial adhesion and infiltration; CTGF activates NF-κB/STAT3 signaling to induce IL-1β and IL-6, promoting M2 macrophage polarization and pro-tumor inflammation; hypoxic oxidative stress further suppresses effector T-cell function within fibrotic tumor nests. For indirect cytokine signaling, CTGF activates JNK/ERK/p38 MAPK pathways to induce IL-8 transcription and mRNA stabilization, recruiting TANs and MDSCs via CXCR1/2; CTGF also upregulates IL-10 to foster M2 TAM polarization. Myeloid populations recruited by IL-8 secrete arginase-1, ROS and TGF-β to suppress $CD8^+$ T cell antitumor function, forming a self-amplifying immunosuppressive loop that accelerates tumor progression. CTGF, connective tissue growth factor; TIME, tumor immune microenvironment; TGF-β, transforming growth factor-β; CAF, cancer-associated fibroblast; ECM, extracellular matrix; NK, natural killer; VEGFA, vascular endothelial growth factor A; NF-κB, nuclear factor-κB; STAT3, signal transducer and activator of transcription 3; IL, interleukin; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; TANs, tumor-associated neutrophils; MDSCs, myeloid-derived suppressor cells; CXCR1/2, C-X-C motif chemokine receptor 1/2; TAM, tumor-associated macrophage; ROS, reactive oxygen species.

CTGF-mediated regulation of indirect cytokines. Indirect cytokines in the TIME mainly include IL-8 (CXCL8), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-10, and IL-4. As a key chemokine, IL-8 has been shown to promote the recruitment of TANs and MDSCs to tumor sites via the CXCR1/2 axis, and was revealed to be closely associated with angiogenesis and the amplification of local inflammation (77,78). These myeloid populations produce immunosuppressive mediators, including arginase-1, ROS, and TGF-β, within the TIME. This suppresses $CD8^+$ T cells, driving the transition of inflammatory signals to an immunosuppressive phenotype, and facilitating the establishment and maintenance of the TIME (79,80). CTGF can induce IL-8 expression by activating the JNK, ERK, and p38 MAPK signaling pathways and by enhancing IL-8 mRNA stability (11). These findings support the existence of a CTGF-IL-8-myeloid cell axis, which may form an inflammation-immunosuppression feedback loop within the TIME. This loop may further amplify the immunosuppressive state and contribute to the aberrant remodeling of the TIME. Beyond IL-8, emerging evidence suggests that CTGF may regulate IL-10, another key immunosuppressive cytokine in the TIME. In glioblastoma, the miR-27a-3p/EZH1/KDM3A/CTGF axis was found to contribute to IL-10 upregulation, which was associated with enhanced M2 macrophage polarization and tumor progression (7). The proposed CTGF-GM-CSF relationship remains inferential and requires direct mechanistic validation.

6. Conclusion

CTGF has emerged as a context-dependent matricellular regulator that integrates tumor cell plasticity, extracellular matrix remodeling, vascular dysfunction, and immune modulation to shape the TIME. Rather than functioning as a linear signaling effector, accumulating evidence supports CTGF as a potential structural-signaling interface that couples stromal mechanics with immune exclusion programs, thereby contributing to spatially constrained antitumor immunity.

Across tumor contexts, CTGF is implicated in ECM remodeling, CAF activation, vascular abnormality, and myeloid- and lymphoid-cell reprogramming, collectively converging on an immunosuppressive and immune-excluded niche. Notably, these effects appear highly context-dependent, with CTGF exerting divergent or even opposing roles depending on tumor type, cellular source, and microenvironmental state, underscoring its non-canonical and non-linear

biology. Representative tumor-specific regulatory mechanisms summarized throughout this review are compiled in Table I for cross-cancer comparison.

Functionally, CTGF-associated stromal and cytokine networks may reinforce resistance to immune checkpoint blockade by promoting physical immune barriers and sustaining immunosuppressive feedback loops involving key inflammatory and fibrotic mediators. This positions CTGF as a potential complementary axis to classical immune checkpoints in the regulation of therapeutic response.

However, most current evidence remains correlative or derived from pathway-level inference, and definitive causal validation of CTGF as a central driver of immune exclusion across tumor types is still lacking. In particular, its context-specific role in defining immune cell spatial organization and functional states requires rigorous *in vivo* and spatially resolved experimental confirmation.

From a translational perspective, CTGF represents a promising candidate for combined stromal-immune targeting strategies aimed at remodeling the tumor microenvironment rather than inhibiting single signaling nodes. Future efforts integrating spatial profiling, functional perturbation, and clinical validation will be essential to determine whether CTGF-directed interventions can effectively convert immune-excluded tumors into immune-permissive states and enhance responsiveness to immunotherapy.

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Authors' contributions

YZ conceived the review framework, collected and organized literature extensively, and drafted the full manuscript as the primary writer. LH conceptualized figures, designed and constructed key mechanism diagrams (Figs. 1 and 2) for the review, and optimized the visual presentation of core research mechanisms. QW assisted in the visualization of research findings, refined the drawing details of the review mechanism diagrams (Figs. 3 and 4), and ensured the accuracy of graphical data expression. HL and FD supervised the overall research and writing process, provided in-depth academic guidance for the manuscript structure and content, revised the manuscript critically for important intellectual content, and finalized the final version of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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