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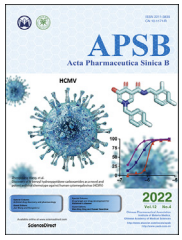

REVIEW

Multifunctional regulatory protein connective tissue growth factor (CTGF): A potential therapeutic target for diverse diseases

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Abstract Connective tissue growth factor (CTGF), a multifunctional protein of the CCN family, regulates cell proliferation, differentiation, adhesion, and a variety of other biological processes. It is involved in the disease-related pathways such as the Hippo pathway, p53 and nuclear factor kappa-B (NF-κB) pathways and thus contributes to the developments of inflammation, fibrosis, cancer and other diseases as a downstream effector. Therefore, CTGF might be a potential therapeutic target for treating various diseases. In recent years, the research on the potential of CTGF in the treatment of diseases has also been paid more attention. Several drugs targeting CTGF (monoclonal antibodies FG3149 and FG3019) are being assessed by clinical or preclinical trials and have shown promising outcomes. In this review, the cellular events regulated by CTGF, and the relationships between CTGF and pathogenesis of diseases are systematically summarized. In addition, we highlight the current researches, focusing on the preclinical and clinical trials concerned with CTGF as the therapeutic target.

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1. Introduction

Connective tissue growth factor (CTGF), a member of CCN family, was first discovered by Bradham et al.[1] from human vascular endothelial cells in 1991. Subsequently, different groups have confirmed that CTGF could be produced by a variety of cells such as fibroblasts, tumor cells, muscle cells, and stellate cells[2–6]. It is composed of four modular domains: insulin-like growth factor-binding protein (IGFBP), von Willebrand factor type C repeat (VWC), thrombospondin type 1 repeat (TSP1), and cysteine knot-containing carboxyl domain (CT). These domains perform various functions by acting on different factors including cell-surface receptors, cytokines and extracellular matrix (ECM) proteins[7]. In the regulation of physiological functions, CTGF plays essential roles[8]. More importantly, the contribution of CTGF to the pathogenesis and progression of diseases has drawn much attention.

Based on numerous studies through the decades, the connection between CTGF and the well-known fibrosis-related growth factor transforming growth factor-β (TGF-β) was revealed. The induction of fibrosis by CTGF through different molecular pathways have been reported in the model of hepatic fibrosis, pulmonary fibrosis, renal fibrosis, cardiac fibrosis, Duchenne muscular dystrophy (DMD) and systemic sclerosis (SSc)[9–14]. Based on these results, many studies tried to block CTGF to treat fibrotic diseases[15–17]. Many drugs targeting CTGF were developed (Table 1), among which FG-3019 was the most striking one. It has already been found that CTGF is effective in treating fibrosis such as pulmonary fibrosis and DMD[18] (NCT01890265, NCT02606136).

With more understanding of CTGF, researchers have noticed the association of CTGF with cancers and other diseases[19–23]. However, the relationship is more complicated. For example, in cancers, elevated CTGF level was found in pancreatic cancer, whereas an inhibited CTGF level was observed in lung cancer, moreover, in breast cancer, CTGF level depended on the specific cases[24–27]. The difference may be caused by mixed effects of CTGF on different cancer cell lines[28,29]. Despite these results, in the cancers overexpressing CTGF, the regulation of CTGF could also be regarded as a therapeutic strategy. In fact, BLR100, BLR200 and FG-3019 have already shown effectiveness in the treatment of pancreatic cancer[30,31]. In the current review, we introduce the structure, related signaling pathways and functions of CTGF both in physiological conditions and in diseases. The therapeutical strategies by targeting CTGF are highlighted, and the related preclinical/clinical studies are summarized.

2. Structure of CTGF

CTGF (also known as CNN2) is a member of CCN family. In 1991, it was initially characterized as a 38 kD cysteine-rich secreted growth factor by Bradham[1]. CTGF consists of four basic domains, they are IGFBP, VWC, TSP1 and CT from N-terminal to C-terminal[32–34]. Each domain could specifically bind with different proteins and thereby play different functions (Fig. 1).

2.1. IGFBP domain

IGFBP domain of CTGF locates in the sequence of Gln27−Lys98. This name was given because IGFBP domain contains a conserved sequence 'GCGCCXXC' which is also found in proteins in IGFBP family[35]. It was observed that the combination of CTGF and insulin-like growth factor was involved in the process of matrix accumulation[36]. Besides, in the development of tubulointerstitial fibrosis, the combination of CTGF and insulin-like growth factor contributes to the progression of the disease[37].

2.2. VWC domain

VWC domain of CTGF locates in the sequence of Ala101−Asp167. It is also called cysteine-rich domain. The conserved sequence 'CXXCXC' and 'CCXXC' exist in this domain. Like other VWC domain-containing proteins, CTGF could bind to BMPs and TGF-β. However, the binding affinity to TGF-β is relatively low, as a result, CTGF could not inhibit the binding between TGF-β and its receptor, but only enhance TGF-β signaling functioning as a chaperone[38,39]. Conversely, in most cases, CTGF is known as a

Table 1 Summary of drugs which have been in clinical trials targeting CTGF in recent years (clinicaltrials.gov).

Drug name	Mechanism	Indication	Development stage	ClinicalTrials.gov identifier
FG-3019	Neutralizing CTGF	Pancreatic cancer (unresectable)	Phase 3	NCT03941093
		Duchenne muscular dystrophy	Phase 3	NCT04632940
		Diabetes mellitus/diabetic nephropathy	Phase 1	NCT00754143
		Diabetes mellitus	Phase 1	NCT00102297
		Idiopathic pulmonary fibrosis	Phase 3	NCT04419558
Pravastatin	Targeting Rho/ROCK /CTGF pathway	Radio-induced fibrosis	Phase 2	NCT01268202
		Breast cancer	Phase 2	NCT04356209
RXI-109	CTGF RNA interference	Age-related macular degeneration/ subfoveal choroidal neovascularization/ subretinal scarring/subretinal fibrosis	Phase 1/ Phase 2	NCT02599064
		Hypertrophic scar	Phase 2	NCT02030275/NCT02246465
		Keloid	Phase 2	NCT02079168
OLX-10010	CTGF RNA interference	Hypertrophic scar	Phase 2	NCT04877756
EXC-001	CTGF antisense oligonucleotide	Skin scarring	Phase 2	NCT01494922/NCT01037985/ NCT01037413/NCT01346969
SHR-1906	Neutralizing CTGF	Idiopathic pulmonary fibrosis	Phase 1	NCT04986540
		Unspecified adult solid tumor	Phase 1	NCT04842630

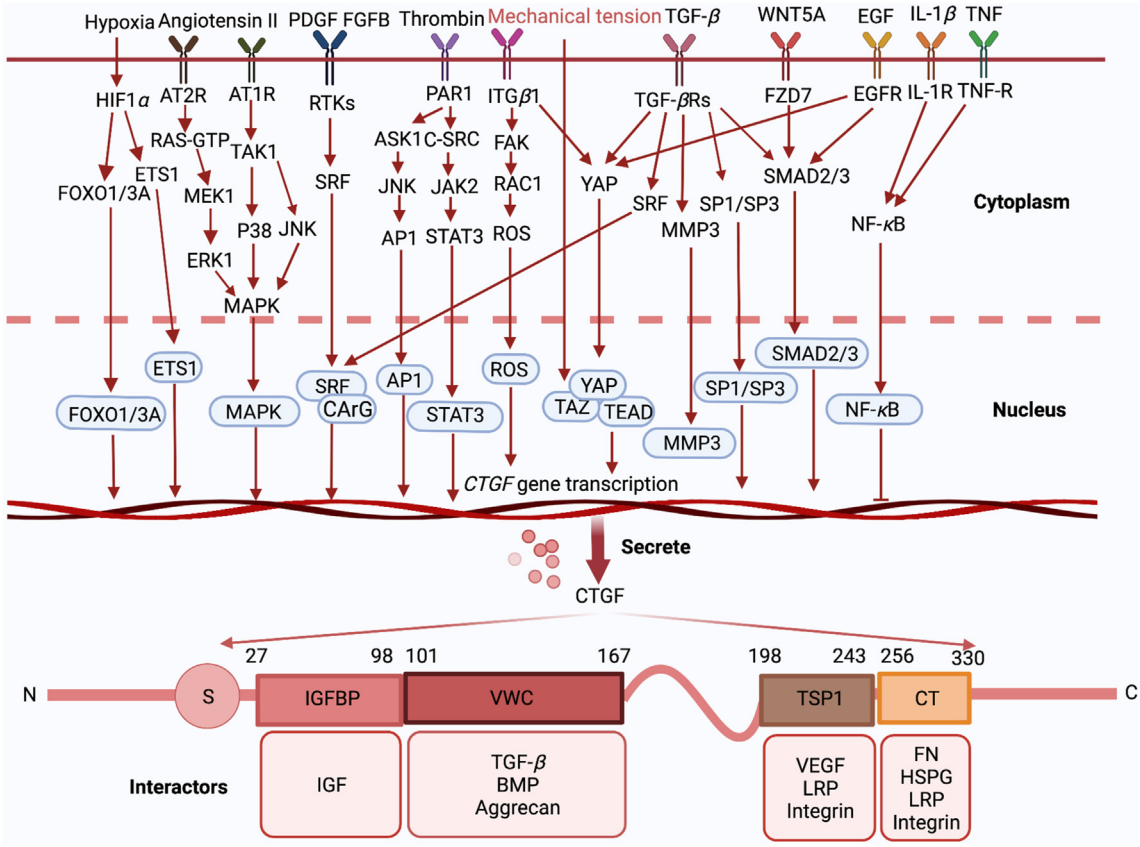

Figure 1 Regulation and the structure of CTGF. Under particular external stimulation and ligand−receptor interaction, the signaling pathways related to CTGF synthesis would be activated. Certain transcription factors would be recruited to the nucleus and finally lead to CTGF transcription and CTGF secretion. After the secretion, four different domains of CTGF containing IGFBP, VWC, TSP1 and CT could interact with various substances and play physiological functions, *i.e.*, insulin-like growth factors interact with IGFBP domain; TGF-β, bone morphogenetic proteins (BMPs) and aggrecan interact with VWC domain; vascular endothelial growth factor (VEGF), low-density lipoprotein-related proteins (LRPs) and integrins interact with TSP1 domain; fibronectin (FN), heparan sulfate proteoglycans (HSPGs), LRPs and integrins interact with CT domain.

BMP antagonist. The activities of BMP-2 and BMP-7 are negatively mediated by CTGF[40,41].

2.3. *TSP1 domain*

TSP1 domain of CTGF locates in the sequence of Asn198−Glu243 which was known as thrombospondin type 1 repeats. It was first identified in thromobospendin-1[42]. It contains both 'CSXXCG' sequence and six cysteines. In TSP1 domain, Trp206, Ser218, Arg220, Gln233 and Arg235 are 100% conserved across the CCN family proteins[43,44]. It was reported that TSP1 domain of CTGF could bind with exon 7-coded region of VEGF165 and negatively regulate the angiogenic activity of vascular endothelial growth factor (VEGF). However, along with the remodeling of some tissues, VEGF would be released from the CTGF−VEGF complex mediated by inactivation of RHOA/Rho-kinase in mesenchymal stem cells[45,46]. Besides, both the adhesion of cells and collagen deposition could be influenced by the interaction between CTGF-TSP1 domain and $\alpha 6\beta 1$ or LRP[47−49].

2.4. *CT domain*

CT domain of CTGF locates in the sequence of Cys256−Pro330. It took its name from a structure in this domain called cystine knot. *In vitro*, low-affinity between low-density lipoprotein receptor-related protein 6 (LRP6) and CTGF-CT domain has been demonstrated. The binding was associated with the wingless-type MMTV integration site family (WNT) signaling pathway and also contributed to the progression of fibrosis[50]. In addition, the CTGF-CT domain could directly combine with LRP4 and then regulate the motor function and nerve terminal maturation[51]. Mediating the adhesion and migration of cells by interacting with integrin or fibronectin (FN) is also one of the important functions of CT domain[52−54]. The interaction between LRP and TSP1 domain could be influenced by HSPGs. And the binding site of HSPGs may also be at CT domain[47,55]. Furthermore, the CTGF-CT domain is associated with the proliferation of cells as well. It is able to facilitate the regeneration of bone defection[56,57]. Moreover, it has been reported that CTGF-CT domain is involved in the process of epithelial−mesenchymal transition (EMT)[58].

3. Regulation of the expression of CTGF

The expression of CTGF is regulated by multiple substances such as growth factors, hormones and cytokines, where TGF-β is known to be a significant regulator (Fig. 1). It has been shown that the treatment of TGF-β to the human peritoneal mesothelial cells

and human diploid fibroblasts promote the expression of CTGF[59,60]. Hormones like angiotensin II, parathyroid hormone, and dexamethasone could also induce the expression of CTGF. Reversely, the use of the antagonist of angiotensin II type 1 receptor (AT-1R) could inhibit the upregulated expression of CTGF[61−63]. Cytokines like IL-20 and hypoxia-inducible factor are the mediators of CTGF as well[8,64,65]. Additionally, CTGF was found hypoxia-inducible in melanomas which means that the microenvironment plays a role in regulating the expression of CTGF[66]. Moreover, the mechanical tension like delayed loading could also increase the expression level of *Ctgf*[67].

The manifold pathways through which transcriptional regulatory proteins induce the expression of CTGF are shown in Fig. 1. Yes-associated protein (YAP), transcriptional enhanced associate domains, transcriptional coactivator with PDZ-binding motif (TAZ) and ETS porto-oncogene 1 (ETS1) are the most essential four factors[68]. YAP, TAZ are downstream effectors of the Hippo pathway. Only the dephosphorylated YAP/TAZ could be translocated into nucleus, and then mediates the expression of CTGF as a transcriptional activator[69−75]. In the recent study, the temperature was found to affect the Hippo signaling pathway and the expression of *CTGF* was increased along with the dephosphorylation of YAP[76]. Besides, the static magnetic field could also upregulate *CTGF* by increasing the nuclear localization of YAP/TAZ[77]. CTGF−YAP/TAZ regulatory loop plays central roles in the processes of vascularization, barrier genesis and even tumor progression. Hence, it might be considered as a therapeutic target for the treatment of multiple diseases[78−80].

ETS1 is another important transcriptional factor to induce *CTGF*. GGAA sequences in the ETS1 binding motifs of *CTGF* proximal promoter binds with ETS1 to activate the promoter and regulate CTGF[81,82]. The same as YAP and TAZ, ETS1 participates in many progressions such as fibrosis, angiogenesis and osteogenesis[83−85]. In addition, mothers against decapentaplegic homolog 2/3 (SMAD 2/3), mitogen-activated protein kinase could also mediate the expression of CTGF through the phosphorylation of SMAD 2/3 or activity of mitogen-activated protein kinase[86−88].

4. Regulation of cellular events by CTGF

As a multifunctional protein, CTGF participates in many cellular events including proliferation, survival, adhesion and migration, differentiation, EMT, as well as the formation of extracellular matrix (Fig. 2A).

4.1. *Proliferation*

In the diseases such as fibrosis and cancer, CTGF always makes the condition worse by promoting the proliferation of fibroblasts, stellate cells or carcinoma cells[89−91]. In addition, CTGF could also mediate the proliferation of cells in skeletal system and cardiovascular system. The study has demonstrated that the induction of proliferation caused by CTGF is related to the destruction of the joint and hypertension[92,93]. Many substances could mediate CTGF to regulate the proliferation of cells such as glucose, growth differentiation factor 8 and even macrophages[94−96]. Furtherly, CTGF would activate the certain downstream proliferation-related signaling pathways. For instance, it has been reported that CTGF activates focal adhesion kinase/SRC/nuclear factor kappa-B p65 (FAK/SRC/NF-κB p65 signaling), which would lead to the upregulation of GLUT3 expression level, by binding directly to an integrin receptor, thereby accelerating the proliferation of tumor cells[97,98]. Nevertheless, sometimes, CTGF is conversely regarded as an antiproliferative factor. The proliferation of WiT49 cells was inhibited when the cells were cultured with human recombinant CTGF *in vitro*[99].

4.2. *Adhesion and migration*

CTGF is a common participant in the regulation of the adhesion and migration of cells[53,55]. Through activating the downstream signaling pathways such as FAK/extracellular signal-regulated kinase (ERK) and FAK/phosphatidylinositol-3-kinase/protein kinase B/NF-κB cascades, CTGF could induce the expression of migration and adhesion-related genes such as matrix metallopeptidase-13[100−102]. Depending on particular conditions, CTGF either blocks or promotes adhesion. $\alpha_v\beta_1$ is known as one of the integrins which could be involved in CTGF-promoted adhesion of osteoblasts[103]. Furthermore, $\alpha_5\beta_1$ has been found to participate in the adhesion of both HCS-2/8 and pancreatic stellate cells induced by CTGF. In pancreatic stellate cells, $\alpha_5\beta_1$ binds to CTGF directly; whereas in HCS-2/8, CTGF binds directly to FN *via* $\alpha_5\beta_1$[53,104]. However, in gastric cancer and colorectal cancer, CTGF blocks the adhesion of cancer cells by interacting with $\alpha_3\beta_1$ and influencing the expression of α_5, respectively[105,106].

4.3. *Differentiation*

CTGF may interact with LRP, integrin, and even fibroblast growth factor receptors to mediate the activation of signaling pathways such as muscle-specific receptor tyrosine kinase and ERK, which are essential for the differentiation of cells[51,103,107]. The differentiation of multiple types of cells is affected by CTGF, such as osteoblasts and chondrocytes[108,109]. The previous study showed that CTGF mediated BMP-9-induced early stage of osteogenic differentiation in a positive way. However, the reversed condition was found when the differentiation potential of committed pre-osteoblasts increased[110]. BMP-2-induced osteoblast differentiation was also negatively regulated by CTGF[41]. Moreover, the differentiation of growth-plate chondrocytes has been proved to be upregulated by CTGF. This characteristic of CTGF could be used to reconstruct elastic cartilage[111]. For other cells, CTGF could also affect relevant physiological states by regulating the differentiation. For instance, the inhibited differentiation of adipocyte caused by CTGF could affect the development of obesity or insulin resistance[112]. On the opposite, CTGF could promote differentiation of mammary epithelial cells to mediate lactogenesis[113]. Last but not least, CTGF could direct the differentiation of human bone marrow mesenchymal stem/stromal cells into fibroblasts which is so important for the enrichment of our understanding of organ fibrosis and cancer[114].

4.4. *Formation of extracellular matrix*

CTGF is known as one of the important extracellular matrix proteins acting essentially in shaping the extracellular microenvironment. Type 1 collagen and FN are two representative components of extracellular matrix. As early as 1996, it has been discovered that CTGF could stimulate the formation of type 1 collagen and FN to induce the synthesis of extracellular matrix[115]. Further, antisense deoxynucleotide for *CTGF* was used to further assess the relationship between CTGF and the formation of extracellular matrix[116]. In molecular level, the SMAD, ERK and

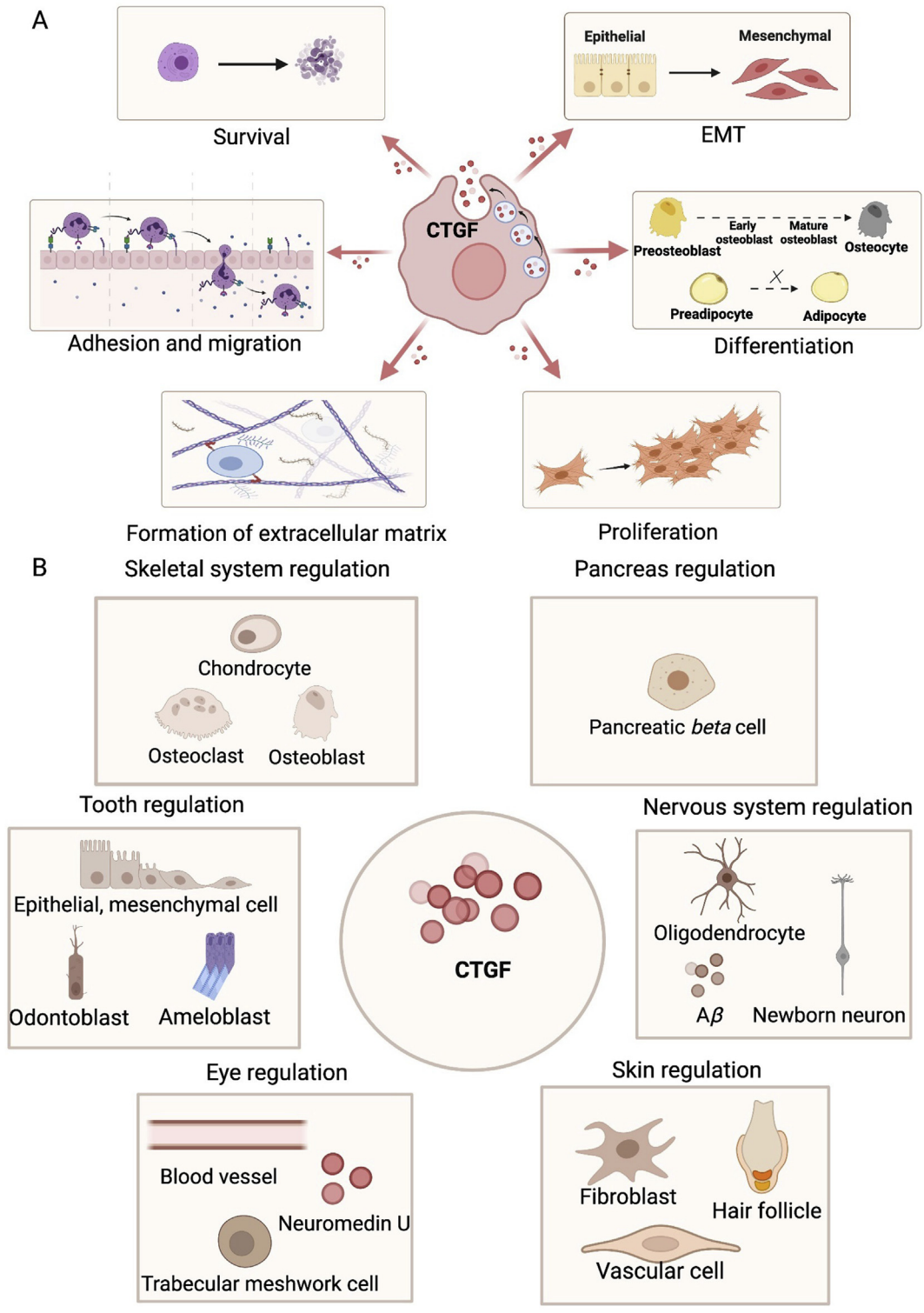

Figure 2 Molecular action of CTGF in cell events and the role of CTGF in physiological regulation. (A) Generally, CTGF could influence cell events at six aspects, including adhesion, migration, proliferation, differentiation, survival, EMT of cells, and formation of extracellular matrix. CTGF is an acknowledged inducer of EMT and the formation of ECM. However, it could play a more mixed role in the adhesion, migration, proliferation, differentiation and survival of cells. (B) CTGF could regulate physiological processes of the skeletal system, nervous system, pancreas, eyes, skin and tooth through mediating certain cells or substance events, which are shown in the square.

P42/44 signaling pathways were found to participate in the CTGF-induced synthesis of extracellular matrix , among which p42/44 signaling pathway was triggered by β3 integrin in human mesangial cells[117–119]. Notably, the synthesis of extracellular matrix could affect pathological progression of fibrosis and cancer.

4.5. *Survival*

It was reported that CTGF could positively mediate apoptosis in ovarian low-grade serous carcinoma and MCF-7, a breast cancer cell line[120,121]. However, in human Tenon capsule fibroblasts and chicken embryo fibroblasts, CTGF was found to negatively mediate the apoptosis[122,123]. Besides, in rat mesangial cells, CTGF could promote the survival of cells by downregulating SMAD7[124]. It was also discovered that CTGF had significant benefit to the survival of osteoclasts. In reverse, the loss of CTGF may cause the decreased survival of chondrocytes and severe chondrodysplasia through CTGF/integrin/NF-κB pathway[125,126]. Moreover, the anti-apoptosis function of CTGF has also been proved in pig granulosa cells *in vitro* by knockdown of *CTGF*[127]. The survival and apoptosis of cells can significantly affect the process of certain diseases, which may be one of the important reasons why CTGF can affect the survival rate of diseases[128–131].

4.6. *Epithelial-mesenchymal transition*

EMT is a significant physiological process that is tightly related to metastasis of tumor, progression of fibrosis and tissue repair[132–134]. Many studies have already revealed that CTGF is a promoter in the regulation of EMT, which usually acts synergistically with TGF-β[22]. The addition of CTGF to MSF-7 culture could induce EMT[135,136]. For lung epithelial cells, the TGF-β1-mediated EMT was found to be dependent on the expression of CTGF[137]. The same induction of EMT by CTGF have been shown in NRK-52E cells as well. Although the comprehensive mechanisms by which CTGF induces EMT are still unclear, some molecular cascades have been found to participate in the CTGF-induced EMT. For instance, compelling evidence suggests that the cellular level of integrin-linked kinase is closely associated with EMT[138]. Liu et al.[139] reported that the interplay between CTGF and its receptor, integrin, could upregulate the expression level of the integrin-linked kinase *via* activating mitogen-activated protein kinase kinase/ERK1/2 and phosphatidylinositol-3-kinase signaling pathway. However, comparing to the complete transition induced by TGF-β, the induction mediated by CTGF may only play a partial role[140,141]. Reportedly, CTGF antibody, micro RNAs (miRs) like miR-212-3p, miR-218, miR-133b and even fucoidans could inhibit EMT and attenuate cancer and fibrosis by blocking CTGF[142–146].

5. Roles under specific physiological conditions

5.1. *Skeletal system regulation*

The development of human skeletal system has two different forms: endochondral ossification and intramembranous ossification. Presently, it is widely accepted that CTGF is involved in these two processes. At first, it has been demonstrated that chondrocytes, pre-osteoblasts and osteoblasts could be affected by CTGF *in vitro*[109,110,147,148]. Moreover, the overexpressed CTGF accelerated the endochondral ossification by promoting the proliferation and differentiation of chondrocytes[149]. The lack of CTGF would cause chondrodysplasia and seriously result in perinatal lethality, as well as the ossification delay in the intramembranous skeletal elements[126,150,151]. Further, CTGF plays a critical role in the regulation of morphogenesis. The function of CTGF to control cartilage morphogenesis is implemented through the regulation of extracellular matrix[74]. Moreover, CTGF could affect both the differentiation and the proliferation of osteoblasts to contribute to the balance between the formation of osteoblastic bone and resorption of osteoclastic bone[71,152].

In addition, CTGF plays a role in skeletal repair as well. During fracture healing, the level of *Ctgf* would increase at first and then decrease in the fracture sites. Besides, it was observed that the expression level of *Ctgf* mRNA was higher during distraction osteogenesis. The upregulated expression level of *Ctgf* was not only found in endochondral ossification area, but also in intramembranous ossification area[153,154]. A nanofibrous mats drug containing a nanofibrous BMP2 core and CTGF surface that could facilitate bone healing has been designed in recent years based on this physiological role[155]. Also, CTGF microencapsulation has been used to promote fibrogenesis in the process of calvarial healing[114]. Besides, as a growth factor that could simultaneously facilitate angiogenesis and osteogenesis, the 2D and 3D bioactive material loaded CTGF was used in bone tissue engineering to optimize scaffold as well[156].

5.2. *Pancreas regulation*

The essential role that CTGF plays in the development of pancreas was illustrated by the discovery of a conserved enhancer in *CTGF* which contains binding sites for transcription factors related to pancreas development[157]. Further, it was shown that the defection of CTGF could disrupt endocrine cell composition and islet morphogenesis[158,159]. It has already been proved that CTGF is necessary for embryonic β-cell proliferation, which is essential for glucose homeostasis[160]. Under non-stimulatory conditions, the overexpression of CTGF could not significantly promote the proliferation of embryonic β-cells[161]. It is plausible because there was no physiological impetus to stimulate the expansion of β-cells. But under the destructive microenvironment for β-cells, CTGF showed considerable functions of increasing the proliferation and mass of β-cells[162]. Further, chemoattractant genes of the macrophage were found to be increased simultaneously after the induction of CTGF when β-cells ablated. Without the participation of macrophages, the CTGF-mediated repair would be blocked[96]. The survival of β-cells would be challenged by inartificial factors like free fatty acids because of its poor adaptability to changing microenvironment. Logically, CTGF might participate in the protection of β-cells from challenges[163].

5.3. *Nervous system regulation*

In 1999, the wide localization of CTGF in the central nervous system of rats was first uncovered[164]. The wide spread of CTGF in the central nervous system indicates a potential role that CTGF plays in the regulation of the nervous system. Many studies have shown the relationship between CTGF and the nervous system in pathological processes[165–167]. However, in this section, important contributions to the regulation of the nervous system made by CTGF would be discussed. The first one is regulating the development of oligodendrocytes. It has been shown that CTGF suppresses the differentiation of oligodendrocytes. The inhibition may be connected with the similarity between CTGF and IGFBP. It is believed as a paracrine regulation of oligodendrocyte development[168]. The second one is changing olfactory behaviors. Olfactory bulb circuitry and olfactory behaviors could be modulated by

the level of CTGF. It has been demonstrated that the increased CTGF stimulated by odorant simulation could lead to the decreased survival of neuron and the habituation of odorant[169–171]. Moreover, during the development of the nervous system, CTGF may also act as a protector. Excessive accumulation of Aβ would cause a progressive neuronal loss in Alzheimer's disease (AD). In the AD model, CTGF could decrease the deposition of Aβ and improve locomotor function. It could reasonably be conjectured that CTGF takes part in Aβ balance in normal physiological process[172]. In addition, based on the observation that zebrafish could regenerate nervous system after spinal cord injury, one could speculate that CTGF might be an essential factor in mediating the repair of spinal cord tissue[173].

5.4. *Skin regulation*

CTGF does not play significant roles in the development of skin[174]. However, it has been revealed that CTGF could affect the regulation of skin in two aspects: wound healing and hair follicle cycling. In the non-human primate burn-wound model, CTGF has been found to contribute to wound healing[175]. In the previous study, it was illustrated that the expression of CTGF dynamically modulated wound healing. Just in the early stage of wound healing, CTGF was upregulated transiently to promote wound repair. This physiological process may be related to fibroblasts and vascular cells regulated by CTGF[176]. If CTGF is not customarily induced, chronic non-healing wounds will occur. Moreover, the loss or redundancy of CTGF would result in the damaged hair cycling. In detail, the deletion of CTGF in cells producing type I collagen could increase the number of hair follicles. The mechanism is related to the blocked binding of WNT and its receptor affected by CTGF[177]. On the contrary, CTGF was previously described as one of participators in L-ascorbic acid 2-phosphate magnesium salt-induced elongation of hair shafts[178]. Anyhow, the induction and deletion of CTGF could be used to mediate the regeneration of hair.

5.5. *Eyes regulation*

The expression of CTGF has been found in cornea, iris, ciliary body and choroid[179]. In the high-throughput study, *CTGF* was identified as one of the candidates for regulators of macular development. Moreover, *CTGF* may mediate early cessation of proliferation in the foveal region acting as an antiproliferative factor[180]. CTGF was also found to have a regulative function in the trabecular meshwork. When human trabecular meshwork cells were under specific short-term stress, the expression of CTGF would be immediately increased and it appeared to increase the viability of human trabecular meshwork[181]. Further, CTGF is necessary for cytoskeletal dynamics and contractile properties of trabecular meshwork cells. CTGF regulated by RHO GTPase could induce neuromedin U on aqueous humor and take part in the homeostasis of aqueous humor drainage and intraocular pressure[182]. In addition, CTGF is one of the regulators of fibroblast-mediated contraction of the stressed matrix, which is tightly related to the response of tissues after injury[183]. At last, the basal expression of CTGF is critical for blood vessel integrity and barrier formation in eyes[80].

5.6. *Tooth regulation*

The influence on tooth development exerted by CTGF is also manifold. It has been observed that many structures and cells in the tooth could be strongly stained by CTGF at a certain period of time[184,185]. The tissue-specific and stage-specific expression of CTGF probably mediates tooth development, including amelogenesis, dentinogenesis and junctional epithelium formation, as well as the development of periodontium like periodontal ligament and cementum[186]. CTGF could take part in the regulation of the proliferation and differentiation of cells which is related to tooth development to affect the regulation of tooth. For example, anti-CTGF treatment could inhibit both the proliferation of epithelial, mesenchymal cells and the differentiation of ameloblasts, odontoblasts[187]. Moreover, when recombinant CTGF was added to the culture medium for MPL cells, the proliferation of cells was stimulated. Periostin mRNA, which is the specific marker of periosteum and periodontium, was also increased[188]. Besides, the tooth is a typical epithelium-mesenchyme organ. CTGF may also regulate EMT during tooth develops[185,189]. In a word, CTGF mainly affects physiological processes, which is mentioned above, through mediating certain cell or substance events (Fig. 2B).

6. Roles under specific pathological condition and related therapies

6.1. *Fibrosis*

6.1.1. *Hepatic fibrosis*

Hepatic fibrosis is an aberrant repairing reaction conducted by hepatic tissue during chronic injury. The activation of hepatic stellate cells (HSCs) is the most iconic link in hepatic fibrosis. It could express abundant α-smooth muscle actin (α-SMA) and synthesize extracellular matrix components especially type I and III collagen after it becomes active and develops to myofibroblast-like cells[190,191]. In other fibrotic diseases, the formation of myofibroblasts could also be observed. However, the source might be different (Fig. 3A)[192–194]. The activation of HSC was found reversible, which means hepatic fibrosis could be attenuated by inhibiting the activation of HSC[195]. CTGF may play an indispensable role in the whole process. The abundant existence of CTGF in HSC indicated that CTGF were overexpressed by HSC[196]. Also, abundant CTGF could induce the production of extracellular matrix in HSC to promote hepatic fibrosis[197].

All the observations have illustrated that CTGF could be a potential target in the treatment of hepatic fibrosis. A siRNA called 483 attenuated the expression of extracellular matrix by reducing more than 90% expression of CTGF. It showed a practical function to reverse the activation of HSC and cure hepatic fibrosis[198,199]. Besides, a virus-like particle-based CTGF vaccine was used to treat hepatic fibrosis induced by carbon tetrachloride in mice. It showed a special protection to the liver through promoting the proliferation of hepatocytes and suppressing apoptosis[16]. In addition, multiple studies tried to find a new impetus for treating hepatic fibrosis through CTGF-related pathways[200,201]. For example, Naringenin was discovered to treat hepatic fibrosis by preserving the TGF-β/SMAD3 and JNK/SMAD3 pathways[202]. Pharmacological inhibition of the YAP pathway could also reduce fibrogenesis[203]. In addition, for hepatic fibrosis caused by helminths like *Schistosoma japonicum*, when Dickkopf1 was used to suppress the WNT signaling pathway, the expression level of CTGF was reduced, and hepatic fibrosis was alleviated[204].

6.1.2. *Pulmonary fibrosis*

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease, which has a high incidence in middle-aged and

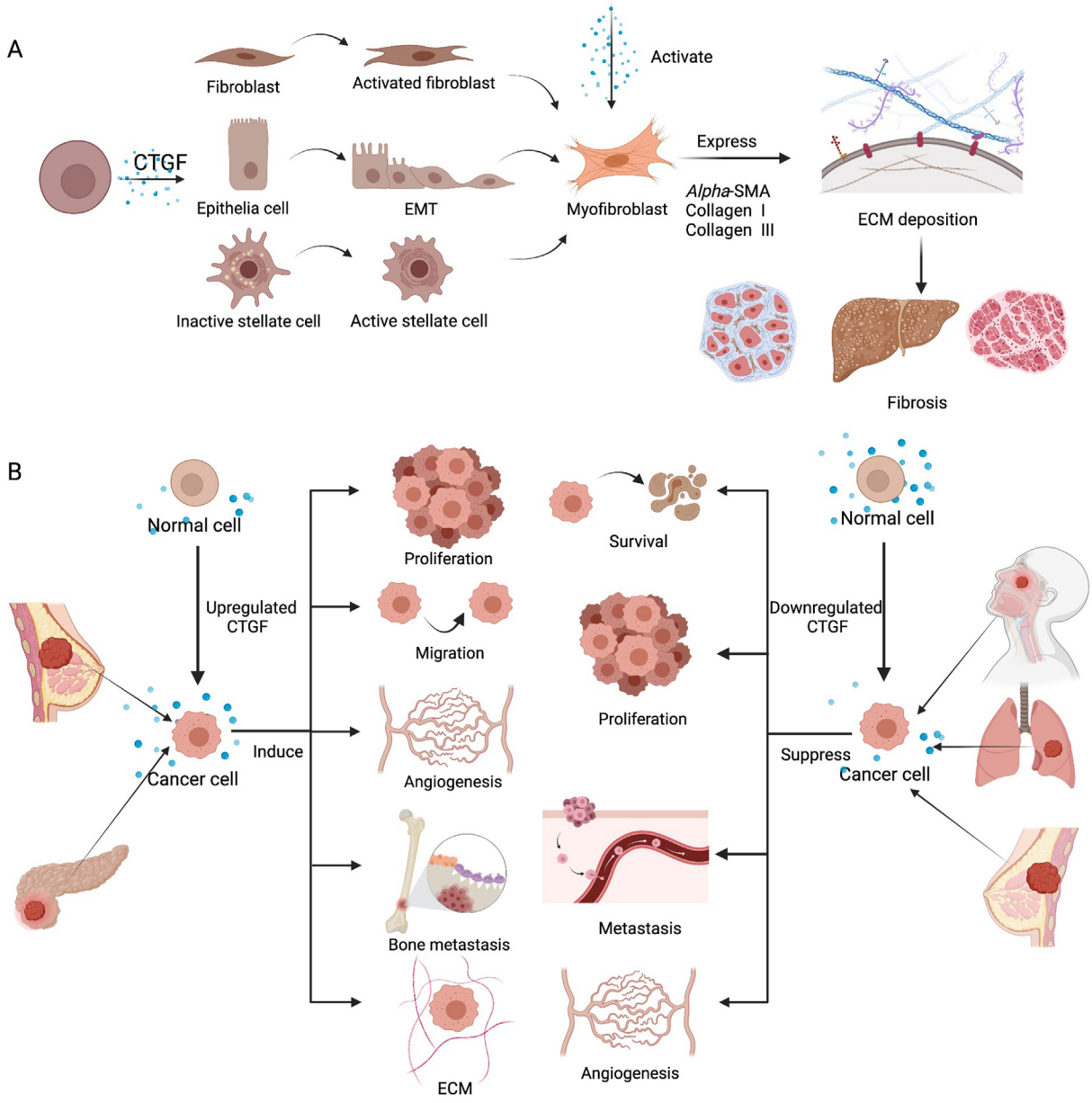

Figure 3 The mechanism of how CTGF contributes to the progression of fibrosis and cancer. (A) Under pathological stimulation, the expression of CTGF would be induced to promote the formation of myofibroblasts which are transdifferentiated from fibroblasts, epithelia cells or stellate cells. CTGF could also activate myofibroblasts to secret ECM components and finally lead to ECM deposition. (B) The contribution of CTGF to the progression of cancer differs into two distinct types. In some cancers like pancreatic cancer or some sub-types of breast cancer, CTGF could be upregulated to induce the proliferation and migration of cancer cells. Besides, changes of tumor microenvironment and the promotion of bone metastasis could also be induced by the upregulated CTGF during the progression of cancer. In other cancers like lung cancer and nasopharyngeal carcinoma, the development of cancer could be supported by the downregulation of CTGF as CTGF could inhibit the proliferation and survival of cancer cells, and suppress the metastasis and angiogenesis under these conditions.

elderly adults. Besides, the incidence and prevalence of IPF is increasing worldwide[205–208]. It has been found that high *CTGF* mRNA level is associated with IPF fibroblasts[13]. Similarly, a high CTGF level has been found in the plasma of IPF patients, making CTGF a potential biomarker for the diagnosis of IPF[209]. TAZ was found to affect IPF a lot by regulating the proliferation and migration of fibroblasts even mediating collagen contraction. As a target gene of TAZ, *CTGF* was thought to mediate part of the function of TAZ to IPF. Furthermore, when YAP was blocked, the expression of *CTGF* would be blocked too. Hence, it may demonstrate that the higher CTGF level could be mediated by the inactivation of the Hippo signaling pathway[210,211].

To treat IPF, some miRs have shown significant efficacies. It has been demonstrated that the enhancement of miR-26a, which could be mediated by CTGF, attenuates pulmonary fibrosis[212]. Besides, based on the fact that trametinib could suppress the activation of myofibroblast by inhibiting CTGF, and astaxanthin (AST) could repair type II alveolar epithelial cell, a synergetic strategy containing trametinib and astaxanthin was designed for the treatment of IPF[213]. Moreover, pamrevlumab showed both safety and efficacy to

reverse the progression of IPF in the phase 2 trial[18]. The effect of the new drug SHR-1916, which is also a CTGF antibody, on the treatment of IPF is going to be assessed by clinical trial (NCT04986540). Other CTGF-related clinic trials would be discussed in the following section and be summarized in Table 1. Pamrevlumab could also treat radiation-induced pulmonary fibrosis. Further, Atorvastatin had the ability to attenuate fibrosis induced by bleomycin. The downregulation of CTGF was one of the vital pathways[214,215]. Since December 2019, corona virus disease 2019 (COVID-19) has made a vast disaster all over the world. Pulmonary fibrosis becomes a common clinical feature of patients infected by COVID-19. The data from patients who were infected by COVID-19 implies that the pulmonary fibrosis induced by COVID-19 may relate to TGF-β, WNT and the Hippo signaling pathway. Therefore, it is important to examine whether CTGF-related therapies could be effective in treating COVID-19[216,217].

6.1.3. *Renal fibrosis*

Chronic kidney disease is now more and more commonly seen. The incidence and prevalence of chronic kidney disease rapidly increased from 1990 to 2016, by 89% and 87%, respectively[218]. During the progression of chronic kidney disease, many profibrotic cytokines and growth factors would be released and myofibroblasts would be activated to create a fibrotic environment[219]. The TGF-β pathway is a crucial pathway for the regulation of renal fibrosis. It could induce the dedifferentiation of epithelial cells after renal injury. Then paracrine signaling factors could be secreted to activate myofibroblast differentiation, proliferation and matrix secretion[220]. Unlike TGF-β, BMP-7 exerts an anti-fibrotic effect on renal fibrosis by affecting the extracellular matrix. As a chaperone and downstream factor of TGF-β signaling and inhibitor of BMP-7 signaling, CTGF is involved in the pathologic progression of renal fibrosis[221−223]. Besides, the Hippo signaling pathway is another important pathway that could affect the process of renal fibrosis. The activation of YAP could induce the expression of CTGF and it is essential to diabetic interstitial fibrogenesis in kidney[224]. Other signaling pathways like the SMAD3 and p53 signaling were also found to be activated in renal fibrosis[225]. Overall, when kidney fibrosis occurred, the expression level of CTGF would be increased[226].

So, it could be reliably predicted that targeting CTGF could mediate the progression of renal fibrosis, and CTGF-targeted treatment would be a potential way to treat renal fibrosis[227]. It was observed that the inflammation of mice was reduced when *Ctgf* was knocked out[226]. Moreover, inhibiting the expression of CTGF by antisense oligonucleotide, the abundant expression of α-SMA and extracellular matrix accumulation induced by unilateral ureteral occlusion (UUO) was markedly suppressed. Fibrotic areas marked by collagen deposition were significantly reduced, demonstrating the amelioration of tubulointerstitial fibrosis[228]. Knocking out megakaryocytic leukemia 1, which could interact with SMAD3 to activate *Ctgf* transcription, also showed the downregulation of UUO-induced collagen and α-SMA[229]. CTGF-siRNA treatment is known to ameliorate fibrosis. To improve the effectiveness of CTGF-siRNA treatment, a nanocarrier called sterically stabilized phospholipid nanoparticles was developed. Higher concentration of siRNA, better efficacy on decreasing collagen and lower toxicity made this nanomedicine a promising option to treat renal fibrosis[15]. In addition, in the UUO-induced renal fibrosis model, the level of hydroxyproline, another marker of collagen deposition, was decreased after the administration of FG-3019[230].

6.1.4. *Cardiac fibrosis*

Cardiac fibrosis is a typical pathologic characteristic of heart failure. The unbalance between the degradation and synthesis of the extracellular matrix in the microenvironment is essential for the occurrence and progression of cardiac fibrosis. The extracellular matrix deposition could be caused by myofibroblasts, whose activation is an important event in cardiac fibrosis[231−234]. It has been reported that the expression of *CTGF* mRNA is positively correlated with myocardial fibrosis. Probably, it is because that CTGF secreted by cardiac myocytes could induce the excessive synthesis of collagen in fibroblasts[12]. In dilated cardiomyopathy, which is fibrosis-related, *CTGF* is a key gene that was upregulated[235]. In the myocardial infarction model of rats that is always accompanied with fibrosis, the level of *Ctgf*, *Fn* and *ColI* were simultaneously increased, too[236]. By evaluating the clinical data from 52 patients with chronic heart failure, it was found that the expression level of CTGF in plasma correlated with heart failure classes and other fibrosis markers. It provides that CTGF concentration in plasma could be a novel biomarker to myocardial fibrosis[237].

MicroRNA is tightly associated with cardiac fibrosis. For instance, miR-125b is necessary for the fibroblast-to-myofibroblast transition[238]. Among them, the mi-RNAs, which are related to CTGF were found to be potential to treat cardiac fibrosis. In particular, miR-26a and miR-455 are in involved in targeting CTGF and collagen in cardiac fibrosis. Also, miR-132 could treat atrial fibrillation, which is featured by atrial fibrosis, through decreasing the expression of CTGF as well[17,239,240]. Further, when a specific antibody of CTGF was administered to the mice with myocardial fibrosis and left ventricular function, the collagen mRNA expression decreased. This is another evidence which proves that CTGF blocking therapy may be a prospective approach to treat fibrosis[241].

6.1.5. *Duchenne muscular dystrophy (DMD)*

DMD is an X-chromosome recessive inheritance disease. It is one of the most prominent diseases caused by the lack of dystrophin. The loss of dystrophin leads to perturbed autophagic flux and then contributes to muscle damage and fibrosis[242]. Hence, skeletal muscle fibrosis is a crucial characteristic of DMD. The data from the biopsies of DMD patients has shown that *CTGF* mRNA level is higher in muscle[14]. By incubating myoblasts with CTGF, it was revealed that extracellular matrix components including some integrins and collagen I a2 were influenced[6]. Further, by using adenovirus to overexpress CTGF in muscles, a strong fibrotic reaction with increasing type III collagen and α-SMA was caused[243]. On the other hand, CTGF could directly cause skeletal muscle deterioration when the development of DMD was underway. Muscles which overexpressed CTGF was found a larger necrotic damage area. Followed by necrotic damage, regeneration of muscle tissues which is also induced by overexpressed CTGF was observed. These necrotic regenerative foci could be decreased by reducing CTGF level artificially[243,244]. To muscle fibrosis caused by other reasons, CTGF is also essential. Treating fibrosis by FG-3019 in a rat model of overuse injury, fibrosis-related proteins were significantly decreased[245,246].

Because of the tight connection between CTGF and DMD, CTGF has been considered as a potential therapeutic target for the treatment of DMD. In mdx mice, after deleting the expression of CTGF, both muscle strength, skeletal muscle impairment, apoptotic damage and fibrosis were found to be improved[247]. Furthermore, a phase 2 trial evaluation has already demonstrated a positive result made by FG-3019 to ameliorate pulmonary and

cardiac dysfunction, which are two of the main reasons leading to DMD mortality. Besides, it could preserve the function of the upper limbs too (NCT02606136). In addition, some other therapies were discovered to have good prospects to treat DMD by downregulating CTGF. Firstly, angiotensin-converting enzyme inhibitors like enalapril could improve skeletal muscle fibrosis in mdx mice by reducing the increment of CTGF level. Next, it has been shown that the AT-1R is associated with the progression of CTGF-dependent skeletal muscle fibrosis. It was reported that the AT-1R was needed when CTGF exerted its biological response. The use of AT-1R blockers could not only decrease the level of CTGF but also block the activity of CTGF and improve fibrosis in mdx model[248,249].

6.1.6. *Systemic sclerosis*

SSc is a complex autoimmune rheumatic disease with fibrotic, inflammatory and vasculopathy manifestations. The disease influences individuals from the skin to organs like lung, renal, heart and even placentas[250–252]. In sclerotic lesions from SSc patients, the expression of *CTGF* could be observed in fibroblasts[10]. The activated CTGF signaling may be affected by fibroblast growth factor receptor 3 signaling[253]. Tight connection between the expression of *CTGF* mRNA and diffuse cutaneous SSc makes *CTGF* mRNA a creditable biomarker for the prediction of skin disease during the progression of diffuse cutaneous SSc[254]. Undoubtedly, CTGF could be considered as an ideal target for the treatment of skin fibrosis in SSc. COA-Cl (6-amino-2-chloro-9-[*trans-trans*-2,3-bis(hydroxy-methyl) cyclobutyl]purine), iloprost and pomalidomide have already been found to control the disease by influencing the expression of CTGF[255–258]. Some studies have tried to analyze the relationship between CTGF and SSc deeply in the level of the gene. In the previous study, the polymorphism (G-945C) in the promoter of *CTGF* gene was tested. It was found that −945G allele was important for the susceptibility to SSc. Notably, in the French population, the situation became a little bit different. The frequency of the rs939905TT genotype was lower in SSc patients than rs6918698 in SSC patients. However, in another study, *CTGF*-945 promoter polymorphism did not show relevance to SSc susceptibility[259–262].

6.2. *Cancer*

6.2.1. *Pancreatic cancer*

As a highly aggressive solid tumor, pancreatic ductal adenocarcinoma is a severe disease with a 5-year survival rate of less than 7%. In 2020, 57,600 pancreatic ductal adenocarcinoma cases were newly diagnosed, while 47,050 patients died in 2020[263]. It has been found that the expression of CTGF is increased in pancreatic cancer, α-SMA-positive and E-cadherin-negative fibroblasts, particularly[26]. In different types of human cell lines of pancreatic cancer, PANC-1 and MIAPaCa-2 have the highest *CTGF* mRNA level[264]. CTGF is important for the activation of pancreatic stellate cells, which could create a fibrotic environment by producing many extracellular matrix proteins to facilitate tumor growth[5]. Thus, it is conceivable that CTGF could be considered as a target for the treatment of pancreatic cancer. The data showed that CTGF-specific mAb could reduce the volume of tumors by inducing apoptosis[265]. Similarly, shRNA was used to knockdown *CTGF* and successfully induced hypoxia-mediated apoptosis of tumor cells[266]. Therapeutic peptides derived from the endogenous inhibitor of CTGF had similar effect on the treatment of pancreatic cancer. The mechanism may be related to the reorganization of the tumor microenvironment[31].

Gemcitabine is the first-line drug for the treatment of patients with pancreatic ductal adenocarcinoma. However, the resistance to chemotherapy, which is tightly related to extracellular matrix proteins and desmoplastic reaction, is a major disadvantage that limits the efficacy of the drug. It was discovered that pentoxifylline could improve the delivery and efficiency of gemcitabine by decreasing the level of extracellular matrix proteins like collagen and CTGF[267]. Besides, CCN1 has been found to suppress deoxycytidine kinase, an enzyme could activate gemcitabine, and induce desmoplastic reaction-promoting factor CTGF to protect pancreatic cancer cells from gemcitabine which means that the combination therapy containing drugs which could suppress CTGF may inhibit the drug resistance[268]. In the phase 3 trial, FG-3019 (pamrevlumab) were administered with or without gemcitabine plus Nab-paclitaxel to treat locally advanced, unresectable pancreatic cancer. Moreover, the clinical data from the phase 2 trial showed a significant improvement of prognosis. Not only the population of patients eligible for surgery, but also the overall survival and progression-free survival were remarkably raised (NCT02210559).

6.2.2. *Breast cancer*

GLOBOCAN reported that the breast cancer was the most common disease in Chinese women. In 2008, the incidence of breast cancer was just lower than lung cancer, gastric cancer, liver cancer, oesophageal cancer and colorectal cancer[269]. For men, the risk of breast cancer is much lower[270]. It has been reported that, in 24 of 44 breast tumor samples, the overexpression of *CTGF* is observed. It was hypothesized that CTGF might contribute to breast cancer by boosting angiogenesis[27,271]. The activation of estrogenic GPR30 signaling by hydroxytamoxifen could lead to the upregulation of the CTGF expression level and it would induce proliferation and migration of oestrogen receptor-negative human breast cancer[272]. In contrast, another study indicated that CTGF might act as a suppressor of the progression of breast cancer[25].

The opposite result may be due to the diverse effects of CTGF on different breast cancer cells. Some studies have found that CTGF could confer drug resistance on human breast cancer by the upregulation of Bcl-xL and cellular inhibitor of apoptosis protein 1. However, when *CTGF* was knocked down, the resistance would reverse[273,274]. Nevertheless, in another study, when *CTGF* was overexpressed in transiently transfected MCF-7 cells, cell viability was significantly decreased. The addition of CTGF increased the number of apoptotic MCF-7 cells and this effect was dose-dependent[121]. In a word, more explorations need to be conducted to elucidate the role CTGF plays in the development of breast cancer.

6.2.3. *Lung cancer*

Lung cancer is a huge threat to human health. Most lung cancer cases could be attributed to non-small cell lung cancer. Unlike other cancers we have already mentioned before, in preliminary studies, CTGF was found to play a collapsin response mediator protein 1-dependent suppressive role in invasion and metastasis of lung adenocarcinoma. The result was consistent with the situation of *CTGF* mRNA level and CTGF protein level in cancerous tissues of non-small cell lung cancer patients[275]. The inhibited function of CTGF may be achieved by promoting the degradation of hypoxia-inducible factor 1α protein and suppressing the VEGF-A-dependent angiogenesis[24,128]. Lung cancer is not the only

cancer that could be negatively influenced by CTGF. Wilms' tumor and nasopharyngeal carcinoma are also repressed by CTGF[99,276,277] (Fig. 3B). However, some other studies found that CTGF could positively regulate the migration and invasion of non-small cell lung cancer cells[278].

6.2.4. *Bone metastasis*

Bone metastasis is a serious complication of cancer. Most tumors metastasize to the spine, pelvis, skull, ribs, proximal humeri and femora[279]. 70% of patients having advanced breast or prostate cancer were found to have bone metastasis[280]. The metastasis has been divided into osteolytic and osteoblastic. However, the osteolytic and osteoblastic lesions could exist at the same time[281]. For bone-metastatic breast and prostate cancer cells like MDA-MB-231 and PC3, the signal intensity of CTGF was higher than nonmetastatic cells. In mtMDA and mtPC3 cells (sublines of MDA and PC3), the expression level of CTGF was higher than that in parental cell lines. It indicated that CTGF may be one of the elements to promote the bone metastasis[282]. The promotion of breast cancer osteolytic metastasis made by CTGF was thought to cooperate with other proteins like IL-11 and osteopontin[283]. Except for breast and prostate cancer bone metastases, the same situation happened in hepatic cancer bone metastasis. 3.63-times higher *CTGF* level was found in hepatic cancer bone-metastatic sample than nonmetastatic sample[284].

CTGF-related treatment has shown efficacy for treating bone metastasis. CTGF antibody was used to treat bone metastasis in mice. It significantly inhibited the osteolytic bone metastasis[285]. MiR-30s could target multiple genes associated with breast cancer bone metastasis to reduce metastasis, and *CTGF* is one of the genes[286]. Besides, in the hepatic cancer bone metastasis model, miR-30a was also effective. It could inhibit migration, invasion and proliferation of hepatic cancer cells *in vitro*, and inhibit the bone metastasis *in vivo*[287]. Affecting the CTGF-related signaling pathway to decrease CTGF could also inhibit bone metastasis. SD-208, a TGF-β receptor I kinase, was used to treat mice with melanoma bone metastasis. After four-week treatment, the development of bone metastasis was inhibited both in therapeutic and preventive protocols[288]. Besides, the blockade of the TGF-β signaling pathway by halofuginone, a plant alkaloid, did the same as SD-208. The bone metastasis and brain metastasis of melanoma were both decreased[289]. Hence, anti-CTGF therapy may not be limited to bone metastasis.

6.3. *Other diseases*

6.3.1. *Major depressive disorder*

More and more studies have found that CTGF dose not just play a role in the progression of fibrosis and cancer. Its contribution to pathological conditions was underestimated. Also, CTGF regulation patterns in many other diseases have already been uncovered (Fig. 4). Major depressive disorder is one of the diseases that has been reported to be linked with CTGF. In the study investigating the association between depression and blood gene expression, *COL1A2*, *RNF150* and *CTGF* were found to be the most relevant genes for depression[21]. Further, the use of CTGF in rats made the condition of depression worse. However, the treatment with FG-3019 has been proven to be antidepressant[290].

6.3.2. *Central neurodegenerative diseases*

Amyotrophic lateral sclerosis (ALS) features the degeneration of motoneurons and waste of skeletal muscles. Not only in the spinal cord but also in the skeletal muscle, the abnormal expression of CTGF was observed. The specimens from patients with sporadic and familial ALS were assessed. The upregulation of CTGF mainly occurred in reactive astrocytes and led to astrogliosis[23]. Moreover, in $hSOD1^{G93A}$ mice, a widely-used murine ALS model, TGF-β signaling pathway and level of CTGF were induced in skeletal muscles[291]. It has been observed that blocking CTGF in $hSOD1^{G93A}$ mice leads to the improvement of both skeletal muscular and neural functions[292].

For the treatment of AD, the opinions are more complicated. It is a common view that the expression level of CTGF is high in plaques-associated place in the brain of AD patients[293,294]. But how CTGF works in the progression of AD is still a matter of debate. In Tg2576, an AD-type amyloid neuropathology mice model, the AD-type amyloid plaque was promoted together with the increase of CTGF and then exacerbated AD. When the level of CTGF was reduced by an endogenous bile acid named TUDCA, amyloid plaques were decreased[295,296]. However, the upregulation of CTGF in amyloid plaques-related tissues is also conversely regarded as a protective reaction that facilitates the uptake and degradation of Aβ[172]. Moreover, the highly-expressed CTGF could bind with substances like DAG peptide. In this way, DAG could be used to deliver therapeutic agents into the brain[297]. In addition, although the mechanism has not been completely understood yet, the connection have been found between neuroinflammation-induced dopaminergic neurotoxicity and CTGF in other neurodegenerative diseases like Parkinson's disease[298].

6.3.3. *Non-healing wounds*

Diabetes is always accompanied by chronic non-healing wounds that would eventually lead to the amputation of organs and limbs. In the diabetic baboon, decreased CTGF was found in wounded tissues[299]. Some CTGF-related treatments have been applied to improve non-healing conditions recently, like CTGF loaded electrospun dual porous core−shell membrane and cold atmospheric plasma. The former used electrospun PLA−PVA core−shell membranes to supply CTGF in a slow and sustained way directly[300]. The latter was based on the inactivation of the Hippo signaling pathway mediated by cold atmospheric plasma[301]. The cold atmospheric plasma therapy has already shown a significant effect on the treatment of diabetic foot ulcers in a randomized clinical trial[302].

6.3.4. *Hypertrophic scar*

On the contrary, the excessive expression of CTGF during wound healing would cause hypertrophic scar (HS). Excessive CTGF stimulated by TGF-β, miR-6836-3p, adipose-derived stem cell, etc. would mediate the profibrotic effects of angiotensin II and lead to the overactivation of the renin-angiotensin system. Eventually, HS and keloids developed[303−306]. Because of the tight connection between CTGF and HS development, *CTGF* mRNA could be used as a prototype genetic target for the early non-invasive detection of wound[307]. The expression level of CTGF was also downregulated by different approaches to treat HS. For instance, a cell-penetrating asymmetric interfering RNA could be used as anti-scar drugs by inhibiting the induction of CTGF and collagen[308]. Besides, EXC 001, an antisense oligonucleotide that could inhibit CTGF has shown great effect on reducing postsurgical skin scars[309].

6.3.5. *Eye diseases*

Expression of CTGF contributes to the progression of many eye diseases of which diabetic retinopathy (DR) and glaucoma are

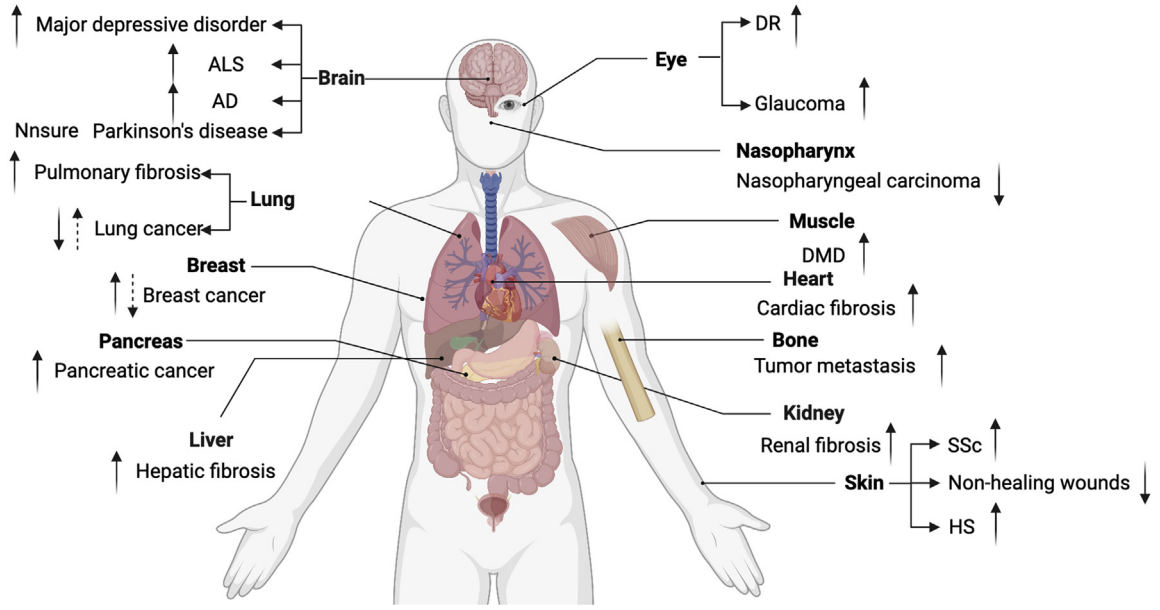

Figure 4 The summary of the expression of CTGF in various diseases compared to normal conditions.

most widely known. In patients with DR, the distribution and level of CTGF were different from that in normal condition[310]. The level of CTGF was significantly increased in retina[311]. Overexpressed CTGF may influence DR through retinal apoptosis and switching angiogenesis to fibrosis[311,312]. ACE inhibitors, SERPINA3K, siRNA, which could decrease CTGF level, were found to be effective in attenuating DR[311,313,314]. When making dual-target intervention with VEGF inhibitor, targeted therapy against CTGF could cause less damage and have greater effectiveness[315]. CTGF level was higher in both tear fluid and aqueous humor in pseudoexfoliative glaucoma patients compared to that in pseudoexfoliation syndrome patients without glaucoma[19,316]. In primary open-angle glaucoma, the level was also increased, and it may be associated with the lack of decorin[19,317]. With regards to the treatment of glaucoma, the efficacy of CTGF intervention has been demonstrated *in vitro*. Some new therapies like hyaluronan-coated nanoparticles combined with RNA interference were designed to treat glaucoma through this rationale. However, the further *in vivo* evaluations are needed[318,319]. In addition, some other diseases like ischemic retinopathy and proliferative vitreoretinal diseases could be possibly treated by downregulating CTGF[320,321].

7. Conclusion and prospect

Overall, CTGF demonstrates its different functions by interacting with certain molecules such as VEGF, TGF-β or BMP *via* four conserved modular. Specific organism conditions would spatiotemporally influence the regulation of CTGF by diverse signaling pathways. Physiologically, the expression of CTGF contributes to the regulation of different systems and organs, *i.e.*, the skeletal system, pancreas, central nervous system, skin, tooth, etc. Moreover, CTGF plays vital roles in the pathogenesis and progression of various diseases. For instance, fibrosis in most of tissues is associated with the upregulation of CTGF. Additionally, the effects of CTGF on cancer progression are more complex, which mainly depend on the cancer types and specific cases.

Although it has been found that CTGF-targeted therapies, such as antibody FG-3019, are effective in treating related diseases in several clinical trials, CTGF is related to a much wider range of diseases and physiological functions. Several points might be addressed for future development of CTGF-targeted therapy. Firstly, the development of a new drug might be underpinned by the uncover of the underlying mechanisms where CTGF contributes to disease progression. Therefore, more efforts should be continuously paid to investigate the basic functions CTGF in various disease. Secondly, the improved understanding of signaling networks, as well as complex microenvironment *in vivo*, might lead to the utilization of combinational therapeutic strategies, like dual pathway inhibitors. Thirdly, the development of nanotechnology platform (nano-delivery systems) and gene editing platform (Cas9) might largely accelerate the translational research of drug candidate targeting CTGF in future.

Under particular external stimulation and ligand interaction, the signaling pathways related to CTGF synthesis would be activated. Certain transcription factors would be recruited to the nucleus and finally lead to *CTGF* transcription and CTGF secretion. After the secretion, four different domains of CTGF containing IGFBP, VWC, TSP1 and CT could interact with various substances and play physiological functions, *i.e.*, insulin-like growth factors interact with IGFBP domain; TGF-β, bone morphogenetic proteins (BMPs) and aggrecan interact with VWC domain; vascular endothelial growth factor (VEGF), low-density lipoprotein-related proteins (LRPs) and integrins interact with TSP1 domain; fibronectin (FN), heparan sulfate proteoglycans (HSPGs), LRPs and integrins interact with CT domain.

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Author contributions

Yuquan Wei and Xiawei Wei offered main direction and significant guidance of this manuscript. Minyang Fu, Dandan Peng and Tianxia Lan drafted the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Bradham DM, Igarashi A, Potter RL, Grotendorst GR. Connective tissue growth factor: a cysteine-rich mitogen secreted by human vascular endothelial cells is related to the SRC-induced immediate early gene product CEF-10. *J Cell Biol* 1991;**114**:1285−94.
2. Makino Y, Hikita H, Kodama T, Shigekawa M, Yamada R, Sakamori R, et al. CTGF mediates tumor−stroma interactions between hepatoma cells and hepatic stellate cells to accelerate HCC progression. *Cancer Res* 2018;**78**:4902−14.
3. Mulsow JJ, Watson RW, Fitzpatrick JM, O'Connell PR. Transforming growth factor-beta promotes pro-fibrotic behavior by serosal fibroblasts *via* PKC and ERK1/2 mitogen activated protein kinase cell signaling. *Ann Surg* 2005;**242**:880−9.
4. Pan LH, Yamauchi K, Uzuki M, Nakanishi T, Takigawa M, Inoue H, et al. Type II alveolar epithelial cells and interstitial fibroblasts express connective tissue growth factor in IPF. *Eur Respir J* 2001;**17**:1220−7.
5. Shen YW, Zhou YD, Luan X, Zhang WD. Blocking CTGF-mediated tumor-stroma interplay in pancreatic cancer. *Trends Mol Med* 2020;**26**:1064−7.
6. Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E. Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. *J Cell Physiol* 2008;**215**:410−21.
7. Chen Z, Zhang N, Chu HY, Yu Y, Zhang ZK, Zhang G, et al. Connective tissue growth factor: from molecular understandings to drug discovery. *Front Cell Dev Biol* 2020;**8**:593269.
8. Kubota S, Takigawa M. Cellular and molecular actions of CCN2/CTGF and its role under physiological and pathological conditions. *Clin Sci* 2015;**128**:181−96.
9. Huang GC, Brigstock DR. Regulation of hepatic stellate cells by connective tissue growth factor. *Front Biosci* 2012;**17**:2495−507.
10. Igarashi A, Nashiro K, Kikuchi K, Sato S, Ihn H, Grotendorst GR, et al. Significant correlation between connective tissue growth factor gene expression and skin sclerosis in tissue sections from patients with systemic sclerosis. *J Invest Dermatol* 1995;**105**:280−4.
11. Ito Y, Aten J, Bende RJ, Oemar BS, Rabelink TJ, Weening JJ, et al. Expression of connective tissue growth factor in human renal fibrosis. *Kidney Int* 1998;**53**:853−61.
12. Koitabashi N, Arai M, Kogure S, Niwano K, Watanabe A, Aoki Y, et al. Increased connective tissue growth factor relative to brain natriuretic peptide as a determinant of myocardial fibrosis. *Hypertension* 2007;**49**:1120−7.
13. Plantier L, Renaud H, Respaud R, Marchand-Adam S, Crestani B. Transcriptome of cultured lung fibroblasts in idiopathic pulmonary fibrosis: meta-analysis of publicly available microarray datasets reveals repression of inflammation and immunity pathways. *Int J Mol Sci* 2016;**17**:2091.
14. Sun G, Haginoya K, Wu Y, Chiba Y, Nakanishi T, Onuma A, et al. Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. *J Neurol Sci* 2008;**267**:48−56.
15. Khaja F, Jayawardena D, Kuzmis A, Onyuksel H. Targeted sterically stabilized phospholipid siRNA nanomedicine for hepatic and renal fibrosis. *Nanomaterials (Basel)* 2016;**6**:8.
16. Li S, Lv YF, Su HQ, Zhang QN, Wang LR, Hao ZM. A virus-like particle-based connective tissue growth factor vaccine suppresses carbon tetrachloride-induced hepatic fibrosis in mice. *Sci Rep* 2016;**6**:32155.
17. Qiao G, Xia D, Cheng Z, Zhang G. miR132 in atrial fibrillation directly targets connective tissue growth factor. *Mol Med Rep* 2017;**16**:4143−50.
18. Richeldi L, Fernández Pérez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, et al. Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2020;**8**:25−33.
19. Browne JG, Ho SL, Kane R, Oliver N, Clark AF, O'Brien CJ, et al. Connective tissue growth factor is increased in pseudoexfoliation glaucoma. *Invest Ophthalmol Vis Sci* 2011;**52**:3660−6.
20. Hinton DR, Spee C, He S, Weitz S, Usinger W, LaBree L, et al. Accumulation of NH_2-terminal fragment of connective tissue growth factor in the vitreous of patients with proliferative diabetic retinopathy. *Diabetes Care* 2004;**27**:758−64.
21. Miao X, Fan B, Li R, Zhang S, Lin H. Network analysis of depression-related transcriptomic profiles. *Neuromolecular Med* 2019;**21**:143−9.
22. Shen YW, Zhou YD, Chen HZ, Luan X, Zhang WD. Targeting CTGF in cancer: an emerging therapeutic opportunity. *Trends Cancer* 2020;**7**:511−24.
23. Spliet WG, Aronica E, Ramkema M, Aten J, Troost D. Increased expression of connective tissue growth factor in amyotrophic lateral sclerosis human spinal cord. *Acta Neuropathol* 2003;**106**:449−57.
24. Chang CC, Lin MT, Lin BR, Jeng YM, Chen ST, Chu CY, et al. Effect of connective tissue growth factor on hypoxia-inducible factor 1alpha degradation and tumor angiogenesis. *J Natl Cancer Inst* 2006;**98**:984−95.
25. Jiang WG, Watkins G, Fodstad O, Douglas-Jones A, Mokbel K, Mansel RE. Differential expression of the CCN family members Cyr61, CTGF and Nov in human breast cancer. *Endocr Relat Cancer* 2004;**11**:781−91.
26. Neesse A, Frese KK, Bapiro TE, Nakagawa T, Sternlicht MD, Seeley TW, et al. CTGF antagonism with mAb FG-3019 enhances chemotherapy response without increasing drug delivery in murine ductal pancreas cancer. *Proc Natl Acad Sci U S A* 2013;**110**:12325−30.
27. Xie D, Nakachi K, Wang H, Elashoff R, Koeffler HP. Elevated levels of connective tissue growth factor, WISP-1, and CYR61 in primary breast cancers associated with more advanced features. *Cancer Res* 2001;**61**:8917−23.
28. Braig S, Wallner S, Junglas B, Fuchshofer R, Bosserhoff AK. CTGF is overexpressed in malignant melanoma and promotes cell invasion and migration. *Br J Cancer* 2011;**105**:231−8.
29. Chien W, Yin D, Gui D, Mori A, Frank JM, Said J, et al. Suppression of cell proliferation and signaling transduction by connective tissue growth factor in non-small cell lung cancer cells. *Mol Cancer Res* 2006;**4**:591−8.
30. Picozzi V, Alseidi A, Winter J, Pishvaian M, Mody K, Glaspy J, et al. Gemcitabine/nab-paclitaxel with pamrevlumab: a novel drug combination and trial design for the treatment of locally advanced pancreatic cancer. *ESMO Open* 2020;**5**:e000668.
31. Resovi A, Borsotti P, Ceruti T, Passoni A, Zucchetti M, Berndt A, et al. CCN-based therapeutic peptides modify pancreatic ductal adenocarcinoma microenvironment and decrease tumor growth in combination with chemotherapy. *Cells* 2020;**9**:952.
32. Kim H, Son S, Shin I. Role of the CCN protein family in cancer. *BMB Reports* 2018;**51**:486−92.
33. Li J, Ye L, Owen S, Weeks HP, Zhang Z, Jiang WG. Emerging role of CCN family proteins in tumorigenesis and cancer metastasis (Review). *Int J Mol Med* 2015;**36**:1451−63.
34. Perbal B. CCN proteins: multifunctional signalling regulators. *Lancet* 2004;**363**:62−4.

35. Sitar T, Popowicz GM, Siwanowicz I, Huber R, Holak TA. Structural basis for the inhibition of insulin-like growth factors by insulin-like growth factor-binding proteins. *Proc Natl Acad Sci U S A* 2006; **103**:13028−33.
36. Wang S, Denichilo M, Brubaker C, Hirschberg R. Connective tissue growth factor in tubulointerstitial injury of diabetic nephropathy. *Kidney Int* 2001;**60**:96−105.
37. Lam S, van der Geest RN, Verhagen NAM, van Nieuwenhoven FA, Blom IE, Aten J, et al. Connective tissue growth factor and IGF-I are produced by human renal fibroblasts and cooperate in the induction of collagen production by high glucose. *Diabetes* 2003;**52**: 2975−83.
38. Abreu JG, Ketpura NI, Reversade B, De Robertis EM. Connective-tissue growth factor (CTGF) modulates cell signalling by BMP and TGF-beta. *Nat Cell Biol* 2002;**4**:599−604.
39. Zhang JL, Huang Y, Qiu LY, Nickel J, Sebald W. von Willebrand factor type C domain-containing proteins regulate bone morphogenetic protein signaling through different recognition mechanisms. *J Biol Chem* 2007;**282**:20002−14.
40. Nguyen TQ, Roestenberg P, van Nieuwenhoven FA, Bovenschen N, Li Z, Xu L, et al. CTGF inhibits BMP-7 signaling in diabetic nephropathy. *J Am Soc Nephrol* 2008;**19**:2098−107.
41. Mundy C, Gannon M, Popoff SN. Connective tissue growth factor (CTGF/CCN2) negatively regulates BMP-2 induced osteoblast differentiation and signaling. *J Cell Physiol* 2014;**229**:672−81.
42. Lawler J, Hynes RO. The structure of human thrombospondin, an adhesive glycoprotein with multiple calcium-binding sites and homologies with several different proteins. *J Cell Biol* 1986;**103**: 1635−48.
43. Tucker RP. The thrombospondin type 1 repeat superfamily. *Int J Biochem Cell Biol* 2004;**36**:969−74.
44. Xu ER, Lafita A, Bateman A, Hyvonen M. The thrombospondin module 1 domain of the matricellular protein CCN3 shows an atypical disulfide pattern and incomplete CWR layers. *Acta Crystallogr D Struct Biol* 2020;**76**:124−34.
45. Inoki I, Shiomi T, Hashimoto G, Enomoto H, Nakamura H, Makino K, et al. Connective tissue growth factor binds vascular endothelial growth factor (VEGF) and inhibits VEGF-induced angiogenesis. *FASEB J* 2002;**16**:219−21.
46. Li C, Zhen G, Chai Y, Xie L, Crane JL, Farber E, et al. RhoA determines lineage fate of mesenchymal stem cells by modulating CTGF−VEGF complex in extracellular matrix. *Nat Commun* 2016;**7**: 11455.
47. Gao R. Low density lipoprotein receptor-related protein (LRP) is a heparin-dependent adhesion receptor for connective tissue growth factor (CTGF) in rat activated hepatic stellate cells. *Hepatol Res* 2003;**27**:214−20.
48. Heng EC, Huang Y, Black Jr SA, Trackman PC. CCN2, connective tissue growth factor, stimulates collagen deposition by gingival fibroblasts *via* module 3 and alpha6- and beta1 integrins. *J Cell Biochem* 2006;**98**:409−20.
49. Tong ZY, Brigstock DR. Intrinsic biological activity of the thrombospondin structural homology repeat in connective tissue growth factor. *J Endocrinol* 2006;**188**:R1−8.
50. Johnson BG, Ren S, Karaca G, Gomez IG, Fligny C, Smith B, et al. Connective tissue growth factor domain 4 amplifies fibrotic kidney disease through activation of LDL receptor-related protein 6. *J Am Soc Nephrol* 2017;**28**:1769−82.
51. Ohkawara B, Kobayakawa A, Kanbara S, Hattori T, Kubota S, Ito M, et al. CTGF/CCN2 facilitates LRP4-mediated formation of the embryonic neuromuscular junction. *EMBO Rep* 2020;**21**:e48462.
52. Gao R, Brigstock DR. Connective tissue growth factor (CCN2) induces adhesion of rat activated hepatic stellate cells by binding of its C-terminal domain to integrin $\alpha_v\beta_3$ and heparan sulfate proteoglycan. *J Biol Chem* 2004;**279**:8848−55.
53. Gao R, Brigstock DR. A novel integrin alpha5beta1 binding domain in module 4 of connective tissue growth factor (CCN2/CTGF) promotes adhesion and migration of activated pancreatic stellate cells. *Gut* 2006;**55**:856−62.
54. Pi L, Ding X, Jorgensen M, Pan JJ, Oh SH, Pintilie D, et al. Connective tissue growth factor with a novel fibronectin binding site promotes cell adhesion and migration during rat oval cell activation. *Hepatology* 2008;**47**:996−1004.
55. Ball DK, Rachfal AW, Kemper SA, Brigstock DR. The heparin-binding 10 kDa fragment of connective tissue growth factor (CTGF) containing module 4 alone stimulates cell adhesion. *J Endocrinol* 2003;**176**:R1−7.
56. Ono M, Kubota S, Fujisawa T, Sonoyama W, Kawaki H, Akiyama K, et al. Promotion of hydroxyapatite-associated, stem cell-based bone regeneration by CCN2. *Cell Transplant* 2008;**17**:231−40.
57. Xu R, Zhang Z, Toftdal MS, Moller AC, Dagnaes-Hansen F, Dong M, et al. Synchronous delivery of hydroxyapatite and connective tissue growth factor derived osteoinductive peptide enhanced osteogenesis. *J Control Release* 2019;**301**:129−39.
58. Liu BC, Zhang JD, Zhang XL, Wu GQ, Li MX. Role of connective tissue growth factor (CTGF) module 4 in regulating epithelial mesenchymal transition (EMT) in HK-2 cells. *Clin Chim Acta* 2006; **373**:144−50.
59. Lv L, Liu FR, Na D, Xu HM, Wang ZN, Jiang CG. Transforming growth factor-beta1 induces connective tissue growth factor expression and promotes peritoneal metastasis of gastric cancer. *Biosci Rep* 2020;**40**:BSR20201501.
60. Kim KH, Park GT, Lim YB, Rue SW, Jung JC, Sonn JK, et al. Expression of connective tissue growth factor, a biomarker in senescence of human diploid fibroblasts, is up-regulated by a transforming growth factor-β-mediated signaling pathway. *Biochem Biophys Res Commun* 2004;**318**:819−25.
61. Ruperez M, Lorenzo O, Blanco-Colio LM, Esteban V, Egido J, Ruiz-Ortega M. Connective tissue growth factor is a mediator of angiotensin II-induced fibrosis. *Circulation* 2003;**108**:1499−505.
62. Meng G, Wuest M, Tang X, Dufour J, McMullen TPW, Wuest F, et al. Dexamethasone attenuates X-ray-induced activation of the autotaxin-lysophosphatidate-inflammatory cycle in breast tissue and subsequent breast fibrosis. *Cancers (Basel)* 2020;**12**:999.
63. Guo Y, Yuan W, Wang L, Shang M, Peng Y. Parathyroid hormone-potentiated connective tissue growth factor expression in human renal proximal tubular cells through activating the MAPK and NF-κB signalling pathways. *Nephrol Dial Transplant* 2011;**26**:839−47.
64. Pap D, Veres-Szekely A, Szebeni B, Rokonay R, Onody A, Lippai R, et al. Characterization of IL-19, -20, and -24 in acute and chronic kidney diseases reveals a pro-fibrotic role of IL-24. *J Transl Med* 2020;**18**:172.
65. Tran CM, Fujita N, Huang BL, Ong JR, Lyons KM, Shapiro IM, et al. Hypoxia-inducible factor (HIF)-1α and CCN2 form a regulatory circuit in hypoxic nucleus pulposus cells: CCN2 suppresses HIF-1α level and transcriptional activity. *J Biol Chem* 2013;**288**:12654−66.
66. Finger EC, Cheng CF, Williams TR, Rankin EB, Bedogni B, Tachiki L, et al. CTGF is a therapeutic target for metastatic melanoma. *Oncogene* 2014;**33**:1093−100.
67. Ruehle MA, Eastburn EA, LaBelle SA, Krishnan L, Weiss JA, Boerckel JD, et al. Extracellular matrix compression temporally regulates microvascular angiogenesis. *Sci Adv* 2020;**6**:eabb6351.
68. Ramazani Y, Knops N, Elmonem MA, Nguyen TQ, Arcolino FO, van den Heuvel L, et al. Connective tissue growth factor (CTGF) from basics to clinics. *Matrix Biol* 2018;**68−69**:44−66.
69. Astone M, Lai JKH, Dupont S, Stainier DYR, Argenton F, Vettori A. Zebrafish mutants and TEAD reporters reveal essential functions for YAP and TAZ in posterior cardinal vein development. *Sci Rep* 2018; **8**:10189.
70. Cao X, Zhao B. Quantitative real-time PCR to measure YAP/TAZ activity in human cells. *Methods Mol Biol* 2019;**1893**:137−52.
71. Yang W, Han W, Qin A, Wang Z, Xu J, Qian Y. The emerging role of Hippo signaling pathway in regulating osteoclast formation. *J Cell Physiol* 2018;**233**:4606−17.

72. Anwar T, Sinnett-Smith J, Jin YP, Reed EF, Rozengurt E. Ligation of HLA class I molecules induces YAP activation through SRC in human endothelial cells. *J Immunol* 2020;**205**:1953−61.
73. Sarmasti Emami S, Zhang D, Yang X. Interaction of the Hippo pathway and phosphatases in tumorigenesis. *Cancers (Basel)* 2020; **12**:2438.
74. Vanyai HK, Prin F, Guillermin O, Marzook B, Boeing S, Howson A, et al. Control of skeletal morphogenesis by the Hippo-YAP/TAZ pathway. *Development* 2020;**147**:dev187187.
75. Wang Z, Liu P, Zhou X, Wang T, Feng X, Sun YP, et al. Endothelin promotes colorectal tumorigenesis by activating YAP/TAZ. *Cancer Res* 2017;**77**:2413−23.
76. Luo M, Meng Z, Moroishi T, Lin KC, Shen G, Mo F, et al. Heat stress activates YAP/TAZ to induce the heat shock transcriptome. *Nat Cell Biol* 2020;**22**:1447−59.
77. Zheng L, Zhang L, Chen L, Jiang J, Zhou X, Wang M, et al. Static magnetic field regulates proliferation, migration, differentiation, and YAP/TAZ activation of human dental pulp stem cells. *J Tissue Eng Regen Med* 2018;**12**:2029−40.
78. Lee TF, Liu YP, Lin YF, Hsu CF, Lin H, Chang WC, et al. TAZ negatively regulates the novel tumor suppressor ANKRD52 and promotes PAK1 dephosphorylation in lung adenocarcinomas. *Biochim Biophys Acta Mol Cell Res* 2020;**1868**:118891.
79. Marquard S, Thomann S, Weiler SME, Bissinger M, Lutz T, Sticht C, et al. Yes-associated protein (YAP) induces a secretome phenotype and transcriptionally regulates plasminogen activator inhibitor-1 (PAI-1) expression in hepatocarcinogenesis. *Cell Commun Signal* 2020;**18**:166.
80. Moon S, Lee S, Caesar JA, Pruchenko S, Leask A, Knowles JA, et al. A CTGF−YAP regulatory pathway is essential for angiogenesis and barriergenesis in the retina. *iScience* 2020;**23**:101184.
81. Geisinger MT, Astaiza R, Butler T, Popoff SN, Planey SL, Arnott JA. Ets-1 is essential for connective tissue growth factor (CTGF/CCN2) induction by TGF-beta1 in osteoblasts. *PLoS One* 2012;**7**:e35258.
82. Van Beek JP, Kennedy L, Rockel JS, Bernier SM, Leask A. The induction of CCN2 by TGFβ1 involves Ets-1. *Arthritis Res Ther* 2006;**8**:R36.
83. Nakerakanti SS, Kapanadze B, Yamasaki M, Markiewicz M, Trojanowska M. Fli1 and Ets1 have distinct roles in connective tissue growth factor/CCN2 gene regulation and induction of the profibrotic gene program. *J Biol Chem* 2006;**281**:25259−69.
84. Yordy JS, Moussa O, Pei H, Chaussabel D, Li R, Watson DK. SP100 inhibits ETS1 activity in primary endothelial cells. *Oncogene* 2005; **24**:916−31.
85. Raouf A, Seth A. Ets transcription factors and targets in osteogenesis. *Oncogene* 2000;**19**:6455−63.
86. Li L, Zhang S, Wei L, Wang Z, Ma W, Liu F, et al. Anti-fibrotic effect of melittin on TRIM47 expression in human embryonic lung fibroblast through regulating TRIM47 pathway. *Life Sci* 2020;**256**: 117893.
87. Reyes-Martinez C, Nguyen QM, Kassan M, Gonzalez AA. (Pro)renin receptor-dependent induction of profibrotic factors is mediated by COX-2/EP4/NOX-4/Smad pathway in collecting duct cells. *Front Pharmacol* 2019;**10**:803.
88. Sun X, Cui X, Chen X, Jiang X. Baicalein alleviated TGF β1-induced type I collagen production in lung fibroblasts *via* downregulation of connective tissue growth factor. *Biomed Pharmacother* 2020;**131**: 110744.
89. Luo H, Li L, Tang J, Zhang F, Zhao F, Sun D, et al. Amygdalin inhibits HSC-T6 cell proliferation and fibrosis through the regulation of TGF-β/CTGF. *Mol Cell Toxicol* 2016;**12**:265−71.
90. Sakai N, Chun J, Duffield JS, Wada T, Luster AD, Tager AM. LPA1-induced cytoskeleton reorganization drives fibrosis through CTGF-dependent fibroblast proliferation. *FASEB J* 2013;**27**:1830−46.
91. Cheng JC, Wang EY, Yi Y, Thakur A, Tsai SH, Hoodless PA. S1P stimulates proliferation by upregulating CTGF expression through S1PR2-mediated YAP activation. *Mol Cancer Res* 2018;**16**: 1543−55.
92. Ding S, Duan H, Fang F, Shen H, Xiao W. CTGF promotes articular damage by increased proliferation of fibroblast-like synoviocytes in rheumatoid arthritis. *Scand J Rheumatol* 2016;**45**:282−7.
93. Wang WB, Li HP, Yan J, Zhuang F, Bao M, Liu JT, et al. CTGF regulates cyclic stretch-induced vascular smooth muscle cell proliferation *via* microRNA-19b-3p. *Exp Cell Res* 2019;**376**:77−85.
94. Chang HM, Pan HH, Cheng JC, Zhu YM, Leung PCK. Growth differentiation factor 8 suppresses cell proliferation by up-regulating CTGF expression in human granulosa cells. *Mol Cell Endocrinol* 2016;**422**:9−17.
95. Liu X, Luo F, Pan K, Wu W, Chen H. High glucose upregulates connective tissue growth factor expression in human vascular smooth muscle cells. *BMC Cell Biol* 2007;**8**:1.
96. Riley KG, Pasek RC, Maulis MF, Dunn JC, Bolus WR, Kendall PL, et al. Macrophages are essential for CTGF-mediated adult β-cell proliferation after injury. *Mol Metab* 2015;**4**:584−91.
97. Kim H, Son S, Ko Y, Shin I. CTGF regulates cell proliferation, migration, and glucose metabolism through activation of FAK signaling in triple-negative breast cancer. *Oncogene* 2021;**40**: 2667−81.
98. Wu SH, Wu XH, Lu C, Dong L, Chen ZQ. Lipoxin A4 inhibits proliferation of human lung fibroblasts induced by connective tissue growth factor. *Am J Respir Cell Mol Biol* 2006;**34**:65−72.
99. Li MH, Sanchez T, Pappalardo A, Lynch KR, Hla T, Ferrer F. Induction of antiproliferative connective tissue growth factor expression in Wilms' tumor cells by sphingosine-1-phosphate receptor 2. *Mol Cancer Res* 2008;**6**:1649−56.
100. Kiwanuka E, Andersson L, Caterson EJ, Junker JP, Gerdin B, Eriksson E. CCN2 promotes keratinocyte adhesion and migration *via* integrin $\alpha_5\beta_1$. *Exp Cell Res* 2013;**319**:2938−46.
101. Hou CH, Yang RS, Tsao YT. Connective tissue growth factor stimulates osteosarcoma cell migration and induces osteosarcoma metastasis by upregulating VCAM-1 expression. *Biochem Pharmacol* 2018;**155**:71−81.
102. Tan TW, Lai CH, Huang CY, Yang WH, Chen HT, Hsu HC, et al. CTGF enhances migration and MMP-13 up-regulation *via* alphav-beta3 integrin, FAK, ERK, and NF-κB-dependent pathway in human chondrosarcoma cells. *J Cell Biochem* 2009;**107**:345−56.
103. Hendesi H, Barbe MF, Safadi FF, Monroy MA, Popoff SN. Integrin mediated adhesion of osteoblasts to connective tissue growth factor (CTGF/CCN2) induces cytoskeleton reorganization and cell differentiation. *PLoS One* 2015;**10**:e0115325.
104. Hoshijima M, Hattori T, Inoue M, Araki D, Hanagata H, Miyauchi A, et al. CT domain of CCN2/CTGF directly interacts with fibronectin and enhances cell adhesion of chondrocytes through integrin $\alpha_5\beta_1$. *FEBS Lett* 2006;**580**:1376−82.
105. Lin BR, Chang CC, Chen RJ, Jeng YM, Liang JT, Lee PH, et al. Connective tissue growth factor acts as a therapeutic agent and predictor for peritoneal carcinomatosis of colorectal cancer. *Clin Cancer Res* 2011;**17**:3077−88.
106. Chen CN, Chang CC, Lai HS, Jeng YM, Chen CI, Chang KJ, et al. Connective tissue growth factor inhibits gastric cancer peritoneal metastasis by blocking integrin $\alpha_3\beta_1$-dependent adhesion. *Gastric Cancer* 2015;**18**:504−15.
107. Aoyama E, Kubota S, Takigawa M. CCN2/CTGF binds to fibroblast growth factor receptor 2 and modulates its signaling. *FEBS Lett* 2012;**586**:4270−5.
108. Nishida T, Kubota S, Yokoi H, Mukoyama M, Takigawa M. Roles of matricellular CCN2 deposited by osteocytes in osteoclastogenesis and osteoblast differentiation. *Sci Rep* 2019;**9**:10913.
109. Takigawa M. CCN2: a master regulator of the genesis of bone and cartilage. *J Cell Commun Signal* 2013;**7**:191−201.
110. Luo Q, Kang Q, Si W, Jiang W, Park JK, Peng Y, et al. Connective tissue growth factor (CTGF) is regulated by Wnt and bone morphogenetic proteins signaling in osteoblast differentiation of mesenchymal stem cells. *J Biol Chem* 2004;**279**:55958−68.
111. Fujisawa T, Hattori T, Ono M, Uehara J, Kubota S, Kuboki T, et al. CCN family 2/connective tissue growth factor (CCN2/CTGF)

stimulates proliferation and differentiation of auricular chondrocytes. *Osteoarthritis Cartilage* 2008;**16**:787−95.
112. Tan JT, McLennan SV, Song WW, Lo LW, Bonner JG, Williams PF, et al. Connective tissue growth factor inhibits adipocyte differentiation. *Am J Physiol Cell Physiol* 2008;**295**:C740−51.
113. Morrison BL, Jose CC, Cutler ML. Connective tissue growth factor (CTGF/CCN2) enhances lactogenic differentiation of mammary epithelial cells *via* integrin-mediated cell adhesion. *BMC Cell Biol* 2010;**11**:35.
114. Lee CH, Shah B, Moioli EK, Mao JJ. CTGF directs fibroblast differentiation from human mesenchymal stem/stromal cells and defines connective tissue healing in a rodent injury model. *J Clin Invest* 2010;**120**:3340−9.
115. Frazier K, Williams S, Kothapalli D, Klapper H, Grotendorst GR. Stimulation of fibroblast cell growth, matrix production, and granulation tissue formation by connective tissue growth factor. *J Invest Dermatol* 1996;**107**:404−11.
116. Yamanaka O, Saika S, Ikeda K, Miyazaki K, Kitano A, Ohnishi Y. Connective tissue growth factor modulates extracellular matrix production in human subconjunctival fibroblasts and their proliferation and migration *in vitro*. *Jpn J Ophthalmol* 2008;**52**:8−15.
117. Ma B, Jing R, Liu J, Yang L, Li J, Qin L, et al. CTGF contributes to the development of posterior capsule opacification: an *in vitro* and *in vivo* study. *Int J Biol Sci* 2018;**14**:437−48.
118. Ma B, Kang Q, Qin L, Cui L, Pei C. TGF-beta2 induces transdifferentiation and fibrosis in human lens epithelial cells *via* regulating gremlin and CTGF. *Biochem Biophys Res Commun* 2014;**447**:689−95.
119. Crean JK, Finlay D, Murphy M, Moss C, Godson C, Martin F, et al. The role of p42/44 MAPK and protein kinase B in connective tissue growth factor induced extracellular matrix protein production, cell migration, and actin cytoskeletal rearrangement in human mesangial cells. *J Biol Chem* 2002;**277**:44187−94.
120. Cheng JC, Chang HM, Leung PCK. Connective tissue growth factor mediates TGF-β1-induced low-grade serous ovarian tumor cell apoptosis. *Oncotarget* 2017;**8**:85224−33.
121. Hishikawa K, Oemar BS, Tanner FC, Nakaki T, Luscher TF, Fujii T. Connective tissue growth factor induces apoptosis in human breast cancer cell line MCF-7. *J Biol Chem* 1999;**274**:37461−6.
122. Gygi D, Zumstein P, Grossenbacher D, Altwegg L, Luscher TF, Gehring H. Human connective tissue growth factor expressed in *Escherichia coli* is a non-mitogenic inhibitor of apoptosis. *Biochem Biophys Res Commun* 2003;**311**:685−90.
123. Bao H, Jiang K, Meng K, Liu W, Liu P, Du Y, et al. TGF-β2 induces proliferation and inhibits apoptosis of human Tenon capsule fibroblast by miR-26 and its targeting of CTGF. *Biomed Pharmacother* 2018;**104**:558−65.
124. Wahab N, Cox D, Witherden A, Mason RM. Connective tissue growth factor (CTGF) promotes activated mesangial cell survival *via* up-regulation of mitogen-activated protein kinase phosphatase-1 (MKP-1). *Biochem J* 2007;**406**:131−8.
125. Nozawa K, Fujishiro M, Kawasaki M, Kaneko H, Iwabuchi K, Yanagida M, Suzuki F, et al. Connective tissue growth factor promotes articular damage by increased osteoclastogenesis in patients with rheumatoid arthritis. *Arthritis Res Ther* 2009;**11**:R174.
126. Hall-Glenn F, Aivazi A, Akopyan L, Ong JR, Baxter RR, Benya PD, et al. CCN2/CTGF is required for matrix organization and to protect growth plate chondrocytes from cellular stress. *J Cell Commun Signal* 2013;**7**:219−30.
127. Guo T, Zhang J, Yao W, Du X, Li Q, Huang L, et al. CircINHA resists granulosa cell apoptosis by upregulating CTGF as a ceRNA of miR-10a-5p in pig ovarian follicles. *Biochim Biophys Acta Gene Regul Mech* 2019;**1862**:194420.
128. Chang CC, Shih JY, Jeng YM, Su JL, Lin BZ, Chen ST, et al. Connective tissue growth factor and its role in lung adenocarcinoma invasion and metastasis. *J Natl Cancer Inst* 2004;**96**:364−75.
129. Kikuchi R, Kikuchi Y, Tsuda H, Maekawa H, Kozaki K, Imoto I, et al. Expression and clinical significance of connective tissue growth factor in advanced head and neck squamous cell cancer. *Hum Cell* 2014;**27**:121−8.
130. Cruzeiro GAV, Lira RCP, de Almeida Magalhães T, Scrideli CA, Valera ET, Baumgartner M, et al. CTGF expression is indicative of better survival rates in patients with medulloblastoma. *Cancer Gene Ther* 2020;**27**:378−82.
131. Zhou ZQ, Cao WH, Xie JJ, Lin J, Shen ZY, Zhang QY, et al. Expression and prognostic significance of THBS1, Cyr61 and CTGF in esophageal squamous cell carcinoma. *BMC Cancer* 2009;**9**:291.
132. Allison SJ. Fibrosis: targeting EMT to reverse renal fibrosis. *Nat Rev Nephrol* 2015;**11**:565.
133. Bakir B, Chiarella AM, Pitarresi JR, Rustgi AK. EMT, MET, plasticity, and tumor metastasis. *Trends Cell Biol* 2020;**30**:764−76.
134. González-Iglesias A, Nieto MA. Proliferation and EMT trigger heart repair. *Nat Cell Biol* 2020;**22**:1291−2.
135. Chen PC, Lee WY, Ling HH, Cheng CH, Chen KC, Lin CW. Activation of fibroblasts by nicotine promotes the epithelial−mesenchymal transition and motility of breast cancer cells. *J Cell Physiol* 2018;**233**:4972−80.
136. Hellinger JW, Schömel F, Buse JV, Lenz C, Bauerschmitz G, Emons G, et al. Identification of drivers of breast cancer invasion by secretome analysis: insight into CTGF signaling. *Sci Rep* 2020;**10**:17889.
137. Sonnylal S, Xu S, Jones H, Tam A, Sreeram VR, Ponticos M, et al. Connective tissue growth factor causes EMT-like cell fate changes *in vivo* and *in vitro*. *J Cell Sci* 2013;**126**:2164−75.
138. Shafieian M, Chen S, Wu S. Integrin-linked kinase mediates CTGF-induced epithelial to mesenchymal transition in alveolar type II epithelial cells. *Pediatr Res* 2015;**77**:520−7.
139. Liu XC, Liu BC, Zhang XL, Li MX, Zhang JD. Role of ERK1/2 and PI3-K in the regulation of CTGF-induced ILK expression in HK-2 cells. *Clin Chim Acta* 2007;**382**:89−94.
140. Burns WC, Twigg SM, Forbes JM, Pete J, Tikellis C, Thallas-Bonke V, et al. Connective tissue growth factor plays an important role in advanced glycation end product-induced tubular epithelial-to-mesenchymal transition: implications for diabetic renal disease. *J Am Soc Nephrol* 2006;**17**:2484−94.
141. Burns WC, Thomas MC. The molecular mediators of type 2 epithelial to mesenchymal transition (EMT) and their role in renal pathophysiology. *Expert Rev Mol Med* 2010;**12**:e17.
142. Yang L, Hou J, Cui XH, Suo LN, Lv YW. MiR-133b regulates the expression of CTGF in epithelial−mesenchymal transition of ovarian cancer. *Eur Rev Med Pharmacol Sci* 2017;**21**:5602−9.
143. Lun W, Wu X, Deng Q, Zhi F. MiR-218 regulates epithelial−mesenchymal transition and angiogenesis in colorectal cancer *via* targeting CTGF. *Cancer Cell Int* 2018;**18**:83.
144. Li X, Wu N, Chen Y, Tan J, Wang J, Geng L, et al. Degradation of different molecular weight fucoidans and their inhibition of TGF-β1 induced epithelial−mesenchymal transition in mouse renal tubular epithelial cells. *Int J Biol Macromol* 2020;**151**:545−53.
145. Dai HY, Ma LN, Cao Y, Chen XL, Shi H, Fan YP, et al. Protection of CTGF antibody against diabetic nephropathy in mice *via* reducing glomerular β-catenin expression and podocyte epithelial−mesenchymal transition. *J Cell Biochem* 2017;**118**:3706−12.
146. Chen JQ, Ou YL, Huang ZP, Hong YG, Tao YP, Wang ZG, et al. MicroRNA-212-3p inhibits the proliferation and invasion of human hepatocellular carcinoma cells by suppressing CTGF expression. *Sci Rep* 2019;**9**:9820.
147. Nakanishi T, Nishida T, Shimo T, Kobayashi K, Kubo T, Tamatani T, et al. Effects of CTGF/Hcs24, a product of a hypertrophic chondrocyte-specific gene, on the proliferation and differentiation of chondrocytes in culture. *Endocrinology* 2000;**141**:264−73.
148. Nishida T, Nakanishi T, Asano M, Shimo T, Takigawa M. Effects of CTGF/Hcs24, a hypertrophic chondrocyte-specific gene product, on the proliferation and differentiation of osteoblastic cells *in vitro*. *J Cell Physiol* 2000;**184**:197−206.
149. Tomita N, Hattori T, Itoh S, Aoyama E, Yao M, Yamashiro T, et al. Cartilage-specific over-expression of CCN family member

2/connective tissue growth factor (CCN2/CTGF) stimulates insulin-like growth factor expression and bone growth. *PLoS One* 2013;**8**:e59226.
150. Kawaki H, Kubota S, Suzuki A, Yamada T, Matsumura T, Mandai T, et al. Functional requirement of CCN2 for intramembranous bone formation in embryonic mice. *Biochem Biophys Res Commun* 2008;**366**:450−6.
151. Kubota S, Takigawa M. The role of CCN2 in cartilage and bone development. *J Cell Commun Signal* 2011;**5**:209−17.
152. Matsumoto Y, La Rose J, Lim M, Adissu HA, Law N, Mao X, et al. Ubiquitin ligase RNF146 coordinates bone dynamics and energy metabolism. *J Clin Invest* 2017;**127**:2612−25.
153. Kadota H, Nakanishi T, Asaumi K, Yamaai T, Nakata E, Mitani S, et al. Expression of connective tissue growth factor/hypertrophic chondrocyte-specific gene product 24 (CTGF/Hcs24/CCN2) during distraction osteogenesis. *J Bone Miner Metab* 2004;**22**:293−302.
154. Nakata E, Nakanishi T, Kawai A, Asaumi K, Yamaai T, Asano M, et al. Expression of connective tissue growth factor/hypertrophic chondrocyte-specific gene product 24 (CTGF/Hcs24) during fracture healing. *Bone* 2002;**31**:441−7.
155. Cheng G, Yin C, Tu H, Jiang S, Wang Q, Zhou X, et al. Controlled co-delivery of growth factors through layer-by-layer assembly of core-shell nanofibers for improving bone regeneration. *ACS Nano* 2019;**13**:6372−82.
156. Honda M, Hariya R, Matsumoto M, Aizawa M. Acceleration of osteogenesis *via* stimulation of angiogenesis by combination with scaffold and connective tissue growth factor. *Materials (Basel)* 2019;**12**:2068.
157. Kapasa M, Serafimidis I, Gavalas A, Kossida S. Identification of phylogenetically conserved enhancer elements implicated in pancreas development in the WISP1 and CTGF orthologs. *Genomics* 2008;**92**:301−8.
158. Crawford LA, Guney MA, Oh YA, Deyoung RA, Valenzuela DM, Murphy AJ, et al. Connective tissue growth factor (CTGF) inactivation leads to defects in islet cell lineage allocation and β-cell proliferation during embryogenesis. *Mol Endocrinol* 2009;**23**:324−36.
159. Wilding Crawford L, Tweedie Ables E, Oh YA, Boone B, Levy S, Gannon M. Gene expression profiling of a mouse model of pancreatic islet dysmorphogenesis. *PLoS One* 2008;**3**:e1611.
160. Guney MA, Petersen CP, Boustani A, Duncan MR, Gunasekaran U, Menon R, et al. Connective tissue growth factor acts within both endothelial cells and beta cells to promote proliferation of developing beta cells. *Proc Natl Acad Sci U S A* 2011;**108**:15242−7.
161. Gunasekaran U, Hudgens CW, Wright BT, Maulis MF, Gannon M. Differential regulation of embryonic and adult beta cell replication. *Cell Cycle* 2012;**11**:2431−42.
162. Riley KG, Pasek RC, Maulis MF, Peek J, Thorel F, Brigstock DR, et al. Connective tissue growth factor modulates adult β-cell maturity and proliferation to promote beta-cell regeneration in mice. *Diabetes* 2015;**64**:1284−98.
163. Deng Y, Matsui Y, Pan W, Li Q, Lai ZC. YAP1 plays a protective role in suppressing free fatty acid-induced apoptosis and promoting β-cell survival. *Protein Cell* 2016;**7**:362−72.
164. Kondo Y, Nakanishi T, Takigawa M, Ogawa N. Immunohistochemical localization of connective tissue growth factor in the rat central nervous system. *Brain Res* 1999;**834**:146−51.
165. Gonzalez D, Brandan E. CTGF/CCN2 from skeletal muscle to nervous system: impact on neurodegenerative diseases. *Mol Neurobiol* 2019;**56**:5911−6.
166. Jones EV, Bouvier DS. Astrocyte-secreted matricellular proteins in CNS remodelling during development and disease. *Neural Plast* 2014;**2014**:321209.
167. Malik AR, Liszewska E, Jaworski J. Matricellular proteins of the Cyr61/CTGF/NOV (CCN) family and the nervous system. *Front Cell Neurosci* 2015;**9**:237.
168. Stritt C, Stern S, Harting K, Manke T, Sinske D, Schwarz H, et al. Paracrine control of oligodendrocyte differentiation by SRF-directed neuronal gene expression. *Nat Neurosci* 2009;**12**:418−27.
169. Buonviso N, Chaput M. Olfactory experience decreases responsiveness of the olfactory bulb in the adult rat. *Neuroscience* 2000;**95**:325−32.
170. Dalton P, Wysocki CJ. The nature and duration of adaptation following long-term odor exposure. *Percept Psychophys* 1996;**58**:781−92.
171. Khodosevich K, Lazarini F, von Engelhardt J, Kaneko H, Lledo PM, Monyer H. Connective tissue growth factor regulates interneuron survival and information processing in the olfactory bulb. *Neuron* 2013;**79**:1136−51.
172. Yang CN, Wu MF, Liu CC, Jung WH, Chang YC, Lee WP, et al. Differential protective effects of connective tissue growth factor against Abeta neurotoxicity on neurons and glia. *Hum Mol Genet* 2017;**26**:3909−21.
173. Mokalled MH, Patra C, Dickson AL, Endo T, Stainier DY, Poss KD. Injury-induced CTGFa directs glial bridging and spinal cord regeneration in zebrafish. *Science* 2016;**354**:630−4.
174. Liu S, Leask A. CCN2 is not required for skin development. *J Cell Commun Signal* 2011;**5**:179−82.
175. Liu LD, Shi HJ, Jiang L, Wang LC, Ma SH, Dong CH, et al. The repairing effect of a recombinant human connective-tissue growth factor in a burn-wounded rhesus-monkey (*Macaca mulatta*) model. *Biotechnol Appl Biochem* 2007;**47**:105−12.
176. Alfaro MP, Deskins DL, Wallus M, DasGupta J, Davidson JM, Nanney LB, et al. A physiological role for connective tissue growth factor in early wound healing. *Lab Invest* 2013;**93**:81−95.
177. Liu S, Leask A, Heldin CH. CCN2 modulates hair follicle cycling in mice. *Mol Biol Cell* 2013;**24**:3939−44.
178. Sung YK, Kwack MH, Kim SR, Kim MK, Kim JC. Transcriptional activation of CCN1 and CCN2, targets of canonical Wnt signal, by ascorbic acid 2-phosphate in human dermal papilla cells. *J Dermatol Sci* 2008;**49**:256−9.
179. van Setten GB, Trost A, Schrodl F, Kaser-Eichberger A, Bogner B, van Setten M, et al. Immunohistochemical detection of CTGF in the human eye. *Curr Eye Res* 2016;**41**:1571−9.
180. Ji S, Liu Q, Zhang S, Chen Q, Wang C, Zhang W, et al. FGF15 activates Hippo signaling to suppress bile acid metabolism and liver tumorigenesis. *Dev Cell* 2019;**48**:460−74.
181. Kuespert S, Junglas B, Braunger BM, Tamm ER, Fuchshofer R. The regulation of connective tissue growth factor expression influences the viability of human trabecular meshwork cells. *J Cell Mol Med* 2015;**19**:1010−20.
182. Iyer P, Maddala R, Pattabiraman PP, Rao PV. Connective tissue growth factor-mediated upregulation of neuromedin U expression in trabecular meshwork cells and its role in homeostasis of aqueous humor outflow. *Invest Ophthalmol Vis Sci* 2012;**53**:4952−62.
183. Garrett Q, Khaw PT, Blalock TD, Schultz GS, Grotendorst GR, Daniels JT. Involvement of CTGF in TGF-β1-stimulation of myofibroblast differentiation and collagen matrix contraction in the presence of mechanical stress. *Invest Ophthalmol Vis Sci* 2004;**45**:1109−16.
184. Li S, Pan Y. Immunolocalization of connective tissue growth factor, transforming growth factor-β1 and phosphorylated-SMAD2/3 during the postnatal tooth development and formation of junctional epithelium. *Ann Anat* 2018;**216**:52−9.
185. Li S, Pan Y. Differential expression of transforming growth factor-β1, connective tissue growth factor, phosphorylated-SMAD2/3 and phosphorylated-ERK1/2 during mouse tooth development. *J Mol Histol* 2017;**48**:347−55.
186. Li S, Ge S, Yang P. Immunohistochemical localization of connective tissue growth factor, transforming growth factor-beta1 and phosphorylated-smad2/3 in the developing periodontium of rats. *J Periodontal Res* 2014;**49**:624−33.

187. Shimo T, Wu C, Billings PC, Piddington R, Rosenbloom J, Pacifici M, et al. Expression, gene regulation, and roles of Fisp12/CTGF in developing tooth germs. *Dev Dyn* 2002;**224**:267−78.
188. Asano M, Kubota S, Nakanishi T, Nishida T, Yamaai T, Yosimichi G, et al. Effect of connective tissue growth factor (CCN2/CTGF) on proliferation and differentiation of mouse periodontal ligament-derived cells. *Cell Commun Signal* 2005;**3**:11.
189. Li S, Pan Y. Immunolocalization of transforming growth factor-β1, connective tissue growth factor, phosphorylated-SMAD2/3, and phosphorylated-ERK1/2 during mouse incisor development. *Connect Tissue Res* 2019;**60**:265−73.
190. Takahra T, Smart DE, Oakley F, Mann DA. Induction of myofibroblast MMP-9 transcription in three-dimensional collagen I gel cultures: regulation by NF-κB, AP-1 and Sp1. *Int J Biochem Cell Biol* 2004;**36**:353−63.
191. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol* 2017;**14**:397−411.
192. Higashi T, Friedman SL, Hoshida Y. Hepatic stellate cells as key target in liver fibrosis. *Adv Drug Deliv Rev* 2017;**121**:27−42.
193. LeBleu VS, Taduri G, O'Connell J, Teng Y, Cooke VG, Woda C, et al. Origin and function of myofibroblasts in kidney fibrosis. *Nat Med* 2013;**19**:1047−53.
194. Willis BC, duBois RM, Borok Z. Epithelial origin of myofibroblasts during fibrosis in the lung. *Proc Am Thorac Soc* 2006;**3**:377−82.
195. Huang Y, Deng X, Liang J. Modulation of hepatic stellate cells and reversibility of hepatic fibrosis. *Exp Cell Res* 2017;**352**:420−6.
196. Paradis V, Dargere D, Vidaud M, De Gouville AC, Huet S, Martinez V, et al. Expression of connective tissue growth factor in experimental rat and human liver fibrosis. *Hepatology* 1999;**30**:968−76.
197. Chen L, Charrier AL, Leask A, French SW, Brigstock DR. Ethanol-stimulated differentiated functions of human or mouse hepatic stellate cells are mediated by connective tissue growth factor. *J Hepatol* 2011;**55**:399−406.
198. Brigstock DR. Strategies for blocking the fibrogenic actions of connective tissue growth factor (CCN2): from pharmacological inhibition *in vitro* to targeted siRNA therapy *in vivo*. *J Cell Commun Signal* 2009;**3**:5−18.
199. Li G, Li D, Xie Q, Shi Y, Jiang S, Jin Y. RNA interfering connective tissue growth factor prevents rat hepatic stellate cell activation and extracellular matrix production. *J Gene Med* 2008;**10**:1039−47.
200. Chen P, Luo Q, Huang C, Gao Q, Li L, Chen J, et al. Pathogenesis of non-alcoholic fatty liver disease mediated by YAP. *Hepatol Int* 2018;**12**:26−36.
201. Xu F, Liu C, Zhou D, Zhang L. TGF-β/SMAD pathway and its regulation in hepatic fibrosis. *J Histochem Cytochem* 2016;**64**:157−67.
202. Hernandez-Aquino E, Quezada-Ramirez MA, Silva-Olivares A, Casas-Grajales S, Ramos-Tovar E, Flores-Beltran RE, et al. Naringenin attenuates the progression of liver fibrosis *via* inactivation of hepatic stellate cells and profibrogenic pathways. *Eur J Pharmacol* 2019;**865**:172730.
203. Mannaerts I, Leite SB, Verhulst S, Claerhout S, Eysackers N, Thoen LF, et al. The Hippo pathway effector YAP controls mouse hepatic stellate cell activation. *J Hepatol* 2015;**63**:679−88.
204. Wang Q, Chou X, Guan F, Fang Z, Lu S, Lei J, et al. Enhanced Wnt signalling in hepatocytes is associated with schistosoma japonicum infection and contributes to liver fibrosis. *Sci Rep* 2017;**7**:230.
205. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J* 2015;**46**:795−806.
206. King TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet* 2011;**378**:1949−61.
207. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018;**378**:1811−23.
208. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *Eur Respir Rev* 2012;**21**:355−61.
209. Kono M, Nakamura Y, Suda T, Kato M, Kaida Y, Hashimoto D, et al. Plasma CCN2 (connective tissue growth factor; CTGF) is a potential biomarker in idiopathic pulmonary fibrosis (IPF). *Clin Chim Acta* 2011;**412**:2211−5.
210. Gokey JJ, Sridharan A, Xu Y, Green J, Carraro G, Stripp BR, et al. Active epithelial Hippo signaling in idiopathic pulmonary fibrosis. *JCI Insight* 2018;**3**:e98738.
211. Noguchi S, Saito A, Mikami Y, Urushiyama H, Horie M, Matsuzaki H, et al. TAZ contributes to pulmonary fibrosis by activating profibrotic functions of lung fibroblasts. *Sci Rep* 2017;**7**:42595.
212. Liang H, Xu C, Pan Z, Zhang Y, Xu Z, Chen Y, et al. The antifibrotic effects and mechanisms of microRNA-26a action in idiopathic pulmonary fibrosis. *Mol Ther* 2014;**22**:1122−33.
213. Chang X, Xing L, Wang Y, Yang CX, He YJ, Zhou TJ, et al. Monocyte-derived multipotent cell delivered programmed therapeutics to reverse idiopathic pulmonary fibrosis. *Sci Adv* 2020;**6**:eaba3167.
214. Sternlicht MD, Wirkner U, Bickelhaupt S, Lopez Perez R, Tietz A, Lipson KE, et al. Radiation-induced pulmonary gene expression changes are attenuated by the CTGF antibody pamrevlumab. *Respir Res* 2018;**19**:14.
215. Zhu B, Ma AQ, Yang L, Dang XM. Atorvastatin attenuates bleomycin-induced pulmonary fibrosis *via* suppressing iNOS expression and the CTGF (CCN2)/ERK signaling pathway. *Int J Mol Sci* 2013;**14**:24476−91.
216. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med* 2020;**8**:807−15.
217. Zhang C, Wu Z, Li JW, Tan K, Yang W, Zhao H, et al. Discharge may not be the end of treatment: pay attention to pulmonary fibrosis caused by severe COVID-19. *J Med Virol* 2020;**93**:1378−86.
218. Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int* 2018;**94**:567−81.
219. Sun YB, Qu X, Caruana G, Li J. The origin of renal fibroblasts/myofibroblasts and the signals that trigger fibrosis. *Differentiation* 2016;**92**:102−7.
220. Humphreys BD. Mechanisms of renal fibrosis. *Annu Rev Physiol* 2018;**80**:309−26.
221. Li RX, Yiu WH, Tang SC. Role of bone morphogenetic protein-7 in renal fibrosis. *Front Physiol* 2015;**6**:114.
222. Liu L, Wang Y, Yan R, Liang L, Zhou X, Liu H, et al. BMP-7 inhibits renal fibrosis in diabetic nephropathy *via* miR-21 downregulation. *Life Sci* 2019;**238**:116957.
223. Lv W, Booz GW, Wang Y, Fan F, Roman RJ. Inflammation and renal fibrosis: recent developments on key signaling molecules as potential therapeutic targets. *Eur J Pharmacol* 2018;**820**:65−76.
224. Chen J, Wang X, He Q, Bulus N, Fogo AB, Zhang MZ, et al. YAP activation in renal proximal tubule cells drives diabetic renal interstitial fibrogenesis. *Diabetes* 2020;**69**:2446−57.
225. Li X, Pan J, Li H, Li G, Liu X, Liu B, et al. DsbA-L mediated renal tubulointerstitial fibrosis in UUO mice. *Nat Commun* 2020;**11**:4467.
226. Toda N, Mukoyama M, Yanagita M, Yokoi H. CTGF in kidney fibrosis and glomerulonephritis. *Inflamm Regen* 2018;**38**:14.
227. Kok HM, Falke LL, Goldschmeding R, Nguyen TQ. Targeting CTGF, EGF and PDGF pathways to prevent progression of kidney disease. *Nat Rev Nephrol* 2014;**10**:700−11.
228. Yokoi H, Mukoyama M, Nagae T, Mori K, Suganami T, Sawai K, et al. Reduction in connective tissue growth factor by antisense treatment ameliorates renal tubulointerstitial fibrosis. *J Am Soc Nephrol* 2004;**15**:1430−40.
229. Mao L, Liu L, Zhang T, Wu X, Zhang T, Xu Y. MKL1 mediates TGF-β-induced CTGF transcription to promote renal fibrosis. *J Cell Physiol* 2020;**235**:4790−803.
230. Wang Q, Usinger W, Nichols B, Gray J, Xu L, Seeley TW, et al. Cooperative interaction of CTGF and TGF-β in animal models of fibrotic disease. *Fibrogenesis Tissue Repair* 2011;**4**:4.

231. Berk BC, Fujiwara K, Lehoux S. ECM remodeling in hypertensive heart disease. *J Clin Invest* 2007;**117**:568−75.
232. Creemers EE, van Rooij E. Function and therapeutic potential of noncoding RNAs in cardiac fibrosis. *Circ Res* 2016;**118**:108−18.
233. Davis J, Molkentin JD. Myofibroblasts: trust your heart and let fate decide. *J Mol Cell Cardiol* 2014;**70**:9−18.
234. Squires CE, Escobar GP, Payne JF, Leonardi RA, Goshorn DK, Sheats NJ, et al. Altered fibroblast function following myocardial infarction. *J Mol Cell Cardiol* 2005;**39**:699−707.
235. Zhao J, Lv T, Quan J, Zhao W, Song J, Li Z, et al. Identification of target genes in cardiomyopathy with fibrosis and cardiac remodeling. *J Biomed Sci* 2018;**25**:63.
236. Chen MM, Lam A, Abraham JA, Schreiner GF, Joly AH. CTGF expression is induced by TGF-β in cardiac fibroblasts and cardiac myocytes: a potential role in heart fibrosis. *J Mol Cell Cardiol* 2000;**32**:1805−19.
237. Koitabashi N, Arai M, Niwano K, Watanabe A, Endoh M, Suguta M, et al. Plasma connective tissue growth factor is a novel potential biomarker of cardiac dysfunction in patients with chronic heart failure. *Eur J Heart Fail* 2008;**10**:373−9.
238. Nagpal V, Rai R, Place AT, Murphy SB, Verma SK, Ghosh AK, et al. MiR-125b is critical for fibroblast-to-myofibroblast transition and cardiac fibrosis. *Circulation* 2016;**133**:291−301.
239. Huang ZW, Tian LH, Yang B, Guo RM. Long noncoding RNA H19 acts as a competing endogenous RNA to mediate CTGF expression by sponging miR-455 in cardiac fibrosis. *DNA Cell Biol* 2017;**36**:759−66.
240. Wei C, Kim IK, Kumar S, Jayasinghe S, Hong N, Castoldi G, et al. NF-κB mediated miR-26a regulation in cardiac fibrosis. *J Cell Physiol* 2013;**228**:1433−42.
241. Chatzifrangkeskou M, Le Dour C, Wu W, Morrow JP, Joseph LC, Beuvin M, et al. ERK1/2 directly acts on CTGF/CCN2 expression to mediate myocardial fibrosis in cardiomyopathy caused by mutations in the lamin A/C gene. *Hum Mol Genet* 2016;**25**:2220−33.
242. Allen DG, Whitehead NP, Froehner SC. Absence of dystrophin disrupts skeletal muscle signaling: roles of Ca^{2+}, reactive oxygen species, and nitric oxide in the development of muscular dystrophy. *Physiol Rev* 2016;**96**:253−305.
243. Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E. CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. *J Pathol* 2011;**225**:490−501.
244. Morales MG, Acuna MJ, Cabrera D, Goldschmeding R, Brandan E. The pro-fibrotic connective tissue growth factor (CTGF/CCN2) correlates with the number of necrotic-regenerative foci in dystrophic muscle. *J Cell Commun Signal* 2018;**12**:413−21.
245. Barbe MF, Hilliard BA, Amin M, Harris MY, Hobson LJ, Cruz GE, et al. Blocking CTGF/CCN2 reduces established skeletal muscle fibrosis in a rat model of overuse injury. *FASEB J* 2020;**34**:6554−69.
246. Rebolledo DL, Gonzalez D, Faundez-Contreras J, Contreras O, Vio CP, Murphy-Ullrich JE, et al. Denervation-induced skeletal muscle fibrosis is mediated by CTGF/CCN2 independently of TGF-β. *Matrix Biol* 2019;**82**:20−37.
247. Morales MG, Gutierrez J, Cabello-Verrugio C, Cabrera D, Lipson KE, Goldschmeding R, et al. Reducing CTGF/CCN2 slows down mdx muscle dystrophy and improves cell therapy. *Hum Mol Genet* 2013;**22**:4938−51.
248. Cabello-Verrugio C, Morales MG, Cabrera D, Vio CP, Brandan E. Angiotensin II receptor type 1 blockade decreases CTGF/CCN2-mediated damage and fibrosis in normal and dystrophic skeletal muscles. *J Cell Mol Med* 2012;**16**:752−64.
249. Morales MG, Cabrera D, Cespedes C, Vio CP, Vazquez Y, Brandan E, et al. Inhibition of the angiotensin-converting enzyme decreases skeletal muscle fibrosis in dystrophic mice by a diminution in the expression and activity of connective tissue growth factor (CTGF/CCN-2). *Cell Tissue Res* 2013;**353**:173−87.
250. Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;**390**:1685−99.
251. Ibba-Manneschi L, Manetti M, Milia AF, Miniati I, Benelli G, Guiducci S, et al. Severe fibrotic changes and altered expression of angiogenic factors in maternal scleroderma: placental findings. *Ann Rheum Dis* 2010;**69**:458−61.
252. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease. *Lancet Respir Med* 2020;**8**:304−20.
253. Chakraborty D, Zhu H, Jüngel A, Summa L, Li YN, Matei AE, et al. Fibroblast growth factor receptor 3 activates a network of profibrotic signaling pathways to promote fibrosis in systemic sclerosis. *Sci Transl Med* 2020;**12**:eaaz5506.
254. Stifano G, Sornasse T, Rice LM, Na L, Chen-Harris H, Khanna D, et al. Skin gene expression is prognostic for the trajectory of skin disease in patients with diffuse cutaneous systemic sclerosis. *Arthritis Rheumatol* 2018;**70**:912−9.
255. Henrot P, Truchetet ME, Fisher G, Taieb A, Cario M. CCN proteins as potential actionable targets in scleroderma. *Exp Dermatol* 2019;**28**:11−8.
256. Nakai K, Karita S, Igarashi J, Tsukamoto I, Hirano K, Kubota Y. COA-Cl prevented TGF-β1-induced CTGF expression by Akt dephosphorylation in normal human dermal fibroblasts, and it attenuated skin fibrosis in mice models of systemic sclerosis. *J Dermatol Sci* 2019;**94**:205−12.
257. Stratton R, Shiwen X, Martini G, Holmes A, Leask A, Haberberger T, et al. Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. *J Clin Invest* 2001;**108**:241−50.
258. Weingartner S, Zerr P, Tomcik M, Palumbo-Zerr K, Distler A, Dees C, et al. Pomalidomide is effective for prevention and treatment of experimental skin fibrosis. *Ann Rheum Dis* 2012;**71**:1895−9.
259. Fonseca C, Lindahl GE, Ponticos M, Sestini P, Renzoni EA, Holmes AM, et al. A polymorphism in the CTGF promoter region associated with systemic sclerosis. *N Engl J Med* 2007;**357**:1210−20.
260. Granel B, Argiro L, Hachulla E, Fajardy I, Weiller PJ, Durand JM, et al. Association between a CTGF gene polymorphism and systemic sclerosis in a French population. *J Rheumatol* 2010;**37**:351−8.
261. Kawaguchi Y, Ota Y, Kawamoto M, Ito I, Tsuchiya N, Sugiura T, et al. Association study of a polymorphism of the CTGF gene and susceptibility to systemic sclerosis in the Japanese population. *Ann Rheum Dis* 2009;**68**:1921−4.
262. Rueda B, Simeon C, Hesselstrand R, Herrick A, Worthington J, Ortego-Centeno N, et al. A large multicentre analysis of CTGF-945 promoter polymorphism does not confirm association with systemic sclerosis susceptibility or phenotype. *Ann Rheum Dis* 2009;**68**:1618−20.
263. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;**70**:7−30.
264. Aikawa T, Gunn J, Spong SM, Klaus SJ, Korc M. Connective tissue growth factor-specific antibody attenuates tumor growth, metastasis, and angiogenesis in an orthotopic mouse model of pancreatic cancer. *Mol Cancer Ther* 2006;**5**:1108−16.
265. Dornhofer N, Spong S, Bennewith K, Salim A, Klaus S, Kambham N, et al. Connective tissue growth factor-specific monoclonal antibody therapy inhibits pancreatic tumor growth and metastasis. *Cancer Res* 2006;**66**:5816−27.
266. Bennewith KL, Huang X, Ham CM, Graves EE, Erler JT, Kambham N, et al. The role of tumor cell-derived connective tissue growth factor (CTGF/CCN2) in pancreatic tumor growth. *Cancer Res* 2009;**69**:775−84.
267. Kim JH, Shin BC, Park WS, Lee J, Kuh HJ. Antifibrotic effects of pentoxifylline improve the efficacy of gemcitabine in human pancreatic tumor xenografts. *Cancer Sci* 2017;**108**:2470−7.
268. Maity G, Ghosh A, Gupta V, Haque I, Sarkar S, Das A, et al. CYR61/CCN1 regulates dCK and CTGF and causes gemcitabine-

resistant phenotype in pancreatic ductal adenocarcinoma. *Mol Cancer Ther* 2019;**18**:788−800.
269. Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, et al. Breast cancer in China. *Lancet Oncol* 2014;**15**:e279−89.
270. Giordano SH. Breast cancer in men. *N Engl J Med* 2018;**378**:2311−20.
271. Shimo T, Kubota S, Kondo S, Nakanishi T, Sasaki A, Mese H, et al. Connective tissue growth factor as a major angiogenic agent that is induced by hypoxia in a human breast cancer cell line. *Cancer Lett* 2001;**174**:57−64.
272. Pandey DP, Lappano R, Albanito L, Madeo A, Maggiolini M, Picard D. Estrogenic GPR30 signalling induces proliferation and migration of breast cancer cells through CTGF. *EMBO J* 2009;**28**:523−32.
273. Lai D, Ho KC, Hao Y, Yang X. Taxol resistance in breast cancer cells is mediated by the Hippo pathway component TAZ and its downstream transcriptional targets Cyr61 and CTGF. *Cancer Res* 2011;**71**:2728−38.
274. Wang MY, Chen PS, Prakash E, Hsu HC, Huang HY, Lin MT, et al. Connective tissue growth factor confers drug resistance in breast cancer through concomitant up-regulation of Bcl-xL and cIAP1. *Cancer Res* 2009;**69**:3482−91.
275. Drzewiecka H, Gałęcki B, Jarmołowska-Jurczyszyn D, Kluk A, Dyszkiewicz W, Jagodziński PP. Decreased expression of connective tissue growth factor in non-small cell lung cancer is associated with clinicopathological variables and can be restored by epigenetic modifiers. *J Cancer Res Clin Oncol* 2016;**142**:1927−46.
276. Yu X, Zhen Y, Yang H, Wang H, Zhou Y, Wang E, et al. Loss of connective tissue growth factor as an unfavorable prognosis factor activates miR-18b by PI3K/AKT/C-Jun and c-Myc and promotes cell growth in nasopharyngeal carcinoma. *Cell Death Dis* 2013;**4**:e634.
277. Zirn B, Samans B, Spangenberg C, Graf N, Eilers M, Gessler M. All-*trans* retinoic acid treatment of Wilms tumor cells reverses expression of genes associated with high risk and relapse *in vivo*. *Oncogene* 2005;**24**:5246−51.
278. Hsu PC, Tian B, Yang YL, Wang YC, Liu S, Urisman A, et al. Cucurbitacin E inhibits the Yes-associated protein signaling pathway and suppresses brain metastasis of human non-small cell lung cancer in a murine model. *Oncol Rep* 2019;**42**:697−707.
279. Coleman RE, Croucher PI, Padhani AR, Clezardin P, Chow E, Fallon M, et al. Bone metastases. *Nat Rev Dis Primers* 2020;**6**:83.
280. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987;**55**:61−6.
281. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004;**350**:1655−64.
282. Kim B, Kim H, Jung S, Moon A, Noh DY, Lee ZH, et al. A CTGF−RUNX2−RANKL axis in breast and prostate cancer cells promotes tumor progression in bone. *J Bone Miner Res* 2020;**35**:155−66.
283. Kang Y, Siegel PM, Shu W, Drobnjak M, Kakonen SM, Cordón-Cardo C, et al. A multigenic program mediating breast cancer metastasis to bone. *Cancer Cell* 2003;**3**:537−49.
284. Gao YB, Xiang ZL, Zhou LY, Wu ZF, Fan J, Zeng HY, et al. Enhanced production of CTGF and IL-11 from highly metastatic hepatoma cells under hypoxic conditions: an implication of hepatocellular carcinoma metastasis to bone. *J Cancer Res Clin Oncol* 2013;**139**:669−79.
285. Shimo T, Kubota S, Yoshioka N, Ibaragi S, Isowa S, Eguchi T, et al. Pathogenic role of connective tissue growth factor (CTGF/CCN2) in osteolytic metastasis of breast cancer. *J Bone Miner Res* 2006;**21**:1045−59.
286. Croset M, Pantano F, Kan CWS, Bonnelye E, Descotes F, Alix-Panabieres C, et al. miRNA-30 family members inhibit breast cancer invasion, osteomimicry, and bone destruction by directly targeting multiple bone metastasis-associated genes. *Cancer Res* 2018;**78**:5259−73.
287. Zhang L, Niu H, Ma J, Yuan BY, Chen YH, Zhuang Y, et al. The molecular mechanism of lncRNA34a-mediated regulation of bone metastasis in hepatocellular carcinoma. *Mol Cancer* 2019;**18**:120.
288. Mohammad KS, Javelaud D, Fournier PG, Niewolna M, McKenna CR, Peng XH, et al. TGF-β-RI kinase inhibitor SD-208 reduces the development and progression of melanoma bone metastases. *Cancer Res* 2011;**71**:175−84.
289. Juarez P, Mohammad KS, Yin JJ, Fournier PG, McKenna RC, Davis HW, et al. Halofuginone inhibits the establishment and progression of melanoma bone metastases. *Cancer Res* 2012;**72**:6247−56.
290. Turner CA, Sharma V, Hagenauer MH, Chaudhury S, O'Connor AM, Hebda-Bauer EK, et al. Connective tissue growth factor is a novel prodepressant. *Biol Psychiatry* 2018;**84**:555−62.
291. Gonzalez D, Contreras O, Rebolledo DL, Espinoza JP, van Zundert B, Brandan E. ALS skeletal muscle shows enhanced TGF-β signaling, fibrosis and induction of fibro/adipogenic progenitor markers. *PLoS One* 2017;**12**:e0177649.
292. Gonzalez D, Rebolledo DL, Correa LM, Court FA, Cerpa W, Lipson KE, et al. The inhibition of CTGF/CCN2 activity improves muscle and locomotor function in a murine ALS model. *Hum Mol Genet* 2018;**27**:2913−26.
293. Kular L, Pakradouni J, Kitabgi P, Laurent M, Martinerie C. The CCN family: a new class of inflammation modulators?. *Biochimie* 2011;**93**:377−88.
294. Ueberham U, Ueberham E, Gruschka H, Arendt T. Connective tissue growth factor in Alzheimer's disease. *Neuroscience* 2003;**116**:1−6.
295. Lo AC, Callaerts-Vegh Z, Nunes AF, Rodrigues CM, D'Hooge R. Tauroursodeoxycholic acid (TUDCA) supplementation prevents cognitive impairment and amyloid deposition in APP/PS1 mice. *Neurobiol Dis* 2013;**50**:21−9.
296. Zhao Z, Ho L, Wang J, Qin W, Festa ED, Mobbs C, et al. Connective tissue growth factor (CTGF) expression in the brain is a downstream effector of insulin resistance-associated promotion of Alzheimer's disease β-amyloid neuropathology. *FASEB J* 2005;**19**:2081−2.
297. Mann AP, Scodeller P, Hussain S, Braun GB, Molder T, Toome K, et al. Identification of a peptide recognizing cerebrovascular changes in mouse models of Alzheimer's disease. *Nat Commun* 2017;**8**:1403.
298. McClain JA, Phillips LL, Fillmore HL. Increased MMP-3 and CTGF expression during lipopolysaccharide-induced dopaminergic neurodegeneration. *Neurosci Lett* 2009;**460**:27−31.
299. Thomson SE, McLennan SV, Hennessy A, Boughton P, Bonner J, Zoellner H, et al. A novel primate model of delayed wound healing in diabetes: dysregulation of connective tissue growth factor. *Diabetologia* 2010;**53**:572−83.
300. Augustine R, Zahid AA, Hasan A, Wang M, Webster TJ. CTGF loaded electrospun dual porous core−shell membrane for diabetic wound healing. *Int J Nanomedicine* 2019;**14**:8573−88.
301. Shome D, von Woedtke T, Riedel K, Masur K. The Hippo transducer Yap and its targets CTGF and Cyr61 drive a paracrine signalling in cold atmospheric plasma-mediated wound healing. *Oxid Med Cell Longev* 2020;**2020**:4910280.
302. Stratmann B, Costea TC, Nolte C, Hiller J, Schmidt J, Reindel J, et al. Effect of cold atmospheric plasma therapy *vs* standard therapy placebo on wound healing in patients with diabetic foot ulcers: a randomized clinical trial. *JAMA Netw Open* 2020;**3**:e2010411.
303. Colwell AS, Phan TT, Kong W, Longaker MT, Lorenz PH. Hypertrophic scar fibroblasts have increased connective tissue growth factor expression after transforming growth factor-β stimulation. *Plast Reconstr Surg* 2005;**116**:1387−92.
304. Deng J, Shi Y, Gao Z, Zhang W, Wu X, Cao W, et al. Inhibition of pathological phenotype of hypertrophic scar fibroblasts *via* coculture with adipose-derived stem cells. *Tissue Eng Part A* 2018;**24**:382−93.
305. Liu F, Chen WW, Li Y, Zhang JQ, Zheng QB. MiR-6836-3p promotes proliferation of hypertrophic scar fibroblasts by targeting CTGF. *Eur Rev Med Pharmacol Sci* 2018;**22**:4069−74.
306. Hedayatyanfard K, Haddadi NS, Ziai SA, Karim H, Niazi F, Steckelings UM, et al. The renin−angiotensin system in cutaneous hypertrophic scar and keloid formation. *Exp Dermatol* 2020;**29**:902−9.

307. Yeo DC, Wiraja C, Paller AS, Mirkin CA, Xu C. Abnormal scar identification with spherical-nucleic-acid technology. *Nat Biomed Eng* 2018;**2**:227−38.
308. Hwang J, Chang C, Kim JH, Oh CT, Lee HN, Lee C, et al. Development of cell-penetrating asymmetric interfering RNA targeting connective tissue growth factor. *J Invest Dermatol* 2016;**136**:2305−13.
309. Jensen J, Gentzkow G, Berman G, Senne L, Jewell M, Connall TP, et al. Anti-CTGF oligonucleotide reduces severity of postsurgical hypertrophic scars in a randomized, double-blind, within-subject, placebo-controlled study. *Plast Reconstr Surg* 2018;**142**:192e−201e.
310. Kuiper EJ, Witmer AN, Klaassen I, Oliver N, Goldschmeding R, Schlingemann RO. Differential expression of connective tissue growth factor in microglia and pericytes in the human diabetic retina. *Br J Ophthalmol* 2004;**88**:1082−7.
311. Yang H, Huang Y, Chen X, Liu J, Lu Y, Bu L, et al. The role of CTGF in the diabetic rat retina and its relationship with VEGF and TGF-β_2, elucidated by treatment with CTGFsiRNA. *Acta Ophthalmol* 2010;**88**:652−9.
312. Kuiper EJ, Van Nieuwenhoven FA, de Smet MD, van Meurs JC, Tanck MW, Oliver N, et al. The angio-fibrotic switch of VEGF and CTGF in proliferative diabetic retinopathy. *PLoS One* 2008;**3**:e2675.
313. Tikellis C, Cooper ME, Twigg SM, Burns WC, Tolcos M. Connective tissue growth factor is up-regulated in the diabetic retina: amelioration by angiotensin-converting enzyme inhibition. *Endocrinology* 2004;**145**:860−6.
314. Zhang B, Zhou KK, Ma JX. Inhibition of connective tissue growth factor overexpression in diabetic retinopathy by SERPINA3K *via* blocking the WNT/β-catenin pathway. *Diabetes* 2010;**59**:1809−16.
315. Hu B, Zhang Y, Zeng Q, Han Q, Zhang L, Liu M, et al. Intravitreal injection of ranibizumab and CTGF shRNA improves retinal gene expression and microvessel ultrastructure in a rodent model of diabetes. *Int J Mol Sci* 2014;**15**:1606−24.
316. Can Demirdogen B, Kocan Akcin C, Ozge G, Mumcuoglu T. Evaluation of tear and aqueous humor level, and genetic variants of connective tissue growth factor as biomarkers for early detection of pseudoexfoliation syndrome/glaucoma. *Exp Eye Res* 2019;**189**:107837.
317. Schneider M, Pawlak R, Weber GR, Dillinger AE, Kuespert S, Iozzo RV, et al. A novel ocular function for decorin in the aqueous humor outflow. *Matrix Biol* 2021;**97**:1−19.
318. Dillinger AE, Guter M, Froemel F, Weber GR, Perkumas K, Stamer WD, et al. Intracameral delivery of layer-by-layer coated siRNA nanoparticles for glaucoma therapy. *Small* 2018;**14**:e1803239.
319. Mietzner R, Breunig M. Causative glaucoma treatment: promising targets and delivery systems. *Drug Discov Today* 2019;**24**:1606−13.
320. Chintala H, Liu H, Parmar R, Kamalska M, Kim YJ, Lovett D, et al. Connective tissue growth factor regulates retinal neovascularization through p53 protein-dependent transactivation of the matrix metalloproteinase (MMP)-2 gene. *J Biol Chem* 2012;**287**:40570−85.
321. Kita T, Hata Y, Kano K, Miura M, Nakao S, Noda Y, et al. Transforming growth factor-β2 and connective tissue growth factor in proliferative vitreoretinal diseases: possible involvement of hyalocytes and therapeutic potential of Rho kinase inhibitor. *Diabetes* 2007;**56**:231−8.