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. 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. 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.

In the regulation of physiological functions, CTGF plays essential roles. 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). Based on these results, many studies tried to block CTGF to treat fibrotic diseases. Many drugs targeting CTGF were developed, 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.

With more understanding of CTGF, researchers have noticed the association of CTGF with cancers and other diseases. However, the relationship is more complicated. In most cases, CTGF is known as a pro-angiogenic factor and an inhibitor of apoptosis. The difference may be caused by mixed effects of CTGF.

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. CTGF consists of four basic domains, they are IGFBP, VWC, TSP1 and CT from N-terminal to C-terminal. Each domain could specifically bind with different proteins and thereby play different functions.

2.1. IGFBP domain

IGFBP domain of CTGF locates in the sequence of Gln27–Lys98. This was named because IGFBP domain contains a conserved sequence ‘GGGCCXXC’ which is also found in proteins in IGFBP family. It was observed that the combination of CTGF and insulin-like growth factor was involved in the process of matrix accumulation. Besides, in the development of tubulointerstitial fibrosis, the combination of CTGF and insulin-like growth factor contributes to the progression of the disease.

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. Conversely, in most cases, CTGF is known as a

| Drug name | Mechanism | Indication | Development stage | ClinicalTrials.gov identifier |
|-----------|-----------|------------|-------------------|-------------------------------|
| FG-3019   | Neutralizing CTGF | Pancreatic cancer (unresectable) | Phase 3 | NCT03941093 |
| Pravastatin | Targeting Rho/ROCK/CTGF pathway | Duchenne muscular dystrophy | Phase 3 | NCT04632940 |
| RXI-109   | CTGF RNA interference | Diabetes mellitus/diabetic nephropathy | Phase 1 | NCT00754143 |
| OLX-10010 | CTGF RNA interference | Diabetes mellitus | Phase 1 | NCT01002297 |
| EXC-001   | CTGF antisense oligonucleotide | Idiopathic pulmonary fibrosis | Phase 1 | NCT04986540 |
| SHR-1906  | Neutralizing CTGF | Unspecified adult solid tumor | Phase 1 | NCT04842630 |
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 I repeats. It was first identified in thrombospondin\(^{142}\). 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 VEGF\(^{165}\) 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 a6β1 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), heparan sulfate proteoglycans (HSPGs), LRP and integrins interact with CT domain.

### 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.\(^{45}\) Reversely, the use of the antagonist of angiotensin II type 1 receptor (AT-1R) could inhibit the upregulated expression of CTGF.\(^{51-53}\) Cytokines like IL-20 and hypoxia-inducible factor are the mediators of CTGF as well.\(^{45,64}\) Additionally, CTGF was found hypoxia-inducible in melanomas which means that the microenvironment plays a role in regulating the expression of CTGF.\(^{56}\) Moreover, the mechanical tension like delayed loading could also increase the expression level of CTGF.\(^{57}\)

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.\(^{69}\) Besides, the static magnetic field could also upregulate CTGF by increasing the nuclear localization of YAP/TAZ.\(^{70}\) 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.\(^{71-80}\)

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.\(^{94-96}\) Furthermore, 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 metalloproteinase-13,\(^{100-102}\) Depending on particular conditions, CTGF either blocks or promotes adhesion.\(^{103}\) In contrast, CTGF is known as one of the integrins which could be involved in CTGF-promoted adhesion of osteoblasts. Furthermore, α\(_v\)β\(_1\) has been found to participate in the adhesion of both HCS-2/8 and pancreatic stellate cells induced by CTGF. In pancreatic stellate cells, α\(_v\)β\(_1\) binds to CTGF directly; whereas in HCS-2/8, CTGF binds directly to FN via α\(_v\)β\(_1\).\(^{53,104}\) However, in gastric cancer and colorectal cancer, CTGF blocks the adhesion of cancer cells by interacting with α\(_v\)β\(_1\) and influencing the expression of α\(_v\) 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.\(^{107,108,109}\) 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 other, 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 I 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
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. Notably, the synthesis of extracellular matrix could affect pathological progression of fibrosis and cancer.

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.
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\(^1\). However, in human Tenon capsule fibroblasts and chicken embryo fibroblasts, CTGF was found to negatively mediate the apoptosis\(^2\). Besides, in rat mesangial cells, CTGF could promote the survival of cells by downregulating SMAD7\(^3\). 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\(^4\). Moreover, the anti-apoptosis function of CTGF has also been proved in pig granulosa cells in vitro by knockdown of CTGF\(^5\). 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\(^6\). \(^7\)–\(^9\).

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\(^10\)–\(^12\). Many studies have already revealed that CTGF is a promoter in the regulation of EMT, which usually acts synergistically with TGF-\(β\)\(^2\). The addition of CTGF to MSF-7 culture could induce EMT\(^13\)\(^–\)\(^15\). For lung epithelial cells, the TGF-\(β1\)-mediated EMT was found to be dependent on the expression of CTGF\(^16\). 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\(^17\). Liu et al.\(^18\) 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\(^19\)\(^–\)\(^21\). 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\(^22\)\(^–\)\(^24\).

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\(^25\)\(^–\)\(^27\). Moreover, the overexpressed CTGF accelerated the endochondral ossification by promoting the proliferation and differentiation of chondrocytes\(^28\). The lack of CTGF would cause chondrodysplasia and seriously results in perinatal lethality, as well as the ossification delay in the intramembranous skeletal elements\(^29\)\(^–\)\(^31\). 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\(^32\). 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\(^33\)\(^–\)\(^35\).

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\(^36\)\(^–\)\(^38\). A nonfibrous mats drug containing a nonfibrous BMP2 core and CTGF surface that could facilitate bone healing has been designed in recent years based on this physiological role\(^39\). Also, CTGF microencapsulation has been used to promote fibrogenesis in the process of calvarial healing\(^40\). 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\(^41\).

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\(^42\). Further, it was shown that the deletion of CTGF could disrupt endocrine cell composition and islet morphogenesis\(^43\)\(^–\)\(^45\). It has already been proved that CTGF is necessary for embryonic \(β\)-cell proliferation, which is essential for glucose homeostasis\(^46\). Under non-stimulatory conditions, the overexpression of CTGF could not significantly promote the proliferation of embryonic \(β\)-cells\(^47\). 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\(^48\)\(^–\)\(^50\). 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\(^51\). 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\(^52\).

5.3. Nervous system regulation

In 1999, the wide localization of CTGF in the central nervous system of rats was first uncovered\(^53\). 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\(^54\)\(^–\)\(^56\). 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\(^57\). 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 (A). 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 (Aβ). 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. 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.

5.4. Skin regulation

CTGF does not play significant roles in the development of skin. 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. 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. 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. On the contrary, CTGF was previously described as one of participants in L-ascorbic acid 2-phosphate magnesium salt-induced elongation of hair shafts. 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. 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. 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. 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. 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. At last, the basal expression of CTGF is critical for blood vessel integrity and barrier formation in eyes.

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. 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. 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. 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 periostium and periodontium, was also increased. Besides, the tooth is a typical epithelium-mesenchyme organ. CTGF may also regulate EMT during tooth development. In a word, CTGF mainly affects physiological processes, which is mentioned above, through mediating certain cell or substance events.

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. In other fibrotic diseases, the formation of myofibroblasts could also be observed. However, the source might be different. The activation of HSC was found reversible, which means hepatic fibrosis could be attenuated by inhibiting the activation of HSC. CTGF may play an indispensable role in the whole process. The abundant existence of CTGF in HSC indicated that CTGF were overexpressed by HSC. Also, abundant CTGF could induce the production of extracellular matrix in HSC to promote hepatic fibrosis.

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. 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. In addition, multiple studies tried to find a new impetus for treating hepatic fibrosis through CTGF-related pathways. For example, Naringenin was discovered to treat hepatic fibrosis by preserving the TGF-β1/SMAD3 and JNK/SMAD3 pathways. Pharmacological inhibition of the YAP pathway could also reduce fibrogenesis. 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.

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...
elderly adults. Besides, the incidence and prevalence of IPF is increasing worldwide\textsuperscript{205–208}. It has been found that high CTGF mRNA level is associated with IPF fibroblasts\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{213}. Moreover, pamrevlumab showed both safety and efficacy to
reverse the progression of IPF in the phase 2 trial\(^\text{18}\). 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. The downregulation of CTGF was one of the vital pathways\(^\text{214,215}\). Since December 2019, corona virus disease 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\(^\text{216,217}\).

### 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\(^\text{218}\). 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\(^\text{219}\). 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\(^\text{220}\). 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\(^\text{221-223}\). 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\(^\text{224}\). Other signaling pathways like the JAK-STAT, WNT and the Hippo signaling pathway are 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\(^\text{224}\). Other signaling pathways like the SMAD3 and p53 signaling were also found to be activated in renal fibrosis\(^\text{225}\). Overall, when kidney fibrosis occurred, the expression level of CTGF would be increased\(^\text{226}\).

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\(^\text{227}\). It was observed that the inflammation of mice was reduced when Ctgf was knocked out\(^\text{228}\). 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\(^\text{229}\). Knocking out megakaryocytic leukemia 1, which could interact with SMAD3 to activate Ctgf transcription, also showed the downregulation of UUO-induced Ctgf and α-SMA\(^\text{230}\). 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\(^\text{15}\). 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\(^\text{230}\).

#### 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\(^\text{231-234}\). 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\(^\text{12}\). In dilated cardiomyopathy, which is fibrosis-related, CTGF is a key gene that was upregulated\(^\text{34}\). In the myocardial infarction model of rats that is always accompanied with fibrosis, the level of Ctgf, Fn and Coll were simultaneously increased, too\(^\text{236}\). 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\(^\text{37}\).

MicroRNA is tightly associated with cardiac fibrosis. For instance, miR-125b is necessary for the fibroblast-to-myofibroblast transition\(^\text{235}\). 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 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\(^\text{17,239,240}\). 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\(^\text{241}\).

#### 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\(^\text{242}\). 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\(^\text{44}\). By incubating myoblasts with CTGF, it was revealed that extracellular matrix components including some integrins and collagen I a2 were influenced\(^\text{6}\). Further, by using adeno virus to overexpress CTGF in muscles, a strong fibrotic reaction with increasing type III collagen and α-SMA was caused\(^\text{243}\). 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\(^\text{12,244}\). 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\(^\text{235,246}\).

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\(^\text{37}\). 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 model248,249.

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 placentas250–252. In sclerotic lesions from SSc patients, the expression of CTGF could be observed in fibroblasts40. The activated CTGF signaling may be affected by fibroblast growth factor receptor 3 signaling43. 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 SSc254. 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 CTGF255–258. 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 susceptibility259–262.

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 2020262. It has been found that the expression of CTGF is increased in pancreatic cancer, α-SMA-positive and E-cadherin-negative fibroblasts, particularly263. In different types of human cell lines of pancreatic cancer, PANC-1 and MIAPaCa-2 have the highest CTGF mRNA level264. 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. 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 apoptosis265. Similarly, shRNA was used to knockdown CTGF and successfully induced hypoxia-mediated apoptosis of tumor cells266. 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 microenvironment17.

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 pentoxyfylline could improve the delivery and efficiency of gemcitabine by decreasing the level of extracellular matrix proteins like collagen and CTGF267. Besides, CCN1 has been found to suppress deoxyxycytidine kinase, an enzyme could activate gemcitabine, and induce desmoplasic 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 resistance268. 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 cancer269. For men, the risk of breast cancer is much lower270. 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 causing angiogenesis17,271. The activation of estrogenic GPR30 signaling by hydroxytamoxtifen could lead to the upregulation of the CTGF expression level and it would induce proliferation and migration of oestrogen receptor-negative human breast cancer272. In contrast, another study indicated that CTGF might act as a suppressor of the progression of breast cancer273. 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 reverse273,274. 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-dependent275. 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 patients276. The inhibited function of CTGF may be achieved by promoting the degradation of hypoxia-inducible factor 1α protein and suppressing the VEGF-A-dependent angiogenesis274,278. Lung cancer is not the only
cancer that could be negatively influenced by CTGF. Wilms’ tumor and nasopharyngeal carcinoma are also repressed by CTGF99,276,277 (Fig. 3B). However, some other studies found that CTGF could positively regulate the migration and invasion of non-small cell lung cancer cells278.

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 femora279. 70% of patients having advanced breast or prostate cancer were found to have bone metastasis280. The metastasis has been divided into osteolytic and osteoblastic. However, the osteolytic and osteoblastic lesions could exist at the same time281. For bone-metastatic breast and prostate cancer cells like MDA-MB-231 and PC3, the signal intensity of CTGF was higher than that in parent cells. It indicated that CTGF may be one of the elements to promote the bone metastasis282. The promotion of breast cancer osteolytic metastasis made by CTGF was thought to cooperate with other proteins like IL-11 and osteopontin283. 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 sample284.

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 metastasis285. MiR-30s could target multiple genes associated with breast cancer bone metastasis to reduce metastasis, and CTGF is one of the genes286. 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 vivo287. 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 protocols288. Besides, the blockade of the TGF-β signaling pathway by halofuginone, a plant alkaldoid, did the same as SD-208. The bone metastasis and brain metastasis of melanoma were both decreased289. 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 depression290. Further, the use of CTGF in rats made the condition of depression worse. However, the treatment with FG-3019 has been proven to be antidepressant290.

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 astrogliosis291. Moreover, in hSOD1G93A mice, a widely-used murine ALS model, TGF-β signaling pathway and level of CTGF were induced in skeletal muscles292. It has been observed that blocking CTGF in hSOD1G93A mice leads to the improvement of both skeletal muscular and neural functions293,294.

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 patients295,296. 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 decreased297,298. 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 Aβ299. 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 brain299. 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 disease299.

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 tissues299. Some CTGF-related treatments have been applied to improve non-healing conditions recently, like CTGF loaded electrosplun dual porous core–shell membrane and cold atmospheric plasma. The former used electrosplun PLA–PVA core–shell membranes to supply CTGF in a slow and sustained way directly300. The latter was based on the inactivation of the Hippo signaling pathway mediated by cold atmospheric plasma301. The cold atmospheric plasma therapy has already shown a significant effect on the treatment of diabetic foot ulcers in a randomized clinical trial302.

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 developed303. 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 brain304. 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 disease299.

6.3.5. Eye diseases
Expression of CTGF contributes to the progression of many eye diseases of which diabetic retinopathy (DR) and glaucoma are...
most widely known. In patients with DR, the distribution and level of CTGF were different from that in normal condition. Overexpressed CTGF may influence DR through retinal apoptosis and switching angiogenesis to fibrosis. ACE inhibitors, SERPIN, siRNA, which could decrease CTGF level, were found to be effective in attenuating DR. When making dual-target intervention with VEGF inhibitor, targeted therapy against CTGF could cause less damage and have greater effectiveness. CTGF level was higher in both tear fluid and aqueous humor in pseudoexfoliative glaucoma patients compared to that in pseudoexfoliation syndrome patients without glaucoma. In primary open-angle glaucoma, the level was also increased, and it may be associated with the lack of decorin. CTGF was higher in both tear fluid and aqueous humor in pseudoexfoliative glaucoma patients compared to that in pseudoexfoliation syndrome patients without glaucoma. In primary open-angle glaucoma, the level was also increased, and it may be associated with the lack of decorin. 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. In addition, some other diseases like ischemic retinopathy and proliferative vitreoretinal diseases could be possibly treated by downregulating CTGF.

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.

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