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Connective Tissue Growth Factor in Normal and Pathological Processes

Abstract

Modern concepts about the role of connective tissue growth factor in various physiological and pathological processes are described in the review. Connective tissue growth factor regulates a variety of cellular functions, including proliferation, migration, adhesion, differentiation and synthesis of extracellular matrix proteins in cells of different types. This factor is also involved in more complex biological processes of angiogenesis, chondrogenesis, wound healing, fibrosis and oncogenesis. Increased expression of connective tissue growth factor is observed in different cardiovascular and oncological diseases. Potential role of this growth factor in regulation of cellular senescence and aging processes is also discussed.

Key words: *connective tissue growth factor, fibrosis, nephrosclerosis, chondrogenesis, osteogenesis, aging*

Conflict of interests

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CHF — chronic heart failure, CTGF — connective tissue growth factor

Connective tissue growth factor (CTGF), also known as CCN2, is a small secreted protein of the CCN family, named after its three original proteins: Cysteine-rich 61 (Cyr61/CCN1), CTGF/CCN2, Nephroblastoma overexpressed (Nov/CCN3) [1, 2]. CTGF is a cysteine-rich extracellular matrix protein with four domains or modules. This protein, like other members of the CNN family, includes four different structural modules: aminoterminal insulin-like growth factor binding domain; cysteine-rich domain; thrombospondin type 1 repeat; carboxyl-terminal cysteine knot domain [3]. The synthesis of CTGF, which was discovered in 1991, stimulates such a profibrotic cytokine as transforming growth factor β [4].

Connective tissue growth factor regulates various cellular functions, including proliferation, migration, adhesion, differentiation and synthesis of extracellular matrix proteins in cells of different types; it is also involved in more complex biological processes of angiogenesis, chondrogenesis, osteogenesis, wound healing, fibrosis and oncogenesis [1]. Increased expression of CTGF is observed primarily in cases of pathological conditions associated with fibrosis [4].

As an extracellular matrix protein, connective tissue growth factor is thought to integrate different extracellular signals into complex biological reactions [2, 5]. CTGF respectively binds to various receptors on the cell surface (in particular, to integrin receptors and surface heparan sulfate proteoglycans), thus controlling the transmission of signals to cells, the recognition of the cell matrix and cell adhesion. This protein also binds growth factors (for example, bone

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morphogenetic protein 4, transforming growth factor β), vascular endothelial growth factor and extracellular matrix proteins [6].

CTGF expression is regulated by growth factors and cytokines, including angiotensin II, bone morphogenetic proteins, endothelin, as well as mechanical stimuli (including high blood pressure and tension in the vascular wall) [3]. Angiotensin II-induced arterial hypertension is an active inducer of CTGF expression in the vascular wall. Transforming growth factor β is the most important regulator of CTGF expression. CTGF expression correlates with the expression of transforming growth factor β in the vascular wall. Vascular endothelial growth factor also induces CTGF, which is of great clinical importance in case of dysregulation of angiogenesis, and, in particular, with underlying diabetic retinopathy [6].

Connective tissue growth factor is actively expressed during the development of the cardiovascular system, while embryos with a deficiency of this factor die soon after birth due to complex development defects. In adults, CTGF apparently plays a role in the development of certain pathological processes, including heart failure, cardiosclerosis and scar formation after myocardial infarction [2]. Increased expression of CTGF in vessels is associated with atherogenesis, apoptosis of smooth muscle cells and the formation of vascular aneurysms [7–9]. In an experiment, angiotensin II, high blood pressure and vascular wall tension enhanced CTGF expression, which contributed to changes in vascular smooth muscle cells [7]. As a result of such remodeling, the structural integrity of the vascular wall is disrupted, which apparently contributes to the formation of aneurysms and aortic dissection or rupture [9].

Stimulation of connective tissue growth factor may be involved in the development of cerebral microbleeding induced by hypertension due to the violation of vascular wall integrity [6]. CTGF is also expressed in atherosclerotic plaques. It is thought to play a role in the regulation of their stability and can also stimulate the migration of monocytes into atherosclerotic plaques [2]. It was demonstrated under experimental conditions that CTGF can play a role in atherogenesis. When mice were injected with a drug that blocks CTGF, the accumulation of macrophages in atheromas and the size of plaques decreased [10].

In cases of such a pathological process as hypertrophic cardiomyopathy (with interstitial fibrosis and excessive accumulation of extracellular matrix proteins), there was an increase in both tissue expression of CTGF and concentration of this factor circulating in the blood, starting from the earliest stages of this disease. It was demonstrated in experimental models that CTGF is a powerful stimulator of the expression of genes that encode extracellular matrix proteins [11]. According to some reports, the suppression of CTGF by transmitting signals of insulin-like growth factor-1 in cases of dilated cardiomyopathy also reduces myocardial fibrosis and improves cardiac function [12].

A significant correlation between the level of connective tissue growth factor in plasma and echocardiographic parameters of diastolic dysfunction was found in the Taiwan registry with 125 patients with diastolic heart failure. The severity of cardiac fibrosis assessed by magnetic resonance imaging also correlated with CTGF concentration in plasma [13].

Another study analyzed the expression of connective tissue growth factor in patients with heart failure who underwent heart transplantation. In the left ventricle tissue of patients with both ischemic and dilated cardiomyopathy, increased expression of CTGF was detected, along with overexpression of transforming growth factor β1, collagen and matrix metalloproteinases, which correlated with the severity of interstitial myocardial fibrosis [14].

In one of the largest clinical studies of connective tissue growth factor involving 1,227 patients with cardiovascular diseases, it was found that an elevated level of this factor in plasma increases the risk of new cardiovascular diseases. In this study, the high concentration of CTFG was associated with ischemic coronary events (1.4 times) and all-cause mortality but was not associated with ischemic stroke. CTGF level in plasma positively correlated with the level of total cholesterol and LDL-cholesterol and negatively correlated with glomerular filtration rate. CTGF concentration in cases of cerebrovascular pathology was significantly lower [15].

High levels of CTGF in the presence of type 2 diabetes mellitus can help to predict subsequent myocardial infarction or death from cardiovascular diseases. A study involving 952 patients with diabetes mellitus and high CTGF concentration showed a higher risk of myocardial infarction (2.4 times), and of cardiovascular mortality and mortality from all causes (2.7 times) compared with individuals with a low concentration of this factor [16]. CTGF is a powerful inducer of chemotaxis and formation of extracellular matrix, which contributes to the progression of inflammatory, proliferative and fibrotic changes with underlying cardiovascular disease [16].

Animal experimental models showed that the increased activity of CTGF in the myocardium after myocardial infarction is associated with the decreased remodeling of the left ventricle, which is achieved due to the inhibition of apoptosis and inflammation [17]. However, in a clinical study involving 988 patients with ST-elevation myocardial infarction, no significant relationship was found between CTGF level in blood and the size of the infarct area, left ventricular ejection fraction, end-systolic and end-diastolic volumes of the left ventricle, and the worsening the prognosis for patients and their mortality [18].

A recent study by Chi H. et al. (2019) involving 114 patients with diastolic heart failure showed that levels of connective tissue growth factor in this group of patients were significantly higher than in the control group and correlated with echocardiographic parameters of diastolic dysfunction [19]. Another study also demonstrated increased CTGF in 52 patients with chronic heart failure (CHF), and a significant correlation of this factor with the severity of CHF, concentration of cerebral natriuretic peptide and echocardiographic parameters of diastolic, but not systolic, dysfunction [20]. According to the authors of this study, the effect of CTGF on diastolic heart failure is a result of its profibrotic action. In a study of CTGF in patients with acute heart failure, maximum increase in CTGF was observed in patients with heart failure and reduced ejection fraction compared to the control group without heart failure or with heart failure and preserved ejection fraction [21].

A number of studies have demonstrated the important role of connective tissue growth factor in the development of atrial fibrosis and dilation and related fibrillation [22, 23]. Analysis of CTGF expression in atrial tissue removed during cardiac surgery revealed a higher content of CTGF in atrial fibroblasts in patients with atrial fibrillation compared with patients with sinus rhythm; moreover, the level of this growth factor positively correlated with the duration of atrial fibrillation and dilation [22]. Another study also revealed increased CTGF expression in fibroblasts and atrial myocytes removed during cardiac surgery; stimulation with angiotensin II further enhanced hyperexpression of this growth factor [23].

It was found that CTGF in atherosclerotic plaques removed during carotid endarterectomy is higher in patients with acute cerebrovascular events than in patients with transient ischemic attacks [24]. In this study, plaques with high CTGF had more collagen and smooth muscle cells. Therefore, the authors concluded that this growth factor is associated with a more stable phenotype of atherosclerotic plaques [24].

As shown in several studies, CTGF expression in the brain in cases of Alzheimer's disease correlates with the progression of the clinical signs of dementia and amyloid accumulation [6]. The experimental model of Alzheimer's disease showed that a diabetic diet leads to a significant increase in CTGF in the brain, along with the increased accumulation of amyloid, which is typical for this type of dementia [6]. Due to impaired maturation and regeneration of oligodendrocytes and inhibition of axon myelination, CTGF can also take part in the pathogenesis of neurodegenerative diseases where the processes of demyelination and axonal degeneration are important [25].

A number of studies have demonstrated the relationship between CTGF and adipose tissue. A recent study showed that CTGF expression was more significant in preadipocytes, not in adipocytes, and the level of this growth factor correlates with the level of adipose tissue and insulin sensitivity [26]. CTGF-positive cells were found primarily in the areas of fibrosis of subcutaneous adipose tissue of the anterior abdominal wall and decreased body weight led to a decrease in CTGF expression in adipose tissue. The authors of the study concluded that increased CTGF expression is associated with adipose tissue, adipose tissue fibrosis, and insulin resistance in obese individuals [26]. At the same time, experimental models showed that CTGF, which affects the differentiation of adipocytes, can play a role in the pathogenesis of obesity and the related insulin resistance [27].

The expression of connective tissue growth factor also increases in presence of many nephropathies. In an experiment, CTGF inhibition slowed disease progression with underlying diabetic nephropathy, unilateral ureteral obstruction and in mice that underwent nephrectomy. CTGF and degradation fragments thereof found in different biological fluids were advanced as risk biomarkers for several nephropathies [28, 29]. The carboxyl terminal module (specifically CCN2 IV) was of particular interest among the fragments. In cell culture, this fragment regulated cell migration and proliferation, increased the production of chemokines and the extracellular matrix, and participated in renal inflammation processes [3].

CTGF was shown to be a key factor in the development and progression of diabetic nephrosclerosis. In cases of experimental diabetic nephropathy, excessive expression of CTGF in glomeruli, tubules, and

interstitial tissue caused glomerulosclerosis, tubulointerstitial fibrosis, and albuminuria [29]. In cases of diabetic nephropathy in humans, overexpression of CTGF, detected by kidney biopsy, was also associated with tubulointerstitial fibrosis, proteinuria and impaired renal function, while CTGF levels in urine correlated with albuminuria [30]. CTGF level in blood can help to predict the onset of end-stage renal failure and death from diabetic nephropathy [31, 32]. The connective tissue growth factor can also be shown to play a certain role with underlying non-diabetic chronic kidney disease. CTGF in blood and urine was significantly high in patients with chronic kidney disease and proteinuria but without diabetes mellitus. The decrease in proteinuria as a result of the appropriate treatment was accompanied by a proportional stepwise decrease of CTGF concentration in urine but had no effect on the high level of this growth factor in the blood [29]. Increased CTGF in urine may be caused by the local synthesis of this protein in kidneys, for example, due to the activation of angiotensin II synthesis or excessive sodium intake. Local production of CTGF in the kidneys was observed in experimental conditions and based on the results of a kidney biopsy in humans [30, 32]. In addition to the local synthesis of CTGF in kidneys, enhanced ultrafiltration of CTGF and its impaired reabsorption in tubules can contribute to the increase in the negative effect of CTGF on the nephron, which further contributes to the stimulation of fibrosis in the kidneys [29].

The CTGF level in kidneys is low under normal conditions, but its expression increases with renal fibrosis. CTGF expression (in both the mesangium and extracapillary) increases with underlying glomerulonephritis. Besides being involved in fibrosis processes, CTGF induces the expression of inflammatory mediators and contributes to the increase in the number of macrophages and cell adhesion. Thus, CTGF can play an important role in the development of glomerulonephritis, causing an inflammatory process [33, 34].

A recent study involving 23 patients with IgA-nephropathy and hemorrhagic vasculitis showed that cytoplasmic expression of CTGF in the cells of renal tubules was significantly higher in these patients compared to the control group. However, there were no differences in CTGF expression in the glomeruli of kidneys. Subsequent follow-up revealed a direct correlation between the rate of nephropathy progression and CTGF expression in tubule cells. The authors of this work suggested that CTGF may be a new, early and sensitive marker of chronic kidney disease [35].

Four hundred and four patients on hemodialysis were enrolled in one of the largest studies of CTGF with underlying nephrological pathology. The results of this study indicate an inverse correlation between the concentration of this growth factor and the glomerular filtration rate. On the other hand, there was a direct relationship between CTGF and cardiovascular diseases, levels of interleukin-6 and β2-microglobulin, as well as the presence of polycystic kidney disease and tubulointerstitial nephritis. Patients with the highest CTGF concentrations were at a higher risk of mortality than patients with the lowest CTGF. It should be noted that the level of this growth factor decreased with hemodiafiltration [36].

Special studies demonstrated that connective tissue growth factor is an important mediator of fibrosis in renal transplant; moreover, CTGF levels in urine correlate with the development of interstitial transplant fibrosis. In a study involving 160 patients with a kidney transplant, tissue expression of CTGF and the level of this protein in urine were predictors of interstitial fibrosis and tubular atrophy. Even in patients with good histology results in the early post-transplant period, significant expression of CTGF was often detected, which could be a predictor of damage development [37].

A number of studies demonstrated the important role of CTGF in lung pathologies. One of the most interesting studies concerning this problem examined CTGF expression in bronchial epithelial cells of human and experimental animals; the results showed that the expression of this growth factor in humans increased with the severity of chronic obstructive pulmonary disease and was associated with accelerated cell aging [38]. According to the authors of this paper, by accelerating the aging of lung epithelial cells, CTGF can inhibit the regeneration of these cells and lead to pulmonary emphysema [38]. Experimental studies showed that CTGF plays a certain role in the development and progression of pulmonary fibrosis due to the activation of type I collagen [5, 39].

A recent study, which results were published in January 2020, showed good efficacy and tolerability of treatment with monoclonal anti-CTGF antibodies in patients with idiopathic pulmonary fibrosis. In the group of patients treated with anti-CTGF antibodies, a significant slowdown in the rate of decrease of lung function was observed (as measured by forced

vital capacity), along with a significant decrease in the progression of pulmonary fibrosis (according to CT results). After 48 weeks, there were fewer patients with disease progression in the treatment group than in the control group. The authors of this work concluded that the treatment of idiopathic pulmonary fibrosis with monoclonal anti-CTGF antibodies could be promising in the treatment of this prognostically unfavorable disease [40].

According to other authors, connective tissue growth factor may be a new target for the management of bronchopulmonary dysplasia in premature infants. This conclusion was made based on the results of experimental studies showing that CTGF contributes to the development of bronchopulmonary dysplasia. CTGF overexpression in alveolar epithelial cells led to impaired alveolar formation and also caused vascular remodeling and pulmonary hypertension. At the same time, CTGF inhibition with monoclonal antibodies stimulated normal formation of alveoli, decreased vascular remodeling and decreased pulmonary artery pressure [41].

In a study involving 95 patients with acute respiratory distress syndrome who were on mechanical ventilation, a direct correlation was revealed between the CTGF level and subsequent pulmonary fibrosis. The authors of this work suggested that connective tissue growth factor and transforming growth factor β1 may be of great prognostic value for assessing the risk of pulmonary fibrosis in patients with acute respiratory distress syndrome [42].

Inflammatory bowel disease is a relatively new area in studying the role of CTGF. A study involving 93 patients with ulcerative colitis showed increased CTGF expression in intestinal mucosa; the concentration of this factor correlated with the severity of colitis. Results of the experimental part of this study showed that CTGF inhibition contributed to a decrease in the severity of inflammatory process in the intestines and the normalization of intestinal microbiota [43].

At the same time, the results of recent experimental and clinical studies demonstrated the high activity of connective tissue growth factor in almost three dozen tumors. It was found that CTGF regulates the proliferation of tumor cells, their migration and metastasis, as well as angiogenesis and drug resistance, which ultimately lead to poor prognosis for a large number of cancer diseases [44]. It was established, for example, that CTGF overexpression predisposes to the progression of endometrial cancer, and this factor itself can be a new prognostic biomarker for this neoplasm [45]. Similar results were also obtained in cases of ovarian cancer when CTGF contributed to the metastasis of tumor cells and resistance to chemotherapy [46].

It was also established that CTGF is an important regulator of skeletogenesis. Studies demonstrated that CTGF is important for the condensation of mesenchymal cells in areas of future bones and the regulation of the proliferation and differentiation of chondrocytes and osteoblasts. Proper regulation of CTGF expression is required for the normal course of mesenchymal condensation, chondrogenesis and osteogenesis [1]. The ability of CTGF to interact with other skeletal growth factors and modulate their effects also plays a critical role for this growth factor in the regulation of skeletal development. The physiological significance of CTGF for normal skeletogenesis was confirmed in experimental mice models without this growth factor (the laboratory animals had craniofacial, axial and appendicular skeleton defects) [1].

In addition, connective tissue growth factor is actively involved in cartilage formation. CTGF significantly increases the production of cartilage matrix proteins, such as type II collagen and aggrecan, and also stimulates the proliferation of chondrocytes and differentiation and maturation of chondrocytes in physiological conditions [47, 48]. At the same time, CTGF increases the adhesion of chondrocytes to fibronectin, as well as angiogenesis by enhancing adhesion and migration of endothelial cells [49]. Skeletal muscle pathology was observed in mice with CTGF deficiency as a result of impaired chondrocyte proliferation and extracellular matrix composition, which indicates that CTGF is a key regulator of the formation of the extracellular cartilage matrix. Moreover, the implantation of CTGF-containing gelatin hydrogel into rat articular cartilage defects accelerated cartilage restoration, and cartilage-specific CTGF overexpression during development and growth reduced age-related changes in articular cartilage [49]. Another study showed that the decrease in the content of CTGF leads to cartilage thickening and has a protective effect against osteoarthritis [50]. Experimental studies showed that CTGF expressed and secreted by osteoblasts during proliferation, differentiation, bone formation and healing of fractures also regulates osteogenesis in osteoblasts [51]. Based on the results of these experiments, it was suggested that the pathological expression of connective tissue growth factor might be a new mechanism for the development of senile osteoporosis by suppressing the function of osteoblasts [51].

As for the regulation of the expression of connective tissue growth factor in skeleton cells, the primary inducer of CTGF in chondrocytes and osteoblasts, as in many other cells, is transforming growth factor β1. Also, glucocorticoids, retinoids, and taurine can stimulate CTGF induction with chondrocytes, while endothelin and cortisol were shown to regulate this growth factor in osteoblasts [1].

Another disease whose pathogenesis can involve CTGF is rheumatoid arthritis. It was established that in this disease, CTGF is secreted by fibroblast-like synoviocytes and stimulates the proliferation of these cells with the formation of pannus and cartilage destruction. In experimental studies, CTGF expression on the synoviocytes of patients with rheumatoid arthritis was shown to be more significant compared with the control group. Results of a clinical study revealed that CTGF serum concentration in patients with rheumatoid arthritis was significantly higher than in the control group [52].

Increased CTGF concentration in blood was also found in a group of 87 patients with Behçet's disease. The CTGF level in this study was much higher with the involvement of internal organs in the pathological process, as well as with severe ophthalmic manifestations. It should be noted that in patients who received treatment with glucocorticosteroids and cytostatics, CTGF concentration was significantly lower [53].

The CTGF level increases significantly with numerous underlying pathological conditions accompanied by fibrosis when excessive production of collagen is thought to be stimulated. CTGF is expressed in normal human dermis, which suggests that this protein is a physiological regulator of collagen expression. It was shown that the CTGF level is significantly lower in dermal fibroblasts, the primary collagen-producing cells, in the skin of individuals older than 80 years. On the other hand, CTGF overexpression stimulated the synthesis of type I procollagen [54].

Experimental data demonstrate that aging is associated with increased expression of connective tissue growth factor in vessels and the heart, which can contribute to the age-related remodeling of the extracellular matrix [6]. CTGF is involved in age-related changes in cardiomyocytes and vascular wall cells by lowering the expression of certain types of micro-RNA [6, 55]. Increased CTGF expression was also found in «aging» fibroblasts. [56]. In connection with these data, CTGF is considered as a possible marker of aging processes.

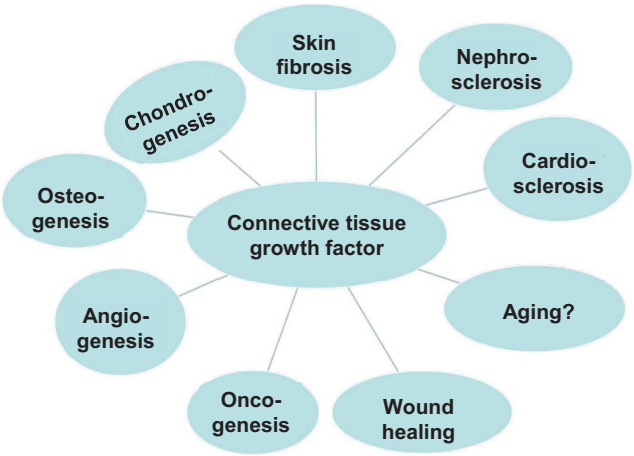

Figure 1. *The effect of connective tissue growth factor on various pathological and physiological processes*

Thus, connective tissue growth factor is a key mediator that modulates the effects of many other growth factors and regulates the formation and remodeling of the extracellular matrix. As a result, this growth factor significantly contributes to various pathological and physiological processes (Figure 1).

There is increasingly more evidence that CTGF is activated with aging. Further studies of this growth factor are required in order to better understand its clinical significance both in aging processes and in various pathological conditions and age-associated diseases.

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