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CTGF/CCN2 from Skeletal Muscle to Nervous System: Impact on Neurodegenerative Diseases

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Abstract

Connective tissue growth factor (CTGF/CCN2) is a matricellular protein that belongs to the CCN family of proteins. Since its discovery, it has been linked to cellular processes such as cell proliferation, differentiation, adhesion, migration, and synthesis of extracellular matrix (ECM) components, among others. The pro-fibrotic role of CTGF/CCN2 has been well-studied in several pathologies characterized by the development of fibrosis. Reduction of CTGF/CCN2 levels in *mdx* mice, a murine model for Duchenne muscular dystrophy (DMD), decreases fibrosis and improves skeletal muscle phenotype and function. Recently, it has been shown that skeletal muscle of symptomatic hSOD1^{G93A} mice, a model for Amyotrophic lateral sclerosis (ALS), shows up-regulation of CTGF/CCN2 accompanied by excessive deposition ECM molecules. Elevated levels of CTGF/CCN2 in spinal cord from ALS patients have been previously reported. However, there is no evidence regarding the role of CTGF/CCN2 in neurodegenerative diseases such as ALS, in which alterations in skeletal muscle seem to be the consequence of early pathological denervation. In this regard, the emerging evidence shows that CTGF/CCN2 also exerts non-fibrotic roles in the central nervous system (CNS), specifically impairing oligodendrocyte maturation and regeneration, and inhibiting axon myelination. Despite these striking observations, there is no evidence showing the role of CTGF/CCN2 in peripheral nerves. Therefore, even though more studies are needed to elucidate its precise role, CTGF/CCN2 is starting to emerge as a novel therapeutic target for the treatment of neurodegenerative diseases where demyelination and axonal degeneration occurs.

Keywords CTGF/CCN2 · Skeletal muscle · Central nervous system · Peripheral nerves · Myelination · Fibrosis

Abbreviations

ALS	Amyotrophic lateral sclerosis
CNS	Central nervous system
CTGF/CCN2	Connective tissue growth factor
DMD	Duchenne muscular dystrophy
ECM	Extracellular matrix
PNS	Peripheral nervous system
TGF-β	Transforming growth factor type β

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Introduction

Connective tissue growth factor (CTGF/CCN2) was discovered more than 25 years ago. Despite the cellular, physiological, and pathological roles of CTGF/CCN2 that have been studied since its discovery, emerging evidence indicate that besides its function in cellular processes such as adhesion, migration, proliferation, differentiation, and extracellular matrix (ECM) deposition, it seems to be also involved in non-fibrotic processes such as demyelination in the central nervous system (CNS).

CTGF/CCN2 is a member of the CCN family that comprises six proteins: cysteine-rich 61 (CYR61/CCN1), CTGF/CCN2, nephroblastoma overexpressed (NOV/CCN3) and Wnt-induced secreted proteins-1 (WISP-1/CCN4), -2 (WISP-2/CCN5), and -3 (WISP-3/CCN6). These proteins share structural similarities with four conserved modules: Module 1 corresponds to an insulin-like growth factor (IGF)-binding domain, module 2 to a von Willebrand type C domain, module 3 to a thrombospondin-1 (TSP-1) domain, and module 4 to a C-terminal domain containing a cysteine

knot. However, despite these conserved CCN protein modules, WISP-2/CCN5 lacks module 4 and biologically active forms of CTGF/CCN2 that lack modules 1 and 2 or 1–3 and of NOV/CCN3 lacking module 1 that has been identified [1, 2]. Moreover, recent studies have shown that CTGF/CCN2 has different isoforms. A study from 2015 shows that CTGF/CCN2 possess a short splice variant encoding only the C-terminal domain that showed to be related with cell proliferation and tumorigenesis in B-linage acute lymphoblastic leukemia [3]. More recently, it has been demonstrated that CTGF/CCN2 is synthesized as an inactive protein that is autoinhibited by its N-terminal domains: the IGF-binding and the von Willebrand type C domain. Interestingly, the TSP-1 and the C-terminal domains appear to carry out the known functions of CTGF/CCN2 [4]. Although several names have been given to the same CCN protein, the HUGO Gene Nomenclature Committee (HGNC) has recently decided to adopt the CCN acronym as the official nomenclature for every CCN protein [5] for avoiding confusion and improving communication among researchers. The role of CTGF/CCN2 in fibrosis is well documented, and it has been investigated in several pathologies that involve a fibrotic response such as kidney, hepatic, lung and skin fibrosis; and skeletal muscular dystrophies, among others [6–10].

We begin this review summarizing the well-studied role of CTGF/CCN2 in skeletal muscular dystrophies, and we will then show recent evidence of its role on demyelination in the central nervous system as well as its potential participation in neurodegenerative diseases such as ALS in the CNS or peripheral nervous system (PNS). We will conclude this review examining the therapeutic possibilities of CTGF/CCN2 on neurodegenerative diseases as well as possible research directions that could help to elucidate its role(s) in the nervous system.

Role of CTGF/CCN2 in Skeletal Muscle

The first insight into CTGF/CCN2 involvement in skeletal muscle biology came from microarray screening studies that identified expression of the CTGF/CCN2 gene in rhabdomyosarcoma cells [11]. A few years later, the same research group showed that CTGF/CCN2 knock-down not only inhibits cell growth by promoting apoptosis but also decreases differentiation of rhabdomyosarcoma cells [12]. In contrast, another study has shown that CTGF/CCN2 induces dedifferentiation of C2C12 myotubes evidenced by a decrease in the number of myogenin-positive nuclei and reduced myosin protein levels [13]. More recently, it has been shown that CTGF/CCN2 not only promotes cell proliferation of C2C12 myoblasts but also inhibits C2C12 differentiation by down-regulating desmin and myosin heavy chain [14]. However, myoblast differentiation from CTGF/CCN2-deficient mice is impaired; thus, CTGF/CCN2 seems to be promoting proliferation and early differentiation but inhibiting terminal differentiation [14]. It has also been shown that CTGF/CCN2 is up-regulated by TGF-β1 stimulation in rat skeletal muscle myotubes [15], and C2C12 myoblasts and myotubes [13]. C2C12 myoblasts and myotubes also express ECM molecules such as fibronectin and collagen-I in response to CTGF/CCN2 stimulation [13]. Skeletal muscle fibroblasts from *mdx* mice, a murine model for Duchenne muscular dystrophy (DMD), which is a disease characterized by loss of muscle strength, degeneration/regeneration cycles of myofibers, and fibrosis [9, 16], express more fibronectin, decorin, and biglycan than wild-type fibroblasts. Paradoxically, treatment with TGF-β1 or CTGF/CCN2 decreases fibronectin levels in *mdx* skeletal muscle fibroblasts, while in the wild-type fibronectin levels are induced, suggesting a mechanism involving protein degradation rather than a decrease in expression, since fibronectin mRNA levels were not altered [17]. Another study has shown that CTGF/CCN2 triggers a pro-fibrotic response via up-regulation of the sphingosine kinase-1/$S1P_3$ signaling axis in C2C12 myoblasts [18]. Thus, it seems that CTGF/CCN2 is able to activate several signaling pathway such as SK-1/$S1P_3$ and extracellular signal-regulated kinases (ERK1/2) [13] to exert its pro-fibrotic role in skeletal muscle.

Another study showed that denervation of hind limb and hemi-diaphragm induces up-regulation of CTGF/CCN2 and CYR61/CCN1 in skeletal muscle. The authors propose that up-regulation of several genes including CTGF/CCN2 and CYR61/CCN1 could be attenuating Wnt signaling pathway [19]. Expression of CTGF/CCN2 and CYR61/CCN1 also seems to be up-regulated in human skeletal muscle after exercise with high mechanical loading, where CTGF/CCN2 appears to be located in myofibers and in the interstitial space [20]. It has also been reported that denervated-sternocleidomastoid muscles show myofiber atrophy accompanied by enhanced expression of CTGF/CCN2, TGF-β1, and α-SMA [21].

Moreover, CTGF/CCN2 is also up-regulated in several dystrophies such as DMD and Becker muscular dystrophy (BMD), among others [9, 22, 23]. CTGF/CCN2 also appears to be located in myofibers and interstitial space, predominantly in the endomysium of DMD muscles. More strikingly, CTGF/CCN2 over-expression in skeletal muscle of wild-type mice triggers a dystrophic phenotype that includes fibrosis and reduction of muscle isometric force [24]. Pharmacological blockade of the angiotensin II receptor (AT1) is able to decrease CTGF-mediated damage and fibrosis in wild-type and *mdx* skeletal muscle [25]. CTGF/CCN2 is also up-regulated in *mdx* mice skeletal muscle, and its genetic reduction in hemizygous $Ctgf^{\pm}$ mice in the *mdx* background leads to improvement of skeletal muscle isometric force and decreased fibrosis and damage [9]. Moreover, it has been shown that CTGF/CCN2 levels are increased in necrotic-regenerative foci of dystrophic muscle from *mdx* mice, where it could be inducing an inflammatory and a fibrotic response [26] (Fig. 1).

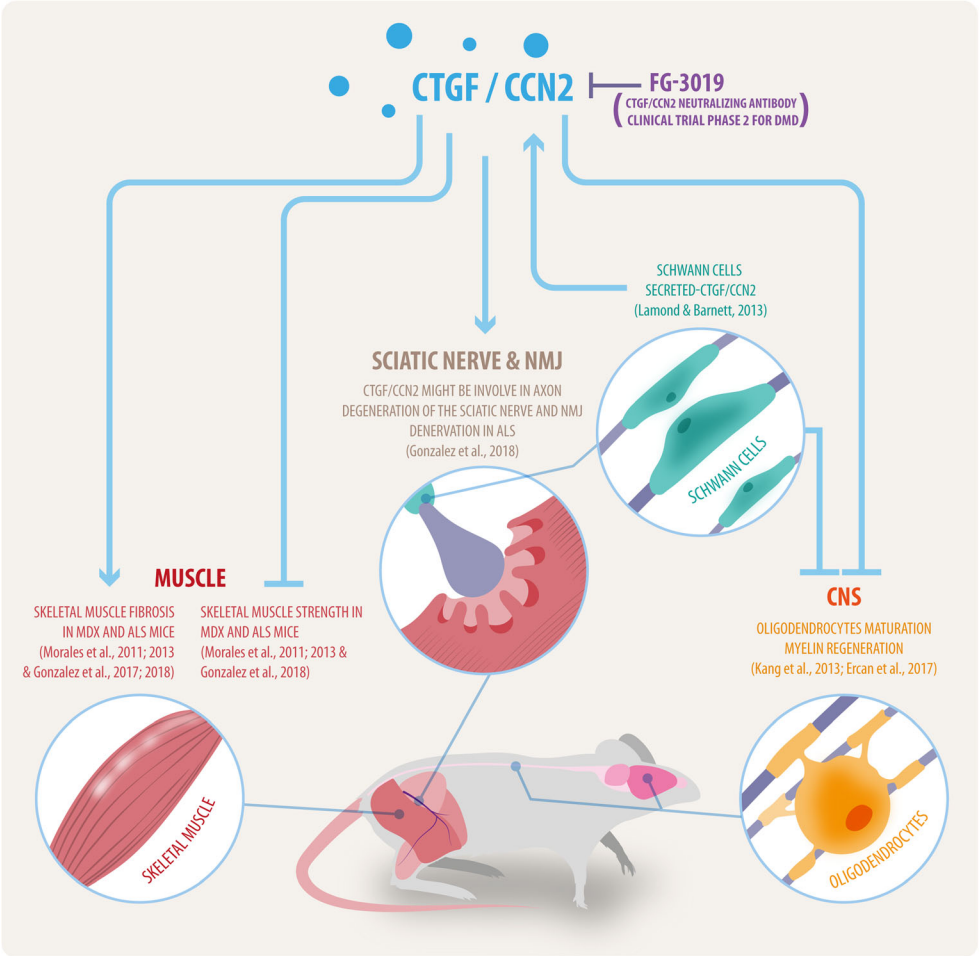

Fig. 1 Proposed CTGF/CCN2-mediated mechanisms involving axonal degeneration and muscle wasting. CTGF/CCN2 is up-regulated in the *mdx* and ALS mice. The inhibition of CTGF/CCN2 activity improves skeletal muscle architecture and function in both *mdx* [9] and ALS mice [27]. Inhibition of CTGF/CCN2 activity also reduces myelin degeneration in the sciatic nerve and improves NMJ innervation in ALS mice [27]. There is evidence showing a role of CTGF/CCN2 as a negative regulator of oligodendrocytes maturation and myelin regeneration in the CNS [28]. Oligodendrocytes maturation and myelin regeneration are also impaired in ALS mice [29], and this phenomenon might be partially explained by a CTGF/CCN2-mediated process as in [28], since elevated levels of CTGF/CCN2 have been found in spinal cord of ALS mice and patients [27, 30]. Interestingly, it has also been found that CTGF/CCN2 secreted by Schwann cells can also modulate CNS myelination in a negative manner. Thus, in a neurodegenerative context, CTGF/CCN2 might be acting as both a pro-fibrotic factor in skeletal muscle and spinal cord, and a negative regulator of myelin regeneration at least, in the CNS. However, further studies are required to elucidate its role at peripheral nervous system

It was recently demonstrated that CTGF/CCN2 is also up-regulated in skeletal muscle from symptomatic hSOD1^{G93A} mice, a murine model for ALS. The up-regulation of CTGF/CCN2 correlates with fibrosis, enhanced TGF-β signaling, and induction of fibro/adipogenic progenitor (FAPs) markers [31], which are cells responsible of high levels of ECM synthesis under different pro-fibrotic conditions [32]. Inhibition of CTGF/CCN2 activity using a blocking antibody (FG-3019; FibroGen, Inc.) improves locomotor and skeletal muscle function in hSOD1^{G93A} mice [27]. Furthermore, in skeletal muscle, FG-3019 treatment reduces levels of fibrosis, improves skeletal muscle architecture, reduces myofiber atrophy, and improves neuromuscular junction (NMJ) architecture [27].

Put together, the evidence indicates that CTGF/CCN2 seems to be involved in the fibrotic process that is triggered in the skeletal muscle as a consequence of varied insults including chronic myofiber degeneration/regeneration cycles as occurs in DMD, traumatic denervation, and pathological denervation occurring in neurodegenerative diseases such as ALS.

Role of CTGF/CCN2 in the Nervous System

Results published in 1999 by Kondo et al. show for the first time the localization of CTGF/CCN2 in the rat central nervous system. The authors showed that the majority CTGF/CCN2

immunoreactivity was localized in astrocytes, but it was also found in a subpopulation of pyramidal neurons. However, they found the strongest immunoreactivity in tanycytes surrounding the central canal of the spinal cord and ependymal cells located in the wall of the cerebral ventricle [33]. Other studies have shown that CTGF/CCN2 is expressed throughout the human central nervous system [34] and also in layer VII neurons throughout the adult cortex [35].

The first studies suggesting a role for CTGF/CCN2 in the CNS were done performing a unilateral kainic acid lesion in the CA3 hippocampus area. In this model, the authors found increased CTGF/CCN2 levels in both astrocytes and neurons, which correlated with an increase in fibronectin levels [36]. It was also shown that CTGF/CCN2 is expressed in astrocytes after human cerebral infarction [37], human traumatic brain injury, and stab wound injury in rat brains [38]. In this study, the authors also found that fibroblasts and endothelial cells express CTGF/CCN2 [38]. On the same line of inquiry, another study shows that there is increased number of CTGF/CCN2-positive cells including GFAP-positive reactive astrocytes, which co-express fibronectin after spinal cord injury [39]. An in vitro study has shown that CTGF/CCN2 increases GFAP-positive and fibronectin deposition in neural progenitors culture. It has also been shown that chronic sciatic nerve compression induces fibrosis, which correlates with induction of TGF-β1, CTGF/CCN2, and ERK1/2 signaling pathway in dorsal root ganglia [40]. More recently, it was demonstrated that silencing CTGF/CCN2 using lentivirus decreases glial scar formation in rats after spinal cord injury by reducing levels of GFAP, vimentin, fibronectin, and laminin [41]. Together, these studies suggest a role for CTGF/CCN2 in glial scar formation in the central nervous system, similar to what has been reported for skeletal muscle and other tissues.

CTGF/CCN2 was also found to be up-regulated, postmortem, in spinal cord of ALS patients [30] and in neurons and astrocytes associated with senile plaques in Alzheimer's disease (AD) patients [42, 43]. Induction of CTGF/CCN2 and matrix metalloproteinase-3 (MMP-3) in ventral midbrain was also observed in lipopolysaccharide-induced dopamine neurodegeneration, suggesting a role in neuroinflammation [44]. Interestingly, it has been shown that CTGF/CCN2 has a neuroprotective role in AD mediating amyloid-β peptide (Aβ) degradation via membrane-bound MMP-14 in glia and membrane-bound MMP-13 in neurons [45].

In recent years, research has also focused on elucidating the non-fibrotic roles of CTGF/CCN2 in the CNS. It was shown that CTGF/CCN2 promotes apoptosis of periglomerular inhibitory neurons by enhancing activity of glial-derived TGF-β2 in the olfactory bulb [46]. CTGF/CCN2 was also identified by genome-wide transcriptomics as a paracrine regulator of oligodendrocyte maturation, where its expression is repressed by serum response factor (SRF). Moreover, adenovirus-mediated CTGF expression in vivo inhibits oligodendrocyte differentiation [47]. It has also been shown that CTGF/CCN2 secreted by neurons negatively regulate the total number and the maturation of oligodendrocytes in a mouse model of tuberous sclerosis complex. Therefore, in this scenario, CTGF/CCN2 seems to be secreted by neurons to regulate myelination and oligodendrocyte development in a paracrine manner [28]. However, a study performed in zebrafish showed that connective tissue growth factor a (*ctgfa*) is up-regulated upon spinal cord injury. Loss-of-function experiments showed that the absence of *ctgfa* leads to aberrant spinal cord repair, while its overexpression accelerates spinal cord regeneration [48]. This contradictory role of CTGF/CCN2 could be partially explained by the inherent regenerative capacities of each biological system.

Interestingly, it has been reported that NOV/CCN3 secreted by regulatory T cells promotes myelination and oligodendrocyte maturation in the CNS [49]. Expression of NOV/CCN3 in the CNS was first described by Su et al., where the authors showed that its expression is increased in the developing brain of rats, and the authors also found that motor neurons from ventral horn of spinal cord were positive for NOV/CCN3 [50]. This evidence indicates that CTGF/CCN2 and NOV/CCN3 have antagonist roles not only in the fibrotic process but also in axon myelination mediated by oligodendrocytes in the CNS ([49, 51]). In this regard, degeneration and impaired regeneration of oligodendrocytes, which result in progressive demyelination, have been identified in hSOD1^{G93A} mice [29]. Therefore, it is likely that axon demyelination and impaired regeneration of oligodendrocytes might be partially explained by a CTGF/CCN2-dependent mechanism, since increased CTGF/CCN2 protein levels have been found in the spinal cord of ALS patients and hSOD1^{G93A} mice [27, 30].

This up-regulation of CTGF/CCN2 in the CNS seems to occur at earlier stages than in skeletal muscle [27], opening the possibility of using CTGF/CCN2 as an early marker of ALS in spinal fluid. More importantly, blockage of CTGF/CCN2 biological activity using FG-3019 in hSOD1^{G93A} mice improved neuromuscular junction (NMJ) innervation and reduced myelin degeneration in the sciatic nerve. FG-3019 was able to reach both skeletal muscle and spinal cord; therefore, the amelioration of symptoms observed in this ALS animal model could be due to inhibition of CTGF/CCN2 activity in skeletal muscle or spinal cord [27]. Nevertheless, inhibition of CTGF/CCN2 could be a very promising therapeutic tool.

An in vitro study showed that CTGF/CCN2 secreted by Schwann cells inhibits oligodendrocyte myelination and promotes astrocyte reactivity. The authors suggest that inhibition of CTGF/CCN2-mediated myelination could be due to its effects on oligodendrocytes and/or by indirect mechanisms involving astrocyte reactivity [52]. Recently, a proteomic analysis demonstrated that CTGF/CCN2 is up-regulated during mesenchymal to Schwann cell transdifferentiation, also

suggesting a role of this factor in myelination [53]. Therefore, although emerging evidence shows that CTGF/CNN2 has a detrimental role in myelination in the CNS, there is no evidence involving CTGF/CCN2 in myelination of peripheral nerves.

Concluding Remarks and Further Directions

Although the role of CTGF/CCN2 has been well-studied in fibrosis of several tissues including skeletal muscle, little is known about its non-fibrotic role, especially in the CNS and PNS. Emerging evidence indicate that CTGF/CCN2 could be acting as a negative regulator of myelination in the CNS. In this scenario, targeting CTGF/CCN2 emerges as a promising therapeutic approach for diseases, which involve neurodegeneration and muscle wasting. Inhibition of CTGF/CCN2 activity by using the neutralizing antibody FG-3019 has shown to ameliorate muscle phenotype in both *mdx* and ALS mice. More strikingly, the treatment with this neutralizing antibody is currently under clinical trial in phase 2 for DMD. Therefore, further studies concerning the role of CTGF/CCN2 in this context are urgently needed, in order to expand these observations to other neurodegenerative diseases. Thus, deciphering the precise roles of CTGF/CCN2 in the nervous system might provide new therapeutic alternatives for neurodegenerative diseases in which demyelination and axonal degeneration occur.

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