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Review

Emerging Mechanisms of Cyr61/CTGF/NOV Secretion in the Nervous System

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The Cyr61/CTGF/NOV (CCN) family is dynamically expressed in various tissues, including the nervous system, from the prenatal period to adulthood. However, major studies have been conducted only in limited fields, such as the cardiovascular and muscular systems, skeletal development, and cancer. In addition, although the CCN family is a secretory protein, very few studies have described its mechanism of secretion. Recently, it has been suggested that overexpression of CCN3 or intracellular accumulation due to problems in the secretory pathway can inhibit neuronal axonal growth. In this review, we have briefly summarized the structure and characteristics of the CCN family and its related diseases, with particular emphasis on the secretory mechanism and modifiers of the CCN family, newly identified in the nervous system.

Key Words: CCN family, Nervous system, Secretory protein, Post-translational modifications, Palmitoylation, zDHHC palmitoyl acyltransferase

INTRODUCTION

The Cyr61/CTGF/NOV (CCN) family consists of six members, CCN1 to CCN6, and the family is named after the initials of the first three members found among them: Cysteine-rich61 (CYR61, CCN1), connective tissue growth factor (CTGF, CCN2), and nephroblastoma overexpressed (NOV, CCN3). The three additional members are Wnt-inducible secreted proteins WISP1 (CCN4), WISP2 (CCN5), and WISP3 (CCN6) (Holbourn et al., 2008; Krupska et al., 2015). The CCN family is a secretory matricellular protein present in the extracellular matrix (ECM) that does not serve as a structural support for the ECM, but performs various regulatory functions by binding to cell surface receptors, activating intracellular signaling pathways, and increasing the intensity of cellular responses. These functions are also related to essential biological processes, such as the differentiation of endothelial cells, the initial development of skeletal bones, the initial formation of a tumor, and wound healing (Holbourn et al., 2008). In contrast, overexpression of many CCN family members has been observed in various cancers, including pancreatic, breast, and lung cancers (Kim et al., 2018a). This suggests that abnormal expression levels of CCN proteins in cells may be linked to various diseases, including those of the nervous system.

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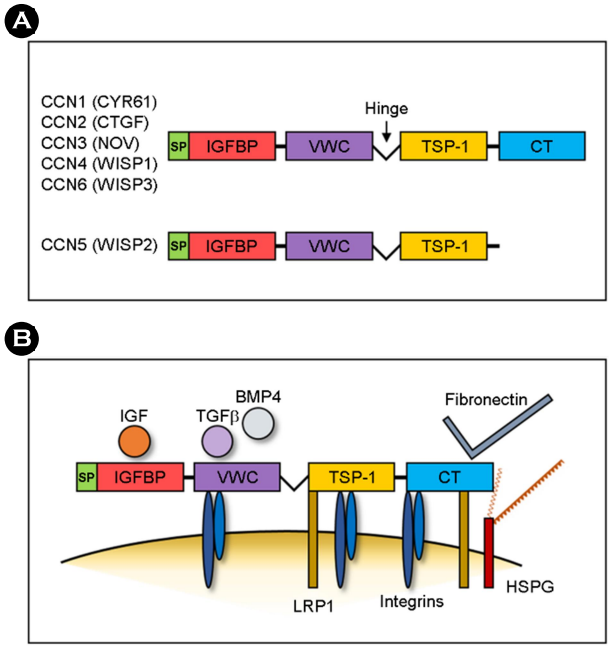

Fig. 1. Structure of CCN family proteins and molecular interactions. (A) Structure of CCN family members. SP, signal peptide; IGFBP, insulin-like growth factor binding protein domain; VWC, von Willebrand factor type C repeat; TSP1, thrombospondin type-1 repeat; CT, cysteine knot containing module. (B) CCN proteins physically interact with several extracellular matrix (ECM) proteins such as fibronectin, growth factors and bone morphogenetic proteins (BMPs). The individual modular domains mediate the interactions with specific proteins. Fibronectin is known to bind to the carboxy-terminal domain while growth factors and BMPs bind to the amino-terminal domain. CCN proteins also bind to and signal through several cell-surface receptors including several integrins, which function in concert with heparan sulphate proteoglycans (HSPGs) or low-density lipoprotein receptor-related proteins (LRPs) as co-receptors in some contexts. IGF, insulin-like growth factor; TGFβ, transforming growth factor-β. Modified from Holbourn et al., 2008; Chen and Lau, 2009; Jun and Lau, 2011.

Structure and molecular interactions of CCN family proteins

The CCN family has a unique mosaic structure composed of modules that share functional identity. A general CCN protein consists of an N-terminal secretory signal peptide (SP) followed by four functional domains. (1) Insulin-like growth factor binding protein (IGFBP)-like domain, (2) von Willebrand factor type C (VWC) repeat domain, (3) thrombospondin type-1 (TSP-1) repeat domain, and (4) cysteine knot-containing (CT) domain. The six CCN family members share ~30-50% identity between their respective structures. However, in the case of CCN5, there is no CT domain, and CCN6 deficiencies 4 cysteine (Cys) residues among the 38 highly conserved Cys residues in the VWC domain. The N-termini (SP, IGFBP, VWC) and C-termini (TSP-1, CT) are connected by a variable hinge, and cleavage occurs easily in this region as it is vulnerable to proteolysis. In truncated molecules each domain displays biological functionality, and the function of an entire protein is determined by the collaboration of each domain (Brigstock, 1999; Holbourn et al., 2008; Krupska et al., 2015).

Each module or domain of the CCN protein interacts with a specific protein. The conserved structure of the CCN family members suggests the utilization of similar mechanisms through which common receptors or factors interact to perform biological functions. CCN family members activate signaling pathways through direct binding of cell surface receptors and multiple co-receptors. Therefore, cell- or time-specific regulation is possible through a combination of various receptors. Additionally, CCN proteins can directly bind to growth factors and cytokines, thereby regulating their intrinsic biological activities (Chen and Lau, 2009; Jun and Lau, 2011) (Fig. 1).

Expression and associated diseases of the CCN family proteins

CCN1 is largely expressed in the heart, blood vessels, and blood during embryonic development (Kireeva et al., 1997). Cardial expression in mice starts from E8.5, and continues until E10.5. Its expression is important for the development of the aorta and pulmonary trunk (Mo and Lau, 2006) CCN1 is strongly associated with cardiovascular disease. Most *Ccn1* null mice embryos die between E11.5-E14.5. Hemorrhage, placental defects, and chorioallantoic fusion have also been reported (Mo et al., 2002). In addition, *Ccn1* null mice showed severe atrioventricular septal defects due to immaturity (Mo and Lau, 2006) and patients with such defects are shown to have a heterozygous missense mutation in CCN1 (Perrot et al., 2015). The *Ccn1* gene is also expressed in the respiratory system, embryonic skeletal system, developing nervous system (spinal cord, mesencephalon, telencephalon), olfactory bulb, and embryonic epidermis (Latinkic et al., 2001).

The expression pattern of CCN2 during development is

similar to that of CCN1, and it appears at high levels in the endothelium, the cardiovascular system, and skeletal tissues (Hall-Glenn et al., 2012). In homozygous *Ccn2* mutant mice, the normal bone skeleton of the chest is not formed, and the chest size is greatly reduced (Ivkovic et al., 2003). *Ccn2* mutant mice show cyanosis and dyspnea, and many die shortly after birth (Partridge et al., 2014). Lung hypoplasia results in decreased cell proliferation and increased cell death (Baguma-Nibasheka and Kablar, 2008), leading to growth retardation in the lungs of *Ccn2* mutant mice. In *Ccn2* deficiency mice, vascular and skeletal defects develop at a later stage of development (Hall-Glenn et al., 2013). At the adult stage, *Ccn2* mRNA is expressed in several organs, including the spleen, gastrointestinal tract, heart, testes, thymus, lung, skeletal muscle, kidney, and pancreas, but not in the central nervous system, liver, and peripheral leukocytes (Xu et al., 2000). Conversely, analysis of diseased tissues of human and animal models revealed enormous accumulation of CCN2 and extracellular matrix components in the fibrotic tissues. Thus, the etiological association of CCN2 in fibroproliferative disorders can be estimated (Leask et al., 2009). In relation to the nervous system, CCN2 expression level correlates with the progression of neurodegenerative diseases like Alzheimer's disease and amyotrophic lateral sclerosis (Ueberham et al., 2003; Zhao et al., 2005).

During development, CCN3 is expressed at high levels in skeletal muscles, vascular smooth muscle cells, the central nervous system and chondrocytes (Su et al., 2001; Perbal, 2015). CCN3 is involved in myogenesis, affecting the formation and stabilization of attachment structures that transmit force from the muscle to tendon (Lafont et al., 2005). In contrast, *Ccn3*-deficient mice develop normally until adulthood and both males and females can reproduce (Shimoyama et al., 2010). Similarly, *Ccn3* mutant mice deficient in the VWC domain displayed good health, albeit with mild skeletal defects (Heath et al., 2008).

During development, CCN4 is expressed in limited amounts in osteoblasts and osteoblastic progenitor cells (French et al., 2004). Adult stage CCN4 is expressed in a wide range of organs, including the epithelium, heart, kidney, lung, pancreas, placenta, ovaries, small intestine, spleen, and brain (Katoh and Katoh, 2005). A CCN4 variant, lacking the VWC domain has been described in a small number of human gastric cancer tissues and normal chondrocytes (Tanaka et al., 2001). Further, CCN4 protects against neurodegeneration by inhibiting primary neuronal injury and apoptosis during oxygen glucose deprivation (Wang et al., 2012).

CCN5 is expressed in most embryonic stages, especially from E4.5, the very early implantation stage in the uterine wall (Myers et al., 2012). *Ccn5*-null mice and *Ccn5*-overexpressing transgenic mice die because of improper implantation at or before the gastrulation stage (Jones et al., 2007). CCN5 is present in several organs such as the kidney, ovary, brain, heart, and lung, and even in adult organs (Gray et al., 2007). It inhibits smooth muscle proliferation and migration in both cell culture and animal models (Lake and Castellot, 2003; Mason et al., 2004). In MCF-7 breast cancer lines, the expression of CCN5 is upregulated by estrogen and it functions as an oncogene (Ray et al., 2005).

CCN6 is a critical protein involved in the keeping of human articular cartilage (Baker et al., 2012). Mutations in the human CCN6 gene causes progressive pseudorheumatoid dysplasia (pseudorheumatic dysplasia). This disease causes articular cartilage loss from infancy and multiple joint and bone abnormalities (Yu et al., 2015). In contrast, *Ccn6* null mice do not show a clear abnormal phenotype (Yu et al., 2015). CCN6 appears to be downregulated in invasive breast cancers and is thought to function as a CCN6 suppressing tumor (Leask and Abraham, 2006).

Post-translational modifications of the CCN proteins for secretion

Post-translational modifications (PTMs) of CCN proteins are important for regulating secretion and function. O-fucosylation is a reaction in which fucose is attached to the hydroxyl group (O-linked) of a serine or threonine residue (Vasudevan and Haltiwanger, 2014). Protein O-fucosyltransferase2 mediates O-fucosylation of CCN1 at the Thr242 residue of the TSP1 domain leading to its secretion from the cell (Niwa et al., 2015). Glucosyl-galactosyl-hydroxylation, which rarely occurs in the Lys residue of collagen family proteins, is found on the Lys203 residue of CCN1 mediated by lysyl hydroxylase 3. This collagen-like glycosylation is

required for secretion (Ishizawa et al., 2019). N-glycosylation is also reported in CCN2 and CCN3 (Bohr et al., 2010) In a later study, it was confirmed that there was an N-glycosylation modification in secreted CCN3. In addition, glycosylation of CCN3 also increases the migration and invasion of Jeg3 choriocarcinoma cells (Yang et al., 2011). Palmitoylation, a reversible PTM that attaches palmitate to cysteine residues via a thioester linkage (Resh, 2006), is known to occur on Cys241 located in the TSP-1 domain of CCN3, and is important for its extracellular secretion (Kim et al., 2018b).

Palmitoylation is an important modification known in other secretory proteins similar to CCN3. In Wnt proteins, one of the typical secretory proteins, glycosylation and palmitoylation are known to aid in the secretion Komekado et al., 2007). Porcupine (PORCN), an acyltransferase, is an important factor regulating normal secretion and signaling of Wnt in vertebrates. PORCN induces palmitoylation of Wnt protein in the endoplasmic reticulum (ER) (palmitoylation at Ser209 is essential for secretion, but requires additional N-glycosylation) (Mikels and Nusse, 2006; Gao and Hannoush, 2014). Another secreted protein, sonic hedgehog (Shh), also requires palmitoylation for secretion. The Shh precursor that enters the ER for processing is separated into two fragments through autocleavage, and palmitate is linked to the N-terminal cysteine residue of the N-terminal fragment by Hedgehog acyltransferase. Lipidated Shh is secreted from cells (Chamoun et al., 2001; Resh, 2021).

zDHHC proteins may act as a palmitoylating enzymes of CCN proteins

Palmitoylation of proteins is associated with various functions, such as membrane attachment, intracellular trafficking, protein localization, and protein secretion. The largest family of palmitoyl acyltransferases mediating this reaction is the aspartate-histidine-histidine-cysteine (DHHC) family, with a variant Cys2His2 zinc finger motif (Putilina et al., 1999; Greaves and Chamberlain, 2011). The DHHC family is a heterogeneous multi-pass transmembrane protein located in various compartments within the cell, such as the ER, Golgi

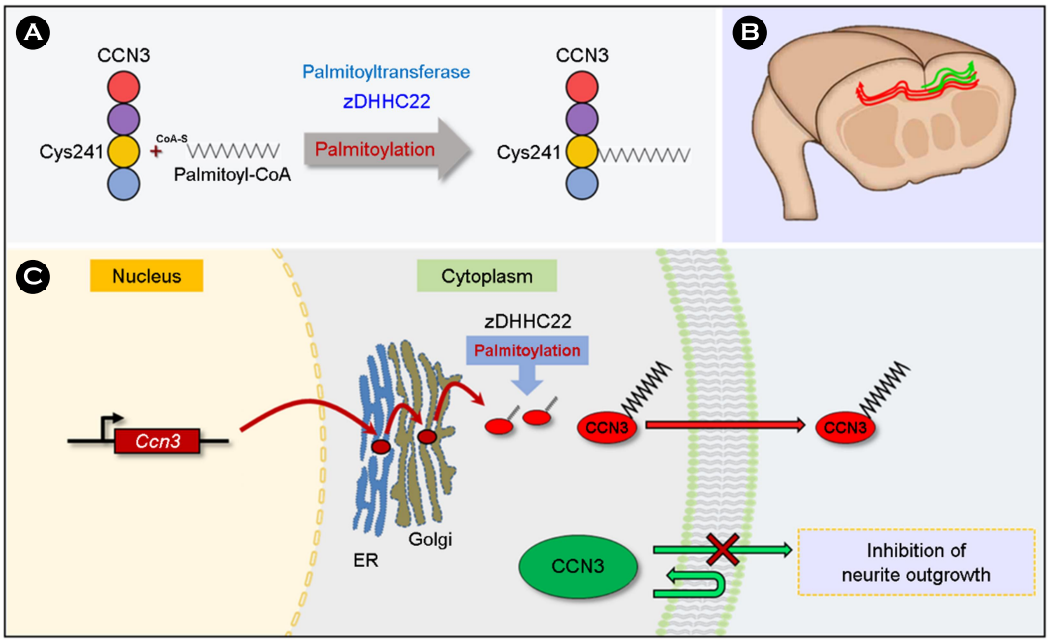

Fig. 2. Secretory mechanism of CCN3 via zDHHC22 in neurons. (A) Palmitoylation of CCN3 by zDHHC22. (B) Inhibition of neuronal axon growth in mouse cortical neurons induced by inhibition of CCN3 secretion (Red: Normal CCN3-secreting Neuron, Green: CCN3-secreted Neuron). (C) The secreted protein CCN3 synthesized in neurons passes through the Golgi apparatus and the endoplasmic reticulum, and palmitoylation occurs at the Cys241 residue by zDHHC22. Palmitoylated CCN3 protein is secreted out of the cell, however, loss of secretion leads to its accumulation inside the nerve cell and induces neuronal defects.

apparatus, endosomes, and plasma membrane (Globa and Bamji, 2017). The palmitoylation at Cys241 of the TSP-1 domain of CCN3 was found to be mediated by zinc finger DHHC type containing 22 (zDHHC22). zDHHC22 had the highest mRNA expression among ZDHHC family members in the neuroblast and Neuro2a cell lines, and directly binds to CCN3 (Kim et al., 2018b). Absence of extracellular CCN3 secretion leads to inhibition of neuronal outgrowth (Fig. 2). This suggest that zDHHC22 is needed for the efficient secretion of CCN3 during the development of neurons, further suggesting a role for the zDHHC family in the secretion of other CCN proteins.

Furthermore, zDHHC mutations also induce a phenotype that can be linked to the disease (Chamberlain and Shipston, 2015). zDHHC5 mutant mice show partial embryonic lethality (Li et al., 2010) while zDHHC8 knockout mice displayed decreased synapse, spine, and dendritic complexity (Mukai et al., 2008). zDHHC13 mutants show decreased lifespan, decreased size, osteoporosis, and muscle loss (Saleem et al., 2010) and zDHHC17 mutant mice resulted in weight loss and decreased brain size (Singaraja et al., 2011). Since this is not a phenotype limited only to neurons, it shows that the CCN substrate-zDHHC enzyme action can also occur in various tissues and cells.

CONCLUSIONS

The processes and mechanisms involved in CCN and its signaling have been extensively studied because they act on numerous cellular processes related to various aspects of development. In particular, changes in the intracellular expression levels of CCN protein have been shown to be associated with various diseases. Although recent studies have shown that palmitoylation of CCN3 is important for the regulation of extracellular secretion, further research is required to determine whether this modification also regulates the secretion of other CCN proteins. Furthermore, evidence of *in vivo* CCN3 palmitoylation induced by zDHHC22 needs to be presented. Considering the expression pattern of CCN in a time- and tissue-dependent manner, it is important to understand the mechanism of several diseases caused by CCN in relation with the mechanism of palmitoylation of each member.

Abbreviations

CCN	Cyr61/CTGF/NOV
CYR61	Cysteine-rich61
CTGF	connective tissue growth factor
NOV	nephroblastoma overexpressed
WISP1	Wnt-inducible secreted proteins
ECM	extracellular matrix
SP	signal peptide
IGFBP	insulin-like growth factor binding protein
VWC	von Willebrand factor type C
TSP-1	thrombospondin type-1
CT	cysteine knot-containing
ER	endoplasmic reticulum
PORCN	porcupine O-acyltransferase
Shh	sonic hedgehog
DHHC	aspartate-histidine-histidine-cysteine
PTM	Post-translational modifications

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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