



WJG 20th Anniversary Special Issues (8): Gastric cancer

Cyr61/CTGF/Nov family proteins in gastric carcinogenesis

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Received: October 29, 2013 Revised: December 7, 2013

Accepted: January 3, 2014

Published online: February 21, 2014

Abstract

Gastric cancer (GC) is the second leading cause of cancer-related death. The poor survival rate may reflect the relatively aggressive tumor biology of GC. Recently, the importance of the tumor microenvironment in carcinogenesis has emerged. In the tumor microenvironment, tumor cells and the surrounding stromal cells aberrantly secrete matricellular proteins capable of modulating carcinogenesis and regulating metastasis. The Cyr61/CTGF/Nov (CCN) proteins are a family of matricellular proteins with variable roles in many physiological and pathological processes. The evidence suggests that CCN family proteins contribute to GC carcinogenic processes. Here, we briefly review recent research on the effects of CCN family proteins in GC carcinogenesis and the development of new targeted agents in this field.

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Key words: Cyr61/CTGF/Nov proteins; Cysteine-rich angiogenic inducer 61; Connective tissue growth factor; Nephroblastoma over-expressed; Gastric cancer; Gastric carcinogenesis

Core tip: Cyr61/CTGF/Nov (CCN) proteins are matricellular proteins responsible for many physiological and pathological processes, including carcinogenesis. The prototypical CCN family protein is composed of an N-terminal secretory signal peptide and four structural modules. Several truncated variants participate in the carcinogenesis of gastrointestinal tract cancers. The role of CCNs in carcinogenesis is tumor-type and context-dependent. The evidence suggests that CCN family proteins play important roles in gastric cancer (GC) carcinogenic processes. Recent CCN targeting agents, including monoclonal antibodies, antisense oligonucleotides and RNA interference compounds, may be helpful in future GC therapeutics.

Cheng TY, Wu MS, Hua KT, Kuo ML, Lin MT. Cyr61/CTGF/Nov family proteins in gastric carcinogenesis. *World J Gastroenterol* 2014; 20(7): 1694-1700 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i7/1694.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i7.1694>

INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer-related death, accounting for approximately 10% of total cancer deaths worldwide^[1]. Despite significant advances in cancer treatment modalities, the prognosis for GC has only modestly improved. The five-year relative survival rate for all stages combined was 28% between 2002 and 2008, compared to 20% between 1987 and 1989^[2]. The poor survival rate may reflect the relatively aggressive tumor biology of GC.

The interplay between the tumor and its microenvironment is crucial for both tumor development and progression. In the tumor microenvironment, tumor cells and the surrounding stromal cells aberrantly secrete matricellular proteins, a group of proteins that function as regulators of cell-cell and cell-matrix interactions that modulate carcinogenesis and the regulatory networks of

Table 1 Nomenclature and characterization of the Cyr61/CTGF/Nov family proteins

CCN proteins (synonyms)	Chromosomal location	Molecular mass, kDa (number of amino acids)
CCN1 (Cyr61; CTGF-2; IGFBP-10/IBP-10; IGFBP-rP4; Cef-10)	1p22.3	42.0 (381)
CCN2 (CTGF; IGFBP-8/IBP-8; IGFBP-rP2; hypertrophic chondrocyte-specific protein 24)	6q23.1	38.1 (349)
CCN3 (Nov; IGFBP-9/IBP-9; IGFBP-rP3)	8q24.1	39.2 (357)
CCN4 (WISP-1; Elm-1)	8q24.22	40.3 (367)
CCN5 (WISP-2; CTGF-3; CTGF-L; Cop-1)	20q13.12	26.8 (250)
CCN6 (WISP-3; LIBC)	6q21	39.3 (354)

CCN: Cyr61/CTGF/Nov; Cyr61: Cysteine-rich angiogenic inducer 61; CTGF: Connective tissue growth factor; IGFBP: Insulin-like growth factor-binding protein; IGFBP-rP: IGFBP-related protein; Cef: Chicken embryo fibroblasts; Nov: Nephroblastoma over-expressed; WISP: Wnt1-inducible signaling pathway protein; Elm: Expressed in low-metastatic cells; Cop-1: Card-only protein 1; LIBC: Lost in inflammatory breast cancer.

metastasis^[3]. The Cyr61/CTGF/Nov (CCN) proteins are a family of matricellular proteins that play pivotal roles in many physiological and pathological processes, including carcinogenesis^[4]. The CCN family proteins include six members, as summarized in Table 1. The expression of CCN family proteins is dependent on cell type and context. CCN family proteins can act both positively and negatively in carcinogenesis for different tumor types. The positive or negative effect depends on whether angiogenic factors are limiting and whether conditions that favor apoptosis or senescence prevail^[5,6]. The prototypical CCN family protein is composed of an N-terminal secretory signal peptide and four structural modules: an insulin-like growth factor binding protein-like module, a von Willebrand factor type C repeat (VWC) module, a thrombospondin-homology type 1 repeat (TSP1) module, and a C-terminal cysteine-knot-containing (CT) module^[7]. Except for CCN5, which lacks the CT module, all CCN proteins contain the four complete structural modules. However, there are biologically active CCN variants with less than four modules after translational processing or alternative splicing. Some of these truncated variants may participate in the carcinogenesis of gastrointestinal tract cancers^[7-10], including GC. More recent evidence suggests that CCN family proteins contribute to GC carcinogenesis (Figure 1). Of the CCN family proteins, only CCN2 has been reported to be involved in *Helicobacter pylori*-associated chronic gastritis. There is a positive correlation between the density of CCN2-producing mononuclear cells and the severity of chronic gastritis. The actual role of CCN family proteins in the initiation stage of GC carcinogenesis will be clarified with future studies^[11]. In this brief review, we focus on the roles that the CCN family proteins play in the promotion and progression of GC, the cell signaling pathways involved in the GC regulatory processes, and the development of new agents in targeted therapy.

INDIVIDUAL CCN FAMILY PROTEINS WITH GC DEVELOPMENT AND PROGRESSION

CCN1

CCN1 was the first cloned member of the CCN family proteins^[12] and has been reported to regulate diverse cellular functions through binding to distinct integrins^[13]. CCN1 supports cell adhesion, stimulates cell migration, augments growth factor-induced DNA synthesis, promotes cell survival, inhibits apoptosis, and enhances angiogenesis^[14]. Although much more data have been reported from cancer cell lines, CCN1 expression is up-regulated in patients with breast cancer, gliomas, hepatocellular carcinoma, prostate cancer, and oral squamous cell carcinoma^[15-20] but is down-regulated in leiomyoma and non-small cell lung cancer^[21,22]. The role of CCN1 in carcinogenesis may be cell type- and context-dependent. CCN1 mediates its activities primarily through interaction with cell adhesion receptor integrins and co-receptor heparan sulfate proteoglycans (HSPGs). CCN1 as a ligand of integrins was first demonstrated by the direct binding of CCN1 to integrin $\alpha v \beta 3$ to mediate endothelial cell adhesion^[23]. Several other integrins, such as $\alpha 2 \beta 1$, $\alpha 6 \beta 1$, $\alpha v \beta 5$, $\alpha II \beta \beta 3$, $\alpha M \beta 2$, and $\alpha D \beta 2$, have also been identified as signaling receptors mediating CCN1 functions^[5].

In patients with GC, high expression levels of CCN1 correlate with more lymph node metastases, more advanced tumor stage, a histologic diffuse type, and early recurrence^[24]. Forced expression of CCN1 can induce angiogenesis, a process essential for nourishing the growing tumor. CCN1 promotes angiogenesis either directly by effects on endothelial cells or indirectly by regulating the angiogenic factors vascular endothelial growth factor (VEGF)-A and VEGF-C^[25,26]. However, there are no data illustrating the relationship among CCN1, VEGF-A and VEGF-C in GC. CCN1 promotes tumor growth and increases tumor vascularization upon over-expression in GC cells in the severe combined immunodeficiency mouse model^[27]. In addition, *in vitro* studies have shown that more invasive GC cell lines contain higher levels of CCN1. The forced expression of CCN1 or treatment with recombinant CCN1 in GC cells significantly increases invasive ability. CCN1 regulates GC cell motility/invasion through integrin $\alpha v \beta 3$ and induces nuclear factor- κB (NF- κB) activation as well as the subsequent cyclooxygenase-2 (COX-2) up-regulation to promote cell invasion^[24]. The importance of COX-2 expression in GC is well established, with its correlation with depth of invasion, lymph node metastasis and advanced stage^[28-30].

In addition to the NF- κB -dependent pathway, CCN1 regulates GC cell invasiveness by the hypoxia-inducing factor-1 α (HIF-1 α)-dependent up-regulation of plasminogen activator inhibitor-1 (PAI-1). Both phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin and extracellular signal-regulated kinase 1/2 signaling pathways are essential for HIF-1 α accumulation^[31]. CCN1 may also contribute to the peritoneal

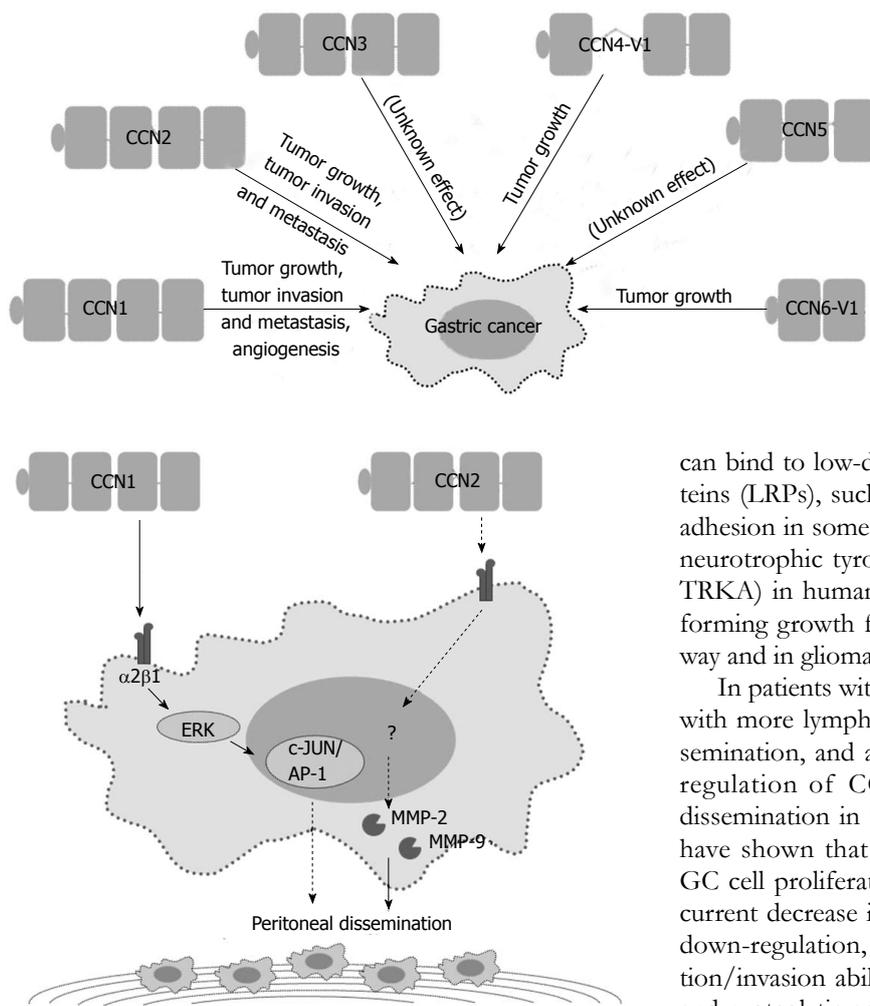


Figure 1 An overview of the roles of individual cysteine-rich angiogenic inducer Cyr61/CTGF/Nov proteins in gastric cancer carcinogenesis based on current evidence. CCN: Cyr61/CTGF/Nov; Cyr61: Cysteine-rich angiogenic inducer 61; CTGF: Connective tissue growth factor; Nov: Nephroblastoma over-expressed.

Figure 2 Summary of the impacts of Cyr61/CTGF/Nov 1 and Cyr61/CTGF/Nov 2 on the peritoneal dissemination of gastric cancer. CCN: Cyr61/CTGF/Nov; Cyr61: Cysteine-rich angiogenic inducer 61; CTGF: Connective tissue growth factor; Nov: Nephroblastoma over-expressed; MMP: Matrix metalloproteinase.

dissemination of GC by promoting tumor-cell adhesion ability. High CCN1 expression levels correlate with peritoneal dissemination in advanced stage GC patients. GC cells over-expressing CCN1 up-regulate integrin $\alpha 2 \beta 1$ via an activator protein-1 (AP-1)-dependent pathway (Figure 2)^[32].

CCN2

CCN2 was first recognized as the major platelet-derived growth factor (PDGF)-related mitogen secreted by human vascular endothelial cells^[33]. CCN2 is involved in a wide variety of regulatory processes, such as angiogenesis, chondrogenesis, osteogenesis, fibrosis formation, diabetic nephropathy, and tumor development^[5]. CCN2 expression is up-regulated in patients with breast cancer, gliomas, esophageal adenocarcinoma, pancreatic cancer, and melanoma^[15,17,34-36] but is down-regulated in lung adenocarcinoma and colon cancer^[22,37,38]. Similar to CCN1, CCN2 achieves functional versatility through its interaction with different integrins, including $\alpha \nu \beta 3$, $\alpha 5 \beta 1$, $\alpha 6 \beta 1$, $\alpha \text{II} \text{b} \beta 3$, and $\alpha \text{M} \beta 2$. In addition to HSPGs, CCN2

can bind to low-density lipoprotein receptor-related proteins (LRPs), such as LRP-1 and LRP-6, to mediate cell adhesion in some cell types. CCN2 can also interact with neurotrophic tyrosine kinase receptor type 1 (NTRK1/TRKA) in human mesangial cells to enhance the transforming growth factor- β (TGF- β)/Smad signaling pathway and in glioma cells to facilitate NF- κ B activation^[5,6].

In patients with GC, high CCN2 expression correlates with more lymph node metastases, more peritoneal dissemination, and a shorter five-year survival^[39-41]. Down-regulation of CCN2 in GC cells reduces peritoneal dissemination in the nude mouse model. *In vitro* studies have shown that down-regulation of CCN2 decreases GC cell proliferation and colony formation with a concurrent decrease in cyclin D1 expression^[42]. After CCN2 down-regulation, GC cells also show attenuated migration/invasion abilities with decreased protein expression and proteolytic activity of both matrix metalloproteinase (MMP)-2 and MMP-9 (Figure 2)^[41].

In GC specimens, CCN2 expression is in agreement with the expression of vascular endothelial growth factor VEGF-C and VEGF-D, as shown by immunohistochemical staining^[39]. CCN2 can induce angiogenesis, and it can also regulate VEGF-induced angiogenesis through the TSP1 and CT modules^[43]. In addition, CCN2 is transcriptionally induced under hypoxia^[44], a condition favoring blood vessel growth by the induction of angiogenic factors such as VEGF. Further studies are necessary to elucidate the complex interaction between CCN2 and the VEGF family proteins in GC.

CCN3

CCN3 was first discovered as an over-expressed gene in a myeloblastosis-associated virus type-1-induced nephroblastoma in chickens^[45]. CCN3 is implicated in many diverse biological processes, such as proliferation, differentiation, and angiogenesis, as well as some pathological conditions, including fibrosis and cancer^[46]. CCN3 is up-regulated in patients with Wilms' tumor with predominantly stromal elements and metastatic Ewing's sarcoma^[47,48] but is down-regulated in malignant adrenocortical tumors and poorly differentiated prostate cancer^[49,50]. CCN3 can mediate its various activities through interacting with integrins, such as $\alpha \nu \beta 3$, $\alpha \nu \beta 5$, $\alpha 5 \beta 1$ and $\alpha 6 \beta 1$ ^[5,6]. CCN3 expression has not been reported in GC samples.

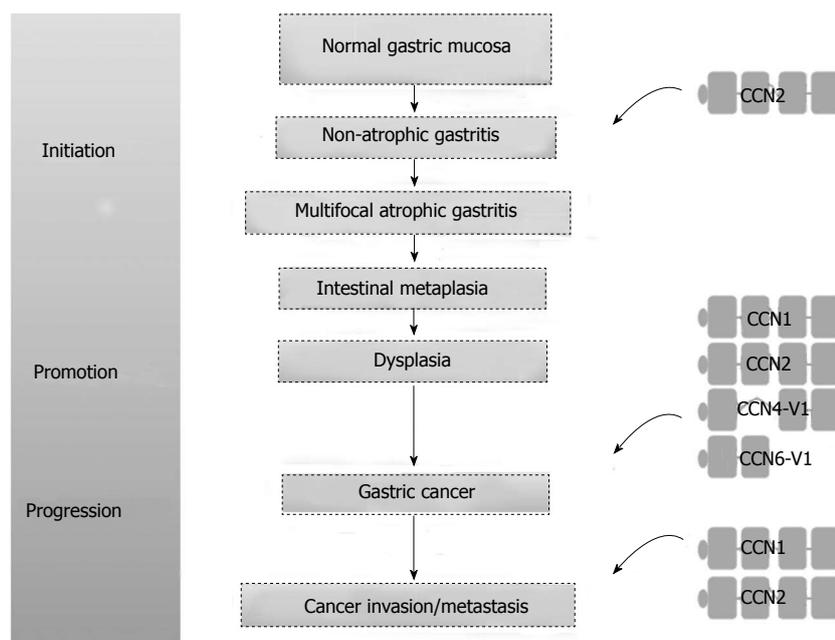


Figure 3 An overview of individual Cyr61/CTGF/Nov proteins in the different stages of gastric cancer carcinogenesis based on current evidence. CCN: Cyr61/CTGF/Nov; Cyr61: Cysteine-rich angiogenic inducer 61; CTGF: Connective tissue growth factor; Nov: Nephroblastoma over-expressed.

CCN4

CCN4 was first identified in low-metastatic cells by comparing mRNA differential display data from high- and low-metastatic murine melanoma cells^[51]. CCN4 is involved in regulating morphological transformation, cell growth, and tumor growth^[52,53]. Although CCN4 overexpression suppresses the growth of melanoma tumors in a mouse model, CCN4 is up-regulated in patients with breast cancer, non-small cell lung cancer, colorectal cancer, esophageal squamous cell carcinoma, endometrial endometrioid adenocarcinoma, and prostate cancer^[15,22,54-59].

In patients with GC, a truncated variant of CCN4-V1 completely lacking the VWC module is up-regulated in scirrhous GC. *In vitro* experiments have shown that forced expression of CCN4-V1 in fibroblast cells induces cellular transformation and a rapid growth characterized by cell piling. CCN4-V1 transfectants can enhance the invasive abilities of co-cultured GC cells^[8].

CCN5

The rat homologue of CCN5 was first reported to be down-regulated in rat embryo fibroblasts transformed by the cooperation of the activated H-ras oncogene and the inactivated p53 tumor suppressor gene^[60]. CCN5 is involved in regulating cell growth, morphological transformation, and attenuating cell migration^[61,62]. CCN5 is down-regulated in patients with colon cancer, pancreatic cancer, and invasive breast cancer^[53,61,62]. CCN5 expression has not been reported in cases of GC.

CCN6

CCN6 was first identified as an expressed sequence tag after database screening for differentially expressed cDNAs after Wnt1-induction in mouse mammary epithelial cells^[54]. CCN6 is involved in regulating morphological transformation, inhibiting cell growth, attenuating cell migration, and inhibiting tumor-induced angiogenesis^[63,64]. CCN6 is down-regulated in patients with inflammatory

breast cancer^[65].

In patients with GC, the truncated variant CCN6-V1 lacking TSP1 and CT modules is noted in 11%-20% of microsatellite unstable GCs. A frameshift mutation in the (A)₉ repeat in exon 4 of CCN6 leads to a premature stop codon in exon 4 and consequently to truncated CCN6-V1. Forced expression of CCN6 in GC cells can inhibit cell invasive abilities, but CCN6-V1 transfectants lose the inhibitory effect^[9,66].

CCN-TARGETED THERAPY

With the greater understanding of the molecular biology of carcinogenesis, more targeted agents have been developed and are associated with improved outcomes in some advanced cancers. Trastuzumab, the first and only targeted agent approved for the treatment of GC, has shown clinical benefits in response rates and survival in combination treatment with chemotherapy for HER-2 positive advanced GC^[67]. Because CCN family proteins are implicated in many processes of carcinogenesis, it is reasonable to develop treatment strategies for these potential targets. For this family of secreted proteins, monoclonal antibodies are good therapeutic candidates. Among the six family members, CCN2 has received the most attention because of previous detailed studies and its strong clinical association with fibrosis. Blocking CCN2 with FG-3019, a CCN2 monoclonal antibody, inhibits pancreatic tumor growth and metastases in both xenograft and orthotopic mouse models^[68,69]. A phase I study that assessed the safety and tolerance of FG-3019 has been performed in patients with idiopathic pulmonary fibrosis, and FG-3019 was shown to be safe and well-tolerated^[70]. Further phase II clinical trials for evaluating its efficacy are underway. For cancer therapy, there is only one ongoing phase I study evaluating FG-3019 therapy in combination with gemcitabine and erlotinib for patients with locally advanced or metastatic pancreatic can-

cer (ClinicalTrials.gov identifier: NCT01181245). There are currently no clinical trials of CCN-targeted therapy in GC.

In addition to monoclonal antibodies, antisense oligonucleotides (EXC 001) and RNA interference compounds (RXI-109) have been recently developed to reduce scar formation by inhibiting CCN2 expression^[6]. Further application of these targeting agents as cancer therapeutics may be helpful for patients with GC.

CONCLUSION

In summary, CCN family proteins play important roles in mediating GC carcinogenesis (Figure 3), including their involvement in cell signaling pathways, angiogenesis, tumor formation, tumor invasion and metastasis. The recognition of the matricellular protein nature of CCNs with a corresponding biological niche in GC carcinogenesis, as illustrated in this review, may allow oncologic issues to be considered in a new way that will have a positive impact on the future management of GC.

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ISSN 1007-9327



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