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Input of microenvironmental regulation on colorectal cancer: Role of the CCN family

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Abstract

Colorectal cancer (CRC) is a major health problem causing significant morbidity and mortality. Previous results from various studies indicate that CRC tumorigenicity encompasses tumor microenvironment, emphasizing the complex interacting network between cancer cells and nearby host cells, which triggers diverse signaling pathways to promote the growth and spread of cancer cells. The CCN family proteins share a uniform modular structure, mediating a variety of physiological functions, including proliferation, apoptosis, migration, adhesion, differentiation, and survival. Furthermore, CCN proteins are also involved in CRC initiation and development. Many studies have shown that CCN members, such as CCN1, CCN2, CCN3, Wnt-induced secreted protein (WISP)-1, WISP-2, and WISP-3, are dysregulated in CRC, which implies potential diagnostic markers or therapeutic targets clinically. In this review, we summarize the research findings on the role of CCN family proteins in CRC initiation, development, and progression, highlighting their potential for diagnosis, prognosis, and therapeutic application.

Key words: Microenvironment; Colorectal cancer; CCN proteins; Tumorigenicity; Cancer progression

Core tip: Colorectal cancer (CRC) is a major health problem causing significant morbidity and mortality. Many studies have revealed that CCN members, such as CCN1, CCN2, CCN3, Wnt-induced secreted protein (WISP)-1, WISP-2, and WISP-3, are dysregulated in CRC, which implied potential diagnostic markers or therapeutic targets clinically. In this review, we summarize the research findings on the role of CCN family proteins in CRC initiation, development, and progression, highlighting their potential for diagnosis, prognosis, and therapeutic application, as well as discussing future perspectives.

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INTRODUCTION

Both mortality and morbidity associated with colorectal cancer (CRC) have been increasing exponentially over the past several decades, and this disease is a major health problem worldwide[1-3]. Although the regulatory events in CRC progression are diverse, microenvironment plays crucial roles in controlling CRC cell proliferation, apoptosis, replication, motility, angiogenesis, and metastasis[4-6]. Though our knowledge about the contents and interactions of the microenvironment in CRC is increasing, the cytokines within this compartment are still not well-understood. Chronic inflammation is also a key predisposing factor in CRC[7], especially inflammatory bowel disease (IBD)-related CRC. The inflammatory-related cytokines secreted from surrounding active stromal cells, immune cells, even tumor cells may stimulate the activation of more inflammation-associated molecules, such as transcription factors or microRNAs which could promote advanced colon carcinogenesis process[7,8]. Furthermore, many studies recently have shown that cancer and host cell-derived cytokines or chemokines drive the transition of tumor-associated macrophages (TAMs) towards an M2 phenotype from M1[9], which exert immnunosuppressive activity and induce cancer proliferation, apoptosis, autophagy, angiogenesis, and distal metastasis[10,11]. These signaling molecules also function to manipulate epigenetic modifications, such as DNA methylation and acetylation, which regulate post-transcriptional activities of possible downstream gene(s) in CRC initiation and progression[12]. The functions and underlying mechanisms of these cytokines are still to be clarified.

The effects of these cytokines in microenvironment are being studied including identification of the targeted and executioner cells of the cytokine, regulatory mechanism(s) of the secreted protein, and protein(s) that are involved in the process. As the understanding of the components and their interactions in microenvironment is important, we aimed to summarize the recent advances in the understanding of the molecular basis of CRC in this review.

MICROENVIRONMENT IN CRC

The characters in microenvironment include cancer cells and host cells, for example, fibroblasts, TAMs, dendritic cells, lymphocytes, monocytes, endothelial and lymphatic cells. The interacting network between cancer cells and host cells is highly regulated, and is not completely defined. Receptors present within cells specifically respond to cytokines and act to form the unique microenvironment. Signaling pathways driven by growth factors, including epidermal growth factor, hepatocyte growth factor, or c-Met, and signaling proteins, such as transforming growth factor (TGF)-α, Wnt, sonic hedgehog, Notch, insulin, integrins, Src, and Ras, can significantly promote the transformation. The transformation process from single crypt lesions through colorectal adenomas to CRC can promote the spread of cancer cells to distal organs[13-20]. Moreover, signaling activates not only tumor cells, but also normal cells in the immediate environment such as TAMs, fibroblasts, and endothelial cells.

Since IBD is a paradigm of cancer-related inflammation, patients affected by IBD are at an increased risk of developing neoplasia. Transformed epithelial cells are able to secrete various inflammatory mediators, such as interleukin (IL)-1, IL-6, COX-2, and TNF-α, to affect proinflammatory leukocytes, endothelial cells, and fibroblasts to further establish a tumor-promoting microenvironment[11]. Therefore, some studies indicated that massive macrophage infiltration is correlated with CRC growth and progression. These TAMs resemble M2-polarized macrophages and have been shown to promote tissue remodeling and angiogenesis to secrete cytokines[21]. CRC cells create or modify a microenvironment that is conducive to metastasis colonization and angiogenesis, which provides a rationale for efforts to enhance cancer progression. Chemokines, cytokines, growth factors, and inflammatory mediators confer the infrastructures of CRC microenvironment, and their concentrations decide the cellular and molecular signaling transduction and functional outcome[22,23]. Thus, these small molecules orchestrate the responses to stimuli and help regulate this unique fine-tuned system.

CCN PROTEINS IN CRC MICROENVIRONMENT

The CCN family was firstly described by P. Bork in 1993, and contains connective tissue growth factor/CCN2, cysteine-rich 61 (Cyr61/CCN1), and nephroblastoma overexpressed/CCN3, as well as Wisp-1/elm1 (CCN4), Wisp-2/rCop1 (CCN5), and Wisp-3 (CCN6). The CCN proteins all show a common multimodular organization, and contain an N-terminal signal peptide followed by four structural domains resembling insulin-like growth factor binding proteins, Von Willebrand factor, thrombospondin, and cysteine knot containing family of growth regulator-like module (CT) (Figure 1). They are involved in various physiological and pathological events, including proliferation, apoptosis, migration, adhesion, differentiation, and survival[24,25]. They also participate in the development of connective tissue such as cartilage and bone, nervous system, muscle, kidney, and bone marrow. Moreover, wound healing, bone fracture repair, pathological fibrosis, and tumorigenesis are all regulated by CCN proteins[26-28]. Recently, many studies have shown that these proteins play crucial roles in CRC progression, including cell migration, invasion, adhesion, and distal metastasis. In this paper we review the current knowledge regarding the implication of CCN proteins in CRC.

CORRELATION OF CCN PROTEIN WITH ADVANCED CRC PROGRESSION

CCN proteins are believed to be multifunctional signaling molecules, and have been found to be involved in a va-

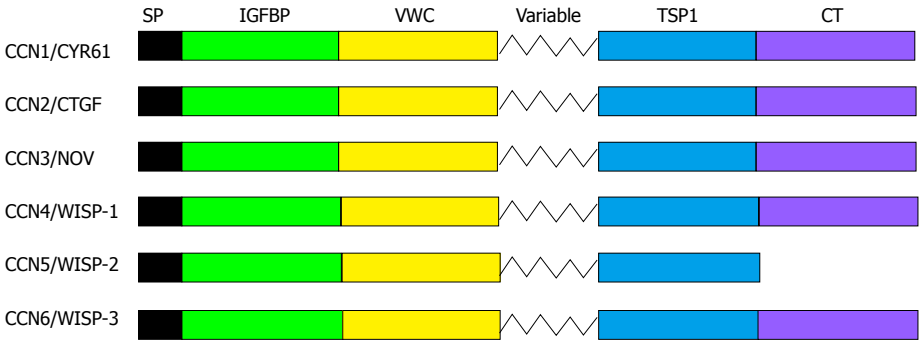

Figure 1 CCN proteins share a conserved multimodular organization. WISP: Wnt-induced secreted protein; Cyr-61: Cysteine-rich 61; NOV: Nephroblastoma overexpressed; CTGF: Connective tissue growth factor; IGFBP: Insulin-like growth factor-binding proteins; VWC: Von Willebrand factor; TSP: Thrombospondin; CT: Cysteine knots.

riety of CRC initiation and development events. Experimental data indicated that CCN1 (also known as Cyr61) overexpression increased Matrigel invasion *in vitro*, which required integrin αvβ5, and promoted lung metastasis formation *in vivo*[29]. Moreover, local recurrence after radiotherapy in CRC often occurs within preirradiated stroma, and CCN1 has been found to be overexpressed in these areas and correlated with invasion and metastasis[29]. However, CCN1 is not highly expressed in advanced stages of CRC, and one may suggest that CCN1 may be crucial in the early stage of CRC development and play a role as an early prognostic biomarker[30,31]. CCN1 is an angiogenic factor, and may function through the ability of CCN1 to bind and activate cell surface integrins[32]. Using SW620, H460, and TE-7 cell lines and their isogenic variants with altered CCN1 expression, Jandova *et al*[33] in 2012 had proved that migration of CRC cells is CCN1- and αώβ5-dependent.

CCN2 (also named CTGF), a 36-38 kD cysteine-rich peptide containing 349 amino acids, is predominantly identified in fibroblasts, endothelial cells, smooth muscle cells, and cartilaginous cells[34]. TGF-β enhances CCN2 synthesis, and CCN2 is a typical downstream mediator of this major inflammatory mediator[34,35]. Although these two proteins share many functions in common, there are still many aspects of tumor regulation which are different. We have found that CCN2 inhibits CRC metastasis and acts as an independent prognostic marker. Mechanistically, CCN2 could inhibit the β-catenin/TCF signaling pathway and cause matrix metalloproteinase 7 down-regulation[36].

Clinically, peritoneal carcinomatosis (PC) has a very poor prognosis and is treated palliatively. CCN2 has been suggested to be a therapeutic agent, and can be used as a predictor of PC in CRC[37]. Low CCN2 expression in tumor samples was associated with an 8-fold increase in the peritoneal recurrence rate compared with tumors with high levels of CCN2 expression[37]. CCN2 alters cellular function, including adhesion which is the first and most crucial step of PC. CCN2 treatment could enhance cell adhesion in normal fibroblast 293T cells, but significantly decreased CRC adhesion ability[37] *in vitro* and *in vivo*. Although high expression of CCN2 is the hallmark of good prognosis of CRC, its roles in CRC cell differentiation and proliferation are still under investigation. In previous studies, Cunningham *et al*[38] showed that CCN2 expression was positively correlated with α-smooth muscle actin expression, which in turn indicated a potential role for CCN2 in myofibroblast-mediated fibrosis associated with ileal carcinoids. Moreover, Kaltsas *et al*[39] in 2010 demonstrated that CCN2 involved in the neoplastic transformation into ileal carcinoids is positively correlated with tumours larger than 1 cm. Jacobson *et al*[40] in 2012 also indicated that CCN2 expression is the hallmark of ileal carcinoids, and potentially is highly related to several functions including cell migration and anti-apoptosis, which proposes an oncogenic role of CCN2 in the progression of well-differentiated CRC and other tumors.

Wnt-induced secreted protein (WISP)-1 is the fourth member of CCN family, which was identified to be a Wnt-1- and β-catenin-regulated protein[41-44]. WISP-1 transcript was reported to be overexpressed in 80 % of human colon carcinomas[43], and immunohistochemistry studies of WISP-1 further supported this result. A comparative study of 47 CRCs exhibited positive interplays between Wnt-1, WISP-1, survivin, and cyclin-D1 proteins in CRC tumorigenicity[41]. Furthermore, WISP-1 may be used as a specific diagnostic and prognostic marker in CRC[42]. However, the precise underlying mechanism is still lacking and needs further investigations. WISP-2 and WISP-3 are parts of the CCN family, and have been showed to play crucial roles in angiogenesis and carcinogenesis[32]. The mRNA expression of WISP-2, but not WISP-1, was significantly decreased in CRC, compared to normal colonic mucosa[43]. Davies *et al*[44] in 2010 also showed that WISP-2 demonstrated the opposite pattern with lower levels of expression in CRC cancer cells compared to normal controls. The *WISP-2* gene is considered a tumor suppressor gene, however, the molecular mechanism is not defined. The *WISP-3* gene is located on 6q22-6q23, and its cellular function is linked to chondrocyte growth and cartilage integrity[45]. Previous studies showed that WISP-3 could be an oncogene in CRC[43,44], especially microsatellite instability subtype of CRC[25]. However, WISP-3 transcript levels showed no significant differences between cancer and normal groups[44]. According to

Table 1 Expression of CCN family members in colorectal cancer

Capital member	Model	Effects	Ref.
CCN1	Periradiated stroma	Positively correlated with metastasis	[29]
CCN1	Clinical sample	Positively correlated with early stage of tumor development	[30,31]
CCN1	Cultured cancer cells	Promoting cancer cell migration	[33]
CCN2	Clinical sample	Positively correlated with early stage of tumor development	[36,37,40]
		Negatively correlated with prevalence of peritoneal carcinomatosis	
		Inhibiting invasion and metastasis	
		Negatively correlated with metastasis and patient survival	
WISP-1	Clinical sample	Promoting cell cycle checkpoint progression, accelerating cell growth and inhibiting apoptosis	[41-45]
		Positively correlated with tumor grade	
WISP-2	Clinical sample	Negatively correlated with tumor grade	[43,44]
WISP-3	Clinical sample	Positively correlated with tumor grade	[43,44]

WISP: Wnt-induced secreted protein.

the findings, WISPs may play crucial but contrasting roles in CRC, which demonstrated that *WISP-1* could be an oncogene, but *WISP-2* might tend to be a tumor suppressor gene and *WISP-3* gene still needs further clarification (Table 1).

CONCLUSION

Microenvironmental regulation is crucial in cancer biology. In this compartment, many effecter host cells, immune cells, cytokines, chemokines, inflammatory proteins, besides intestinal microbiota (not discussed), are orchestrated to form the infrastructure of CRC. The interaction is complicated and but has potential therapeutic applications. In this review, we have extensively discussed the secreted proteins called CCN family, which function in many physiological and pathological processes, and showed their important regulatory roles in CRC microenvironment. Although genetic and epigenetic alternations drive the transformation of normal enterocytes into neoplasia, CCN family proteins mediate significant communications between CRC and host cells.

Understanding the detailed mechanisms involved in CCN-mediated regulation will provide further insight into the progression and metastasis of CRC. Furthermore, the utility of CCN family proteins to regulate metastasis and invasion/angiogenesis suggests that these growth factors may be relevant candidates or targets for CRC treatment.

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