Biological functions and role of CCN1/Cyr61 in embryogenesis and tumorigenesis in the female reproductive system (Review)

RUI YANG, YING CHEN and DAOZHEN CHEN

Wuxi Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu 214002, P.R. China

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Abstract. Cysteine-rich angiogenic inducer 61 (CCN1/Cyr61) is a prompt response transcription product activated by growth factors. As a member of the CCN family, it mediates cell survival, proliferation, differentiation, migration, adhesion and synthesis of the extracellular matrix by binding directly to the integrins and heparin sulfate proteoglycans or activating multiple signaling transduction pathways. It has previously been demonstrated that CCN1/Cyr61 exhibits an important role in the female reproductive system during embryogenesis and tumorigenesis. However, the functions of CCN1/Cyr61 in the female reproductive system have not been systematically investigated, therefore, the primary aim of the present review is to introduce the role and function of CCN1/Cyr61 in the female reproductive system. The current review presents the molecular structure and biological function of CCN1/Cyr61 and provides detailed data on its expression pattern and contribution to the female reproductive system, including the role in embryogenesis and tumorigenesis.

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1. Introduction

Cysteine-rich angiogenic inducer 61 (CCN1/Cyr61) was originally revealed to act as a growth factor-inducible immediate-early gene, present in serum and platelet-derived growth factor-stimulated mouse BALB/c 3T3 cells (1). As a member of the CCN family, it was first cloned by O'Brien in 1990 via differential hybridization screening of a cDNA library from BALB/c 3T3 clone A31 cells (2). The CCN family is composed of six members including CCN1/Cyr61, connective tissue growth factor, nephroblastoma overexpressed, Wnt-1-induced secreted protein (WISP) -1, WISP -2 and WISP -3 (3). CCN1/Cyr61 is a basic secreted protein localized on the cell surface, cell interior and the extracellular matrix (ECM). CCN1/Cyr61 targets cells including fibroblasts, epithelial cells, endothelial cells, smooth muscle cells and neurons through integrins and heparin sulfate proteoglycan (HSPG) receptors. CCN1/Cyr61 exhibits a variety of functions in differing target cells. The biological properties of CCN1/Cyr61 in the regulation of cell survival, proliferation, differentiation, migration, adhesion and synthesis of ECM have been demonstrated to be important in the progression of embryogenesis and tumorigenesis in the female reproductive system.

2. CCN1/Cyr61 molecular structure

Complementary DNA encoding the human CCN1/Cyr61 protein was isolated by Jay et al (4) from human embryonic tissues in 1997. It is located on human chromosome 1p22.3 and contains 5 exons, interspaced with 4 introns. As presented in Fig. 1, the first exon encodes the mRNA that is translated into secretory signal peptide protein. The following 4 exons (E2-E5) encode a mosaic Cyr61 domain. The transcription of Cyr61 may be promptly induced by a wide range of environmental stimulatory factors, including vascular
endothelial growth factor (VEGF), fibroblast growth factor, platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, sphingosine 1-phosphate, angiotensin II and lipopolysaccharides, in addition to physical and environmental inputs including shear stress, mechanical stretch and oxygen deprivation (5-7). The open reading frame of CCN1/Cyr61 encodes a protein of 381 amino acid including 38 conserved cysteines.

Sequence analysis revealed the presence of a mosaic structure to the CCN1/Cyr61 protein, including four highly conserved modules (3). As presented in Fig. 1, from the N- to the C-terminal, the four structurally distinct modules of CCN1/Cyr61 are insulin-like growth factor binding protein (IGFBP)-like domain, von Willebrand factor type C repeats (vWC) domain, thrombospondin type 1 (TSP-1) repeat homology domain, and the C-terminal domain that contains a cysteine-knot (8). Currently, the four structurally distinct modules of CCN1/Cyr61 have been important targets to explore the biological function of the protein. Module I is the binding domain of IGFBP which consists of 68 amino acids and shares homology with the cysteine-rich N-terminal region of traditional IGFBPs. A previous study suggested that CCN1/Cyr61 demonstrates a low affinity to IGFs (9). Module II consists of 68 amino acids and includes a vWC domain which exists in vWC factor, mucoprotein, thrombospondin and collagenous fiber. Module II may additionally have a role in oligomerization (3). Module III contains a motif firstly identified in TSP-1 repeat homology and subsequently observed in various extracellular proteins, TSP-1 homology is involved in binding to soluble and matrix sulfated glyco-conjugates (10). A previous study revealed that Module III contains cell attachment sites (11). Module IV, the C-terminal domain, is present in PDGF, nerve growth factor and TGF-β. It has been hypothesized that Module IV may be involved with cell surface receptors (12). The modular structural organization of the CCN1/Cyr61 protein suggests that its diverse biological functions may result from the combined actions of individual modules, either acting independently or in conjunction. The interaction of the module and different factors endows CCN1/Cyr61 with complex biological effects in the organism tissues, cell environment and at all developmental stages.

3. CCN1/Cyr61 biological functions

CCN1/Cyr61 coordinates the essential activities of life and demonstrates a diverse functional pattern in various pathological and physiological conditions, in addition to its role in various tissues and cells. CCN1/Cyr61 primarily binds to integrins and HSPGs in a cell-type specific manner, and thus mediates various biological activities via these interactions.

CCN1/Cyr61 mediates cellular processes. CCN1/Cyr61 has been reported to mediate numerous cellular activities, including cell adhesion, migration, proliferation and apoptosis. CCN1/Cyr61 is a cell adhesion protein, which is associated with the adhesion activities of endothelial cells, fibroblasts cells, smooth muscle cells, monocytes and platelets, through binding to particular integrins (Table I) (13-18). Integrin αβ1, αβ6, αβ3, αβ4, and αβ3, serve as adhesion receptors for CCN1/Cyr61 on different cell types which are summarized in Table I. It has previously been demonstrated that cell adhesive properties of CCN1/Cyr61 in human umbilical vein endothelial cells are mediated through interaction with integrin αβ1 (14). In addition, it was demonstrated that CCN1/Cyr61 mediates endothelial cell adhesion through interaction with αβ6 (13). CCN1/Cyr61 promotes cell adhesion indirectly by altering the structure of the ECM protein. Kireeva et al (19) reported that CCN1/Cyr61 mediates cell and ECM- and cell-cell adhesion by connecting with ECM and the cell membrane.

Cell migration is a complex biological process which involves a series of stimulating factors, signaling pathways and molecular mechanisms. It has been demonstrated that CCN1/Cyr61 regulates cell migration of fibroblasts and endothelial cells. Zhang et al (20) firstly verified that PDGF-induced CCN1/Cyr61 exhibits a key role in regulating smooth muscle cell migration by connecting intracellular PDGF-extracellular signal-regulated kinase and jun N-terminal kinase signals with integrin/focal adhesion kinase (FAK) signaling. Fibroblasts may suppress the inflammatory response, and may be considered as a novel target for the therapy of inflammation. Huang et al (21) demonstrated that CCN1/Cyr61 markedly facilitates rheumatoid arthritis (RA) fibroblast-like synovioyte invasion and migration and may act as a promising therapeutic target for RA treatment. Wei et al (22) suggested that CCN1/Cyr61 expression is significantly associated with the metastasis of gastric cardiad adenocarcinoma (GCA). It has therefore been hypothesized that CCN1/Cyr61 may act as a metastatic biomarker for evaluating the prognosis of GCA and a potential molecular target for anti-metastatic therapy of GCA.

In addition to promoting cell adhesion and migration, CCN1/Cyr61 regulates cell survival and apoptosis. The overexpression of CCN1/Cyr61 activates the nuclear factor (NF)-κB pathway and induces hepatic stellate cell apoptosis through endoplasmic reticulum stress and initiation of the unfolded protein response (23). Conversely, CCN1/Cyr61 expression promotes kidney tubular epithelial cell proliferation and cell apoptosis is inhibited (21). The functions of CCN1/Cyr61 in promoting cell survival or inducing apoptosis in different cell-types is important to elucidate its role in tissue reconstruction.

CCN1/Cyr61 and angiogenesis. Previous studies have suggested CCN1/Cyr61 is a primary physiological mediator of angiogenesis. CCN1/Cyr61 modulates vascular formation in vitro directly through binding to αβ3 to enhance the endothelial cell adhesion, migration, proliferation and micro-tube formation, or indirectly by accommodating the activity of VEGF/VEGF receptor. You et al (24) suggested that CCN1/Cyr61 induces the expression of monocyte chemoattractant protein-1 to mediate angiogenesis via the αβ3 integrin, FAK, phosphoinositide-3-kinase/Akt Serine/Threonine Kinase 1 (Akt) and the IKB kinase signaling pathways in monkey chorioretinal vessel endothelial cells (25). A previous study investigating pancreatic neuroendocrine tumors revealed a positive correlation between CCN1/Cyr61 expression levels and tumor angiogenesis, which suggests an ancillary function of CCN1/Cyr61 in vascular development. CCN1/Cyr61 was revealed to be expressed in the placenta, cardiovascular,
skeletal and nervous systems during embryonic development. CCN1/Cyr61 expression levels are additionally significantly decreased in pre-eclamptic placentas (26). This suggests that CCN1/Cyr61 is involved in placental angiogenesis and may be important in the pathogenesis of pre-eclampsia. CCN1/Cyr61-deficient mice lead to a placental vasculogenesis deficiency with incomplete vascular nets. A previous study reported >30% of mice died from the chorioallantoic junction defect in the early stage of pregnancy and the others died in the middle of pregnancy due to placental vascular insufficiency and extensive loss in the vasculature integrity (27). Overall, these results demonstrate that CCN1/Cyr61 is critically involved in developmental angiogenesis.

**CCN1/Cyr61 and chondrogenesis.** CCN1/Cyr61 is important in cartilage cell differentiation and chondrogenesis. The expression of CCN1/Cyr61 is closely associated with angiogenesis and the process of the differentiation from narrow stromal cells (MSC) to chondrocytes during embryogenesis (28). In adult cartilage, Chijiwa et al (29) demonstrated that CCN1/Cyr61 is involved in chondrocyte cloning in osteoarthritic cartilage by inhibiting the activity of ADAM metallopeptidase with thrombospondin type 1 motif 4 (ADAMTS; aggrecanase-1). Conversely, the emergence of CCN1/Cyr61 may lead to the replacement of bone tissue by cartilage through inducing angiogenesis. A previous study revealed that CCN1/Cyr61 may be associated with the induction of a passage-dependent decrease in chondrogenic differentiation and a passage-dependent increase in osteogenic potential of tonsil-derived MSC (30).

**4. CCN1/Cyr61 and the female reproductive system**

**CCN1/Cyr61 and reproduction.** Mammalian reproduction is a complex process involving ovulation, fertilization, embryo development and implantation and the failure of any process may result in sterility, malformations or adverse pregnancy outcomes. Previous studies demonstrated that CCN1/Cyr61 is expressed on the corpus luteum (CL) (31), conceptus and endometrium in early pregnancy (32), trophoblastic origin of the placenta (33), midterm fetal smooth muscle vessel walls of the arterial circulatory system (34), endothelial cells of vessels surrounding the cloaca, embryonic hippocampal neurons (35) and mesodermal and ectodermal mesenchymal cells (28). It contributes to the process of embryogenesis including the implantation (36), fetal neovascularization (34), fetal brain development (35), fetal cartilaginous development (28) and fetal-maternal cross-talk (32). The abnormal expression of CCN1/Cyr61 may result in pre-eclampsia, epispidias, embryonic death resulting from disability of allantoic fusion and the disturbance of vascular dysplasia (34,37).

CL, which is a glandular-like structure rich in blood vessels and exhibits a key role in mammalian reproduction. The development of the follicle into the CL involves neovascularization, and previous studies have demonstrated that CCN1/Cyr61 may mediate this process (Fig. 2). Zhang et al (31) suggested that CCN1/Cyr61 is expressed in the CL of cows and the expression is upregulated at days 4, 6, 10 and 16 of CL. It was therefore hypothesized that the upregulation may be associated with the angiogenesis of the CL. A further study conducted by Romereim et al (38) demonstrated that the CCN1/Cyr61 gene is highly expressed in small luteal cells isolated from cows. These findings support the hypothesis that CCN1/Cyr61 is important in the development of the CL. However, the expression pattern, regulation and function of CCN1/Cyr61 in human CLs still remains unclear and requires further investigation.

Implantation is an important process during the early development of embryos. CCN1/Cyr61 has previously been suggested to act as a mediator for embryo implantation. It has previously been detected to be upregulated in the invasive extravillous trophoblasts and unclosed endometrial luminal epithelium surrounding the embryo (39). Pre-eclampsia is one of the common complications of pregnancy, which originates in the placenta and results in complication of maternal and fetal health (40). The hypothesis of the etiology has been recognized as insufficient invasion of trophoblast cells into the decidua and the obstruction of maternal spiral artery remodeling (41). This leads to an inadequate blood flow in the placenta and may result in the inhibition of placental development and intrauterine growth restrictions (42). Recombinant CCN1/Cyr61 protein-stimulated trophoblast cells demonstrate a stronger invasion ability compared with cells without the stimulus (43). Chen et al (33) revealed that CCN1/Cyr61 mRNA expression levels in placentas of pre-eclampsia cases are decreased compared with those in normal pregnancies. Furthermore, Kipkeew et al (36) indicated that CCN1/Cyr61 and CCN3 promote the migration capability of trophoblast cells by activating FAK and Akt kinase. This evidence verified the hypothesis of a negative correlation between the expression of CCN1/Cyr61 and pre-eclampsia. These findings may act as a research foundation for the early diagnosis and prediction of pre-eclampsia through screening for expression of CCN1/Cyr61. Zhang et al (44) suggested that that micro (mi)RNA 155 contributes to pre-eclampsia development by downregulating CCN1/Cyr61. MiRNAs are relatively stable and the identification of circulating miRNAs involved in promoting the development of pre-eclampsia by regulating the expression of CCN1/Cyr61 in the plasma of pregnant woman, may aid in the clinical prediction of pre-eclampsia.

CCN1/Cyr61 is additionally important in the maintenance of the pregnancy and the embryonic development. Klein et al (32) demonstrated that CCN1/Cyr61 is co-expressed on the conceptus and endometrium in the early stage of pregnancy and involved the maintenance of the early pregnancy. It contributes to the cross-talk of the conceptus and endometrium through affecting the proliferation and differentiation of endometrial and trophoderm cells and stimulation of endometrial angiogenesis. Furthermore, previous studies have demonstrated that CCN1/Cyr61 regulates neovascularization and matrix remodeling in the process of embryogenesis. CCN1/Cyr61 gene knock-out mice often suffer from vascular anomalies of placenta and embryonic fatalities (34). The expression of CCN1/Cyr61 may be detected in endothelial cells of vessels surrounding the cloaca and the umbilical cord on gestational days 10 and 11.5 in mice, which suggests it may be involved in the development of human epispidias (37). In addition, the expression of CCN1/Cyr61 in fetal hippocampal neurons has been demonstrated to be increased compared with mature hippocampal neurons, which suggests it may exhibit an important role during development of the embryonic brain (35). Overall,
CCN1/Cyr61 is important role in the female reproductive system.

**CCN1/Cyr61 and female reproductive tumors.** It was previously demonstrated that CCN1/Cyr61 acts as a tumor-suppressor or promoter in different types of tumors depending on the complex external environment (45-47). CCN1/Cyr61 is involved in the occurrence and development of tumors through its role in tumor angiogenesis, tumor cell proliferation and apoptosis and tumor metastasis (25,47-49). An overview of the expression and function of CCN1/Cyr61 in female reproductive tumors is presented in Table II (50 -61). Further research and understanding of the function of CCN1/Cyr61 in different types of cancer may provide a promising basis for cancer prognosis and therapy.

Uterine leiomyoma (UL) is the most common benign tumor of the female reproductive system, which is hormone dependent and results from smooth muscle cell proliferation (62). Molecular genetic studies have provided compelling evidence that abnormally expressed genes have an important influence on UL occurrence (63,64). CCN1/Cyr61 expression in UL is downregulated when compared with matched normal uterine smooth muscle cells, suggesting it may exhibit a tumor-suppressor role (50). Di Tommaso et al (51) revealed that estrogen upregulates the expression of the CCN1/Cyr61 gene in myometrium tissue, however has no influence on the expression of the CCN1/Cyr61 gene in fibroid tissue, detected via gene expression analysis. The results indicated that the expression of CCN1/Cyr61 may not be regulated by the estrogen receptor in uterine fibroids. Fundamental research was conducted by Wallace et al (52) to determine if hypoxia induced CCN1/Cyr61 secretion through the Endothelin-A (ETA) receptor in UL. However, the results identified that blockade of the ETA receptor demonstrated no significant influence on the increase of CCN1/Cyr61 expression under normoxic or hypoxic conditions and the secretion of CCN1/Cyr61 may not be regulated by the ETA receptor in UL. The exact mechanism still remains unclear and further investigation is required in the future.

Endometriosis (EMT) is one of the most common diseases of obstetrics and gynecology, and commonly associates with infertility in women of child-bearing age (65-67). The specific pathogenesis of EMT remains to be fully elucidated. Although EMT is a frequently occurring benign disease, it is characterized by malignant behaviors including recurrence and metastasis (68,69). At present, various pharmacotherapies and other methods have been proposed to treat EMT (70,71). However, their usage has been limited due to strong and obvious adverse effects (65,72). It was previously demonstrated that the expression of the CCN1/Cyr61 gene is controlled by estrogen and is enhanced in endometria of women suffering from EMT and in endometriotic lesions, suggesting that CCN1/Cyr61 may act as a useful maker gene for EMT (53). A further study identified that estrogen promotes the expression of the CCN1/Cyr61 gene during the early stages of EMT-like establishment and the CCN1/Cyr61 gene contributes to regulation of cell proliferation and the generation of vasculature in the development of lesions, using the conditional knockout mice lacking uterine CCN1/Cyr61 (54). Furthermore, Gashaw et al (73) demonstrated that the expression level of CCN1/Cyr61 is upregulated by hypoxia-inducible factor 1-α, through use of the benign endometrial cell line. The study suggests that targeting CCN1/Cyr61 signaling during the early stages of lesion establishment may provide a novel treatment method for EMT.

**Table I. Adhesion receptor for CCN1/Cyr61 on different cell types.**

| Author, year   | Cell types        | Integrins (Refs.) |
|----------------|-------------------|-------------------|
| Heng, 2006     | Endothelial cells | α3β3, α6β1        |
| Kireeva, 1998  | Fibroblasts cell  | α6β1              |
| Grzeszkiewicz, 2002 | Smooth muscle cells | α5β2          |
| Schober, 2002  | Monocytes         | α5β3              |
| Jedsadayanmata, 1999 | Platelets  | α6β1              |

Cyr61/CCN1, cysteine-rich angiogenic inducer 61.
Endometrial cancer (EC) is a common malignant gynecological tumor, however non-invasive diagnostic tools for early and accurate diagnosis are still limited (74). Hormonal dysregulation is believed to contribute to the etiology of EC (75). Previous studies demonstrated that long-term replacement estrogen therapy is associated with a type I EC and progesterational hormone is not sufficient to prevent this (56). Estrogen may upregulate the expression of CCN1/Cyr61 and current data indicate that there is a significant increase of CCN1/Cyr61 expression in the endometrium of women with polycystic ovarian syndrome and premalignant lesions. Hence, measures to detect the expression of CCN1/Cyr61 may result in its use as an early diagnostic marker of type I EC cancer. However, Chien et al (55) demonstrated that the expression level of Cyr61 is decreased in endometrial tumors compared with normal endometrium. At present, little is known regarding the anti-thetical function of CCN1/Cyr61 in EC. Previous findings from Witek et al (76) revealed that CCN1/Cyr61 genes expressed in all cancer grades and their expressions levels are potentially correlated with the survival of patients. Therefore, detecting the expression level of CCN1/Cyr61 may act as a novel non-invasive diagnostic tool for early and accurate diagnosis of EC.

Cervical cancer is one of the most common gynecological tumors occurring in women worldwide, with >190,000 newly diagnosed cases per year (77). The human papillomavirus infection is an important factor in the development of cervical cancer, and vaccination against it provides an effective way to prevent development of cervical cancer. However, the pathogenesis underlying cervical cancer remains unknown, and its incidence is increasing each year. Xie et al (58) demonstrated that CCN1/Cyr61 gene expression is downregulated in cervical cancer compared with normal tissues and its expression level is inversely correlated with miR-205 expression. miR-205 has been reported to contribute to the development of cervical cancer and regulate cell proliferation and migration in human cervical cancer cells. The identified inverse expression pattern between CCN1/Cyr61 and miR-205 suggests that CCN1/Cyr61 may act as a novel non-invasive diagnostic tool for early and accurate diagnosis of EC.

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Table II. Expression and function of CCN1/Cyr61 in female reproductive tumors.

| Author, Year | Female reproductive tumors | Expression level | Function (Refs.) |
|-------------|-----------------------------|-----------------|-----------------|
| Arslan, 2005; Di Tommaso, 2013; Wallace, 2014 | UL | Downregulated | Suppressor of UL (50-52) |
| Zhao, 2014; Klein, 2012 | EMT | Upregulated by estrogen or HIF-α | Promoter of EMT cell proliferation, generation of vasculature (53,54) |
| Klein, 2012 | EC | Downregulated in endometrial tumors; Up-regulated in PCOS | Suppress growth of endometrial cancer cells, expression is correlated with patient survival (55,56) |
| Joy, 2014; Xie, 2012 | Cervical cancer | Downregulated | Target therapy, clinical diagnosis (57,58) |
| Bartel, 2012; Lee, 2012; Lin, 2014 | Ovarian cancer | Upregulated | Promotes ovarian cancer cell proliferation and inhibits apoptosis, associated with lymph node metastases (59-61) |

Cyr61/CCN1, cysteine-rich angiogenic inducer 61; UL, uterine leiomyoma; EMT, endometriosis; EC, endometrial cancer; PCOS, polycystic ovarian syndrome; HIF-α, hypoxia-inducible factor-α.
syptoms are insidious in onset (78,79). The search for novel biomarkers for early diagnosis in ovarian carcinoma may provide effective medical support. Lee et al (60) demonstrated that CCN1/Cyr61 promotes ovarian cancer cell proliferation and inhibits apoptosis by regulating p53 and NF-κB expression through the phosphoinositide-3-kinase/AKT Serine/Threonine kinase/mechanistic target of rapamycin signaling pathways. Bartel et al (59) revealed that CCN1/Cyr61 is preferentially expressed in high grade serous carcinomas. It was demonstrated that CCN1/Cyr61 expression is significantly upregulated in ovarian epithelial carcinoma tissue compared with benign ovarian tumor tissue samples and the levels of CCN1/Cyr61 are associated with lymph node metastases (61). CCN1/Cyr61 may therefore be useful in targeted diagnosis and therapy in ovarian epithelial carcinoma.

5. Conclusions

The present review systematically clarified the biological functions of CCN1/Cyr61 and its associated roles in the female reproductive system, including embryogenesis and tumorigenesis. CCN1/Cyr61 may regulate numerous cellular activities, angiogenesis and chondrogenesis. It is important in the reproduction and the occurrence and development of tumors in the reproductive system. However, the underlying mechanism that results in CCN1/Cyr61 acting as a tumor-suppressor or tumor-promoter in different types reproductive system tumors, remains to be fully elucidated, due to the complicated external environment, including complex crosstalk of intracellular molecules and multi-module activated signal transduction pathways.

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