CCN5/WISP-2 Expression in Breast Adenocarcinoma Is Associated with Less Frequent Progression of the Disease and Suppresses the Invasive Phenotypes of Tumor Cells

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Abstract

Although previous in vitro studies predicted that CCN5/WISP-2 may act as an anti-invasive gene in breast cancer, the distribution pattern of CCN5 in breast cancer samples is conflicting. Thus, we systematically investigated the CCN5 expression profile in noninvasive and invasive breast tumor samples and its functional relevance in breast cancer progression. The studies showed that CCN5 expression is biphasic, such that in normal samples CCN5 expression is undetectable, whereas its expression is markedly increased in noninvasive breast lesions, including atypical ductal hyperplasia and ductal carcinoma in situ. Further, CCN5 mRNA and protein levels are significantly reduced as the cancer progresses from a noninvasive to invasive type. Additionally, we showed that CCN5 mRNA and protein level was almost undetectable in poorly differentiated cancers compared with the moderately or well-differentiated samples and its expression inversely correlated with lymph node positivity. The result was further supported by evaluating the RNA expression profile in microdissected sections using real-time PCR analysis. Therefore, our data suggest a protective function of CCN5 in noninvasive breast tumor cells. This hypothesis was further supported by our in vitro studies illuminating that CCN5 is a negative regulator of migration and invasion of breast cancer cells, and these events could be regulated by CCN5 through the modulation of the expression of genes essential for an invasive front. These include Snail-E-cadherin signaling and matrix metalloproteinase (MMP)-9 and MMP-2. Collectively, these studies suggest that the protective effect of CCN5 in breast cancer progression may have important therapeutic implications. [Cancer Res 2008;68(18):7606–12]

Introduction

Breast cancer, a genetically heterogeneous disease (1), is the most commonly identified malignant disease in Western women after nonmelanocytic skin cancer. Breast cancer attacks one in seven women, affecting nearly every family worldwide. Approximately 60% of these women will develop the invasive form of the disease, which is ultimately fatal. Fortunately, the breast cancer mortality rate has decreased recently due, in part, to early diagnosis and decreased intake of carcinogenic hormones or other unknown factors. However, our current therapeutic options for the advanced stages of breast cancer are still fairly limited and ineffective. Thus, there is a need to better understand the molecular basis of the genesis of breast cancer and its progression to design targeted, molecularly based therapies.

Like other cancers, the genesis of ductal carcinoma in the breast is the result of unprogrammed genetic and epigenetic changes, which lead to the malregulation of cellular growth (2). But a key clinical turning point in the progression of this disease is the formation of an invasive front (invasion and metastatic spread) through the changes in the adhesive and migratory capabilities of the noninvasive breast cancer cells (3). The invasive front is a complex, multistep process in which primary tumor cells invade adjacent tissue, enter the systemic circulation (intravasation), translocate through circulation, extravasate into a secondary site, recolonize, and expand (3, 4). In recent years, multiple studies have revealed the participation of several protein-encoding genes and noncoding genes, such as miRNA, in the formation of an invasive front (3). However, the specific molecular changes needed to execute the initial step of the noninvasive to invasive phenotypic switch remain an enigma. Loss of cellular adhesion and increased cell motility are essential features of the invasive front (5). Therefore, identification and characterization of molecules that control adhesion and cell motility are critical to our understanding of cancer dissemination.

CCN5 (which is also known as WISP-2) is a 29-kDa secreted protein identified as a member of the CCN [Cyr61 (cysteine rich as a protein), connective tissue growth factor, and Nov (nephroblastoma overexpressed gene)] family of growth factors, a family that shares conserved multimodal domains with diverse biological functions (6, 7). These include angiogenesis, stem cell differentiation, and cancers (6–8). Nucleotide and protein sequences of CCN5 show a 30% to 40% sequence homology within other members of the family, predominantly CCN4 (WISP-1) and CCN6 (WISP-3). The modular architectures [i.e., an insulin-like growth factor (IGF)-binding protein type domain, a von Willebrand type C domain, a thrombospondin-1 domain, and a COOH-terminal cysteine-knot domain] of these genes are similar except in their COOH-terminal domains, which are absent in the CCN5 gene (6). CCN5 has both growth-promoting and growth-arresting competence depending on cell types and the microenvironment of the cells. For example, overproduction of CCN5 by epidermal growth factor or IGF-1 is required for the mitogenic action of these growth factors in estrogen receptor–positive (ER⁺), noninvasive breast
tumor cells (9–11), whereas it acts as a growth arrest–specific gene in vascular smooth muscle cells and prostate cancer cells (12). In addition, it is most likely that CCN5 plays a preventive role in the progression of pancreatic cancer as it participates in morphologic alterations from mesenchymal to epithelial transition of pancreatic adenocarcinoma cells (13). Our studies have shown for the first time that CCN5 is differentially expressed in breast tumor cell lines and human breast samples (14). Its expression is mainly detected in noninvasive breast cancer cell lines and noninvasive lesions [i.e., atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS)] and almost undetected in invasive lesions (9). Our in vitro results were further supported by two independent studies (15, 16). However, the in vivo results in one of these two studies contradicted its own in vitro data and our in vivo results. It does not corroborate our claim and proposed opposite reports (15).

Therefore, the objective of the present work was to explore the expression profile of CCN5 accurately in different breast tumor samples with various disease conditions and the functional role of this gene in the development of breast cancer.

Materials and Methods

Tissue samples. The snap-frozen tissues (normal and tumor; n = 52) were obtained from the University of Kansas Medical Center Tissue Repository Bank. The normal tissues were collected from patients who underwent breast reduction mammoplasty. Tissue microarray slides were obtained from Imgenex Corp. In these slides (silane coated), 60 serial 4-μm sections were mounted. Of 60 tissue samples, 50 samples were infiltrating ductal carcinoma samples with different stages of tumor grades and lymph node status. The remaining 9 samples were nonneoplastic breast tissue. All of this information is provided by the manufacturer. The study was approved by the Veterans Affairs Medical Center Institutional Review Board.

Cell lines and culture condition. The noninvasive (i.e., MCF-7 and ZR-75-1) and invasive (i.e., MDA-MB-231 and HCC70) human breast carcinoma cell lines, purchased from the American Type Culture Collection, were used for this study. Both cell lines were maintained in DMEM (Sigma) supplemented with 10% fetal bovine serum (Hyclone) at 37°C in a humidified chamber.

Laser capture microdissection. The laser capture microdissection (LCM) was carried out as described (17). Briefly, the paraffin-embedded breast tissue sections were stained with H&E and specific areas (DCIS and tumor invasive) were captured by an Arcturus AutoPix laser capture microscope (Molecular Devices), which is available in the Breast Cancer Prevention Center research laboratory at the University of Kansas Medical Center. Individual areas from the six serial sections were dissected from the slides, captured by the Macro LCM caps (MDS Analytical Technologies), and transferred to sterile 0.5 mL PCR tubes (Applied Biosystems) for RNA extractions.

Extraction of RNA from cell lines and tissue sections by LCM. Cytoplasmic RNA was extracted from breast tumor cell lines using the Trizol extraction procedure (Invitrogen), as described previously (18). This RNA was used for the nonradioactive digoxigenin-labeled probe preparation (9).

RNA extraction was performed from the laser microdissected samples according to the RNeasy Micro kits (Qiagen, Inc.). Briefly, cells lysates were prepared by adding the buffer RLT into the microdissected tissue sections and digested with proteinase K for 30 min at 55°C. The cell lysates were centrifuged to collect the supernatant. Ethanol was added and mixed properly. The lysates were collected into the spin column and centrifuged at 8,000 × g, and the flow through was discarded. The column was washed with washing buffer (RW1) followed by a DNase treatment. Total RNA was eluted in RNase-free water and quantitated in a spectrophotometer.

Amplification of the RNA. For the RNA amplification procedure, the TargetAmp 1-Round aRNA Amplification Kit 103 was used (Epitome Technologies). The TargetAmp TT-Oligo(dt) Primer A was annealed with the RNA sample at 65°C for 5 min in a thermocycler. After annealing, the first-strand cDNA synthesis master mix (1.5 μl TargetAmp Reverse Transcription PreMix, 0.25 ml of DTT, and 0.25 ml of SuperScript III reverse transcriptase) was added in each reaction and incubated at 50°C for 30 min in a thermocycler. To prepare the second-strand cDNA synthesis, the second-strand synthesis master mix (4.5 μl TargetAmp DNA Polymerase PreMix and 0.5 μl polymerase) was prepared and added into each reaction tube. The samples were incubated at 65°C and 80°C for 10 and 3 min, respectively. After the cDNA synthesis, the in vitro transcription master mix was added in each tube and incubated at 42°C for 4 h. The amplified RNA was purified using the Qiagen RNeasy Micro kit according to the manufacturer’s protocol and quantitated.

cDNA synthesis and real-time PCR. cDNA was synthesized according to the previous methods (19). The real-time PCR was performed from the cDNA of unamplified as well as from amplified RNA using SYBR Green DNA detection dye by Applied Biosystems StepOne Real-Time PCR System. PCR was performed for 15 s at 95°C and 1 min at 60°C for 40 cycles followed by the thermal denaturation protocol. The primers for CCN5 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) are the same as used previously (10, 11, 20). C(T) values for CCN5 are normalized to human GAPDH by subtracting the average Ct value for each sample. Relative quantification values for the CCN5 mRNA in DCIS and invasive carcinoma were determined using the 2-ΔΔC(T) method (21). Each PCR was performed in triplicate.

CCN5 in situ hybridization and scoring. CCN5 mRNA expression in paraffin-embedded tissue sections was performed according to the manufacturer’s instruction (Biogenex) with minor modification as previously reported (9, 22). The slides were evaluated independently by two different pathologists.

Western immunoblot analysis. The Western blot analysis was performed according to the previous method (23). Signals were detected with SuperSignal Chemiluminescent Substrate (Pierce) by using ID Image Analysis Software version 3.6 (Eastman Kodak Co.).

Gelatin zymographic assay for matrix metalloproteinases. Gelatin zymographic assay was performed as described earlier (24–26). Briefly, parental MCF-7 cells, CCN5-nullified MCF-7 cells, or MDA-MB-231 cells (positive control) were seeded on six-well plates and grown to ~90% confluence in 1.5 mL of growth medium. After 48 h, the conditioned medium was collected and matrix metalloproteinase (MMP)-2 and MMP-9 activities were determined by substrate gel electrophoresis (zymography) with the use of 7.5% SDS-PAGE containing gelatin (2 mg/mL). Following electrophoresis, the gels were washed with 2.5% Triton X-100 for 1 h followed by incubation with an enzyme assay buffer [25 mmol/L Tris (pH 7.5), 5 mmol/L CaCl2, 0.9% NaCl, 0.05% Na2CO3] for 48 h. The gels were stained with 0.05% Coomassie brilliant blue G-250. Areas of gelatinase activity were detected as clear bands against the blue-stained gelatin background.

CCN5 immunohistochemistry. CCN5 protein expression was performed by immunostaining using Zymed broad range immunohistochemical kits (Zymed Laboratories), as previously described (9). The immunoreactivity was detected by conjugated streptavidin. The sections were counterstained by hematoxylin.

Short hairpin RNA knockdown. To knock down CCN5, MCF-7 cells were transiently transfected with the pSilencer vector (1.0-U6) containing growth arrest–specific gene (AS) with their companion six-well plates (Corning) were used for transfection. For the RNA knockdown experiments, the pSilencer vector (1.0-U6) containing shRNA targeting CCN5 was transiently transfected with the pSilencer vector (1.0-U6) containing shRNA targeting CCN5. The nontransfected cells were used as control. The cells were then incubated in anti-BrdUrd peroxidase. Finally, the cells were incubated in a substrate solution at room temperature, and proliferation was assessed by colorimetric detection.

In vitro migration and invasion assay. Transwell culture inserts (Corning) were used for in vitro migration and invasion assays. The methods were the same as described previously (19).
Statistical analysis. All the statistical analyses were performed with Prism 4.0 software (GraphPad Software, Inc.) using χ² or two-tailed unpaired Student's t test. Significance is indicated by an asterisk when P < 0.05.

Results

CCN5 expression is inversely correlated with breast cancer progression. Previously, we reported that CCN5 is overexpressed in the noninvasive lesions, including ADH and DCIS, and the expression of CCN5 is sporadic in the invasive lesion (9). Identical results were found in different breast tumor cell lines (9, 14–16, 20). We extended our work and systematically reevaluated the expression profile of CCN5 mRNA and protein in 112 samples (archival normal and cancerous breast tissue samples and tissue array samples) using in situ hybridization and immunohistochemical analysis (Fig. 1). Consistent with our previous studies, we found that the intensity of CCN5 (mRNA or protein) is inversely correlated (χ² ANOVA) with the disease progression from noninvasive to invasive lesions. CCN5 expression is significantly higher in ADH and DCIS compared with invasive cancer where the CCN5 expression is gradually decreased to none as the disease progresses from the well-differentiated to poorly differentiated stage. Moreover, subsequent quantitative discriminatory studies grading the staining intensity of CCN5 (i.e., none to dark) showed an inverse correlation between staining intensity of CCN5 and lymph node positivity (Fig. 1D). Our studies were further confirmed by real-time PCR analysis using amplified mRNA isolated from microdissected sections from noninvasive and invasive samples as indicated in Fig. 2. We found that CCN5 mRNA expression was markedly higher in DCIS areas compared with invasive areas.

Suppression of CCN5 induces an invasive front in breast tumor cells. The goal of this study was to uncover the functional significance of the basal level of CCN5 in noninvasive breast tumor cells. To test this, MCF-7 cells were transiently transfected with CCN5-specific shRNA and grown in the presence or absence of IGF-I. We exposed the cells to IGF-I because it is well established from decade’s findings that IGF-I exhibits either proliferative or differentiation effect on cancer cells depending on their micro-environments (i.e., noninvasive or invasive phenotypes). IGF-I shows the mitogenic effect on ER-α⁺, noninvasive cells and this effect is mainly depending on the up-regulation of CCN5 expression (10). We found that the suppression of basal expression of CCN5 in MCF-7 cells by RNA interference (Fig. 3A) does not impede the regular growth of noninvasive breast cancer cells but blocks the IGF-I–induced cell proliferation (Fig. 3B). Interestingly, the silencing of CCN5 enhances the motile behavior of MCF-7 cells under normal or IGF-I environment (Fig. 3C). We found that after 48 h of transfection, migration was increased significantly in shRNA1 transiently transfected MCF-7 cells compared with mismatched vector after 8 h of seeding these cells on the upper

Figure 1. Analysis of the CCN5 expression profile in different human breast tumor samples. A, CCN5 mRNA and protein were detected in breast tumor sections using in situ hybridization and immunohistochemistry. Magnification, ×200. Inserted box, selected portions of some figures in higher magnification. B, intensity profile of CCN5 expression in different breast tumor samples. C, schematic representation of the summary of the expression profile of CCN5 in different breast tumor samples. Note that the intensity of CCN5 expression increased markedly in noninvasive lesions compared with normal ducts and invasive lesions in the breast. D, relation of CCN5 expression with the lymph node (LN) status.
was highly expressed in ZR-75-1 noninvasive breast cancer cells, but its expression is undetected in MDA-MB-231 and HCC70 CCN5 breast carcinoma cell lines. The endogenous expression profile of Snail was reverse in these cells compared with E-cadherin. Snail was detected in MDA-MB-231 and HCC70 cells, whereas it was underexpressed in ZR-75-1 cells (Fig. 5C). This result persuaded us to explore whether CCN5 regulates Snail expression in breast tumor cells. To do so, MCF-7 cells were transiently transfected with CCN5 shRNA to silence the CCN5 insert of the Boyden chamber (Fig. 3C). IGF-I exhibits an additive effect (Fig. 3C). The other two shRNAs also showed similar effects on the migration of MCF-7 cells (data not shown). This result was further confirmed by in vitro migration and invasion of MDA-MB-231 invasive breast cancer cells in different culture environments (Fig. 4). The motility and invasion of MDA-MB-231 cells can be suppressed significantly by MCF-7 (noninvasive) conditioned medium. However, this suppressive effect of the conditioned medium can be impaired by shRNA-induced knockdown of the CCN5 expression. Collectively, these studies, along with a recent publication (16), suggest that the CCN5 signaling may be a negative regulator of tumor cell invasion. Further studies are warranted.

**CCN5 is a positive regulator of E-cadherin and negative regulator of MMPs.** Attenuation of adhesive property followed by migration of a cancer cell is the hallmark of an invasive/metastatic phenotype. This feature is regulated by multiple factors, including E-cadherin repression and MMPs, and notably the gelatinases MMP-2 and MMP-9 induction. Our studies show that shRNA-mediated silencing of CCN5 in MCF-7 cells potently blocked E-cadherin expression and simultaneously promoted MMP-2 and MMP-9 expressions in MCF-7 cells (Fig. 5A and B). These studies, therefore, speculate that CCN5 may play a preventive role in the progression of breast cancer by modulating E-cadherin and MMP expression in noninvasive breast cells.

**E-cadherin and CCN5 expressions in breast tumor cells are inversely correlated with Snail.** Recently, it has been shown that E-cadherin expression can be suppressed by Snail, a zinc finger transcription factor and a labile protein, via its binding to E-box in the E-cadherin promoter (27). Snail protein is mostly undetected in various cancer cells and it may be tightly regulated by an ubiquitin-proteasome pathway (28). In this study, we found that E-cadherin was highly expressed in ZR-75-1 noninvasive CCN5 breast cancer...
expression and Snail expression profile was determined. Because transfection efficiency of shRNA vectors is reasonably very satisfactory in MCF-7 cells compared with ZR-75-1, we intentionally selected MCF-7 noninvasive breast tumor cells for this study. The results show that the Snail level increased significantly in CCN5-nullified cells (Fig. 5D). Collectively, we assumed that the CCN5-dependent up-regulation of E-cadherin may be mediated through the suppression of Snail or its upstream signaling molecules.

Discussion

Our studies show convincingly that CCN5 expression is biphasic such that in normal ducts and lobules CCN5 expression is undetectable, whereas its expression is markedly increased in noninvasive breast lesions, including ADH and DCIS. Further, CCN5 mRNA and protein levels are significantly reduced as the cancer progresses from a noninvasive to invasive types. Additionally, we showed that CCN5 mRNA and protein levels were almost undetectable in poorly differentiated cancers compared with the moderately or well-differentiated samples. CCN5 expression inversely correlated with lymph node positivity. Therefore, our studies suggest a potentially protective contribution of CCN5 signaling to the invasive front. This hypothesis is further supported by our subsequent in vitro studies indicating that silencing of CCN5 enhanced the invasive phenotypes in noninvasive cells through the regulation of pertinent gene signatures, including Snail, E-cadherin, and MMP.

The development of human breast cancer and its invasion and metastatic spread is a complex, multistep process, which has not yet been fully elucidated. Several growth factors, oncogenes, and tumor suppressor genes have been known to participate in regulating the progression of this fatal disease. Several breast cancer models have recently been developed and have already yielded new information on the molecular network of the progression of breast cancer. However, their effect in terms of offering new concepts of the molecular network of human breast cancer development, diagnostics, or therapeutic modalities remains limited. Over the last several years, after the identification of CCN5 in noninvasive human breast tumor cells and samples by using RNA differential display analysis (14), CCN5 has been implicated as having an important role in human breast disease and other cancers as well (9, 10, 14, 20, 29–33). The present immunohistochemical and in situ hybridization analysis studies have shown a differential expression profile of CCN5 in human breast samples. Under normal conditions, its expression is undetected. Once healthy cells are assaulted by some unknown factors, which cause noninvasive lesions (ADH or DCIS) in breast cells, the CCN5 expression increases (Fig. 1). In contrast, the expression of CCN5 gradually decreases as the breast cancer progresses from the well-differentiated to poorly differentiated stage. Moreover, the expression pattern of CCN5 shows an inverse correlation with lymph node positivity. We therefore suspect that the distinct patterns and variable expression of CCN5 may not be a secondary consequence of differences among these tumor samples.
It may play a protective effect against the progression of the disease as it was implicit by previous in vitro studies (13, 16). The present studies are not in agreement with the recent work of Davies and colleagues (15). Interestingly, previous work of Davies and colleagues (15) contradicted their own in vitro data and our in vivo results. It does not corroborate our claim and proposed opposite reports. This is because their studies were not designed to evaluate the CCN5 expression profile in the entire spectrum of noninvasive and invasive breast tumor samples.

If overexpression of CCN5 definitely plays a role in limiting breast cancer progression, how might it perform? An obvious possibility is that the apparent protective effect of CCN5 may be related to its ability to prevent the formation of an invasive front via regulating the molecular pathways associated with this event. Inhibition of an adhesive property followed by migration of a cancer cell is the hallmark of an invasive front (3). This feature is regulated by multiple factors, including E-cadherin repression and MMPs, and notably the gelatinases MMP-2 and MMP-9 induction (3, 34). Moreover, E-cadherin expression is frequently suppressed by MMPs, and notably the gelatinases MMP-2 and MMP-9 induction is regulated by multiple factors, including E-cadherin repression and cancer cell is the hallmark of an invasive front (3). This feature is regulated by multiple factors, including E-cadherin repression and MMPs, and notably the gelatinases MMP-2 and MMP-9 induction (3, 34). Moreover, E-cadherin expression is frequently suppressed by MMPs, and notably the gelatinases MMP-2 and MMP-9 induction is regulated by multiple factors, including E-cadherin repression and cancer.

CCN5 by shRNA up-regulates Snail expression in these cells. Thus, we anticipate that the suppression of E-cadherin expression in CCN5-nullified MCF-7 cells could be mediated through the activation of Snail. Consequently, one intriguing possibility is that the anti-invasive activity of CCN5 might be mediated through the suppression of Snail signaling.

MMP-2 and MMP-9 (gelatinase A and B) are zinc-dependent endopeptidases of the MMP family (39). These two gelatinases are involved in cancer invasion and metastasis by tissue remodeling through the degradation of extracellular matrix and basement membrane (39). They are secreted aszymogens and then cleaved as active forms to perform their function, which is tightly regulated by different mechanisms (39). In breast cancer, both MMP-2 and MMP-9 are differentially overexpressed in cancer cells, stromal cells, and circulation (40–45). Our studies found that both MMP-2
and MMP-9 expression are increased in CCN5-nullified MCF-7 cells. Therefore, we suggest that the anti-invasive activity of CCN5 may also exert through the regulation of MMP-2 and MMP-9.

In summary, these studies along with earlier findings (9–11, 13, 14, 16, 18, 20, 30–33, 46) suggest that CCN5 is a two-faced cancer gene that may be one of the key regulators of invasive phenotype of breast tumor cells. Therefore, the protective effect of CCN5 in breast cancer progression may have important therapeutic implications, particularly in the design of targeted therapy against breast cancer. However, the precise mechanism of action of CCN5 in the protection of the invasive phenotype remains to be elucidated.

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14. Sengupta K, Banerjee S, Guangyan Q, et al. CCN5-nullified MCF-7 cells. Therefore, we suggest that the anti-invasive activity of CCN5 may also exert through the regulation of MMP-2 and MMP-9.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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