CCN1 Expression in Ductal Proliferations: A Preliminary Study

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ABSTRACT

CCN 1 is one the matricellular proteins that is aberrantly expressed in infiltrating duct carcinoma. We studied its possible role in intraepithelial duct proliferations. 6 Low Risk Ductal Intraepithelial Neoplasia, 18 Ductal Intraepithelial Neoplasia 1 (DIN1), 9 DIN2 and 10 DIN3 were studied by immunohistochemistry. All of the intermediate and high grade DIN cases showed either focal or diffuse positivity. 7 DIN1 cases were negative, 5 DIN1 were focally and 6 DIN1 were diffusely positive. The staining pattern was mostly cytoplasmic except in high grade DIN which had both cytoplasmic and nuclear staining. CCN 1 expression was independent of ER/PgR status of non-invasive lesions in this limited sample size.

BACKGROUND

CCN (Cysteine rich protein 61/Connective tissue growth factor / Nephroblastoma overexpressed gene) family has several biologic roles including cell survival, differentiation, adhesion, migration and angiogenesis. Expression of CCN genes can enhance or suppress tumor cells, depending on the specific tumor type. Aberrant expression of CCN1 is observed in many cancers, including infiltrating ductal carcinoma of the breast. The expression of CCN1 in pre-invasive ductal lesions, however, has not been studied in detail.

AIMS

1. Explore possible role of CCN 1 in DCIS pathogenesis
2. Correlate CCN 1 expression with grade of DCIS
3. Correlate CCN 1 expression with hormone receptor status of the lesions

METHODS

6 cases of UDH (Usual Duct Hyperplasia), 7 of Atypical Intraductal Hyperplasia (AIDH), 11 Ductal Carcinoma *In Situ* (DCIS) grade 1, 9 DCIS grade 2 and 10 DCIS grade 3 cases were studied for CCN1 expression by immunohistochemistry. Solid, cribriform, micropapillary and papillary subtypes of DCIS were represented. All 11 DCIS 1, 4 of 9 DCIS 2 and 5 of 10 DCIS 3 were ER+/PgR+. 3 DCIS 2 were ER+/PgR-. The remaining cases were ER-/PgR-. Staining for CCN1 in > 50% of cells was reported as “diffuse”, staining in 1-50% of cells was considered “focal”, and staining in <1% of tumor cells was “negative”. Cytoplasmic and nuclear staining were recorded separately.

FIGURE

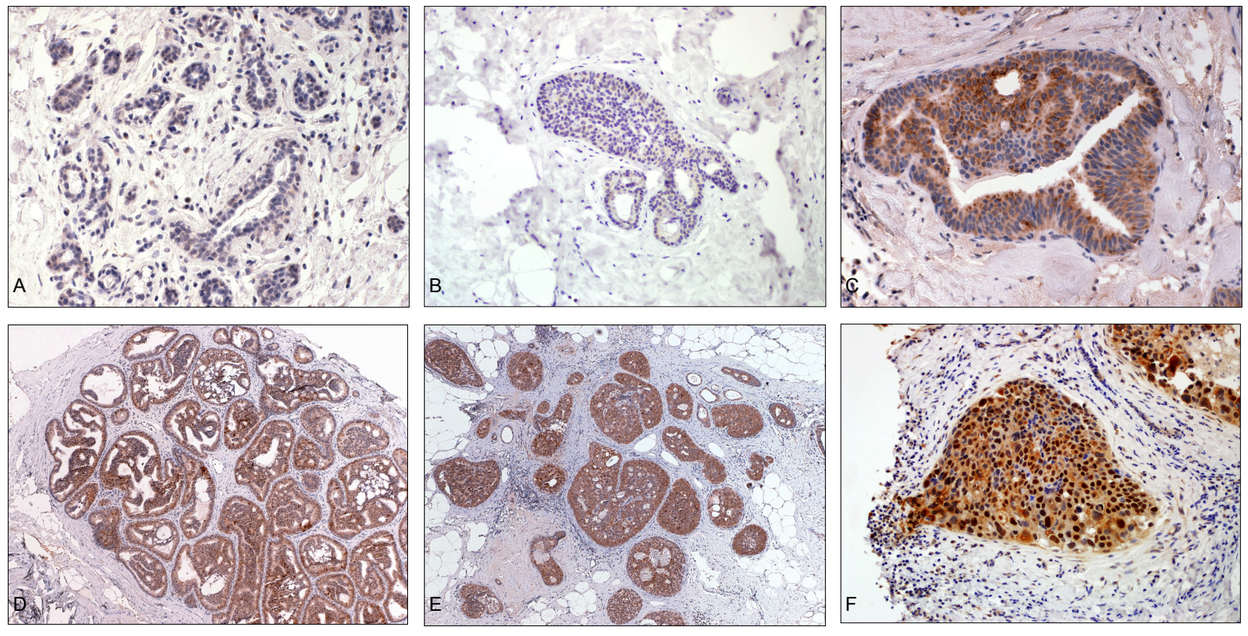

Figure 1: CCN 1 Immunostain. **A:** Benign mammary epithelium, **B:** Usual Duct Hyperplasia, **C:** Atypical Intraductal Hyperplasia, **D:** Ductal Carcinoma *In situ* (DCIS) grade 1, **E:** DCIS grade 2, **F:** DCIS grade 3.

RESULTS

- CCN1 immunostaining was primarily cytoplasmic, with focal nuclear staining limited to DCIS grade 3.
- UDH and surrounding benign breast tissue were negative for CCN1 AIDH was negative in 4, focal in 2 and diffusely positive in 1 case.
- DCIS grade1 was negative in 3, focal in 3 and diffusely positive in 5 cases.
- DCIS grade 2 was focal in 2 and diffusely positive in 7 cases.
- DCIS grade 3 was diffusely positive in all 10 cases. (Figure 1).

CONCLUSIONS

1. CCN1 is not expressed in normal or hyperplastic breast ductal epithelium.
2. The frequency of CCN1 expression correlates with the grade of the *in situ* lesion, being present in all DCIS grade 3 cases examined.
3. CCN1 expression is independent of ER or PgR expression.

REFERENCES

1. Chong HC, Tan CK, Huang RL et al. *Matricellular proteins: a sticky affair with cancers.* J Oncol. 2012;2012:351089. doi 10.1155/2012/351089.
2. Brigstock DR. *The CCN family: a new stimulus package*. J Endocrinol. 2003 Aug;178(2):169-75.
3. Tsai MS, Bogart DF, Catan JM. *Cyr61 promotes breast tumorigenesis and cancer progression.* Oncogene. 2002;21: 8178–8185.
4. Menedez JA, Vellon L, Mehmi I et al. *A novel CYR61-triggered ‘CYR61-avb3 integrin loop’ regulates breast cancer cell survival and chemosensitivity through activation of ERK1/ERK2 MAPK signaling pathway*. Oncogene. 2005;24:761–779.
5. Lester FL. *CCN1/CYR61: the very model of a modern matricellular protein.* Mol. Life Sci. 2011; 68:3149–3163.