ORIGINAL ARTICLE

CD10-A new prognostic stromal marker in breast carcinoma, its utility, limitations and role in breast cancer pathogenesis

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ABSTRACT

Background and Aims: Breast cancer is one of the leading causes of mortality in Indian women. Although breast cancer is an epithelial malignancy, stroma plays a key role in its development and pathogenesis. Stromal markers are now emerging as novel markers in assessing the prognosis of invasive breast cancer and have not been studied extensively till date. The aim of the present study is to study the stromal expression of CD10 in breast carcinoma, find its relationship with other prognostic markers and study the role stroma plays in breast cancer pathogenesis. **Materials and Methods:** A total of 70 cases of breast cancer were included in the study. Representative sections were taken and hematoxylin and eosin staining was done. Immunohistochemistry was performed with ER, PR, Her2neu and CD10. Stromal expression of CD10 (>10% stromal positivity was considered positive) in invasive breast carcinoma was noted and was statistically analyzed with different known prognostic markers of breast carcinoma. **Results:** Stromal expression of CD10 was found to be significantly associated with increasing tumor grade (P = 0.04), increasing mitotic rate (P = 0.33), worsening prognosis (P = 0.01), ER negativity (P = 0.0001), Her2neu positivity (P = 0.19) and with molecular subtypes (CD10 positivity with the HER2 type, and CD10 negativity with Luminal type). No correlation was found between CD10 overexpression and PR, age, menopausal status, tumor size, lymph node positivity and tumor stage. **Conclusions:** This study gives substantial proof to the various models/research papers explaining the role of stroma/CD10 in breast cancer pathogenesis. Keeping the role stroma plays in predicting prognosis and tumor response, CD10 should be included as a routine pre-chemotherapy marker in breast carcinoma. Further studies should be performed to see the role stroma plays in hormonal expression and the usefulness of CD10 to predict treatment failure in breast carcinomas receiving neoadjuvant therapy.

KEY WORDS: Breast carcinoma, CD10, pathogenesis, stromal marker

INTRODUCTION

Breast cancer is one of the most common cancers among women globally. According to the population based national cancer registry (India),[1] it is one of the major cancers in Indian females. As breast cancer is an epithelial malignancy, the prognosis of breast cancer is related to the number and types of oncogenes activated in the epithelial cells. Various hormonal markers, such as ER, PR and Her2 neu are routinely used to study this oncogene expression or amplification in breast cancer epithelial cells. However, stroma plays a key role in modulating tumor invasion and metastasis. A better understanding of stromal contribution to cancer progression will identify specific signals that promote growth, dedifferentiation, invasion, and ectopic survival of tumor cells and may eventually result in the identification of new therapeutic targets for future treatment. Stromal markers are now emerging as novel markers in assessing the prognosis of invasive breast cancer and have not been studied extensively till date. This justifies the current study of new stromal marker CD10 for prognostification and possible therapeutic intervention in invasive breast carcinoma.

MATERIALS AND METHODS

Patients and sample collection

A total of 70 cases of breast carcinoma were studied, including 69 cases of radical mastectomy and 1 case of trucut biopsy. Relevant history, like age of patient, menopausal status, prior chemotherapy was taken.

Histopathological examination

Grossing and reporting were done according to the CAP (College of American Pathologists) protocol for the examination

of specimens from patients with invasive carcinoma of the breast (Based on AJCC/UICC TNM, 7th edition).[2] All specimens were formalin-fixed (in 10% neutral buffered formalin). Representative sections were taken and after proper tissue processing, were paraffin embedded, and stained with hematoxylin–eosin stain. The grading of breast carcinoma was done according to the Nottingham combined histologic grade (Elston–Ellis modification of Scarff–Bloom–Richardson grading system). Nottingham's Prognostic index (NPI) was calculated, and patients were divided in six NPI groups (as advocated by Blamey *et al*).[3]

(EPG) Excellent Prognostic group-2.08 to 2.4
(GPG) Good Prognostic group- >2.42 to = <3.4
(MPG I) Moderate I Prognostic group- >3.42 to </ = 4.4
(MPG II) Moderate II prognostic group- >4.42 to = <5.4
(PPG) Poor prognostic group- >5.42 to = <6.4
(VPG) Very poor prognostic group- >6.5 to 6.8

Ratio of positive to total lymph nodes dissected (LNR) was calculated in 57 cases. LNR was not calculated if total number of dissected lymph nodes were less than six. Staging was attempted in 69 cases based on the pTNM status of the breast carcinomas.

Immunohistochemistry (IHC) for ER, PR, Her2neu and CD10

3 μ sections were taken on poly-L-Lysine coated slides. Sections were deparaffinized in xylene followed by hydration in descending ethanol grades. Antigen retrieval was performed by heating sections at 95°c (3 cycles of 5 min each for Her2 neu and CD10) in citrate buffer (pH 6.0 for Her2neu) and Tris–EDTA buffer (pH 9.0 for CD10) and at 100°c (2 cycles, 1st for 15 min and 2nd for 7 min for ER and PR) in citrate buffer (pH 2.5 for ER, PR) using an EZ antigen retriever system (BioGenex, USA). Sections were then incubated with power block (BioGenex, USA) for 10 min to reduce the non-specific antibody binding followed by incubation at 4°C with primary antibodies for 1 h. Rabbit monoclonal antibody against human ER (Dako Anti-human ERα (EP1-clone)(Ready to use-RTU), mouse monoclonal antibody against human PgR (Dako Anti-human PgR Receptor (PgR 636-clone)(RTU), Rabbit monoclonal antibody against human Her2 (BioGenex Anti-ErbB 2/Her2(EP1045Y) (RTU) and mouse monoclonal antibody against human CD10 (Dako AntiHuman CD10 (56C6clone)(RTU) were used. After three washes with TBS, secondary antibody was added for 30 min. After three washes with TBS(trisphosphate buffer solution), 3,3'-diaminobenzidine substrate (DAB tetrahydrochloride) was applied to the sections for 10 min and sections were counterstained with hematoxylin, dehydrated with ethanol and xylene and mounted permanently with DPX. Negative control sections were processed by omitting primary antibody. Positive controls were (1) fibroadenoma for ER, PR (2) Previously known positive cases of Her2 neu positive breast cancer for Her2neu (3) Periductal stromal cells in fibroadenoma for CD10.

Evaluation of staining

Reporting of ER, PR and Her2neu was done according to the CAP protocols.[2] CD10 was considered positive if more than 10% of stromal cells showed cytoplasmic and membranous positivity [Figure 1].

Statistical analysis

Statistical analysis was performed by using Graph Pad software (Prism 6 version) for Windows 7. Chi-square test was carried out to see the correlation between CD10 expression and different prognostic parameters of breast cancer. A *P*-value <0.05 was considered as statistically significant.

RESULTS

A total of 70 cases of breast carcinoma were included in the study. Correlation between stromal CD10 expression and clinicopathological data of the cases is shown in Table 1.

Stromal CD10 positivity was found to have statistically significant trend with increasing grade of tumor ($P = 0.04$), increasing mitotic rate ($P = 0.33$) and with worsening prognosis ($P = 0.01$). CD10 positivity was also significantly associated with ER negativity ($P = 0.0001$) and Her2neu positivity ($P = 0.1902$). No correlation was found between CD10 overexpression and PR staining of tumor cells. Also, CD10 immunostaining had a significant association with the molecular subtypes ($P = 0.0004$) of breast cancer, with CD10 positivity having a strong association with the HER2 subtype, and CD10 negativity with the Luminal subtype. However, CD10 positivity was found more in the triple negative group, no significant difference was found from the non-triple negative breast cancer. Age, menopausal status, tumor size, lymph node positivity (including LNR), tumor stage did not have any correlation with CD10 positivity. The findings of the present study correlated with the studies of Makretsov *et al.*,[4] Iwaya *et al.*,[5] Thomas *et al.*[6] [Table 2].

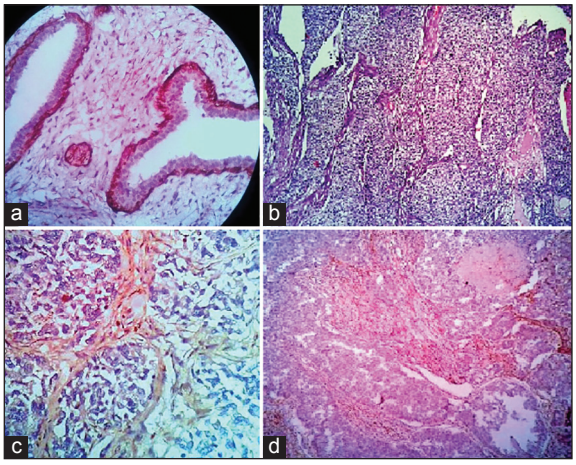

Figure 1: (a) CD10 positivity in periductal stromal cells in fibroadenoma (positive control) (b) H and E section of breast carcinoma-grade3 (400×) (c and d) Stromal CD10 positivity in breast cancer

Table 1: Correlation of CD10 expression with prognostic factors in breast

Stromal	*CD10 positivity (%)*	*CD10 negativity (%)*	*P value*	*Significance*
Age group				
<40	8 (61)	5 (39)	0.3572	No
40-60	19 (42)	26 (58)		
>60	7 (58)	5 (42)		
Menopausal status				
Pre	22 (52)	20 (48)	0.4729	No
post	12 (43)	16 (57)		
LNR (lymph node ratio)				
<0.2	13 (43)	17 (57)	0.1864	No
>0.2	17 (63)	10 (37)		
Tumour size				
T1	1 (25)	3 (75)	0.5325	No
T2	15 (50)	15 (50)		
T3	9 (50)	9 (50)		
T4	9 (53)	8 (47)		
Stage				
1	1 (33)	2 (67)	0.8600	No
2A	5 (36)	9 (64)		
2B	7 (58)	5 (42)		
3A	8 (53)	7 (47)		
3B	9 (53)	8 (47)		
3C	4 (50)	4 (50)		
Mitotic grade as in Nottingham's grading				
1	13 (36)	23 (64)	0.0331	Yes for trend
2	10 (62.5)	6 (37.5)		
3	11 (65)	6 (35)		
Tumour grade (Nottingham's Grade)				
1	5 (26)	14 (74)	0.0413	Yes for trend
2	16 (57)	12 (43)		
3	13 (68)	9 (32)		
NPI (prognosis)[3]				
EPG	0	2 (100)	0.0140	Yes for trend
GPG	2 (18)	9 (72)		
MPG1	3 (37.5)	5 (62.5)		
MPG2	15 (62.5)	9 (37.5)		
PPG	7 (58)	5 (42)		
VPG	7 (58)	5 (42)		
ER				
Negative	26 (70)	11 (30)	0.0001	Yes Sensitivity-77% Specificity-70%
Positive	8 (24)	25 (76)		
PR				
Positive	7 (35)	13 (65)	0.1902	No Sensitivity-21% Specificity-64%
Negative	27 (54)	23 (46)		
Her2				
Negative	18 (72)	7 (28)	0.0057	Yes Sensitivity-53% Specificity-80%
Positive	16 (35)	29 (65)		
Molecular subtype				
ER neg, Her 2 pos	15 (75)	5 (25)	0.0004	yes
Negative for ER, PR, Her 2	11 (65)	6 (35)		
ER pos., Her 2 neg	5 (18)	23 (82)		
ER pos Her 2 pos.	3 (60)	2 (40)		

Table 2: Correlation of present study with other studies

Name of study	*Sample size*	*Positive correlation CD10*	*No correlation*	*Uncertain*
Present study (2013)	70	Higher Grade Increasing Mitosis Bad Prognosis ER - Her2 + Molecular subtype	Age Tumour Size Stage/TNM Lymph node positivity PR	Histological type Chemotherapy
Makretsov NA *et al*[4] (2007)	453	Higher Grade Decreased survival ER -	Tumour Size Lymph node status PR, Her 2 Histologic subtype	
Iwaya K *et al*[5] (2002)	123	Lymph node mets Decreased DFS/OS	age tumor size histologic grade clinical stage	
Thomas S *et al*[6] (2013)	29	ER - Her 2 + Chemotherapy and clinical response		

DISCUSSION

Although breast cancer is an epithelial malignancy arising in the epithelial cells of the terminal ductal lobular unit, stromal microenvironment plays an important role in breast cancer evolution and metastasis. It has been proved beyond doubt that tissue microenvironment plays a key role in controlling cell survival, proliferation, migration, polarization, and differentiation.[7,8]

The continuous and bilateral molecular crosstalk between normal epithelial cells and cells of the stromal compartment is disrupted by several factors secreted by the tumor cells themselves or by stromal cells under the influence of cancer cells.[7,9-12] One such important factor is the matrix metalloproteinase (MMPs). MMP plays an important role in tumor progression and in defining the role of stromal microenvironment in tumor invasion and metastasis.[13] Up-regulated extracellular matrix (ECM) gene expression and elevated MMP activities correlate with poor patient prognosis.[13] Also, high expression of estrogen receptors is associated with enhanced activity of MMP-2, while high expression of progesterone receptors is correlated with low TIMP-1(tissue inhibitor of MMPs) protein levels.[12] MMPs also play an important role in the formation of active TGF-β (tissue growth factor-β-a cytokine produced by carcinoma associated fibroblasts) which promotes tumorigenesis and stromal cell functions associated with angiogenesis, immunosuppression and tumor progression.[13] Cleavage products of matrix components (*e.g.*, collagen, laminin) (produced by MMPs) and some growth factors (*e.g.*, IGFs I & II) have chemotactic activity for tumor cells, and thus help in tumor cell migration through matrix.[14]

CD10 in normal breast

CD10 is a membrane-bound zinc-dependent endopeptidase (a type of MMP), which regulates the physiological action of various peptides by lowering their extracellular concentration available for receptor binding.[15,16] CD10 protease maintains the early progenitor population in the human mammary lineage by cleaving signaling proteins that would otherwise promote differentiation of ECPs (early common progenitors) to LEPPs (luminal epithelial progenitor) or MEPPs (myoepithelial progenitor), which ultimately gives rise to luminal and myoepithelial cells, respectively [Figure 2]. Therefore, CD10 by its enzymatic functions (along with the help of β1-integrin) acts largely as a Stem cell (SC) regulator in the breast preventing the unchecked proliferation of mammary SC.[16-18]

CD10-its role in breast cancer progression

In breast carcinoma, CD10 expression has apparently contradictory findings. On one hand its disappearance from myoepithelial cells and the basement membrane leads to the progression of DCIS to invasive carcinoma and on the other hand, CD10 expression by the stromal cells surrounding the breast tumor is correlated with poor prognosis, oestrogen receptor negativity, and high grade.[4,5,19,20] This can be explained on the model proposed by Maguer-Satta *et al.*,[15] [Figure 2], that an early oncogenic events in stem cells modulate the expression of CD10-enzyme in the altered cells or even in the neighboring cellular environment. A resultant decrease in CD10-enzymatic function after the neoplastic transformation of early common progenitors (ECP) or progenitors (P) could induce an accumulation of unprocessed peptides in the SC (stem cell) microenvironment, resulting in their lineage commitment and malignant proliferation.[15] This is the proposed basis for progression of DCIS into invasive malignancy with CD10 loss [Figure 2a].

However, in invasive breast carcinoma, an upregulation of CD10 (mutated) enzymatic activity (mostly from mesenchymal SCs/or from proliferation of transformed epithelial cancer SCs expressing CD10) could lead to an accumulation of local CD10-cleaved peptides that inhibit epithelial cell differentiation and maintain cancer SCs[15] [Figure 2b]. This explains the increased expression of CD10 in undifferentiated carcinomas (*i.e.*, with high histological grade and subsequently higher NPI) in our study.

CD10 and mitotic rate, prognosis and chemotherapy response

In normal tissue, CD10 associates with the tumor suppressor PTEN leading to decreased PIP3 (phosphatidylinositol 3,4,5-trisphosphate) phosphorylation, which prevents activation of the Akt pathway (implicated in tumor cell growth), and leads to cell apoptosis (via MDM2 pathway).[15,21–25] CD10 also cleaves growth factors such as fibroblast growth factor 2 (FGF2), which induces Akt signaling in favor of endothelial cell growth and angiogenesis.[24] CD10 also prevents cancer cell migration

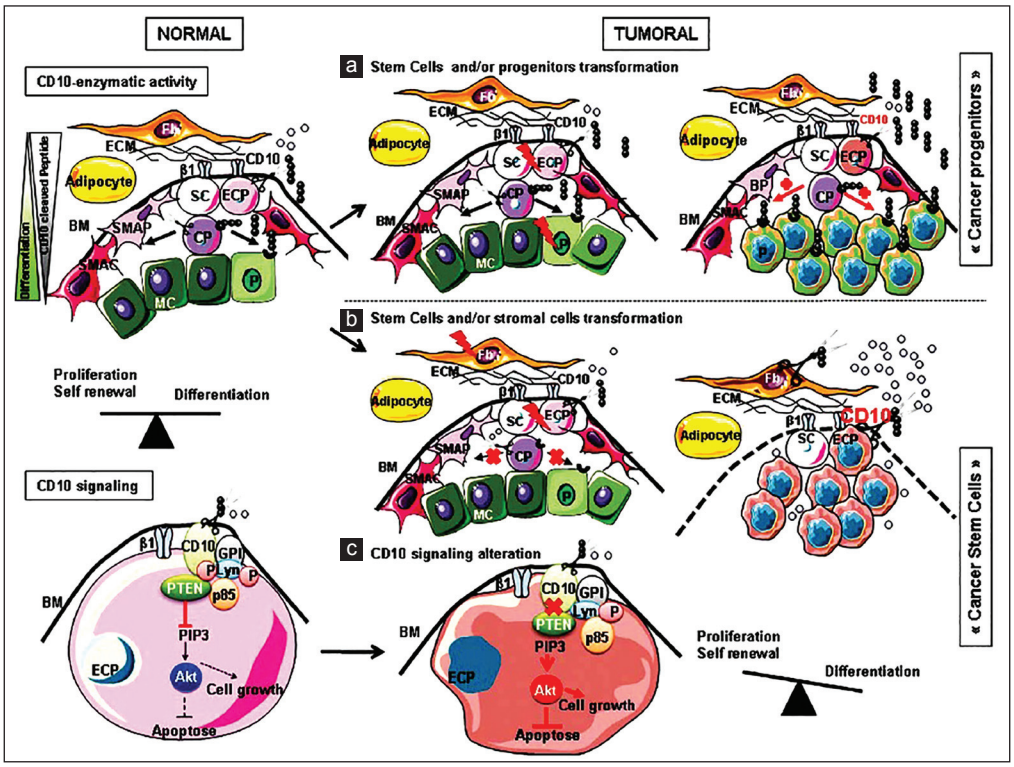

Figure 2: Role of CD10 in normal (left panel) and tumoral (right panel) context with a CD10-enzymatic deregulation (upper (a) and middle (b) panel) or an alteration in the CD10 signaling (lower (c) panel). (a) Transformation of ECP and/or P induces the decrease of the CD10-enzymatic activity and/or the decrease of the number of CD10-expressing cells that induce the accumulation of peptides, normally cleaved by the CD10, which mediate the proliferation of progenitor cells. (b) Transformation of ECP induces their proliferation and an increase in CD10-expressing cells, which cleaved differentiating signaling peptides. (c) CD10 signaling deregulation in transformed ECP cells could block PTEN activity and induce cell growth by the activation of Akt pathway.

BM: Basal membrane; CP: Common progenitors; ECM: Extracellular matrix; ECP: Early common progenitors; Fb: Fibroblast; GPI: Glycosylphosphatidylinositol; MC: Mature cells; P: Progenitors; PTEN: Phosphatase and TENsin homolog; SC: Stem cells; SMAC: Smooth muscle actin cells; SMAP: Smooth muscle actin progenitors.

(Adapted with permission from Maguer-Satta V, Besançon R, Bachelard-Cascales E. Concise review: Neutral endopeptidase (CD10): A multifaceted environment actor in stem cells, physiological mechanisms, and cancer. Stem cells. 2011;29:389-96)

(via PI3K-FAK pathway)[15,21–25] [Figure 3]. In breast cancer, CD10 signaling could be modified in cancer progenitors or SCs, independently of its enzymatic activity. These signaling alterations could block PTEN functions leading to apoptosis inhibition, cell proliferation and angiogenesis through the Akt pathway[15] [Figure 2c]. This can explain our finding that CD10 positivity is associated with increasing mitotic grade (*i.e.*, increasing cell proliferation) and poor prognosis. Also, the poor response of chemotherapy drugs in some CD10 positive cases (as shown by Thomas *et al.* and few cases (five cases) in our study) may be due to this modified signaling pathway of CD10 leading to decreased apoptosis and hence resistance to chemotherapy.[6]

CD10 and hormonal status and molecular subtypes

Explaining the association between CD10 positivity and hormonal status of breast cancer is much more difficult. Most studies [Table 2] (including ours) have shown that CD10 positivity to be associated with ER negativity and Her2 positivity. In our study, CD10 positivity was associated with the HER2 subtype while negativity with luminal subtypes. Molecular studies have shown that in human breast cancer, basal like (ER-/PR-/Her2-) and HER2E(ER+/HER2+) subtype are more associated with PTEN loss, than luminal type (ER+).[26] CD10 positivity in basal and HER2E subtype can be explained by assuming that in spite of high CD10 expression, defective signaling by CD10 in cancer cells leads to defective PTEN function, causing cancer progression and angiogenesis.

Also, the initial oncogenic events in progenitor cells that cause PTEN loss may upregulate CD10 function in mesenchymal stem cells, leading to accumulation of CD10 cleaved peptides that prevent epithelial differentiation. That both CD10 positivity and PTEN loss are found more in the basal and HER2 subtype and absent in luminal subtype raises the suspicion that there is some relation between CD10 and PTEN in causing breast cancer. However further research is required to see the exact role played by CD10 and PTEN in breast carcinoma and their influence on the hormonal signature of tumor cells.

CD10 and stromal signature

A recent gene expression profiling study of breast carcinoma stroma identified two clinically significant types of stromal

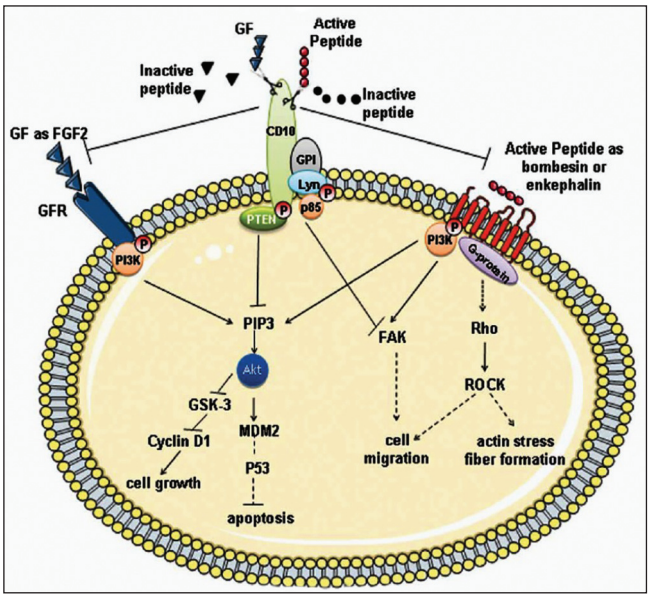

Figure 3: CD10 signaling pathways. CD10 associates with p85, a PI3K subunit, and Lyn kinase indirectly prevents FAK activation by PI3K. Simultaneously, the association between CD10 and the tumor suppressor PTEN simultaneously leads to decreased PIP3 phosphorylation, which activates the Akt pathway. CD10 catalytically inactivates a variety of peptides like bombesin in prostate cancer cells, which induces FAK or Rho signaling by their fixation onto G-coupled protein receptor. CD10 also cleaves growth factors such as fibroblast growth factor 2 (FGF2), which induces Akt signaling in favor of endothelial cell growth and angiogenesis.
(Adapted with permission from Maguer-Satta V, Besançon R, Bachelard-Cascales E. Concise review: Neutral endopeptidase (CD10): A multifaceted environment actor in stem cells, physiological mechanisms, and cancer. Stem cells. 2011;29:389-96.)

signatures in breast cancer, namely, solitary fibrous tumor (SFT) type and desmoid type fibromatosis (DTF) type, where the first was associated with poor outcome.[27] CD10 expression was associated preferentially with desmoid-type fibromatosis stromal signature, and, possibly, contributed to a number of negative outcomes in invasive carcinoma of the breast with this type of stromal signatures. Further studies have shown that, CD10 positive stroma signature includes, among others, genes involved in matrix remodeling (MMP11, MMP13, and COL10A1) and genes related to osteoblast differentiation (periostin). This stromal signature is present in DCIS but absent in invasive carcinoma-proving the fact that progression from *in situ* to invasive breast cancer is dependent upon the tumor microenvironment.

CD10 and Her2neu

CD10 positive stromal signature also carried prognostic value in the HER2 positive breast cancer, and is associated with a poor response to therapy.[28] A possible explanation, offered by Desmedt *et al.* and Cabioglu *et al.* is that positive stromal expression of CD10 is associated with increased expression of CXCL12 which causes transactivation of Her2, leading to increased levels of Her2.[28,29] Our study also showed a significant correlation between CD10 positivity and Her2 overexpression. However, the exact tumor–epithelium interactions explaining the specific clinical relevance of the stroma in HER2 Positive breast cancer is still a mystery and needs further research. All these points to the fact that stroma plays an important role in breast cancer progression and prognostification, and in coming days new markers such as CD10, TGF-β, SPARC, integrins and laminins are to be used for better prognostification of breast cancer.

However, CD10 did not have any correlation with tumor stage (and its components-size, nodal involvement), but had a significant correlation with tumor grade (and its components-mitosis) and prognosis (NPI). This points to the fact that both tumor stage and grade are independent prognostic parameters.

CD10 and drug development

Another important role of CD10 immunostating is its role in drug designing. Treatment of breast cancer no longer depends on designing drugs against the cancer epithelial cells, but drugs that can have better delivery system, with maximum efficacy, least toxicity and that can modify the tumor microenvironment/stroma. This has led to development of peptide prodrugs cleavable by peptidases present in the tumor environment, thus increasing maximum efficacy with least toxicity. CD10, being a cell surface metalloprotease expressed in breast cancer, is capable of cleaving CPI-0004Na and related peptide prodrugs, such as N-succinyl- alanyl-L-isoleucyl-L-alanyl-Lleucyl-Dox (sAIAL-Dox). This proteolytic cleavage generates leucyl-Dox, which is capable of entering cells and generating intracellular Dox, with a higher potency than Dox alone. Cytotoxicity of CPI-0004Na is inhibited by phosphoramidon, a known inhibitor of CD10 enzymatic activity.[30] Therefore routine staining of CD10 will be helpful in deciding the line of treatment of patients, especially in Triple negative breast cancer.

CONCLUSION

To conclude, stroma plays an important role in development, progression, hormonal expression and response to chemotherapy in breast cancer. This has necessitated for the study of stromal markers in breast cancer. CD10, a novel stromal marker plays an important role in normal breast involution and in the development and progression of breast carcinoma. Stromal expression of CD10 in breast cancer correlates with poor tumor grade, bad prognosis, ER negativity and Her2 positivity, besides acting as a potential target for newer drug development. Further studies are required to see the correlation between stroma and hormonal expression in breast cancer, and the usefulness of CD10 to predict treatment failure in breast carcinomas receiving neoadjuvant therapy.

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