Research Article

Immunohistochemical expression of PELP1 in breast cancer, with focus on triple negative cases – a south Indian study

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Abstract

Introduction: Triple negative cases account for 10 to 20% of breast cancers and remain a challenge to the treating physician. Recognition of molecular pathways involved in tumorigenesis may unravel newer therapeutic options. Proline, glutamic acid-, and leucine-rich protein PELP1 (MNAR- Modulator of Nongenomic Actions of estrogen Receptor), a novel nuclear receptor coregulator, is deregulated in many cancers including breast. With this background we assessed the PELP1 expression pattern in different molecular subtypes of breast cancer. **Materials and Methods:** Eighty three cases of infiltrating ductal carcinoma, who underwent modified radical mastectomy were reviewed and subtyped using molecular classification. PELP1 immunostain was done. Nuclear and cytoplasmic positivity was assessed by modified Quick score. Results were analysed using standard statistical methods. **Results:** Luminal A was the most common type followed by Triple negative. A higher incidence of triple negative cases was noted (p value 0.018). Nottingham grade 2 was the most common grade irrespective of molecular subtype. Her 2 and triple negative types occurred in a relatively younger age group. T2 N0 was the most common stage at presentation. The mean tumor size of triple negative cases was 4.05cm which was larger than the others. Luminal B showed the highest mean nuclear and cytoplasmic PELP1 Quick Score. The nuclear and cytoplasmic Quick score of triple negative cases was the lowest (p value 0.0005). Grade 2 tumors showed a Quick score greater than grade 3. **Conclusion:** The incidence of triple negative breast cancers was higher in our study, compared to reported incidence. The lower PELP1 expression in triple negative cases indicates a possible down regulation of PELP1 gene. These findings need to be further confirmed by molecular studies.
Keywords: Breast cancer, triple negative, PELP1.

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Received Date: 10/12/2014 Revised Date: 17/12/2014 Accepted Date: 22/12/2014

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 06 February 2015

INTRODUCTION

Breast cancer is the most frequent cancer among women and is one of the leading causes of cancer deaths in women worldwide[1]. Immunostaining for estrogen receptor, progesterone receptor and Her- 2/neu forms the basis for designing the treatment protocols for carcinoma breast. About 10 - 20 % of breast cancers, are found to be triple negative[2] and they do not respond to hormonal therapy[3,4]. In addition, a subset of estrogen receptor[5] positive patients are also found to be resistant to tamoxifen therapy. Finding ideal treatment options for these patients is a challenge faced by the treating physician. Unlike traditional chemotherapy and irradiation, targeted therapies work by blocking a specific process the malignant cells use, to divide, thrive and spread. Understanding the various molecular pathways involved in tumour biology is essential for the recognition of these specific molecular targets. This would enable the development of new therapeutic strategies which would

How to site this article: Archana K, Sandhya Sundaram, Ganesh Venkatraman, Ravi Shankar, Prathiba D. Immunohistochemical expression of PELP1 in breast cancer, with focus on triple negative cases – a south Indian study. *International Journal of Recent Trends in Science and Technology* February 2015; 14(1): 116-121 http://www.statperson.com (accessed 08 February 2015).

be focused, personalised and more effective. Proline-, glutamic acid-, and leucine-rich protein PELP1[6,7], also known as modulator of nongenomic actions of the estrogen receptor (MNAR), is a unique nuclear receptor coregulator with numerous functions. PELP1/MNAR serves as a scaffolding protein that integrates different signaling complexes. Deregulation of PELP1/MNAR gene is observed in many cancers including breast, ovary, endometrium and prostate. PELP1/MNAR interacts with many oncogenes and various enzymes that modify the cytoskeleton. Deregulation of PELP1/MNAR in metastatic breast tumors indicates its vital role in tumor cell migration. With this background, we proposed to assess the PELP1 expression pattern in different molecular subtypes of breast cancer cases.

MATERIALS AND METHODS

A total of Eighty three cases of infiltrating ductal carcinoma for whom modified radical mastectomy cases were retrived from the surgical pathology files of the Department of Pathology, Sri Ramachandra Medical College and Research Institute, Chennai. Approval from the Institutional Ethics Committee was obtained prior to commencing the study [IEC-NI/11/FEB/21/10]. Gross findings were recorded and clinical data was obtained from the medical record section and available local area computer network in-service at Sri Ramachandra Medical College and Research Institute, Chennai. Formalin fixed paraffin embedded tumour tissue samples were used for this study. Formalin fixed paraffin embedded tissue samples were sectioned to five micron thickness and stained with hematoxylin and eosin. Tumors were graded using Nottingham grading system for breast cancer[8,9]. Lymph node involvement was assessed, and pathological staging was done. Immunostaining for estrogen receptor (ER), progesterone receptor (PR) and Her 2 neu was performed using prediluted monoclonal antibodies Ab.no.272M, Clone PR88 and Ab.no.134M respectively procured from Biogenex laboratories. Complete membrane stain was recorded as positive for Her2neu[10]. The cases were classified according to the molecular classification based on the ER, PR and Her2neu receptor status[11] Immunostaining for PELP1/MNAR, P160, was done. Affinity purified antibody using an epitope specific to PELP1/MNAR immobilized on solid support, was procured from Bethyl Laboratories and used. Immunostaining intensity was assessed as grade negative, low, moderate and strong for the staining intensity of 0, 1+. 2+, 3+ respectively [12] A modified Quick's score[13,14] was done to score PELP1 immunohistochemical staining in all the molecular subtypes. The scores were obtained by multiplying the percentage of positive cells (P) by the intensity (I)[15,16]. Formula for quick score Q=P x I. Maximum = 300. Results were analysed and statistical significance was assessed.

RESULTS

A total of 83 cases of invasive ductal carcinoma were retrieved from Department of Pathology, Sri Ramachandra Medical College and Research Institute, Chennai and studied .In this study patient's age were ranged from 32 to 75years with a median age of 53 years. The highest number of cases were seen between the age group of 51 to 60 years .Out of 82 cases, 36 % were of Luminal A molecular subtype which was found to be the most common subtype. Followed by Luminal A; 30% were Triple negative, 19% were Luminal B and 15% were Her2. This was based on immunostaining with ER, PR, Her2 Neu staining pattern (Table 1). Tumors showing nuclear positivity for ER and PR were recorded as positive (Figure.1). This difference in presentation was not statistically significant by Chisquare test. However the higher incidence of triple negative cases noted in our study (30%) was statistically significant with a p value of 0.018. In this study irrespective of molecular subtype Nottingham grade 2 was the most common (60%), followed by grade 3 (25%) and grade 1 (15%). Luminal A and Luminal B most commonly occurred in the age group of 51 to 60years. Her2 and triple negative type occurred more commonly in a relatively younger age group between 41 and 50years. Six positive controls were stained along with the test cases. The adjacent normal breast tissue was used as control. Positivity for PELP1 immuno staining in the cytoplasm and nucleus of the tumour cells was recorded (Figure.2) T2 N0 was the most common stage at presentation for all the four molecular subtypes. The mean tumor size of triple negative cases in our study was 4.05cm which was larger than the other subtypes. However this was not statistically significant.

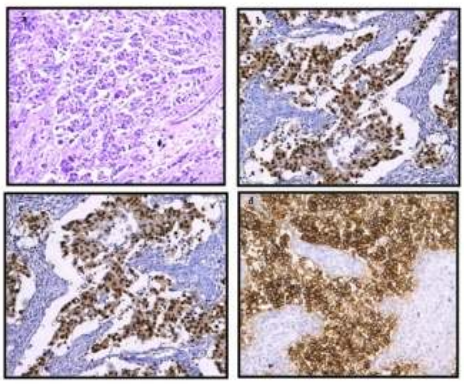

Figure 1: a: Infiltrating Duct Carcinoma Hand E X100, b: ER Positive IHC X100, c: PR Positive IHC X100, d: Her-2/neu 3+ Positive IHC X100

Table 1: Molecular subtype classification of ductal carcinoma

Molecular subtype	ER	PR	Her2neu
Luminal A	+	+	-
LuminaL B	+	+	+
HER 2 Neu	-	-	+
Triple negative	-	-	-

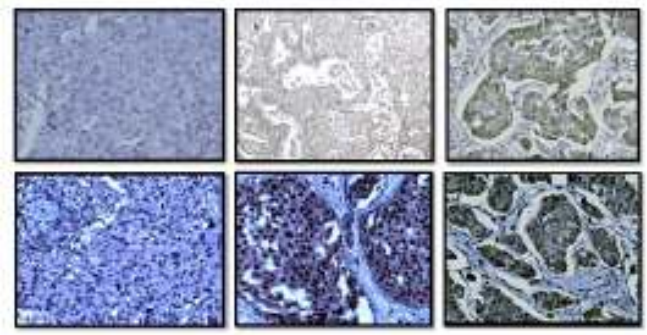

Figure 2: a: PELP1 Nucleus Negative, Cytoplasm Positive 1+, IHC X100, **b:** PELP1 Cytoplasm Negative, Nucleus Positive 1+ IHC X100, **c:** ELP1 Nucleus Positive 2+ IHC X100, **d:** PELP1 Cytoplasm Positive 2+ IHC X100, **e:** PELP1 Nucleus Positive 3+ IHC X100, f: PELP1 Cytoplasm Positive 3+ IHC X100.

PELP1 IMMUNOSTAINING PATTERN

NUCLEAR IMMUNOSTAINING PATTERN

Luminal B type showed the highest mean Quick Score of 236.6. This was followed by Her2 with a mean Quick Score of 220.7. The mean quick score of Luminal A and triple negative were 215.6 and 138.9 respectively (Figure.3)

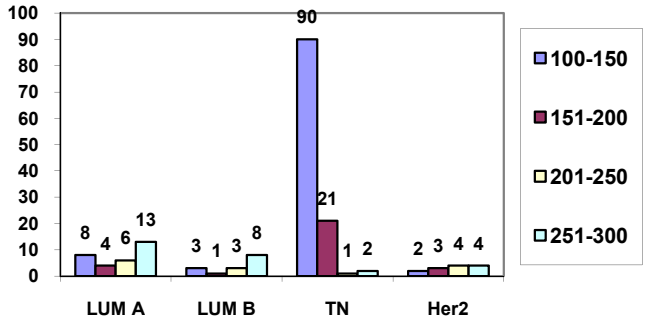

Figure 3: PELP1 Quick score- Nucleus

CYTOPLASMIC IMMUNOSTAINING PATTERN

Luminal B type showed the highest mean Quick Score of 218.6, followed by Luminal A (216.7), Her2(199.2) and triple negative (129.1). (Figure.4) the results were subjected to statistical analysis by Post Hoc test. On comparing the nuclear and cytoplasmic Quick score of triple negative subtype with the others triple negative cases showed a lower mean Quick score, with a statistically significant p value of 0.0005. But none of the other pairings were statistically significant. The mean difference was significant at the 0.05 level. On comparing the nuclear Quick score of grade 2 with grade 3, grade 2 tumors showed a higher Quick score with a statistically significant p value of 0.023. The cytoplasmic Quick score of grade 2 was higher, when compared with other grades with a significant p value of 0.11 on comparison with grade 3 (Table.2). But none of the other pairings were statistically significant. The mean difference is significant at the 0.05 level.

Table 2: Summary of immunoreactive staining of PELP1 in breast tumors

No staining	Positive staining	Nuclear staining	Cytoplasmic staining	Nuclear andCytoplasmic staining
7 of 83 (8.4%)	76 of 83 (91.5%)	2 of 76 (2.6%)	4 of 76 (5.2%)	70 of 76 (92.1%)

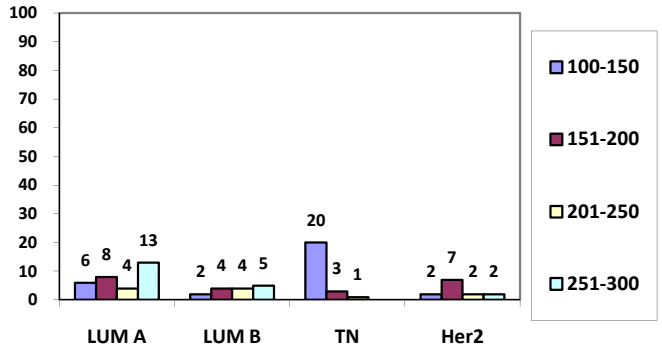

Figure 4: PELP1 Quick score- Cytoplasm

DISCUSSION

A shift of general disease pattern has been observed in developing countries in the recent years. Non communicable diseases like life style diseases and malignancies[17,18] are on the rise. Younger age at presentation is also reported in developing countries. India's National Health Profile 2010 predicted that by 2020, breast cancer will overtake cervical cancer as the most common type of cancer among women in India[19] (ICMR data)[20]. The therapeutic modalities and prognosis of breast cancer is influenced by several factors like age, tumor size, histological subtype and grade, axillary lymph node status, lymphatic/vascular invasion and hormone receptor status[21]. In India the average age of breast cancer diagnosis is 25 to 69 years [22]. In our study the age ranged from 32 years to 75 years with a median age of 53 years. The highest number of cases were seen between the age group of 51 to 60 years. This is in concurrence with the study by Terfa S. Kene *et al* [23] done in Nigerian population. In our study, triple negative and Her 2 subtype of breast cancers presented most commonly in the age group of 41 to 50 years. Luminal A and Luminal B subtypes presented commonly at 51 to 60

years. Mean age at presentation of triple negative breast cancer was 53years [24] in the study reported by Rebecca Dent *et al* in Canada. Triple negative patients presented at a relatively younger age (mean age 49years) in our study. Statistically significant difference in the age of presentation of triple negative breast cancer cases compared to other molecular subtypes was observed in our study, with a p value of 0.018. Triple negative tumors are reported to be of larger size in the earlier studies[25,26]. The mean tumor size of triple negative cases in our study was 4.05cm which was larger than the other subtypes though this was not statistically significant. Histological variants like tubular, cribriform, mucinous and adenoid cystic carcinomas carry a good prognosis, whereas medullary, secretory and invasive lobular cancers have an intermediate prognosis. Infiltrating ductal carcinoma, NOS has a poor prognosis compared to the above mentioned variants. In addition, it is the most common histological type. Eighty percent of breast cancers reported, belong to this type. Therefore we chose to study this subset of breast cancer. In our study, Nottingham grade 2 was the most common grade across the various molecular subtypes followed by grade 3 and grade 1. This data was analysed statistically and a significant p value of 0.011 was obtained. WD Foulks *et al*[27] in their study found that majority of triple negative cases were grade 3, ductal/no-specific-type carcinomas. In contrast to this we found grade 2 to be the commonest grade among triple negative cases. N0 was the most common nodal status at presentation for all the molecular subtypes. Among triple negative cases 41% presented in N0 stage. The difference in the presentation of nodal status between different molecular subtypes was not statistically significant. This is in concordance with the study by Andre Albergaria *et al*. Molecular classification of breast cancer was devised based on the ER, PR and Her 2 neu expression status[11]. According to Adedayo[28] A. Onitilo *et al* Luminal A is the most common molecular subtype of breast carcinoma. This is in concordance with our study where 36 % were Luminal A molecular subtype of breast cancer. However this was not statistically significant. In this study, 25 cases out of 83 were triple negative. This accounts to 30% of the total number of cases. This is much higher than the incidence reported by Rakha *et al*[29] who found 16.3% were of the triple-negative phenotype. This higher incidence of triple negative cases in our study was statistically significant (p value 0.018). The therapeutic options were also developed based on this. The basal type of breast cancers do not express these markers. However triple negative cases have been described as a separate subtype since they have subtle variations at the molecular level. Tamoxifen, Herceptin etc. do not act on this subset. Only systemic chemotherapy is available for these patients. In addition, few ER positive cases have been shown to be of poor prognosis[30,10]. Targeted therapeutic options which would effectively manage these subsets of patients is the need of the hour. PELP1 is one of the recently described molecular marker, aberrant expression of which can play an important role in tumor biology. According to Hany Onsy Hapashy *et al*, PELP1 protein expression can independently predict the disease free interval in breast carcinoma[12]. Its increased expression indicates a poor prognosis. Hence PELP1 may play an important role in evaluating the prognosis of both ER-positive and negative breast cancer. PELP1 expression has been shown to influence the metastatic potential of breast cancers. However we found a lower PELP 1 expression in the triple negative cases which generally have a poor outcome. Correlation of molecular subtype of invasive ductal carcinoma with PELP1 nuclear and cytoplasmic expression pattern has shown statistically significant difference between different subtypes in our study. It is of interest to note that triple negative cases have a significantly lower expression of PELP1 which indicates a possible dysregulation in PELP1/MNAR axis. PELP1 plays a critical role in ER genomic, ER non-genomic and ER signalling cross talk with growth factor signalling pathways. Although PELP1 is important for normal functions of ER, the possibility to target ER-PELP1 axis appears to be an effective strategy for preventing hormonal carcinogenesis and resistance to therapy[6]. According to Sudipa Roy *et al*[31] PELP 1 is an estrogen receptor co regulator that has been implicated as a proto-oncogene whose expression is deregulated in metastatic breast tumors and whose expression is retained in ER-negative tumors. Roy *et al* suggested that PELP1 knock down reduced the in-vivo metastatic potential of ER negative breast cancer cells and significantly reduced lung metastatic nodules in a xenograft assay. This suggests that PELP 1 may regulate metastasis by promoting cell motility or epithelial mesenchymal transition. With this background information we under took this study to find the expression of PELP1 in breast cancer in our Indian subset of IDC, NOS patients. However, we found a lower nuclear and cytoplasmic expression of PELP1 by immunohistochemistry in our south Indian subset of patients. The findings in our study support the possibility of deregulation of PELP1-MNAR axis with a statistically significant reduced expression of PELP1 protein in triple negative cases. This expression pattern is different from the previous studies on PELP1 expression reported in the literature.

CONCLUSION

Triple negative breast cancers were relatively more common, they presented at a relatively younger age and

showed predominantly a lower histological grade (grade 2) in our subset of patients compared to reports in the literature from the Western studies. A statistically significant difference between PELP1 nuclear and cytoplasmic expression pattern in different subtypes of infiltrating duct carcinomas indicates a dysregulation of PELP1/MNAR axis in these patients with a possible down regulation of PELP1 gene in triple negative subset. These findings need to be confirmed by further molecular studies in a larger number of cases.

ACKNOWLEDGEMENT

We thankfully acknowledge the financial assistance provided by Indian Council of Medical Research.

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Source of Support: None Declared
Conflict of Interest: None Declared