Original Article

Is it Time to Include p40 as a Standard Myoepithelial Marker of Breast? A Comparative Study of Expression of p63 and p40 in Benign Breast Diseases and Invasive Ductal Carcinomas of the Breast

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Abstract

Context: The expression of p40 in breast tissue as a myoepithelial marker is not extensively studied. This study was designed to find the expression of two markers p63 and p40 in benign breast diseases and Invasive ductal carcinomas (IDCs) of the breast. **Aim:** A series of cases of fibroadenoma and IDC of breast were studied for expression of p40 and compared to the p63 staining profile. **Settings and Design:** A total of 118 cases of breast disease were selected for this study from the archives of a tertiary care hospital, which included 41 cases of benign and 77 cases of malignant etiology. After the exclusion, 30 cases of fibroadenoma and 68 cases of IDC, were selected for the study. **Subjects and Methods:** Samples (n = 98) included fibroadenoma (n = 30) and IDC (n = 68). IDC was studied as a whole group and was also divided as triple negative breast cancer (TNBCs, n = 12) and Non-Triple TNBCs (NTNBC, n = 56). The expression of p63 and p40 was assessed in myoepithelial cells (MECs) in fibroadenoma and tumor cells in IDC. **Results:** Both the antibodies performed similarly to highlight MECs in fibroadenoma in all 30 cases. In IDC, TNBC and NTNBC subgroups p63 stained the tumor cells more than p40. None of the tumor cells in the NTNBC group exhibited positivity for p40. **Conclusions:** As a MEC marker, both p63 and p40 perform similarly but in IDC (TNBC and NTNBC), the tumor cells of IDC stain significantly more for p63 than p40. It appears that p40 does not come positive in the tumor cells of NTNBC.

Keywords: *Fibroadenoma, invasive ductal carcinoma, myoepithelial cell, p40, p63*

Introduction

Breast carcinomas form the second largest group of malignancy-related deaths in women. The incidence increases with age and reaches to about 1 in 8 women, at 90 years of age. Younger women too, constitute a significant burden of this disease.[1-4] Immunohistochemistry is a valuable tool not only for accurate diagnosis of breast cancer but also to know the predictive and prognostic factors in an individual case. There is a plethora of studies on the pathobiology of breast cancers, many centered on finding a more sensitive and specific myoepithelial immunohistochemical marker. The presence or absence of myoepithelial cells (MECs), goes without saying, is the cornerstone for the place a breast lesion in the benign or malignant category.[2] The luminally located epithelial and the abluminally located MECs are different as regards their function and hence antigen expression profiles. The arrangement of these MECs differs within the various benign breast proliferation (haphazard in sclerozing lesions), *in situ* lesions (absent or reduced frequency, only in the peripheral layer) and frankly malignant lesions (absent).[5]

Immunohistochemistry for MECs is routinely used in breast resection as well as core biopsies specimens. Numerous IHC markers for MECs are in use, the important ones being smooth muscle actin (SMA),[6] p63,[7] CD10,[8] smooth muscle myosin heavy chains (SMMHCs),[9] along with h-caldesmon, calponin, S100, basal type and high-molecular-weight cytokeratins, glial fibrillary acid proteins.[5] Each has their inherent sensitivity, specificity, and cellular localization. Of these immunohistochemical markers, the most commonly used are CK5/6, SMA and p63. SMA is a cytoplasmic marker and though sensitive for MECs (88%–100%) cannot be completely

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relied upon as it stains vascular smooth muscles, pericytes and myofibroblasts, all of which are present in the tumor stroma, and also in few cases of IDC.[10,11]

The basal type high molecular weight cytokeratins are localized to the cytoplasm as well as the cell membrane. Of them, CK5/6 is a popular choice but also it stains epithelial cells besides MECs and also various cases of ductal carcinoma *in situ* (DCIS) and high-grade IDC. As a result, the latter alone does not seem to be a dependable option.[12,13]

P63 a homolog of p53 delineates nearly 100% of MECs in the normal breast as well as benign proliferation. Is appears to be better than SMA as it does not stain the myofibroblasts as well as vascular smooth muscle cells. It is a nuclear marker and hence easier to discern[7,14] It has two drawbacks. Like CK5/6, p63 also stains tumor cells in IDC (15%–25%).[15] Some studies claim that the expression of p63 is reduced in old blocks.[16]

p40 is a newer antibody and a product of the p63 gene. In many studies, the p40 antibody has shown better and specific staining, compared to p63 in lung squamous cell carcinoma than in lung adenocarcinoma.[17] p40 is also emerging as an important diagnostic marker in malignancies of prostate, head and neck, squamous cell carcinomas, and sinonasal undifferentiated carcinomas.[18,19] There are few studies to evaluate the utility of p40 as a marker of MECs in the breast.[20]

Carcinomas of the breast, based on gene expression profiling have been slotted into luminal, HER2 enriched, basal-like, and normal-like. The surrogate markers for the gene expression profiling are based on IHC for estrogen receptor (ER), progesterone receptor (PR), HER2 and MIB 1 labeling index.[2] Among these the basal-cell like are high-grade tumors, affect younger women show poor response to therapy, harbor higher frequency of BRCA 1 mutations and thus have the worse prognosis.[3]

Triple-negative breast cancers (TNBC) are not synonymous with but a subgroup of basal-like molecular subtype characterized by ER, PR, and HER2 negativity on IHC.[21] Other IHC used to characterize the TNBC are CK5/6, EGFR, SMA, CD 117, and p63.

Subjects and Methods

AIM:

(1) In this study, our aim was to find out the expression of p40 in the MECs of benign breast proliferation and compare it with p63.

(2) Study cases of IDC to know the expression of p40 in the tumor cells, in our subpopulation and compare it with p63.

A total of 118 cases of breast disease were selected for this study from the archives of a tertiary care hospital, which included 41 cases of benign and 77 cases of malignant etiology. Cases where benign diagnosis was other than fibroadenoma were excluded. Of 97 malignant cases only cases of invasive ductal carcinoma (IDC), NST was considered. Cases with a diagnosis other than IDC, where tissue blocks were unavailable or when the tissue was insufficient for IHC were excluded from the study. Post chemotherapy excision cases were also excluded from this study. Biopsies included Tru-cut breast biopsies, excision biopsies, breast conservation surgery and modified radical mastectomies. Tumor and normal breast parenchyma interface block was chosen for H and E stain and IHC which also sufficed for internal positive control purposes.

The cases were independently assessed by two pathologists and the histopathological diagnosis was reconfirmed. The ER, PR, Her2 receptor status, and Ki-67 labeling index was evaluated. Any case, where diagnosis or hormone receptor status was in disagreement, was removed from this study. Finally, 30 cases of fibroadenoma and 68 cases of IDC, were selected for the study.

Tissue sections were routinely fixed in neutral buffered formalin and thereafter paraffin-embedded. Tissue sections of 4–5 μm thickness were done and subsequently stained for Hematoxylin and Eosin stain and IHC for ER, PR, Her2, Ki-67, p63, and p40. Suitable positive and negative controls were run with each batch of immunohistochemistry. The following monoclonal antibodies were used for IHC:

API 3066 AA, H (clone BC28, mouse) ready to use, anti-p40 (BioCare, Calif., USA); PM 163 AA, H (clone 4A4, mouse) ready to use, anti-p63 (BioCare, Calif., USA);

PR042 (clone EP1, Rabbit monoclonal) ready to use anti-ER (Path-*in situ*, Calif., USA); PR068(clone EP2, Rabbit) ready to use, anti-PR (Path-*in situ*, Calif., USA); PR047(clone EP 3, rabbit monoclonal) ready to use, anti-Her2/Erb2(Path-*in situ*, Calif., USA); FLEX monoclonal mouse (clone MIB-1) ready to use anti-human Ki-67(DAKO, Glostrup, Denmark).

Antigen retrieval was done after deparaffinization and rehydration at room temperature (Envision Flex Target Retrieval system TRIS/EDTA buffer, pH 9.0, for 30 min at 94°C; Dako, Glostrup, Denmark). For slides, rinsing was done with Tris-buffered saline (EnVision FLEX Wash) and the sections subsequently stained Immunohistochemical staining was done standard protocols. For counterstaining Mayer's Hematoxylin was used. Positive controls were run using relevant archival sections while for negative controls, the primary antibody step was done away with. The interpretation of ER, PR, HER2, and MIB1 labeling index was done as per standard teaching.[2-4] P63 and p40 staining were interpreted by both the pathologist separately and was considered positive when localized to the nucleus

and at least 1% of cells stained. The staining intensity was recorded as absent, weak, moderate, and strong.[18] The results were analyzed using.

Results: Clinico-Pathological Parameters

The samples included in the study were from December 2019 to August 2020, a total period of 09 months during which 118 breast biopsies were received, of which 41 benign lesions (34.7%) and 77 (65.3%) malignant lesions were diagnosed during the above-mentioned duration. One was a male patient with gynecomastia while the rest were females. The spectrum of benign disease included fibroadenoma (n = 31), fibrocystic breast disease (n = 2), benign phyllodes tumor (n = 1), granulomatous mastitis (n = 3), duct ectasia (n = 1), sclerozing adenosis (n = 1), gynecomastia (n = 1), fibromatosis (n = 1), and a case of benign myoepithelial proliferation. The malignant tumors were predominantly IDC, NST (n = 71), mixed mucinous carcinoma and IDC (n = 2), lobular carcinoma (n = 1), micropapillary IDC (n = 1), carcinoma with medullary features (n = 1), encysted papillary carcinoma (n = 1), and a case of malignant solitary fibrous tumor (n = 1).

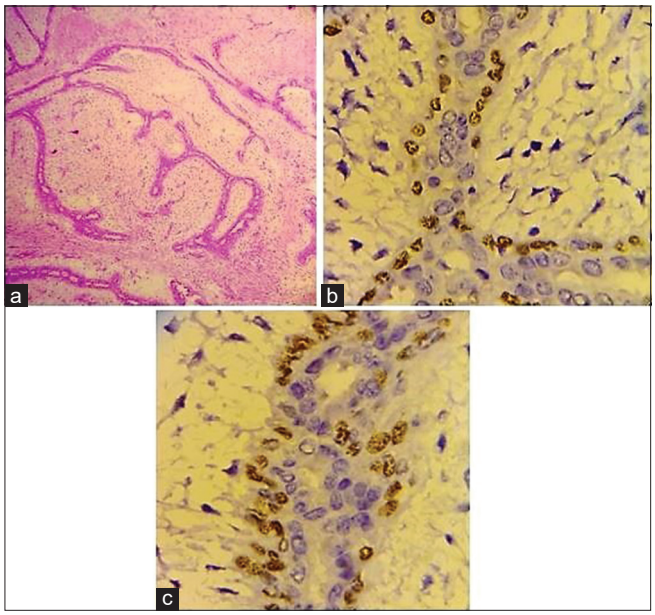

Figure 1: Photographic illustration Fibroadenoma, IHC staining of p40 and p63 markers. (a) Hematoxyline & Eosin stain of Fibroadenoma. (b) Strong nuclear staining of p40. (C) Strong nuclear staining of p63

Following the inclusion criteria, 98 cases (n = 98) formed part of the study, of which 30 were of fibroadenoma (n = 30) and 68 cases were of IDC, NST (n = 68). All the patients were females with an age range of 15–58 years for benign lesions and 27-72 years for the malignant lesion. The mean age for benign and malignant tumors was 36.2 years and 53.8 years, respectively.

Of the 68 cases of IDC, NST tumors with luminal A differentiation were predominant (n = 37, 54.4%), followed by TNBC (n = 12, 17.60%), luminal B (n = 11, 16.2%), and HER 2 enriched type (n = 8, 11.8%).

An observation was that the malignant diseases outnumbered benign breast diseases, the ratio being 1.9:1.

Immunohistochemistry for p63 and p40. The staining for both p63 and p40 was present in all our 30 cases of fibroadenoma (n = 30, 100%). The staining was nuclear, unambiguous, crisp and without any background stains. All the cases lit up brightly with p63 and p40 [Figure 1a-c].

For purpose of computing the result, we divided our IDCs as TNBC and Non-TNBC (NTNBC). Among all IDCs 82.35% (n = 56) did not stain for p63 or p40, 17.6% stained for p63 (n = 12) in the tumor cells and 2.9% (n = 2) exhibited positivity for p40. In the TNBC subgroup (n = 12), 75% (n = 9 were negative for both the markers while 25% (n = 3) stained for p63 and 16.6% (n = 2) stained for p40. Among the NTNS category (n = 56) 83.9% (n = 47) did not exhibit stain for either markers while 16% (n = 9) showed p63 positivity. None of the NTNBC showed staining for p40. The IHC results are tabulated in Table 1. Another observation was that the number of tumor cells showing positivity for either p63 or p40 was between 1% and 5%. The staining was weak and at best could be graded as moderate in intensity [Figure 2a and c]. There were three cases where we had DCIS and IDC coexisting in the sections. All the

Table 1: IHC for P63 and p40 : results in tumor groups

Category	Negative staining for p63 & p40 (%)	Positive p63 (%)	Positivep40 (%)
IDC combined (n=68)	82.3	17.6	2.9
TNBC (n=12)	75.0	25.0	16.6
NTNBC (n=56)	83.9	16.0	0.0

Table 2: Comparison of p63 and p40 positivity in tumor cells in various studies

Study	Cases considered	P63(% positivity)	P40(% positivity)
Sang Kyum *et al*…	IDC and Metaplastic carcinoma	2.7%	1.9-11.7%
Bence Kovari *et al*…	TNBC only	42.1%	94.7%
Present study	IDCc	17.6%	2.9%
	TNBC	25%	16.6%
	NTNBC	16%	0%

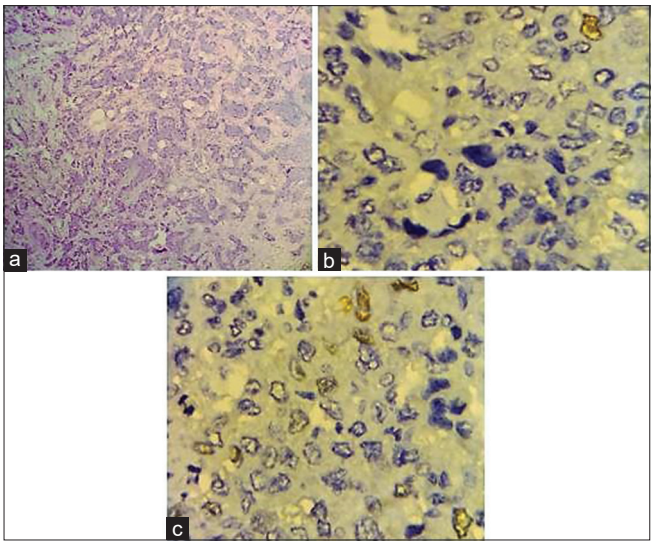

Figure 2: Photographic illustration of TNBC and IHC staining of p40 and p63 markers. (a) Hematoxyline & Eosin stain of TNBC. (b) Negative for p40. (c) weak nuclear staining of p63

latter DCIS areas exhibited focal, noncontinuous and weak-to-moderate peripheral positivity of p63, but the same cases were negative for p40 [Figure 2b].

Discussion

Without doubt, accurate identification of MEC is the most important feature to be looked for, when deciding about the nature of a breast lesion. Robust IHC markers are available and perform well to delineate the MEC. Usually, a cocktail of markers is suggested, and depending on the institutional protocols and the "pathological question," these markers are applied. The most common and easily available are CD 10, basal cytokeratins, calponin, *P* cadherin, SMMHC, and p63.[5,22,23] The sensitivity, specificity, robustness, cross-reactivity, cellular localization, and hence, ease of interpretation differs with every antibody used. The positive stain can be nuclear (p63, S100), cytoplasmic (SMMHC, SMA, S100, CK5/CK6) or membranous (CD10).[7,22,23] P63 is an IHC marker which delineates MEC of the breast, basal cells of the prostate and also in certain cancers of the head and neck, urinary bladder, and lungs. P40 is the product of the same gene, with a different composition of N terminal. The p63 gene is located on chromosome 3q27-29. There are two different promoters of this gene, one of which makes p63-a the full-length protein transactivation domain (TA) p63 harboring an N-terminal TA while the other forms-p40. The latter is the isoform Δ N having a transcriptionally inactive Δ N domain.[24] P63 performs well as a MEC marker of the breast with a sensitivity and specificity of 90% and up to 100%, respectively, in benign lesions of the breast.[17,25] p63 protein is thus a frequently used MEC marker, providing with the additional advantage of being nuclear, and not exhibiting cross-reactivity with vascular smooth muscle or myofibroblasts (unlike SMA).[26] An important concern is the expression of p63 in cases of IDC, NST. Various studies have quoted a range of positivity, from 15% to 23% in the tumor cells, implying its use with caution.[15,27]

In studies done on squamous cell carcinomas of the lung, P40 has proved to be a better marker when compared to p63 for diagnosis and is widely used by practicing pathologists.[17,18] It also fares marginally better than p63, to highlight the basal cells of prostatic glands. In the breast, there have been very few studies done to compare of p63 and p40 as a myoepithelial marker.[20,25] A study by Bence *et al*. and by Sang *et al*., both conclude that p63 and p40 are good MEC markers in the setting of benign breast diseases with the expression of up to 100%. For some reason, p40 is still not the preferred MEC marker in the breast. Our study brings forth the point and reconfirms, that p40 is an excellent marker of MECs in benign breast diseases.

There are even fewer studies which have examined and compared the expression of p63 and p40 in breast carcinoma cells. By definition the cases of IDC, NST breast should not have MECs and therefore should be negative for either p63 or p40. Usually, the diagnosis of IDC is clear cut and we do not routinely do a MEC stain in an IDC breast. To complicate matters p63 is expressed in tumor cells of the breast, especially in the TNBC subgroup. P63 is one of the markers of TNBC though the sturdier ones are CK 5/6, CK 7, CK 17, 34 β E12, EGFR, CD117, and SMA.[21] A comparative study found that the positivity of p63 ranges from 15.7-23% in the tumor cell.[5,15] The available studies on the expression of p63 and p40 in tumor cells have been done on IDC, myoepithelial carcinoma of the breast, and TNBC.[20,21,25] They have found a wide range of expression of p63 and p40 in tumor cells. Sang *et al*.(studied IDC and metaplastic carcinomas) found 2.7% of cases expressing p63 and 1.9%–11.7% of cases (depending on the type of antibody used) positive for p40.[25] Bence *et al*. (studied exclusively TNBCs) and found that 42.1% and 94.7% of tumor stained for p63 and p40 respectively.[20] We can see that the range of positivity in tumor cells is wide, from 2.7-42.1% for p63 and 1.9%–94.7% for p40 [Table 2].

As far as the percentage of tumor cells staining positive, a single study dealt with this issue and found it to be as low as 1% to as high as 70%, for both these markers. It was also brought out that the intensity of staining was "generally weak" and needed "scrutinous search."[20]

The present study divided the cases of IDC into three groups (IDC, TNBC, Non-TNBC) and found that as an undivided group, IDC shows 17.6% of p63, which is in concurrence with Rajan *et al*.[5] P40 was positive in 2.9% of the undivided IDC group, similar to Sang *et al*.[25]

As far as TNBC goes we found a positivity of 25% for p63 and 16.6% for p40, compared to 42.1% (p63) and 94.1% (p40) in the Bence *et al*. study, both of which were

significantly less (P = 0.005) in our study. No study has been done till date evaluating the percentage positivity of p63and p40 in tumor cells of NTNBC subgroup of IDC and we found that p63 stained 16% of tumor cells in NTNBC cases. An interesting observation was that in NTNBC no case showed positivity for p40.

We had three cases of IDC in which DCIS was admixed. All the three cases showed faint positivity for MEC while p40 was negative. This was in contrast to the observation by Sang *et al*. who found p40 to be better expressed that p63 in their DCIS cases[25] There has been no study on comparison of p63 and p40 as a MEC marker and its expression in IDC, in the Indian subpopulation.

As regards the observation that cases of the benign disease were much less than malignant, could be explained by the fact that the reduction in benign breast surgeries was due to the prevailing pandemic of SARS-COVID-19.

Conclusions

We would like to drive home that for benign breast diseases, p40 performs equally well compared to p63 and the use is highly recommended as a stand-alone marker or in combination with other MEC markers. As a marker of basal cell carcinomas, the results of this study suggest that p63 fares better than p40. It is also concluded that if for some reason we put up a stain for p63 and p40 in a diagnosed case of IDC breast, p63 is likely to be much more positive in tumor cells (however it stains faintly) in a subgroup of IDC (TNBC, NTNBC) and thus has to be interpreted with caution. We found that to pick up areas of DCIS surrounding IDC p63 stain was better than p40, though we had only 3 such cases in our study. A larger study is required to validate the same. A very interesting and novel finding of this study is that p40 does not stain the tumor cells in the NTNBC subgroup of IDC. The latter however needs to be studied in a larger cohort. It is highly recommended that the usage of these markers has to be done in the context of the query at hand.

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Conflicts of interest

There are no conflicts of interest.

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