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Original contribution

Expression of lymphoid enhancer-binding factor 1 in breast fibroepithelial lesions☆

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Summary Phyllodes tumors (PTs) are rare epithelial-mesenchymal tumors of the breast with malignant potential. Here, we evaluate the nuclear expression of lymphoid enhancer-binding factor 1 (LEF-1), a transcription factor downstream of Wnt/β-catenin signaling, in fibroepithelial lesions of the breast. Excised fibroepithelial lesions of the breast were retrospectively reviewed, blinded to the original diagnosis, and classified according to World Health Organization (WHO) criteria. A tissue microarray (TMA) was composed with two representative cores from each case, including 24 benign lesions, 11 borderline phyllodes, and 8 malignant PTs. β-Catenin, LEF-1, p120, and E-cadherin immunohistochemistry was performed on the TMA, and staining was quantified. The malignant/borderline PTs showed higher stromal LEF-1 expression than benign tumors ($P < 0.001$). Stromal cells expressed LEF-1 in 100% (16/16 of core TMA) of malignant phyllodes, compared with 73% (16/22) borderline and 27% (13/48) benign tumors. The average LEF-1 H-score was 24.9, 6.1, and 1.5 for malignant, borderline, and benign tumors, respectively. Nuclear expression of β-catenin in the stromal component was more often seen in malignant than in borderline and benign tumors (44% versus 32% and 23%, respectively). Nine TMA cores of malignant tumors without nuclear β-catenin staining demonstrated LEF-1 expression. Both LEF-1 and nuclear β-catenin showed expression in the majority of borderline/malignant PTs suggesting a biological progression of Wnt/β-catenin pathway activation in the stromal component from benign to malignant tumors. Inhibitors for the Wnt/β-catenin pathway may provide alternative treatment options in the future for malignant or metastatic PTs.

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1. Introduction

Phyllodes tumors (PTs) are rare epithelial-mesenchymal tumors of the breast with malignant potential. Current understanding suggests that PTs arise from epithelial-stromal interaction, in which epithelial-derived Wnt drives β-catenin—induced signaling in the stroma [1—4]. Recently, genomic studies have identified recurrent mutations in the *MED12* and *TERT* promoter: the former as part of the giant mediator complex essential in transcription and the latter as part of the telomerase complex that protects the ends of chromosomes [5—8]. Both MED12 and telomerase have been implicated in modulating β-catenin to regulate gene expression [9—11]. Karim et al. suggest increasing β-catenin signaling in the stroma from benign to borderline but decreases from borderline to malignant tumors. Sawyer et al. noticed increasing nuclear β-catenin in the stroma of benign PTs compared with borderline and malignant PTs [2,4]. In malignant PTs, it has been postulated that the stromal component proliferation overrides the epithelial component, at which point the stromal component becomes independent of epithelial-derived Wnt [2,4].

Lymphoid enhancer-binding factor 1 (LEF-1) is a transcription factor downstream of Wnt/β-catenin signaling [12]. LEF-1 normally binds to TLE-1 to form a transcription repressor complex; when β-catenin accumulates in the nucleus, β-catenin competitively displaces TLE-1 for LEF-1 binding and drives transcription of Wnt target genes. LEF-1 has been shown to be expressed in an increasing number of neoplasms such as synovial sarcoma, solid pseudopapillary neoplasm of pancreas, and acute myeloid leukemia, among others [13—15].

Although LEF-1 plays critical roles in Wnt/β-catenin pathway activation, its expression in breast fibroepithelial lesions has not been tested. Owing to its primary nuclear localization, LEF-1 offers a clean staining pattern for interpretation. In this article, we examined the expression of LEF-1 in breast fibroepithelial lesions, ranging from benign tumors to malignant phyllodes. We also tested LEF-1 as a surrogate marker for nuclear β-catenin signaling using cases of fibromatosis which are known to have nuclear β-catenin localization.

2. Methods

2.1. Case selection

After Institutional Review Board approval, a retrospective review of the electronic pathology database was performed to identify resected fibroepithelial lesions and fibromatosis of the breast. Hematoxylin and eosin (H&E) slides from each case were reviewed by one observer, blinded to the original diagnosis, and classified according to the WHO criteria [16]. The specific microscopic features listed in Table 1 were used to definitively categorize difficult cases. Cases with a different classification rendered from the original diagnosis were reviewed by an additional pathologist and a consensus reached.

2.2. Immunohistochemistry

A tissue microarray (TMA) was made with two representative 1-mm cores from each case, composed of benign fibroepithelial lesions (including fibroadenomas, cellular and juvenile, and benign PTs), borderline (including one periductal stromal tumor), malignant (including one metastatic) PTs, and fibromatosis of the breast. Immunohistochemistries (IHCs) of β-catenin (Biocare, clone 14, 1:100), E-cadherin (Dako, clone NHC-38, 1:20), p120 (BD Transduction Labs, clone 98/pp120, 1:500), and LEF-1 (Abcam, clone EPR2029Y, 1:500) were performed on the TMA, and the extent and intensity of staining was evaluated by H-scores (intensity score 0-3 x % cells staining = 0—300). Stromal and epithelial components, when present, were scored separately. LEF-1 staining was also performed on representative sections of normal breast tissue from the resection specimens of randomly selected benign, borderline, and malignant fibroepithelial lesions.

2.3. Statistical analysis

One-way analysis of variance was used to compare distributions of H-scores for independent samples. Statistical significance was achieved when the p value was <0.05.

3. Results

3.1. Pathologic features of PTs

We identified 48 cases to include 24 benign fibroepithelial lesions, 11 borderline PTs, eight malignant PTs, and five fibromatosis. For each case, two cores were obtained for the TMA. After discarding unsatisfactory cores (folded tissue or no tumor present), we obtained 48 benign, 22 borderline, and 16 malignant cores for each TMA slide. Overall, the benign, borderline, and malignant fibroepithelial lesions account for 50%, 23%, and 17% of our case series, respectively, compatible with frequencies of each tumor type reported in the literature.

The benign fibroepithelial lesions showed well-defined borders, usually low to moderate stromal cellularity with rare to few atypical cells, none to rare mitotic figures, and lack of stromal overgrowth. Intracannalicular or pericanalicular growth patterns were easily identified (Fig. 1A). The borderline PTs, in comparison with benign tumors, demonstrated areas of leaf-like stromal overgrowth. The stroma was more cellular than benign tumors with mild pleomorphism, and few mitotic figures were identified (Fig. 1B). In general, these cases shared some but not all features of malignant PTs. The eight malignant PTs

Table 1 Microscopic criteria for categorization of fibroepithelial lesions.

Benign fibroepithelial lesion (4 or 5 of following criteria):

- Low stromal cellularity
- Rounded margin
- No more than mild pleomorphism (pleomorphism without hyperchromasia or > 2-fold enlargement compared with normal fibroblasts)
- No stromal overgrowth (2 areas in which the epithelium is absent within a ×10 field or one area of ×4 field by WHO criteria)
- Mitotic count of 2 or less per 10 high power fields (HPFs) (×40 objective)

Borderline phyllodes tumor:

- Does not meet criteria of benign or malignant phyllodes

Malignant phyllodes tumor (4 or 5 of following criteria):

- High stromal cellularity
- Stromal overgrowth (overgrowth as defined previously)
- Highly pleomorphic stromal nuclei (pleomorphism with hyperchromasia and up to 3-fold cell enlargement)
- Mitotic count 5 or more per 10 HPFs (×40 objective)
- Infiltrative margin (percolation of tumor-associated collagen and or cells between fatty stroma at the periphery of the lesion creating an irregular tumor-host interface)

displayed features of stromal overgrowth, increase in mitotic figures (up to 18/10 high power field (HPF)), nuclear pleomorphism, infiltrative tumor border, and marked stromal cellularity. One case of liver metastasis consisted of a 6-cm mass with sarcomatous overgrowth of dedifferentiated liposarcoma. Another case demonstrated marked nuclear pleomorphism, anaplastic changes, and infiltrative borders (Fig. 1C).

3.2. LEF-1 IHCof PTs

To show that LEF-1 can serve as a surrogate for Wnt/β-catenin pathway activation, we included five cases of fibromatosis, which is a soft tissue neoplasm classically featuring nuclear β-catenin staining pattern. Histologically, fibromatosis shows hypocellular spindle cells in a collagenous background; the spindle cells demonstrate indistinct cell borders that merge imperceptibly with background collagen, consistent with myofibroblastic differentiation. To validate LEF-1 as a useful surrogate biomarker for Wnt/β-catenin pathway activation, we compared the LEF-1 with β-catenin which served as a positive control. For LEF-1, strong nuclear staining was observed in four of five cases with little to no background staining; for the same cases, nuclear staining of β-catenin ranged from 1 to 3+ with variable cytoplasmic and membranous staining.

Epithelial−mesenchymal junction regions were specifically chosen in the TMA composition to better evaluate the staining patterns in these two compartments. LEF-1 was expressed in the tissue cores of 100% (16/16 of TMA cores) of malignant PTs, 73% (16/22 cores) of borderline PTs, and 27% (13/48 cores) of benign fibroepithelial neoplasms. The average H-scores were 24.9, 6.1, and 1.5 for malignant, borderline, and benign tumors, respectively (Table 2). This staining pattern corresponds to an overall positive stromal LEF-1 result in 42%, 91%, and 100% of benign, borderline, and malignant cases, respectively (Table 3). Three features of LEF-1 staining were identified. First, there was nearly universal absence of nuclear staining in the luminal epithelial compartment, suggesting lack of Wnt/β-catenin−activated LEF-1 activation in the epithelial component. Consistent with this finding, the epithelium showed mainly normal membranous staining of β-catenin (Fig. 2) and no nuclear localization. Second, the pattern of staining for LEF-1 was predominantly subepithelial in PTs, in the nuclei of round to spindle periepithelial stromal cells. Third, we noted an increase in LEF-1 staining from benign to malignant PTs (mean H-score of 1.5, 6.1, and 24.9 for benign, borderline, and malignant PTs, respectively). Heterogeneity of staining (i.e. one negative core and one positive core from the same tumor) was seen more frequently in benign and borderline tumors (Table 3). LEF-1 staining on full tissue sections of adjacent normal breast tissue of representative benign, borderline, and malignant tumors showed only rare, weak nuclear staining of stromal cells immediately adjacent to a malignant PT.

3.3. β-catenin IHC

The epithelial component of benign tumors expresses membranous β-catenin more frequently than borderline and malignant ones (70% versus 55% and 44% of cores; 83% versus 72% and 63% of cases); in contrast, nuclear expression of β-catenin in the stromal component is more often seen in malignant than in borderline and benign tumors (44% versus 32% and 23% of cores; 63% versus 55% and 29% of cases). For most tumors, a thin subepithelial band of nuclear staining was typically seen, similar to that observed in LEF-1 staining. Interestingly, nine TMA cores of malignant tumors that did not stain for β-catenin demonstrated strong LEF-1 expression (an example shown in Fig. 2). Heterogeneous epithelial and stromal staining with β-catenin was seen in all tumors, regardless of grade (Table 3).

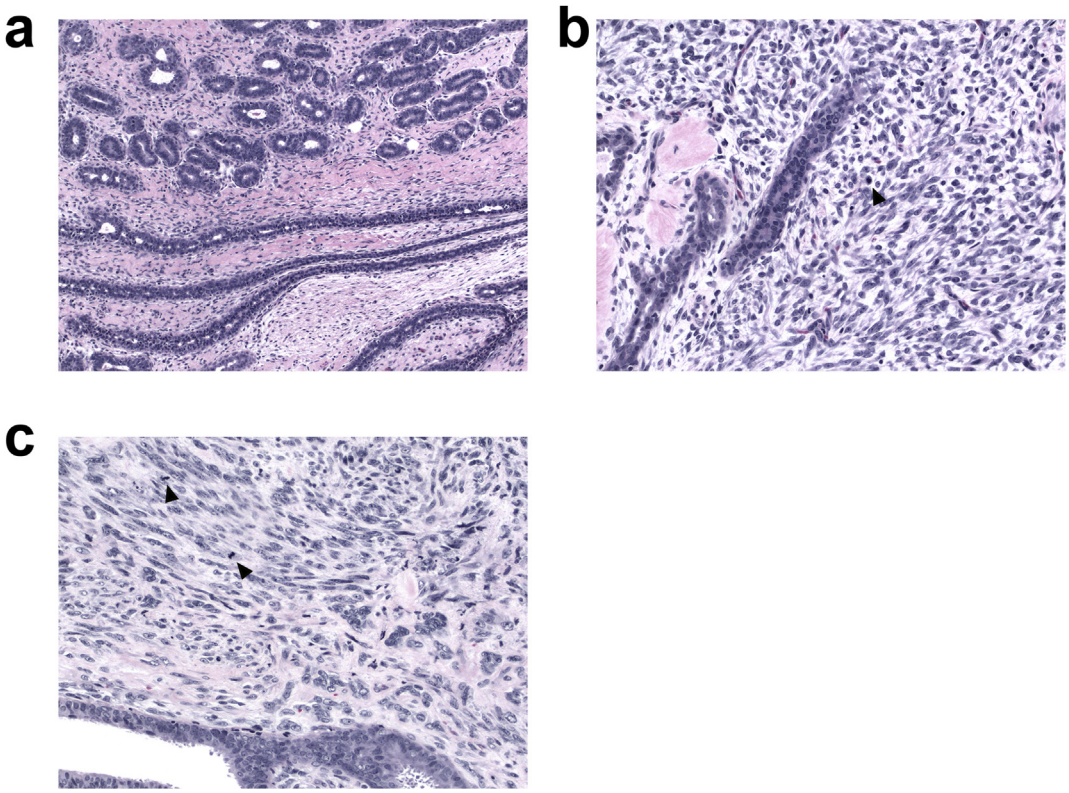

Fig. 1 Microscopic features of fibroepithelial tumors. A, Pericanalicular and intracanalicular growth patterns in a fibroadenoma (original magnification ×100 H&E); B, cellular stroma and rare mitotic figure indicated by arrowhead in a borderline phyllodes tumor (×200 H&E); C, malignant phyllodes tumor with marked stromal atypia and mitoses indicated by arrowheads (×200 H&E).

3.4. E-cadherin and p120 IHC

We evaluated E-cadherin and p120 immunostains because of their association with β-catenin signaling. E-cadherin and p120 play important roles in maintaining the integrity of cell-cell junction. E-cadherin was expressed in a membranous pattern in the epithelial component and not in the stromal component, regardless of tumor grade.

Interestingly, p120 showed cytoplasmic expression in the stromal component of 83% of fibroepithelial lesions and in 75% of fibromatosis cases with cores adequate for evaluation. The average H-scores increased from benign to borderline to malignant PTs (15, 31, and 97, respectively). A cytoplasmic dot-like pattern was most commonly observed. Similar to LEF-1 and β-catenin, the staining was strongest in the periepithelial regions and gradually decreased toward the center of stroma-rich regions.

4. Discussion

We showed that LEF-1 is expressed in breast fibroepithelial lesions. Because LEF-1 colocalizes and interacts with nuclear β-catenin as a transcription complex, LEF-1 detection could function as a surrogate for activation of Wnt/β-catenin signaling, which has traditionally relied on the interpretation of β-catenin nuclear staining pattern. The positive LEF-1 staining in fibromatosis in our series is consistent with this observation. Furthermore, due to simultaneous cytoplasmic and nuclear localizations, interpretation of β-catenin stain has not always been straightforward; LEF-1 circumvents the localization issue because it is a nuclear protein.

Previously, although β-catenin was found to be expressed in PTs, its association with tumor grade varied between studies. Ho et al. [3] noticed increased *cytoplasmic* expression of β-catenin in the stromal cells with increasing tumor grade, whereas three other studies showed initial increase of *nuclear* β-catenin in stromal cells from benign to borderline PTs but decreased β-catenin from borderline to malignant PTs [1,2,4]. The latter studies reasoned that as the PTs become malignant, they become independent of β-catenin signaling. In contrast, both β-catenin and LEF-1 in our study demonstrated higher H-scores in malignant/borderline compared with benign tumors, suggesting increased rather than decreased Wnt/β-catenin pathway signaling as PTs progress from benign to malignant. Most recently, we have seen a case of metastatic malignant PT to the bone, in which the tumor contains only the sarcomatous component that diffusely and strongly expresses LEF-1 (unpublished result), a finding that further corroborates the results in the present study. Possible sources of

Table 2 Summary of staining pattern by core.

	Fibromatosis (n = 10)	Benign (n = 48)	Borderline (n = 22)	Malignant (n = 16)	p-value
β-catenin epithelial membranous staining					
Mean H-score (range)	N/A	41.1 (0−210)	13.6 (0−120)	11.7 (0−90)	0.0108
Mean intensity (range)	N/A	1.1 (0−3)	0.7 (0−2)	0.5 (0−2)	
Mean % staining (range)	N/A	24.0 (0−90)	9.1 (0−60)	10.3 (0−90)	
β-catenin stromal nuclear staining					
Mean H-score (range)	81.4 (20−100)	1.2 (0−10)	1.0 (0−10)	11.2 (0−120)	<0.0001
Mean intensity (range)	1.7 (1−2)	0.3 (0−3)	0.3 (0−1)	0.7 (0−2)	
Mean % staining (range)	44.3 (20−50)	0.9 (0−10)	1.1 (0−10)	6.7 (0−60)	
LEF1 stromal nuclear staining					
Mean H-score (range)	150 (0−270)	1.5 (0−20)	6.1 (0−20)	24.9 (1−150)	<0.0001
Mean intensity (range)	2.0 (0−3)	0.4 (0−2)	1.1 (0−2)	2.0 (1−3)	
Mean % staining (range)	52 (0−90)	1.1 (0−10)	4.2 (0−20)	9.7 (1−50)	
p120 stromal cytoplasmic staining					
Mean H-score (range)	67.5 (0−105)	15 (0−160)	31.3 (0−80)	97.8 (30−180)	<0.0001
Mean intensity (range)	1.0 (0−1.5)	0.9 (0−2)	1.4 (0−2.5)	2.0 (1−3)	
Mean % staining (range)	50 (0−70)	10.8 (0−80)	23.9 (0−80)	50.6 (20−90)	

differences between prior and current studies include different antibody clones used in the studies, intrinsic heterogeneity even within the same tumor, and potentially inconsistent interpretations of β-catenin localizations.

In our study, 100% (16/16 cores) of malignant PTs showed at least 1+ stromal LEF1 staining, whereas only 44% (7/16) demonstrated β-catenin staining. For borderline tumors, 73% (16/22) versus 32% (7/22) showed stromal LEF-1 and β-catenin staining, respectively. The number of cores that stained for LEF-1 and β-catenin was not significantly different for benign tumors (11/48 vs 13/48). The differences in LEF-1 and β-catenin stains in higher grade tumors (e.g. borderline and malignant PTs) were not entirely clear but may suggest LEF-1 functions that are not directly associated with Wnt/β-catenin pathway. The classic example of such dichotomous LEF-1 and β-catenin staining pattern occurs in chronic lymphocytic leukemia, in which LEF-1 positivity is a defining feature but only rare instances of nuclear β-catenin stain have been identified [17].

Overexpression of LEF-1 in malignant and metastatic PTs could be clinically significant in terms of utilization of LEF-1 as a predictive biomarker for therapeutic interventions targeting the Wnt pathway. Although the mainstream treatment of malignant PTs does not differ significantly from benign and borderline PTs, that is, resection with negative margins, malignant PTs can metastasize in up to 20% of cases and in such circumstances chemotherapy may be instituted [18]. Novel therapies targeting the β-catenin-LEF-1 transcription complex are now in development [19−22], which offers alternative options for treating solid tumors harboring dysregulation of the Wnt/β-catenin pathway. A wide range of tumors has been found to contain an altered Wnt/β-catenin pathway. In synovial sarcoma, *SS18-SSX* fusion leads to increased Wnt pathway activation and LEF-1−mediated signaling [23]. TLE-1, which competes with β-catenin for LEF-1 binding, is overexpressed in synovial sarcoma and a variety of soft tissue tumors in a recent study [24]. A significant portion of prostate cancers, particularly castration-resistant prostate cancers, has been shown to have increased β-catenin nuclear localization [25]. Key Wnt pathway regulators such as LGR5 and RSPO are overexpressed in Ewing sarcoma [26]. LEF-1 expression could potentially stratify tumors amenable for targeted Wnt pathway therapy.

We also found strong p120 staining in the stromal component of almost all fibroepithelial lesions and fibromatosis. E-cadherin and p120 are key mediators of intact cellular junctions whose loss of functions are important mechanisms of epithelial-to-mesenchymal transition (EMT) implicated in tumor invasiveness. Loss of E-cadherin and p120 functions is important in the pathogenesis of lobular carcinoma of the breast. E-cadherin is a single-pass transmembrane receptor that binds to p120 and β-catenin via different binding motifs in its cytoplasmic tail, and together they stabilize epithelial cell-cell junctions. E-cadherin and p120 are both localized to the epithelial cell membrane and normally produce a membranous staining pattern. While E-cadherin and p120 are normally expressed in the epithelial component of breast tissue, in our study, p120 shows cytoplasmic expression in the stromal component of almost all fibroepithelial lesions and fibromatosis. It is known that there are multiple isoforms of p120, and the so-called p120 isoform 1 predominates in motile mesenchymal tissue [27]. In addition, the so-called *mesenchymal cadherins* such as cadherin-11 and N-cadherin can bind to p120 and is implicated in EMT. Furthermore, in our study, the expression of p120 increased with increasing tumor grade. The specificity of p120 stromal stain for fibroepithelial lesions remains to be determined. Together, LEF-1 and p120 may be useful as an adjunct to help distinguish malignant from borderline and benign PTs.

Table 3 Summary of staining pattern by case.

	Fibromatosis (n = 5)	Benign (n = 24)	Borderline (n = 11)	Malignant (n = 8)
β-catenin epithelial membranous staining				
# positive cases (%)	N/A	20 (83)	8 (72)	5 (63)
# cases with heterogeneity[a] (%)		4 (17)	4 (36)	3 (38)
β-catenin stromal nuclear staining				
# positive cases (%)	4 (80)[b]	7 (29)	6 (55)	5 (63)
# cases with heterogeneity[a] (%)	0 (0)	3 (12)	5 (45)	3 (38)
LEF1 stromal nuclear staining				
# positive cases (%)	4 (80)	10 (42)	10 (91)	8 (100)
# cases with heterogeneity[a] (%)	1 (20)	7 (29)	4 (36)	0 (0)
p120 cytoplasmic stromal staining				
# positive cases (%)	3 (60)[b]	17 (71)[b]	10 (91)	8 (100)
# cases with heterogeneity[a] (%)	1 (20)	9 (38)	0 (0)	0 (0)

[a] Heterogeneity defined as 2 cores from the same tumor demonstrating 1 core with no staining and 1 core with staining of any level.
[b] Some stained cores could not be evaluated due to tissue folding/washing.

One weakness in our study design is the use of TMAs for staining. Stromal heterogeneity in fibroepithelial lesions is a well-recognized phenomenon and heterogeneous staining seen within individual cases in this study further support the biologic heterogeneity of these tumors. To control for this variability, we used cores from two representative areas of each tumor. TMA cores were sampled from areas morphologically representative of the tumor to include both epithelial and stromal elements when possible. In addition, one may argue against our grouping of all fibroadenomas and benign phyllodes into a single benign fibroepithelial tumor category. The primary indication for distinguishing fibroadenomas from benign phyllodes is the difference in clinical behavior and therefore management. Follow-up studies of these lesions, however, have failed to show a significant difference in recurrence rates or outcomes in patients with overlapping fibroadenoma and phyllodes features, even if not widely excised [28–30]. One potential explanation for the lack of difference in behavior is the documented lack of interobserver agreement between these two diagnostic entities. In a study by Lawton et al. [31], an independent review of 21 fibroepithelial lesions by 10 subspecialty breast pathologists showed uniform agreement in the classification of fibroadenoma versus PT on only two cases. To categorize the tumors in our study, we established specific definitions for each tumor category (as outlined in the methods section and Table 1) with consensus review of any categorization discrepancy between the observer and original diagnosis.

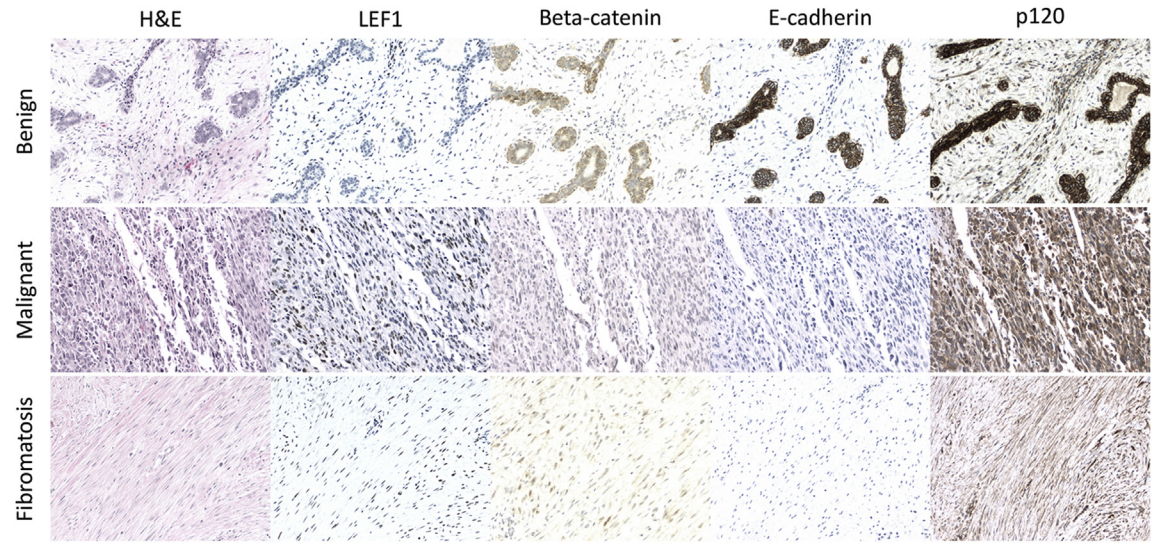

Fig. 2 Stromal and epithelial staining patterns of representative benign fibroepithelial lesion, malignant phyllodes tumor, and fibromatosis (original magnification ×200).

In conclusion, our study further supports the potential role of Wnt/β-catenin in EMT and progression of PTs. LEF-1 is expressed in breast fibroepithelial lesions. LEF-1 staining and p120 staining correlated with tumor grade. LEF-1 IHC may be helpful as a future biomarker to evaluate the use of novel inhibitors targeting the Wnt/β-catenin pathway in the treatment of high-grade and metastatic PTs.

Author contributions

P.C. contributed in data curation, writing, reviewing, and editing. E.R. contributed in conceptualization, data curation, writing, reviewing, and editing. V.B. contributed in conceptualization, reviewing, and editing.

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