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# Diagnostic utility of p75 neurotrophin receptor ($p75^{NTR}$) as a marker of breast myoepithelial cells

Nikolay K Popnikolov, Sharon M Cavone, Pauline M Schultz and Fernando U Garcia

*Department of Pathology and Laboratory Medicine, College of Medicine, Drexel University, Philadelphia, PA, USA*

**We evaluated the low affinity neurotrophin receptor ($p75^{NTR}$) as a marker of breast myoepithelial cells. Immunohistochemical staining for $p75^{NTR}$ was performed on paraffin sections of 122 malignant breast lesions, 28 benign lesions and the adjacent normal breast tissue. The staining pattern was compared to those of myosin heavy chain and p63. $p75^{NTR}$ immunostain was consistently positive and compatible with p63 and myosin immunoreactivity in the myoepithelial cells of the normal mammary gland, benign breast lesions (six usual ductal hyperplasias, six specimens with sclerosing adenosis, eight intraductal papillomas, six fibroadenomas), and carcinoma *in situ* (18 ductal carcinomas *in situ*, two noninvasive papillary carcinomas, two lobular carcinomas *in situ*). The luminal cells were negative for $p75^{NTR}$, but rare positive cells were noticed in the solid areas of some of the usual ductal hyperplasias. Four of 64 invasive ductal carcinomas (6%) and all metaplastic carcinomas ($n=3$, 100%) showed a variable degree of $p75^{NTR}$ positivity. No $p75^{NTR}$ expression was found in the malignant cells in all *in situ* carcinomas, invasive lobular carcinomas ($n=11$), tubular carcinomas ($n=10$), invasive papillary carcinomas ($n=6$), mucinous carcinomas ($n=4$), and medullary carcinomas ($n=2$). No myosin imunoreactivity was seen in the luminal/tumor cells, but p63 pattern of staining in the luminal/tumor cells was quite similar to that of $p75^{NTR}$. Although significant $p75^{NTR}$ immunoreactivity was noticed in the vessels, nerves, and stromal component of fibroadenomas, no difficulties in the evaluation of the immunostain of myoepithelial cells were encountered. Our study shows that $p75^{NTR}$ is a useful marker for breast myoepithelial cells and can be used to rule out invasive disease as well as to evaluate difficult for diagnosis sclerosing lesions. Our data suggest a role of neurotrophins in the development of fibroepithelial breast tumors and some of the breast carcinomas.**
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The presence of myoepithelial cells in a breast lesion is used as a criterion to distinguish invasive mammary carcinoma from carcinoma *in situ* or from sclerosing benign breast lesions. However, this distinction is sometimes difficult to be made on hematoxylin–eosin-stained sections, and it often requires immunohistochemical visualization of the myoepithelial cells. A variety of myoepithelial markers have been used for this purpose including several smooth muscle-associated proteins,[1,2] cytokeratin subtypes,[3,4] S-100 protein,[5,6] CD10,[7] maspin,[8] and p63.[9,10] The immunohistochemical studies have shown that the interpretation of myoepithelial markers can be complicated by their crossreactivity with the stromal compartment of mammary gland or luminal/tumor cells. We believe that these difficulties can be overcome by the use of a combination of carefully selected complementary myoepithelial markers.

Neurotrophins (nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, neurotrophin-4/5) play critical roles in the development, maintenance, survival, and apoptosis of the nervous system.[11] In addition, they also elicit a wide range of responses in certain non-neural tissues.[12] Neurotrophins' effects are initiated by interactions with specific receptors with low or high affinity (Huang *et al*[11] and references herein). $p75^{NTR}$ is a transmembrane glycoprotein member of the TNF-receptor superfamily. It binds with low affinity all of the neurotrophins and can mediate cellular survival or apoptosis directly or indirectly through interaction

Correspondence: Dr NK Popnikolov, MD, PhD, Department of Pathology and Laboratory Medicine, College of Medicine, Drexel University, 1800 Lombard Street, Graduate Hospital, Suite 400, Pepper Pavilion, Philadelphia, PA 19146, USA.
E-mail: npopniko@drexelmed.edu
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with the high affinity neurothrophin receptors (Trks). $p75^{NTR}$ is expressed in neural as well as in non-neural tissues including breast myoepithelial cells.[13,14] However, its diagnostic utility as a marker of breast myoepithelial cells has not been evaluated. Here we examine $p75^{NTR}$ expression in benign and malignant breast lesions and compare its expression pattern with those of well-established myoepithelial markers such as p63 and myosin heavy chain.

## Materials and methods

### Tissues

Immunohistochemical staining for $p75^{NTR}$ was performed on paraffin sections of 64 invasive ductal carcinomas, 11 invasive lobular carcinomas, 10 tubular carcinomas, six invasive papillary carcinomas, four mucinous carcinomas, two medullary carcinomas, three metaplastic carcinomas (two spindle cell carcinomas and one matrix producing carcinoma), 18 ductal carcinomas *in situ*, two lobular carcinomas *in situ*, two noninvasive papillary carcinoma, eight intraductal papillomas, six usual ductal hyperplasias, six specimens with sclerosing adenosis, two specimens with fibroadenomatoid change, and six fibroadenomas. The adjacent normal breast tissue was also studied. Sixty-four of the invasive carcinomas and seven of the *in situ* carcinomas were included in a tissue microarray. Two different areas from those tumors were sampled.

### Immunohistochemical Analysis

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections by using an automatic immunostainer (Ventana Medical System Inc., Tucson, AZ, USA) and a streptavidin–biotin–peroxidase complex technique (LSAB2 system, DAKO, Carpinteria, CA, USA). Heat-induced epitope retrieval was performed in a Handy Steamer Plus (Black and Decker, Shelton, CT) in citrate buffer, pH 6.0 (DAKO) for 20 min. The following primary antibodies were used: anti-$p75^{NTR}$ (clone ME20.4; dilution 1:100; Santa Cruz Biothechnology, Santa Cruz, CA, USA), anti-smooth muscle myosin

**Table 1** Expression of $p75^{NTR}$, p63, and myosin heavy chain in normal breast parenchyma, benign breast lesions and carcinoma *in situ*

| *Lesion* | *Cell type* | *$p75^{NTR}$ positive/total (%)* | *p63 positive/total (%)* | *Myosin positive/total (%)* |
|---|---|---|---|---|
| Normal ($n=14$) | Myoepithelial | 14/14 (100) | 14/14 (100) | 14/14 (100) |
| | Luminal | 0/14 (0) | 0/14 (0) | 0/14 (0) |
| | Fibroblasts | 0/14 (0) | 0/14 (0) | 0/14 (0) |
| Usual ductal hyperplasia ($n=6$) | Myoepithelial | 6/6 (100) | 6/6 (100) | 6/6 (100) |
| | Luminal | 2[a]/6 (33) | 3[a]/6 (50) | 0/6 (0) |
| | Fibroblasts | 0/6 (0) | 0/6 (0) | 0/6 (0) |
| Sclerosing adenosis ($n=6$) | Myoepithelial | 6/6 (100) | 6/6 (100) | 6/6 (100) |
| | Luminal | 0/6 (0) | 0/6 (0) | 0/6 (0) |
| | Fibroblasts | 0/6 (0) | 0/6 (0) | 0/6 (0) |
| Intraductal papilloma ($n=8$) | Myoepithelial | 7/8 (100) | 8/8 (100) | 8/8 (100) |
| | Luminal | 0/8 (0) | 0/8 (0) | 0/8 (0) |
| | Fibroblasts | 0/8 (0) | 0/8 (0) | 0/8 (0) |
| Fibroadenomatoid change ($n=2$) | Myoepithelial | 2/2 (100) | 2/2 (100) | 2/2 (100) |
| | Luminal | 0/2 (0) | 0/2 (0) | 0/2 (0) |
| | Fibroblasts | 2/2 (100) | 0/2 (0) | 0/2 (0) |
| Fibroadenoma ($n=6$) | Myoepithelial | 6/6 (100) | 6/6 (100) | 6/6 (100) |
| | Luminal | 0/6 (0) | 0/6 (0) | 0/6 (0) |
| | Fibroblasts | 6/6 (100) | 0/6 (0) | 0/6 (0) |
| Ductal carcinoma *in situ* ($n=18$) | Myoepithelial | 18/18 (100) | 18/18 (100) | 18/18 (100) |
| | Luminal/tumor | 0/18 (0) | 1[a]/18 (6) | 0/18 (0) |
| | Fibroblasts | 0/18 (0) | 0/18 (0) | 0/18 (0) |
| Lobular carcinoma *in situ* ($n=2$) | Myoepithelial | 2/2 (100) | 2/2 (100) | 2/2 (100) |
| | Luminal/tumor | 0/2 (0) | 0/2 (0) | 0/2 (0) |
| | Fibroblasts | 0/2 (0) | 0/2 (0) | 0/2 (0) |
| Noninvasive papillary carcinoma ($n=2$) | Myoepithelial | 2/2 (100) | 2/2 (100) | 2/2 (100) |
| | Luminal/tumor | 0/2 (0) | 0/2 (0) | 0/2 (0) |
| | Fibroblasts | 0/2 (0) | 0/2 (0) | 0/2 (0) |

The positive cases in this table showed a score $\geq 2$.
[a]Low intensity of staining.

**Table 2** Expression of $p75^{NTR}$, p63, and myosin in invasive breast carcinomas

| *Invasive carcinoma type* | *$p75^{NTR}$ score* | | | | *p63 score* | | | | *Myosin score* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *0* | *1* | *2* | *3* | *0* | *1* | *2* | *3* | *0* | *1* | *2* | *3* |
| Ductal ($n=64$) | 60/64 (94%) | 3/64 (5%) | 0/64 (0%) | 1/64 (2%) | 60/64 (94%) | 3/64 (5%) | 0/64 (0%) | 1/64 (2%) | 64/64 (100%) | 0/64 (0%) | 0/64 (0%) | 0/64 (0%) |
| Lobular ($n=11$) | 11/11 (100%) | 0/11 (0%) | 0/11 (0%) | 0/11 (0%) | 11/11 (100%) | 0/11 (0%) | 0/11 (0%) | 0/11 (0%) | 11/11 (100%) | 0/11 (0%) | 0/11 (0%) | 0/11 (0%) |
| Tubular ($n=10$) | 10/10 (100%) | 0/10 (0%) | 0/10 (0%) | 0/10 (0%) | 10/10 (100%) | 0/10 (0%) | 0/10 (0%) | 0/10 (0%) | 10/10 (100%) | 0/10 (0%) | 0/10 (0%) | 0/18 (0%) |
| Mucinous ($n=4$) | 4/4 (100%) | 0/4 (0%) | 0/4 (0%) | 0/4 (0%) | 4/4 (100%) | 0/4 (0%) | 0/4 (0%) | 0/4 (0%) | 4/4 (100%) | 0/4 (0%) | 0/4 (0%) | 0/4 (0%) |
| Metaplastic ($n=3$) | 0/3 (0%) | 2/3 (67%) | 1/3 (33%) | 0/3 (0%) | 0/3 (0%) | 0/3 (0%) | 1/3 (33%) | 2/3 (67%) | 3/3 (100%) | 0/3 (0%) | 0/3 (0%) | 0/3 (0%) |
| Medullary ($n=2$) | 2/2 (100%) | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) | 2/2 (100%) | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) | 2/2 (100%) | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) |
| Papillary ($n=6$) | 6/6 (100%) | 0/6 (0%) | 0/6 (0%) | 0/6 (0%) | 6/6 (100%) | 0/6 (0%) | 0/6 (0%) | 0/6 (0%) | 6/6 (100%) | 0/6 (0%) | 0/6 (0%) | 0/6 (0%) |

heavy chain (clone SMMS-1; ready-to-use, BioGenex, San Ramon, CA, USA), and anti-p63 (clone 4A4; dilution 1:50; NeoMarkers, Fremont, CA, USA). Negative controls were obtained by omitting the primary antibodies. Benign breast parenchyma adjacent to the lesion served as an internal positive control.

### Scoring

The immunostainings of the myoepithelial, luminal cells/tumor cells, and stromal cells were scored separately. The results of immunostaining were graded on a 4-point scale (0–3): 0, no staining; 1+, <25% of target cells positive; 2+, 26–75% of target cells positive; 3+, 76–100% of target cells positive.

## Results

The results of immunostainings for $p75^{NTR}$, p63 and myosin are summarized in Tables 1 and 2.

### $p75^{NTR}$ Expression in Myoepithelial Cells

Myoepithelial cells of the normal mammary ducts and acini were consistently positive for $p75^{NTR}$ (Figure 1). $p75^{NTR}$ immunoreactivity was observed on the cell membrane and in some cases in the cytoplasm. $p75^{NTR}$ was always found in the myoepithelial layer of usual ductal hyperplasia, sclerosing adenosis (Figure 2a), intraductal papilloma (Figure 3a–c), and fibroadenoma. Ductal carcinoma *in situ* (Figure 2g), noninvasive papillary carcinoma (Figure 3d), and lobular carcinoma *in situ* showed a continuous or focally discontinuous layer of $p75^{NTR}$-positive myoepithelial cells.

### $p75^{NTR}$ Expression in Luminal/Tumor Cells

In two of the six usual ductal hyperplasias included in this study, weak membranous $p75^{NTR}$ immunoreactivity was observed in the cells in the solid areas. Ductal carcinoma *in situ* (Figure 2g), noninvasive papillary carcinoma (Figure 3d), and lobular carcinoma *in situ* do not show $p75^{NTR}$ positivity in the luminal/tumor cells. None of the invasive lobular carcinomas, tubular carcinomas (Figure 2d), invasive papillary carcinomas (Figure 3g), mucinous carcinomas, or medulary carcinomas expressed $p75^{NTR}$. Four of the 64 invasive ductal carcinoma (6%) and all metaplastic carcinomas ($n=3$; 100%) showed a variable degree of mostly membranous $p75^{NTR}$ immunoreactivity.

### $p75^{NTR}$ Expression in Stromal Cells

$p75^{NTR}$ immunoreactivity was noticed in some endothelial cells, vascular adventitia, nerves, and few spindle stromal cells. In rare cases, few weakly

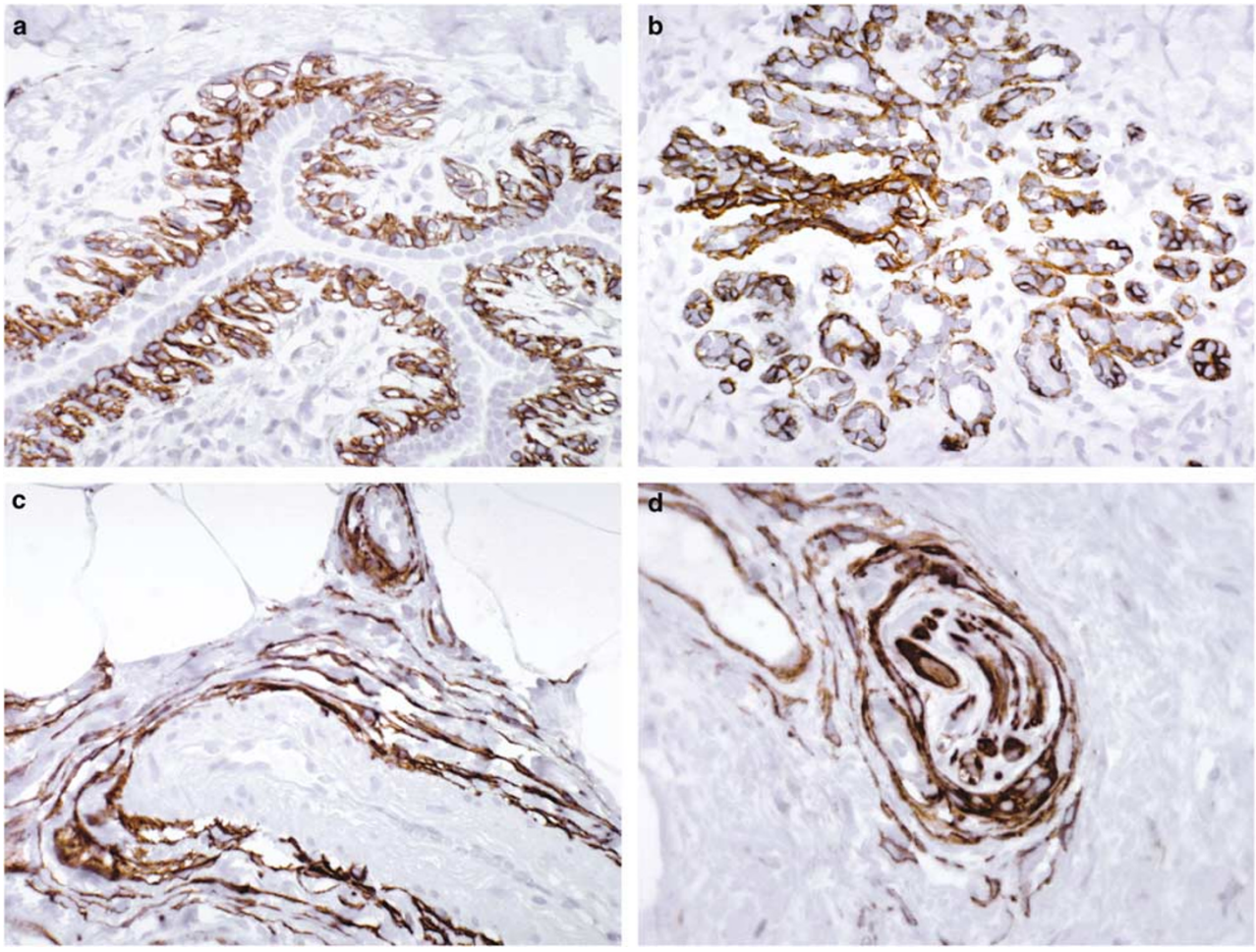


**Figure 1** Expression of $p75^{NTR}$ in normal breast tissue. Myoepithelial cells of normal mammary ducts (**a**) and acini (**b**) were consistently positive for $p75^{NTR}$. $p75^{NTR}$ immunoreactivity was noted in pericytes and vascular adventitia (**c**), nerves (**d**), and in few spindle stromal cells. Original magnification, $\times 400$ for **a**, **b**, and **c**; $\times 600$ for **d**.

positive stromal cells were found in the specimens with invasive carcinoma. In most of the cases, it was difficult to establish if those positive cells are fibroblasts or part of the vascular bed. A positive staining for $p75^{NTR}$ was seen in the fibroblast of the expanding intralobular stroma (fibroadenomatoid change) and in the nonhyalinized stromal components of all fibroadenomas ($n=6$) included in our study. Despite this pattern of staining, no difficulties in the evaluation of the immunostain of myoepithelial cells were encountered.

### Correlation of $p75^{NTR}$ Expression with p63 and Myosin

In myoepithelial cells, the expression pattern of $p75^{NTR}$ was compatible with those of p63 and myosin (Table 1). None of the cases with $p75^{NTR}$-positive luminal/tumor cells show immunoreactivity for myosin (Tables 1 and 2). Two of the three usual ductal hyperplasias with p63-positive cells in the lumen also showed $p75^{NTR}$-positive cells in the same areas. All metaplastic carcinomas included in this study expressed both $p75^{NTR}$ and p63. Similar double expression was found in two invasive ductal carcinomas. Two invasive ductal carcinomas and one ductal carcinoma *in situ* showed focal p63 positivity in the tumor cells, but were negative for $p75^{NTR}$ Two invasive ductal carcinomas with focal $p75^{NTR}$ positivity did not show expression of p63. The $p75^{NTR}$-positive stromal cells in the specimens with fibroadenomatoid change and fibroadenoma were negative for p63 and myosin.

## Discussion

Similarly to the previous reports,[13,14] we found that $p75^{NTR}$ is consistently expressed in the myoepithelial cells of the human mammary gland. We also showed that $p75^{NTR}$ always highlighted the myoepithelial cells in the benign breast lesions (slerosing adenosis, ductal hyperplasia, intraductal papilloma) and carcinoma *in situ* and was absent in the majority of the invasive carcinomas. The data support the notion that $p75^{NTR}$ can be used to evaluate difficult

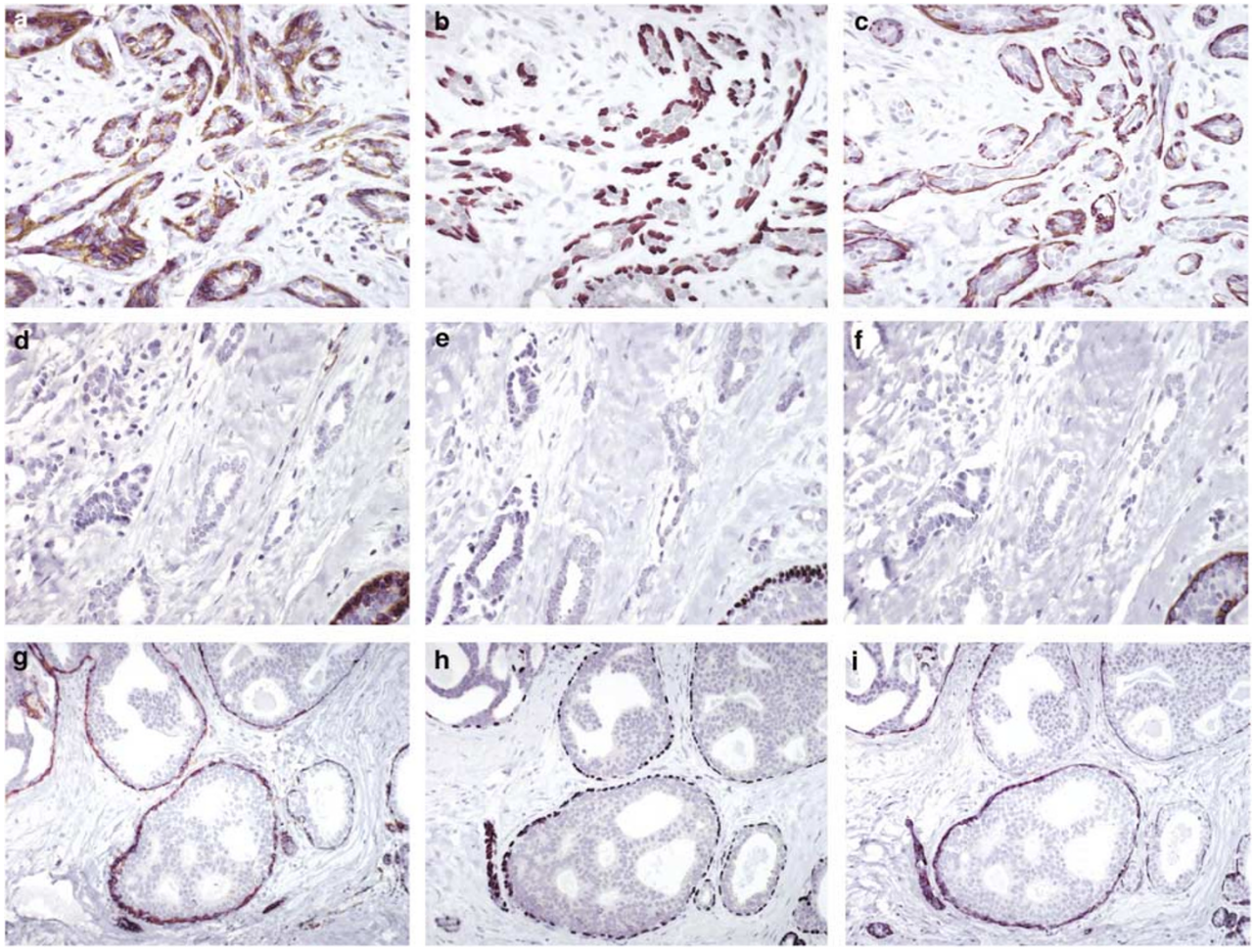


**Figure 2** Expression of p75$^{NTR}$ p63, and myosin heavy chain in sclerosing adenosis, tubular carcinoma, and ductal carcinoma *in situ*. (**a–c**) sclerosing adenosis; (**d–f**) tubular carcinoma; (**g–i**) ductal carcinoma *in situ*; (**a**, **d**, and **g**) p75$^{NTR}$ immunostain; (**b**, **e**, and **h**) p63 immunostain; (**c**, **f**, and **i**) myosin immunostain. Original magnifications, ×400 for (**a–f**) ×200 for (**g–i**).

sclerosing lesions or to distinguish between *in situ* and invasive disease.

All metaplastic carcinomas included in our study as well as a small portion of invasive ductal carcinomas, showed expression of p75$^{NTR}$ Similarly, Aragona *et al*,[14] who used the same monoclonal antibody on frozen sections, have found that 15% of the breast cancers included in their study are positive for p75$^{NTR}$ However, using a polyclonal antibody on paraffin sections, Sakamoto *et al*[15] have reported that 73% of the breast carcinomas express p75$^{NTR}$ in more than 15% of cancer cells. Those discrepancies might be explained with the use of different antibodies and different tissue preparation techniques. In addition, Aragona *et al*[14] have shown that p75$^{NTR}$ expression is associated with estrogen receptor positivity and more differentiated histologic grade. This result is unexpected since the tumors that express myoepithelial/basal markers usually lack estrogen receptors and are poorly differentiated.[16,17] Our previous study has shown that the metaplastic breast carcinomas are estrogen receptor negative and express a variety of myoepithelial/basal markers.[18] In our current study, all metaplastic carcinomas were positive for p75$^{NTR}$ which supports the prediction that p75$^{NTR}$ will be expressed in the estrogen receptor negative basal-like breast carcinomas. Obviously, larger studies addressing the correlation of p75$^{NTR}$ with other phenotypic characteristics of the tumors (which is not the focus of this publication) will resolve this issue.

p75$^{NTR}$ expression in myoepihelial cells correlates well with p63 and myosin immunoreactivity. However, the overall p75$^{NTR}$ expression in breast parenchyma/tumors showed greater similarity to p63 rather than to myosin. None of the p75$^{NTR}$-positive carcinomas or the p75$^{NTR}$-positive cells in the florid usual ductal hyperplasia showed myosin expression. Discrepancy between p75 and p63 immunostains was observed in four invasive ductal carcinomas, one ductal carcinoma *in situ*, and one usual ductal hyperplasia. However, the immunoreactivity in these cases was focal and this inconsistency may represent a sampling artifact. Our experience showed that the membranous and cytoplasmic pattern of p75$^{NTR}$ immunoreactivity was

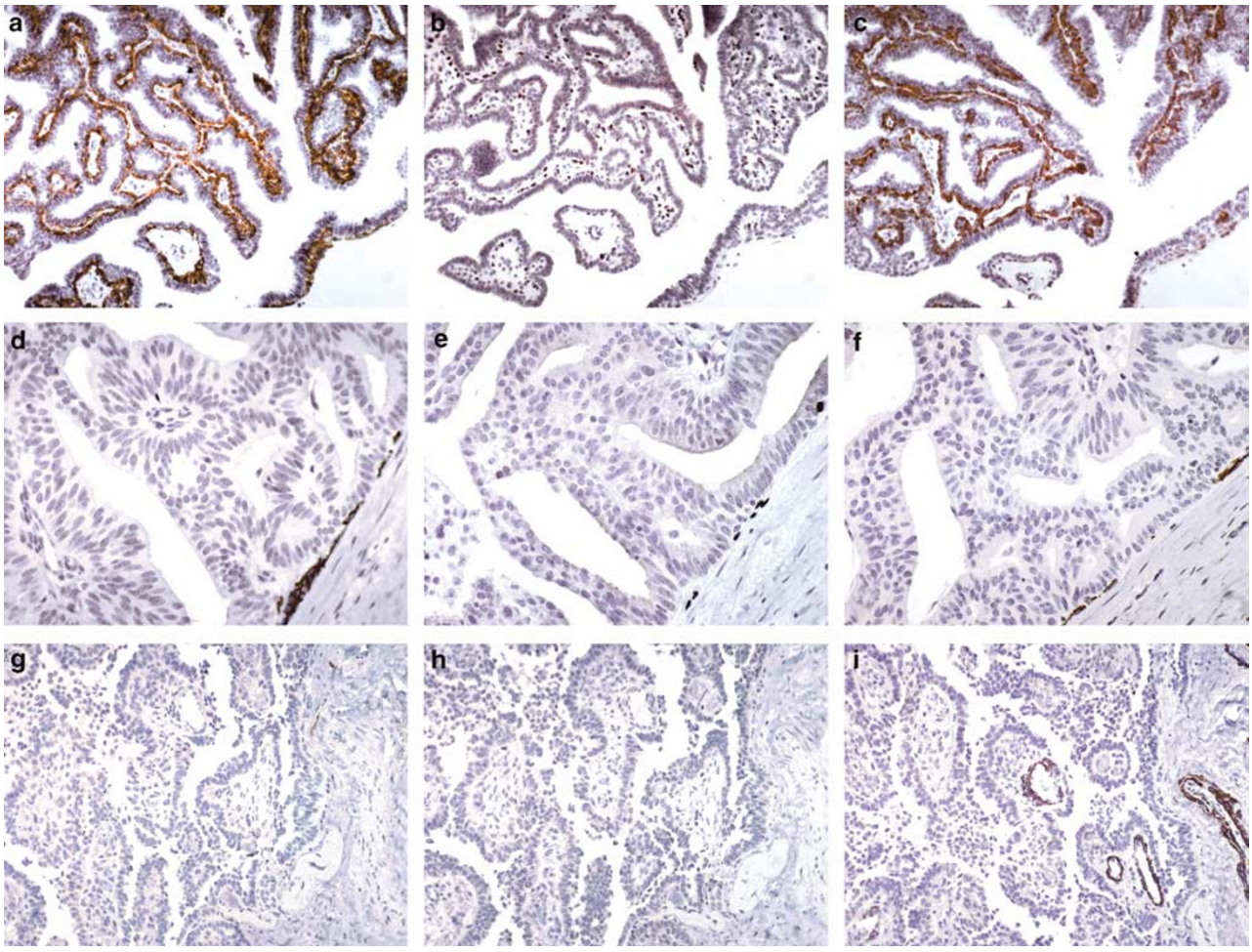


**Figure 3** Expression of $p75^{NTR}$, p63, and myosin heavy chain in papillary breast lesions. (**a–c**) intraductal papilloma; (**d–f**) noninvasive papillary carcinoma; (**g–i**) invasive papillary carcinoma; (**a**, **d**, and **g**) $p75^{NTR}$ immunostain; (**b**, **e**, and **h**) p63 immunostain; (**c**, **f**, and **i**) myosin immunostain. Original magnifications, $\times 200$ for (**a–c**) and (**g–i**) $\times 400$ for (**d–f**).

often more easily appreciated than the nuclear pattern of p63. The expression of $p75^{NTR}$ on the cell membrane and in cytoplasm nicely complemented p63 immunoreactivity when a cocktail of the two antibodies was used (data not shown).

Several experimental studies have shown that under different conditions breast myoepithelial cells may change their immunophenotype. For example, Stingl *et al*[19] have demonstrated that, in culture conditions, mammary epithelial cells with myoepithelial features lack SMA. Similarly, other authors have reported decreased CD10 and SMA expression in continuously passaged purified human breast myoepithelial cells.[20] We have found that the myoepithelial component of adenomyoepitheliomas often does not express CD10 and/or myosin, while SMA expression often decreases.[18] All of these facts suggest that a panel containing complementary myoepithelial markers should be used when an evaluation of myoepithelial cells or tumor phenotype is required. In this respect, $p75^{NTR}$ can also be included in the panel of immunohistochemical stains necessary for establishment of myoepithelial/basal origin or differentiation of breast lesions.

$p75^{NTR}$ immunoreactivity was noticed in the vascular adventitia, nerves, few spindle stromal cells in benign and malignant lesions. $p75^{NTR}$ has been previously detected in the nerves[13,14,11–23] and vessels.[13,14] Although we did not observe significant $p75^{NTR}$ expression in the fibroblast in normal breast stroma and in the stroma around the carcinoma, we found strong $p75^{NTR}$ expression in the fibroblasts of the expanding intralobular stroma (fibroadenomatoid change). In addition to the myoepithelial positivity, further immunohistochemical staining performed on six fibroadenomas revealed similar strong stromal $p75^{NTR}$ expression. These findings suggest that neurotrophins play a role in the development of mammary fibroepithelial tumors. Despite the nonepithelial expression of $p75^{NTR}$ no difficulties were encountered during the evaluation of the immunostain of myoepithelial cells.

In summary, p75 neurotrophin receptor is a useful marker for breast myoepithelial cells and can be used to rule out invasive disease or to evaluate

difficult sclerosing lesions. $p75^{NTR}$ has a pattern of expression in breast parenchyma/tumors more similar to that of p63 than to that of the myosin heavy chain. The membranous and cytoplasmic expression of $p75^{NTR}$ was often more easily appreciated than the nuclear expression of p63. $p75^{NTR}$ expression in the stroma of fibroadenoma suggests a role of neurotrophins in the development of fibroepithelial breast tumors and some of the breast carcinomas.

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