USE OF BASAL/MYOEPIHELIAL MARKERS IN BREAST PATHOLOGY: NHSBSP CO-ORDINATING GROUP OVERVIEW AND RECOMMENDATIONS

The increasing use of needle core biopsy for non-operative diagnosis and the nature of lesions identified mammographically can result in diagnostic difficulties. Interpretation may be helped by the use of immunohistochemistry used to detect basal/myoepithelial markers. A recently circulated questionnaire showed that there were variations in the type and frequency of markers used diagnostically in the UK and Ireland. This paper summarises current knowledge of the various markers, discusses the diagnostic areas where they are of value and makes recommendations for a suitable diagnostic panel.

Basal/Myoepithelial Markers

The myoepithelial cell has traditionally been distinguished from luminal epithelial cells by the presence of smooth muscle fibres. However, many more proteins have now been identified that are expressed in myoepithelial cells and these fall into three groups: smooth muscle related; cytokeratins; others.

**Smooth Muscle Related**

- Smooth muscle actin (SMA)-antibodies detect actin microfilaments; good sensitivity but specificity poor since will detect myofibroblasts.\(^1\)

- Smooth muscle myosin heavy chain (SMMHC)-structural component of smooth muscle myosin. SM2 isoform is expressed in breast myoepithelial cells. Sensitivity and specificity are high with SMMHC being present in periductal and periacinar myoepithelial cells and not stromal myofibroblasts\(^2\), although sensitivity reported to be slightly lower than SMA.\(^3\)

- Calponin – 34 KD polypeptide, modulates actomyosin ATPase activity. Excellent sensitivity but present in a subset of myofibroblasts.\(^1,2\)

- H-caldesmon-smooth muscle actin binding protein. Only detectable in myoepithelial cells of ducts but not found in myofibroblasts.\(^2,3\)


**Cytokeratins**

- Myoepithelial cells express cytokeratins (CK) characteristic of basal layer of stratified epithelium – CK5, CK10, CK14 and CK17.\(^4,5\)

- CK5/6 in normal breast can be detected in both myoepithelial and luminal epithelial cells.\(^6\)

- The antibody 34\(\beta\)12 recognises CKs 1, 5, 10 and 14 but is not specific for myoepithelial cells.\(^7\)

**Other markers**

- S100 – has low specificity since detectable in epithelial cells.\(^8\)

- CD10 (Common Acute Lymphoblastic Leukaemia Antigen CALLA) – endopeptide expressed in myoepithelial cells. Antibodies now available that work on fixed tissue; high sensitivity in normal breast.\(^10\)

- P cadherin – cell adhesion molecule with high sensitivity for myoepithelial cells in normal breast, no reactivity with myofibroblasts.\(^11\)

- P63-p53 homologue, differs from other markers in being nuclear\(^12\), with high sensitivity for myoepithelial cells.\(^13\)

- 14-3-3\(\sigma\)- protein associated with apoptosis and cell cycle control, present in myoepithelial cells in normal breast.\(^14\)

- Maspin – serine protease inhibitor present in myoepithelial cells\(^15\), with both cytoplasmic and nuclear reactivity.
Diagnostic Areas

**Radial Scar v Tubular Carcinoma**

Highly sensitive and specific markers are required due to myoepithelial cells in central parts of radial scars being attenuated, plus the presence of myofibroblasts. The requirements favour SMMHC and p63 as markers of choice. SMA and, to a lesser extent calponin, will be present in myofibroblasts.

**Papillary Lesions**

Immunohistochemistry can reduce the variability in reporting of core biopsies of papillary lesions, particularly in relation to B3 and B4. Intraduct papillomas have a complete layer of myoepithelial cells, whether detected by SMMHC, calponin, p63 and CK5/6 or SMA, p63, CD10 and CK14. However, findings for intracystic papillary carcinomas differ, with Collins et al failing to detect any myoepithelial cells and Tse et al finding them to be scattered and discontinuous. p63 had the highest sensitivity; CK14 was also present in florid hyperplasia, SMA showed stromal staining and CD10 epithelial and stromal staining.

**Hyperplasia v Atypia v Ductal Carcinoma in Situ**

High molecular weight basal cytokeratins are of use particularly in interpretation of core biopsies enabling a B2 rather than a B3 diagnosis. Myoepithelial cells form a useful internal positive control. Hyperplasia of usual type and hyperplasia in papillomas show reactivity for CK5/6 and CK14 whereas atypical hyperplasia and ductal carcinoma in situ epithelium do not.

**Non-Invasive v Invasive Carcinoma**

Myoepithelial cell markers can be of value in assessing whether or not invasion is present but myofibroblast reactivity, discontinuity of staining of myoepithelial cells and staining of vascular smooth muscle cells can cause problems in interpretation. Discontinuous staining can occur with p63, but it has greater sensitivity and specificity. SMMHC has been found to be more sensitive than CD10 in assessing invasion but is in vascular smooth
muscle cells. Due to the advantages and disadvantages it is better to use two myoepithelial markers that complement one another e.g. p63 and SMMHC or calponin.

**Myoepithelial Tumours**

SMA, CK5/6, CK14, p63 and other markers are all suitable for analysing possible (adeno) myoepithelial tumours, both benign and malignant.\(^{23}\)

**Other lesions**

Myoepithelial markers can aid differentiation of adenoid cystic carcinoma from collagenous spherulosis and cribriform carcinoma.

**Basal-like Carcinomas**

There is increasing interest in basal-like breast carcinomas, partly due to the finding that BRCA1-related breast cancers can have these features\(^ {24}\) and to their poorer response to anthracycline chemotherapy.\(^ {25}\) There is no consensus as to the definition of basal-like which probably reflects the view that they are a heterogeneous group of cancers. Nielsen et al\(^ {26}\) consider them to express CK5/6, HER-1 (EGFR) and/or c-kit and lack ER and HER2. Others have used CK14\(^ {27}\) or P-cadherin\(^ {28}\) as a basal marker to identify these tumours. Rakha et al\(^ {29}\) have proposed that basal-like carcinomas can be defined based on the expression of basal cytokeratins (CK 5/6 and CK14) irrespective of other markers.

**Recommendations for a Diagnostic Panel**

It is important not to rely on just one marker, as discussed above.

- SMMHC or calponin are sensitive and specific cytoplasmic myoepithelial markers. SMA can be used but care has to be taken in interpretation in the presence of myofibroblasts.
• P63 is a sensitive and specific nuclear myoepithelial marker but staining can be discontinuous, so use of a cytoplasmic myoepithelial marker, such as SMMHC or calponin, as well will aid interpretation.

• When trying to identify the presence/absence of myoepithelial cells use p63 and SMMHC/calponin

• CK5/6 is of value in several diagnostic situations, such as analysis of hyperplasias or basal-like breast cancers.

REFERENCES


23. Hungermann D, Buerger H, Oehlschregel C, Hersst H, Boecker W. Adenomyoepithelial tumours and myoepithelial carcinomas of the breast – a spectrum of


