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What is triple-negative breast cancer?

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ABSTRACT

Triple-negative (ER-negative, PR-negative, HER2/neu not overexpressed) breast cancer has distinct clinical and pathologic features, and is a clinical problem because of its relatively poor prognosis, aggressive behaviour and lack of targeted therapies, leaving chemotherapy as the mainstay of treatment. Most triple-negative tumours fall into the basal-like molecular subtype of breast cancer, but the terms are not completely synonymous. Among the intriguing characteristics of triple-negative breast cancer is its association with cancers arising in BRCA1 mutation carriers, in young women and in African–American women. The reasons for these associations are unclear but may ultimately provide avenues for prevention and targeted therapy. This review discusses the definitions and characteristics of as well as current and evolving therapies for triple-negative and basal-like breast cancer.

1. Introduction

In 2007, 1.3 million women worldwide were diagnosed and 465,000 died from breast cancer making this the most common cancer in women and the leading cause of death.[1] Though impressive, these statistics treat breast cancer as a homogeneous entity, which we increasingly recognise as inaccurate. Gene expression studies have identified several major subtypes of breast cancer[2]: the luminal subtypes, which typically express hormone receptor-related genes, and two hormone receptor-negative subtypes – the human epidermal growth factor receptor 2 (HER2) positive/oestrogen receptor (ER) negative subtype and the basal-like subtype. The subtypes vary in prognosis, with worse outcomes traditionally seen among the two hormone receptor-negative subgroups compared with the luminal subgroups[3–5]; however, improvements in chemotherapy, endocrine therapy and HER2-targeted therapy may change the prognostic landscape of breast cancer.

A subtype of particular interest is the basal-like breast cancer BBC. In population-based studies, this subtype comprises approximately 15–20% of breast cancers.[6–8] In research studies, BBC has been reproducibly identified using gene expression methods[4,5] and immunohistochemistry,[9–11] however, a validated method to identify BBC and other intrinsic subtypes of breast cancer for clinical use does not exist. In arrays, BBCs are characterised by low expression of ER-related genes and HER2-related genes; for this reason in clinical specimens they are usually ER-negative, progesterone receptor (PR) PR-negative and lack HER2 overexpression. This is called the 'triple-negative' phenotype.

Since triple-negative breast cancer is resistant to our current HER2-targeted therapies such as trastuzumab, and hormonal therapies such as tamoxifen and aromatase inhibitors, chemotherapy is the mainstay of treatment. This lack of targeted therapies has intensified the interest in this group of patients. This review will focus on the definition and features of triple-negative breast cancer, current treatment strategies and future directions for treatment.

2. Nomenclature

As mentioned above, most triple-negative breast cancers cluster with the BBC,[10] however, these are not synonyms. 'Triple negative' is a term based upon clinical assays for ER, PR

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and HER2, while 'basal-like' is a molecular phenotype. The 'basal-cell phenotype' was first described by Wetzels et al. by using immunohistochemical markers to identify cytokeratins in breast tumours that normally were found only in the cell layer lying closest to the basement membrane of the mammary gland epithelium.[12] These markers are also expressed in BRCA1-associated cancers, as discussed below. The original basal-like intrinsic subtype was defined using cDNA microarrays[2,3]; however, it has been reproducibly identified using other gene expression platforms,[5,13–15] mean expression-based and similar approaches to subtype categorisation,[16–18] and multiplex immunohistochemical profiling involving either multiple markers[9,11] or a simpler surrogate (ER-negative, PR- negative, HER2-negative, plus either cytokeratin 5 positive or EGFR-positive),[10] which is 76% sensitive and 100% specific.[10] The triple-negative proxy is the least accurate; although most triple-negative tumours have basal-like expression profiles and most BBCs are triple negative, both categories have up to 30% discordance.[19,20] The interest in developing other diagnostic tools to identify subtypes is because although RNA-based microarrays are the gold standard to identify breast cancer subgroups, these assays are not routinely used in clinical environments for both technical reasons and the need for frozen tumours.

3. Molecular features of triple-negative breast cancer

'Unsupervised' (heedless of clinical characteristics or outcome) gene expression array profiling studies on breast tumours have allowed breast cancers to be clustered according to their intrinsic gene expression patterns, revealing at least five intrinsic subtypes[2–5]: luminal A and B, HER2+/ER-negative, normal breast-like, basal-like and potentially a 'claudin-low' subtype.[21] These breast cancer subtypes are highly reproducible,[3–5] persist before and after therapy, are concordant between the primary tumour and the metastasis[22] and are found in the preneoplastic lesion ductal carcinoma *in situ*.[23–26]

Gene expression of the novel 'basal cluster' includes HER1 (epidermal growth factor receptor, EGFR), high molecular weight cytokeratins 5, 14 and 17, vimentin, p-cadherin, fascin, caveolins 1 and 2 and alpha-B-crystallin.[3,10,11,16,27–32] The hormone receptor cluster of genes is underexpressed, and the proliferation cluster is highly expressed, befitting the largely grade 3 nature of these tumours.[6] Myoepithelial markers SMA, p63 and CD 10 are generally expressed[27] and have been suggested as a means of identifying BBC. Some of these characteristic markers are potentially targetable. As mentioned, HER1/EGFR is expressed in approximately 60% of triple-negative tumours.[10,33] c-Kit expression is higher in basal-like tumours; in one study, 31% of tumours expressing basal cytokeratins had c-kit staining compared to 11% in basal cytokeratin-negative tumours ($p < 0.001$).[10] Several molecules integrally important in response to DNA damage are aberrantly expressed in BBC, which may have implications for chemosensitivity. For example, high p53 IHC expression or TP53 gene mutations are common in BBC[3,11,34,35]; in one study 82% of BBC had p53 mutations compared with only 13% in the luminal A subtype ($p < 0.001$).[3] In addition, the strong association of BBC with BRCA1 mutation carriers, described further below, raises the question of whether this pathway, which is integrally involved in repair of DNA damage, may be dysfunctional in both sporadic and BRCA1-associated BBC.[36] These observations, as well as the high grade nature and the high proportion of gene copy number aberrations speak to underlying genomic instability in BBC.[37] In BBC, mRNA levels of p16, cyclin E and E2F3 are elevated compared to other tumour types, while the levels of Rb and cyclin D1 are lower; this suggests that Rb inactivation is integrally linked to BBC.[38] The Rb pathway is a key component of the response to cellular stress. Deranged p16/Rb signalling and abnormal stress response are also characteristics of BBC.[38] Table 1 summarises these molecular features.

Table 1 – Summary of relevant molecular features in triple-negative tumours.

Increased	Decreased or not found
c-kit	ER
p53 protein /TP53 gene mutations	PR
cyclin E	HER2
p16	Cyclin D1
EGFR	Rb
Basal cytokeratins 5, 14, 17	
αB crystallin	

Updated examination of the gene expression portraits of large numbers of breast cancers suggests that there may be other smaller subtypes. Among these is the 'claudin-low' subtype,[21] which is typically triple-negative so it warrants a discussion here. The relationship of breast cancer subtypes and the controversial area of mammary stem cells is of great interest because of the implications for treatment.[39,40] There are several lines of evidence in support of mammary stem cell involvement in breast cancer pathogenesis. Al-Hajj and colleagues isolated CD 44+/CD24$^{-/low}$ tumourigenic breast cancer cells that were capable of generating phenotypic heterogeneity[41]; another suggested that the loss of BRCA1 contributes to the development of such tumourigenic cells.[42] While some studies have suggested shared characteristics cancer cells with myoepithelial/basal cell phenotype with breast progenitor cells,[43,44] this does not necessarily imply derivation. More recent studies suggest that there exists a subpopulation of CD44+/CD24$^{-/low}$ cells that share some characteristics with the basal-like subtype, including triple-negative status, but are biologically distinct and more phenotypically consistent with 'stemness'.[21,40,45]

4. Clinical features and risk factors

Triple-negative tumours typically have a higher histologic grade, elevated mitotic count, scant stromal content, central necrosis, pushing margins of invasion, a stromal lymphocytic response and multiple apoptotic cells[27,46]; histologically they are largely ductal,[6] but several unusual histologies are also overrepresented, including metaplastic,[27,47,48] atypical or typical medullary,[27,49] or adenoid cystic carcinomas.[50] A case series evaluating 65 metaplastic breast cancers by