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REVIEW

Patho-biological aspects of basal-like breast cancer

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Abstract Breast cancer comprises a remarkably diverse group of diseases in terms of presentation, morphology, molecular profile and response to therapy. Recent gene expression profiling of breast cancer has identified specific molecular subtypes of clinical significance. Basal-like cancers (*BLC*) comprise a group of tumours that are characterised by an expression signature similar to that of the basal/myoepithelial cells of the breast and cluster together with BRCA1 associated tumours. Although *BLC* has fascinated oncologists and scientists alike due to its enigmatic clinical and pathological parameters, there is no consensus about the definition and method of identification in routine practice of this rather heterogeneous group of cancers. Furthermore, the prognostic significance of *BLC*s and response to specific chemotherapy regimens are still a matter debate. In this review, we discuss the molecular and morphological features, prognostic significance of *BLC*, and explore its impact on the concept of the breast cancer stem cell.

Keywords Breast cancer · Basal-like · Definition · Morphology · Prognosis

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Introduction

Breast cancer comprises an extraordinarily diverse group of diseases in terms of presentation, morphology, molecular profile and response to therapy. This heterogeneity poses significant challenges in tailoring therapy to individual patients, given that current methods of diagnosis and classification fall short of delivering a sufficiently accurate categorisation. The identification of classes of tumours with differing biological behaviour or responsiveness to specific therapies is needed. Despite the numerous studies employing single markers to stratify breast cancer, only oestrogen receptor (ER) and HER2 have been translated into companion diagnostics methods for therapy with anti-oestrogens or SEERMs and anti-HER2 therapy. The fact that single markers cannot accurately account for the heterogeneity of breast cancer is not surprising. The degree of cellular and molecular heterogeneity in breast cancer and the large number of molecular events involved in controlling cell growth, differentiation, proliferation, invasion and metastases [1] emphasise the importance of studying multiple molecular alterations in concert. The introduction of high-throughput technologies that survey hundreds to thousands of genes and their products in a single assay, coupled with powerful analytical tools, has offered new opportunities for classifying breast cancer into biologically and clinically distinct groups based on gene expression patterns [2–8].

Microarray-based class discovery studies pioneered by Perou et al. [2] have paved the way for a new era in breast cancer research. This series of landmark studies [2–4] established that breast cancer could be classified into molecularly distinct groups based upon gene expression profiles and their similarity to those of normal cell counterparts. Multiple independent studies have confirmed and expanded the original results [2–4, 9]. It is currently accepted

that based on microarray analysis, breast cancer can be divided into two broad groups: oestrogen (ER) positive and ER negative groups, which can be subdivided into multiple distinct biologically and clinically significant subgroups. One of the subgroups comprises the basal-like breast carcinomas (*BLC*s), which have been shown to have a more aggressive clinical behaviour when compared to tumours pertaining to the ER-positive subgroups [2–4, 10, 11].

Molecular features of basal-like tumours (*BLC*)

Although tumours characterised by expression of markers characteristic of basal/myoepithelial cell [i.e. high molecular weight (basal) cytokeratins] and associated with poor prognosis were described two decades ago [12, 13], *BLC*s have only received the deserved attention by the research community after their re-discovery by gene expression profiling studies [2]. The terminology "basal-like" stems from the similarity between the molecular profile of tumours pertaining to this molecular subgroup with that of basal/myoepithelial cells (termed *basal-like* cells in this review) of normal breast [2]. This class of breast cancer is characterised by its poor prognosis and the lack of specific targeted therapies. Furthermore, the pathogenesis of *BLC* is still poorly understood and it remains unclear what drives these tumour cells to proliferate and metastasise.

Most studies have shown that *BLC*s are mainly included within a cluster in the ER negative and HER2 negative tumours and are largely characterised by positive expression of *basal* cytokeratins (CK) and other genes characteristic of *basal-like* cells of the breast [2–4, 11]. Several *BLC* gene products identified are important structural elements of the *basal-like* cells of the breast [2, 14–16] and extracellular matrix (ECM) receptor proteins [17]. Other gene products in the *BLC* cluster included several proteins that activate signalling pathways, which are commonly deregulated in cancer [18] and gene products that have been implicated in cellular proliferation, suppression of apoptosis, cell migration, invasion and extracellular remodelling have been identified [19–21]. Furthermore, *BLC*s often express genes associated with proliferation, including cyclin E1, BUB1, topoisomerase II α, CDC2, and PCNA [2, 3, 11]. The continuous proliferation of *BLC* and possible potential block in their differentiation might be due to an abnormal balance of transcription factors such as GATA transcription factors [22]. These findings imply that similar molecular pathways drive these cancers and to some extent justify a focused therapeutic research strategy.

In a previous study, Fan et al. [23], assessed gene expression profiles of 295 tumours and compared the different molecular classes of breast cancer with the different prognostic gene signatures. Importantly, they found that all *BLC* (53 cases) have a high recurrence score [24] and a poor 70-gene profile [25], 50 cases were classified as having an activated wound-response signature [26] and 42 (79%) tumours have a high two-gene ratio [27]. These results confirm that *BLC*s not only express a set of genes that allow clustering of these tumours together, but also express different genes associated with tumours of poor prognosis. However, these results were not confined to the *BLC* class of breast cancer as they also found a nearly identical finding for the HER2 and Luminal-B subtypes highlighting the biological and prognostic importance of proliferation genes in these subgroups as already reported by others [28, 29]. Alternatively, these results also suggest that it is rather challenging to identify subgroups of ER-negative breast cancers associated with good prognosis signatures.

Several gene products in the *basal* cluster are also expressed in stem cells of various tissue types [30]. Collectively, the gene-expression profile of *BLC* provides a myriad of candidate genes that might contribute to their aggressive phenotype and may suggest a less differentiated "stem/progenitor" cell origin for these tumours. In fact, one could argue that *BLC*s have several features of a stem cell-like transcriptome; however, it remains to be determined whether the final phenotype of these cancers is a mere reflection of that of their cell of origin.

On close scrutiny, the results of hierarchical clustering analysis of breast cancer provide circumstantial evidence that *BLC*s are not a homogeneous entity [31]. When defined on the basis of cDNA expression, the *BLC* group is not homogenous with sharp outlines but has a degree of overlap of genes within the *BLC* cluster as well as between the *BLC* cluster and other clusters. Cases that display all the transcriptomic features of basal-like breast cancers are located in the centre of the cluster, whereas cases located at the periphery of the dendrogram branch fail to express all '*basal*' markers. Therefore, it is not surprising that some genes can be shared with other clusters, for example with those pertaining to the HER2 subtype, and may be a function of the shared high histological grade or high proliferation indices of those cancers. In addition, there are data to suggest that a subgroup of HER2 amplified breast cancers may display a basal-like phenotype [32–34].

Immunohistochemical (IHC) definition and IHC features of *BLC*

Although the gene-expression profiling is still considered the 'gold standard' for the identification of *BLC*s, this technology is not readily available for large-scale clinical applications or for retrospective studies using formalin

fixed, paraffin-embedded samples. In these situations protein expression characteristics bases on immunohistochemical staining (IHC) can be a useful surrogate of gene expression analysis. However the optimum IHC profile of *BLC* is still under investigation and several IHC combinations have been proposed. Nielsen et al. [31] have identified an IHC surrogate based on four markers (ER and HER2 negative, CK5/6 and/or EGFR positive). In their study, this panel showed a sensitivity of 76% and a specificity of 100% to identify breast carcinomas with a *BLC* phenotype as defined by expression profiling analysis. These criteria for definition of *BLC* were adopted by many other authors [35–40]. In addition, other criteria have been used in the definition of *BLC* such as "ER, PR, HER2-negative, and CK5/6 and/or EGFR-positive" [36], "ER-negative, HER2-negative/positive and [CK6 and/or P-cadherin and or p63]-positive" [41, 42], and "ER, PR and HER2-negative" [43]. Other markers that have been included in the panel of "*basal*" biomarkers to distinguish the *BLC* group include vimentin and laminin [35, 44], c-KIT [45], p63 [46], nestin [47] and osteonectin [48]. Moreover, some, including our group, but not all IHC studies [46, 49–53] have used *basal* CKs alone to defined *BLC* and this definition is supported by (i) prevalence of *basal* CKs expression among tumours identified as *BLC* in expression microarray studies and by (ii) association between *basal* CKs expression and poor prognosis [54–56] even within the triple-negative tumours [57, 58]. However, it is important to mention that this definition is not complete and has some important shortcomings: (i) some tumours which express *basal* CKs also express hormone receptors or HER2 [57–59] and (ii) some tumours identified as *BLC* by expression microarrays do not express *basal* CKs [49, 60, 61]. Most of these studies have also suffered a degree of variability in using these *basal* CKs to identify *BLC*. For instance, either single [41, 49, 52, 62–64] or a combination of *basal* CKs [2, 34, 45, 46, 48, 50, 53, 60, 61, 65–69] have been used. They also varied in the type of *basal* CK used (CK5, CK5/6, CK14 and CK17). In addition, it has been shown that the staining patterns of these basal CKs can be highly variable and heterogeneous [34, 51, 67] and some tumours may express on *basal* CK but not the others [46, 59, 67, 70]. Hence, it is difficult to assess the degree of misclassification of *BLC*s when basal keratins are used as the definition of these cancers. Furthermore, the variability and heterogeneity of the expression of basal CKs has created some degree of discordance and contradictory results, in particular due to the use of tissue microarrays (TMA) to assess the expression of these *basal* CKs.

One important misconception related to the expression of basal/ high molecular weight cytokeratins in *BLC* refer to cytokeratins 5 and 6. Some experts have recently claimed that "basal breast tumours are characterized as being ER−, PR−, HER2−, epidermal growth factor receptor (EGFR)+ and keratin 6+ and/or 17+." [71]. Whilst cytokeratins 5 is part of the microarray-based definition of *BLC* [2, 3] and has been shown to be expressed in breast cancer [33, 34, 41, 45, 46, 62], cytokeratin 6 mRNA expression does not correlate with basal like phenotype. Furthermore, there is evidence to suggest that cytokeratins 6 is not expressed in normal breast and basal-like breast cancer [72, 73].

The immunophenotype of *BLC*, as defined by gene expression profiling or by IHC surrogate markers, is characterised by positive expression of EGFR, p53, P-cadherin, caveolins 1 and 2, cyclin E, c-KIT, fascin, moesin, vimentin, nestin, laminin and Ki-67. They are predominantly negative for ER, PgR and HER2 (triple-negative), FHIT protein, cyclin D1, p27 and MUC1 [14, 31, 38, 45, 49, 53, 59, 60, 74–78]. Compared to luminal and HER2 groups, *BLC*s show reduced but still frequent expression of luminal CKs and increased positivity for myoepithelial (ME) markers (e.g., SMA and CD10) [44, 59].

BLC and triple-negative breast cancer

BLC is characterised by certain common features including the triple-negative phenotype. Some authors have claimed that *BLC*s are composed almost entirely of triple negative [43, 79] breast cancers, that triple negative phenotype could reliably be used as a surrogate for *BLC*s [79] and that 'basal-like' and triple negative phenotype would be synonymous [80]. From the oncologist standpoint, triple-negative tumours are undeniably one of the most relevant subgroups of breast cancer, given the lack of targeted therapies for this group and their aggressive clinical behaviour. However, there are several lines of evidence that triple negative phenotype is not an ideal surrogate for the identification of basal-like breast cancers. In fact, there are several lines of evidence that both BLC and triple-negative are not exactly the same [58, 81–83]. In two expression profiling studies where the expression of hormone receptors were analysed in tumours classified according to the 'intrinsic gene list', ER expression was seen in 5–45% of *BLC*s. In addition, Rouzier et al. [84] have demonstrated that 14% of *BLC*s express HER2. On the other hand, triple-negative tumours are not necessarily *BLC*. A recent study by Tan et al. [85], found that 6/31 (19%) of the triple negative tumours were negative for both EGFR and basal CKs, whilst 15/207 (7.3%) of non-triple negative tumours were positive for basal markers. In addition, they found that four cancers that were classified as *BLC* using the Nielsen criteria expressed PR (even in both TMAs and whole tissue sections—Tan & Reis-Filho

personal communication) and therefore, were classified as pertaining to the ER/PR+ ('luminal') group [58].

Another confounding issue is that a significant proportion of 'normal breast-like cancers' as defined by expression arrays would also lack hormone receptors and HER2 (i.e. triple negative) [2–4]. Although the normal breast-like cancers are still poorly characterised, they are reported to have a prognosis that is better than that of *BLC*s [3, 23] and do not seem to respond to neoadjuvant chemotherapy [84, 86]. In fact, in one study, 45% of patients with *BLC* showed pathological complete response following anthracycline + taxanes neoadjuvant chemotherapy, whereas none of the normal breast like cancers did so [84]. We [81] and others [57] have demonstrated that the expression of basal markers (i.e. basal cytokeratins and EGFR) identifies a clinically significant subgroup within the triple-negative group. Furthermore, expression of basal cytokeratins and/or EGFR [57, 81, 87], regardless of the expression of ER or PR status, identifies a subgroup of cancers which display a particularly poor prognosis; emphasising the prognostic value of these basal markers expression irrespective of the hormone receptors status.

Whether or not triple negative phenotype is a reliable surrogate for basal-like breast cancers is not a mere academic issue. In fact, defining an entity based on the lack of a combination of markers may be misleading. As stressed by Nielsen et al., "lack of staining for ER and HER2 alone to identify *BLC* risks misassignment based on technical failures" [31]. In fact, ER has a documented technical false negative rate [88] and problems with HER2 interpretation, in particular when data are retrieved from pathology reports without a central review [89]. Thus, correlative studies which use triple-negative phenotype as the definition of *BLC* are likely to include in the study group a mixture of basal-like and non-basal-like tumours (e.g. normal breast-like cancers) with varying histology and clinical behaviour. Similarly using single 'basal markers' to define *BLC* is likely to identify a proportion of *BLC* and tumours which have some but not all molecular features of *BLC* and therefore, should not be assigned to the class of *BLC*.

Pathological features of *BLC*

*BLC*s, as defined by mRNA expression profile or expression of *basal* IHC markers, represent 8% to up to 37% of all breast cancer cases [2, 3, 11, 25, 26, 45, 51–53, 59, 64, 67, 90, 91], depending on the proportion of grade III cases included in the population. The average age of patients with *BLC* ranged from 47 to 55 [36, 45, 91], and they are usually younger [36, 49, 59, 92] and premenopausal [36] than those with non-basal tumours. Preliminary data from a population based study [91], suggest that there may be significant differences between the *BLC* and other molecular subtypes regarding the distribution of breast cancer risk factors with reduced risk of *BLC* associated with increasing age at menarche, increased risk with positive family history and lack of association with body mass index.

The majority of *BLC*s are ductal of no special type [33, 44, 59], but occasionally either tubular mixed [59]. In addition, the vast majority of metaplastic [65] or medullary-like cancers [93–95] display a basal-like phenotype. BLC is rarely found in other special types of breast cancer [59].

*BLC*s are usually of high histological grade. According to gene expression microarrays, 75–100% of *BLC* are grade 3 [44, 92] and similar figures have been reported in IHC studies [45, 53, 59]. BLCs have common morphologic features including marked cellular pleomorphism, high nuclear-cytoplasmic ratio, vesicular chromatin, prominent nucleoli, lack of tubule formation, high mitotic index, frequent apoptotic cells, scant stromal content, pushing invasion borders, central geographic or comedo-type necrosis and stromal lymphocytic infiltrate. They are also characterised by the presence of metaplastic elements such as spindle cells and squamous cell metaplasia, presence of a central scar, glomeruloid microvascular proliferation and a stromal lymphocytic response [49, 50, 59, 63, 64, 96]. Mitotic figures frequencies of more than 25/10hpf [44] and up to 40/10hpf [63] have been reported. Although these features are strongly associated with *BLC* and can help in the identification of these tumours [59, 65, 93], they are generally not specific and individual feature can be seen in other high grade tumours regardless of their immunophenotype, thus emphasising the importance of IHC detection of specific (*basal*) markers as a realistic and simple method to identify these tumours (invasive ductal carcinomas NST with basal-like phenotype) in routine practice.

Some reports have suggested that *BLC* may achieve extraordinarily rapid clinical growth rates [97]. The high proliferative activity of *BLC* may probably explain why these tumours are over-represented amongst the so-called interval breast cancers (e.g., cancers arising between annual mammograms) [98]. The reported association between *BLC* and lymph node stages varied between different studies. Some authors did not find association [33, 49, 50, 60, 92], while others have reported association with lymph node negativity [45, 57–59]. Some studies have reported as association between *BLC* and larger primary tumour size [49, 59]. In addition, there is compelling evidence that there is a link between *BLC* and either *BRCA1* germline mutations or a dysfunctional BRCA1 pathway [99, 100]. Many phenotypical, immunohistochemical, clinical characteristics and molecular features are shared by

BLC and tumours that arise in carriers of *BRCA1* germline mutations [99]. These include high histological grade, high proliferative activity, features of medullary-like carcinoma and triple-negative phenotype. The majority of breast cancers arising in *BRCA1* germline mutation carriers express basal CKs, in addition to other markers commonly seen in *BLC*s such as p53, P-cadherin and EGFR [4, 46, 49, 101–105] and, in most studies, both patient groups have a poor outcome [49, 106]. In keeping with these similarities, clustering analyses of microarray expression profiling data have shown that familial *BRCA1* mutant tumours tend to fall into the *BLC* category. This latter observation also suggests that the carcinogenic pathways or causes of these two subtypes of breast cancer [4] may be similar.

Prognostic significance of *BLC*

Despite differences in the definition and prevalence of *BLC* in various studies, the poor outcome of patients with *BLC* has been reported in many different patient populations [3, 4, 31, 36, 57, 59, 61, 75]. *BLC* is associated with an aggressive clinical history, development of recurrence, distant metastasis, shorter survival and a relatively high mortality rate [3, 4, 11, 36, 49, 50, 53, 58, 59, 61, 67]. Previous studies have demonstrated that *BLC* phenotype is an independent marker of poor prognosis in breast cancers as a whole [1, 9–11], in the lymph node (LN) negative [49, 53, 67], and LN positive groups [31, 54]. *BLC* phenotype was found to predict a particularly aggressive course in patients with grade 3 who are lymph node negative [61], have metastatic disease [51] or treated with adjuvant anthracycline chemotherapy [58].

Despite the numerous studies demonstrating the poor prognosis of patients with BLCs, there is some evidence to suggest that this may not be as uniform as previously anticipated. Some studies did not find prognostic significance for *BLC* in LN positive [49, 53, 67], LN negative disease [31, 54] or lower grade tumours [61]. Jumppanen et al. [33] have investigated 375 breast tumours and found that CK5/6/14 positive *BLC*s did not do worse than other ER-negative cancers. Similar findings were reported by Potemski et al., using CK5/6 and CK17 [53]. Fulford et al. [51] have also reported that CK14-positive *BLC*s have a prognosis similar, or slightly better than, other grade III, CK14-negative breast cancers. Although some reports have demonstrated that the worse survival and most of the relapses in the *BLC* occurred in the first 3–5 years [33, 36], one study showed that the reduction in survival increased with time, becoming more pronounced at 10 years than at 3 years [57]. It has also been reported that *BLC* is not associated increased risk for locoregional relapse after conservative surgery [107] or after adjuvant-anthracycline therapy [58]. To understand the actual prognostic significance and reason for this degree of variation of the prognostic value of *BLC*, it is important to mention the following points:

(i) In gene expression microarrays the prognosis of *BLC* was compared to that of luminal/ER positive tumours [3, 11, 23, 108], which are already known to have a better prognosis and therefore, association of *BLC* (ER negative, high grade tumours) with a worse prognosis is not surprising. When *BLC*s have been compared to HER2 positive tumours, they showed similar outcome [23, 92, 108]. However, it should also be noted that in most of these studies, HER2 positive patients did not receive specific anti-HER2 therapy. Lack of association between *BLC*s and poor survival in ER negative tumours [33] can also be explained by the presence of the majority of HER2 positive tumours within the ER-negative group. Thus, both *BLC* and the majority of non-*BLC* ER-negative cancers are expected to have poor outcome. It should be noted that with the introduction of Trastuzumab + chemotherapy as first line therapy for HER2-positive breast cancers, the prognosis of patients with HER2-positive cancers will significantly improve. It is, therefore, likely that if HER2 positive breast cancer patients receive anti-HER2 targeted therapy, they will have survival advantage over *BLC* leaving patients with *BLC* with the worst outcome.

(ii) The observed discrepancies on the prognostic significance of *basal-like* cancer as defined by IHC may be related to differences between the studies in patient cohorts, treatment modalities, analytic methods and perhaps most importantly, the IHC definitions of *BLC*. For instance, some studies, which used single basal CK (i.e. CK14) to define *BLC*, did not find an association with survival [51, 52]. This may be the result of an incomplete definition of *BLCs* in those studies. Incomplete definitions may lead to paradoxical results which stem from the allocation of elements from one group to another, leading to dramatic changes in the average values of both sets [109]. This is supported by our findings [59] in which we demonstrated that two *basal* markers did not identify exactly the same tumours when used alone and the associations with overall survival were different between tumours defined either by CK14, CK5/6 or by both CKs (CK14 and/or CK5/6) expression. Consistent with our observation, similar finding with CK5/6 and 14 [46, 70] and CK5 and CK17 [67] have been reported. In addition, it has been reported that the staining patterns of these basal CKs can be highly variable and heterogeneous [34,

51, 67]. Another important point is that some studies have used a triple-negative phenotype to define *BLC* [43] and reported specific findings as being associated with or feature of *BLC*.

(iii) *BLC* is not a homogenous class of tumours with differences at molecular, morphological and prognostic levels. This may, in fact, be a reflection of variation in the definition of *BLC*. For instance, typical medullary carcinomas are often classified as *BLC* because they have the same molecular and immunophenotypic features of *BLC* [93–95]; however, there is evidence to suggest that this group of cancers has a favourable prognosis [110] or at least lack any adverse effect on patients' outcome [111, 112]. Likewise, myoepithelial and salivary-gland like tumours (see below) are associated with a rather indolent clinical behaviour despite the fact that these cancers often harbour a basal-like immunophenotype. However, these tumours have distinct morphologic features that can be used to identify and manage them as separate entities. Therefore, it may be important to emphasise that the commonest form of *BLC* as originally identified in gene expression microarray studies has particular morphological and molecular characteristics, as described above, but is one of several sub-types of basal phenotype breast cancer entities. Other known good prognostic classes of basal phenotype tumours such as myoepithelioma (see below) merit greater recognition and improved definition in order not to confuse patients and clinicians. Some of the IHC markers used to define *BLC* (i.e. basal CKs and EGFR) are expressed in lower grade tumour and although in a low proportion of cases and the significance of this is currently unknown, inclusion of these tumours may affect the outcome results [45, 46, 61]. Furthermore, the survival of patients with *BLC* is expected to be different in cases where particular additional features, such as ER negativity, are used as a defining feature of those tumours.

Metastatic pattern

*BLC*s have been shown to have a specific pattern of metastatic spread, with an increased propensity for visceral metastases to brain (CNS) and lung; sites know to be associated with a poorer prognosis [113]. Conversely, these cancers are less likely metastasise to bone, liver and axillary lymph nodes [50, 51, 75, 96, 114]. CNS or brain metastases traditionally occur in 10–16% of metastatic breast cancer patients and are associated with a dismal prognosis. In a recent study, Gaedcke et al. [115] found that the majority of breast cancer that developed CNS metastases are *BLC* and HER2 positive. These CNS metastatic tumours are usually hormone receptor negative, EGFR and basal CKs (CK5/14) positive [116, 117]. These findings may suggest that *BLC* might also posses a distinct mechanism of metastatic spread. Further studies to unravel the underlying molecular mechanisms for this distinct pattern of spread are warranted.

Myoepithelial and salivary gland-like tumours

Breast carcinomas showing true ME features, including pure myoepithelial carcinoma, adenomyoepithelioma, adenoid cystic carcinoma, low grade adenosquamous (syringomatous) carcinoma, poorly differentiated myoepithelial-rich carcinoma and malignant adenomyoepithelioma, are rare tumours but have been increasingly reported in the literature [118–122]. Apart from adenomyoepithelioma, adenoid cystic carcinoma and low grade adenosquamous (syringomatous) carcinoma, which have been shown to be low malignant potential tumours, the definition, natural history and clinical behaviour of other malignant myoepithelial lesions of the breast remain controversial. Interestingly, the metastatic pattern of some malignant myoepithelial tumours is remarkably similar to that of *BLC* in that they usually skip axillary lymph nodes and preferentially disseminate to lung and brain. Furthermore, all of these lesions are consistently characterised by the lack of ER and HER2 expression and the expression of basal/ myoepithelial markers, including basal CKs. In addition, differentiation between malignant myoepithelioma/myoepithelial carcinoma and some forms of metaplastic breast cancer is not achievable. Hence, from an immunohistochemical and molecular perspective, it would be reasonable to suggest that these lesions should be included in the spectrum of *BLC*.

The hypothetical morphological spectrum of *BLC* encompasses not only grade III invasive ductal carcinomas and carcinomas with medullary features, but also at the low end of the spectrum adenoid cystic carcinomas and, at the upper end of the spectrum, high grade, malignant tumours with overt myoepithelial differentiation, such as malignant myoepitheliomas and metaplastic breast carcinomas. Fortunately, the identification of lesions in the low and upper end of the spectrum can be easily achieved by means of morphological analysis alone.

Within the group of grade III invasive ductal carcinomas and carcinomas with medullary features with *BLC* phenotype, the expression of some SM markers characteristic of ME cells has been documented and may have a prognostic or biological value related to the type or degree of differentiation of the cells from which these tumours arise or to the peculiar differentiation pattern these tumours acquire [44, 59, 65]. However, the actual clinical and

biological significance of the expression of myoid markers and other markers related to terminal myoepithelial differentiation still remains as a matter of speculation. In a previous study, we have shown that breast tumours that express ME specific markers only (8.6%) for example SMA and/or p63 without expression of CK5/6 and/or 14 have a better outcome than tumours that express basal CKs (*basal-like*) including tumours that express basal CKs only (13.6%) or combined ME specific markers and basal CKs (4.8%) [59]. These results were confirmed in another study [44, 49] which reported infrequent expression of ME markers (SMA, p63 and CD10) in *BLC*. In addition, although some of *BLC*s show areas with spindle cell morphology that show unequivocal myoepithelial differentiation [123], these might be considered as metaplastic elements within these aggressive high grade "ductal" breast tumours similar to other types of metaplasia seen in high grade cancer such as squamous, chondroid and clear cells. In other words, although it is acceptable to include these cancers within the subgroup of *BLC*, the special type needs to be emphasised, in particular in the case of low malignant potential entities such as low grade adenomyoepithelioma or adenoid cystic carcinoma.

BLC and cancer stem cell: the dilemma

The relationship between the newly recognised breast cancer subtypes, as identified by gene expression microarrays, to the cell of origin and whether these *basal-like* cells belong to mammary stem/progenitor cell lineage is not yet known. However, it has been hypothesised that there are distinct epithelial cell types and lineages within the breast with probably several intermediate states [124–126] and rapid progress is being made concerning the characterisation of the various mammary epithelial cell types and putative cancer stem cells. The precise sequence of the stages linking these cell types to each other and to cancer arising from them is under investigation leading to proposals for several hierarchical branching models of differentiation [125, 127] (Fig. 1).

Although it has been suggested that tumours pertaining to different breast cancer subtypes may originate from different cell stages in differentiation lineages of the mammary stem/progenitor cells (i.e. *BLC* would originate from differentiated "*basal-like*" cells), there is no direct evidence to prove that this is the case. Also, *BLC* is unlikely to be derived from differentiated myoepithelial cells because the majority of these tumours (duct carcinoma NST with basal-like phenotype) do not express myoid markers (i.e. SMA) or other myoepithelial specific markers (i.e. p63) and usually express luminal CKs in addition to the *basal* CKs [44, 59]. Based on the remarkable degree of genetic instability of *BLC*s and their extremely complex karyotypes, some have hypothesised that the expression profile of *BLC* would not be a mere reflection of that of their cells of origin, as genomic changes have been shown to lead to significantly altered expression of genes mapping to affected regions [128]. However, there are several lines of evidence to suggest that the effects of genetic changes have been shown to be context and cell dependent, hence, it would be reasonable to speculate that perhaps some genetic changes could only lead to tumour development in certain cell types (i.e. in other cell types it would lead to cell death) [71]. In that case, the final phenotype of a tumour would depend on a combination of the type of genetic change and the constitution of the target cell.

In addition, BRCA1, which is commonly altered in *BLC*, has been reported to function in normal differentiation pathways in breast tissue [99, 129, 130]. It might possible, therefore, that the loss of *BRCA1* gene expression in a breast cancer stem/progenitor cell may result in deregulated differentiation, leading specifically to the development of tumours with *basal-like* characteristics. The model proposed by Behbod and Rosen [127] considers myoepithelial differentiation as being end-stage and *BLC* arising from ER-negative long-term stem cells. This model would indicate that the stratified cytokeratins are markers of more than one cell population in the normal breast. Alternatively, given that BRCA1 also works as a transcription factor, it is possible that lack of BRCA1 expression leads to expression of '*basal-like*' genes regardless of the cell type. This concept is in part supported by a recently developed mouse model. McCarthy et al. [131], have used germline manipulation to generate a conditional mouse model of *BRCA1* deficiency in luminal epithelial cells of the mouse mammary gland and that has lead to the development of tumours that recapitulate human *BLC*s.

Furthermore, the concept of tumour histogenesis has been called into question at least in the field of soft tissue tumours [132, 133]. There is circumstantial evidence to suggest that it is unreliable to rely on the expression of markers such as CKs to indicate cells of origin of a given tumour. During neoplastic transformation, cells display considerable variability and plasticity and therefore, cancer cells may remain stable, lose, or acquire new features of differentiation that are different to that of cells of origin. Hence, it remains to be determined whether the expression profiles identified by microarray analysis are a true reflection of the cell of origin or identify the patterns of differentiation of a given tumour. Noteworthy, in the field of soft tissue tumour biology and pathology, the concept of histogenesis has been almost entirely replaced by the concept of tumour differentiation; the latter seems more appropriate in this era of tailored therapies and predictive classification systems.

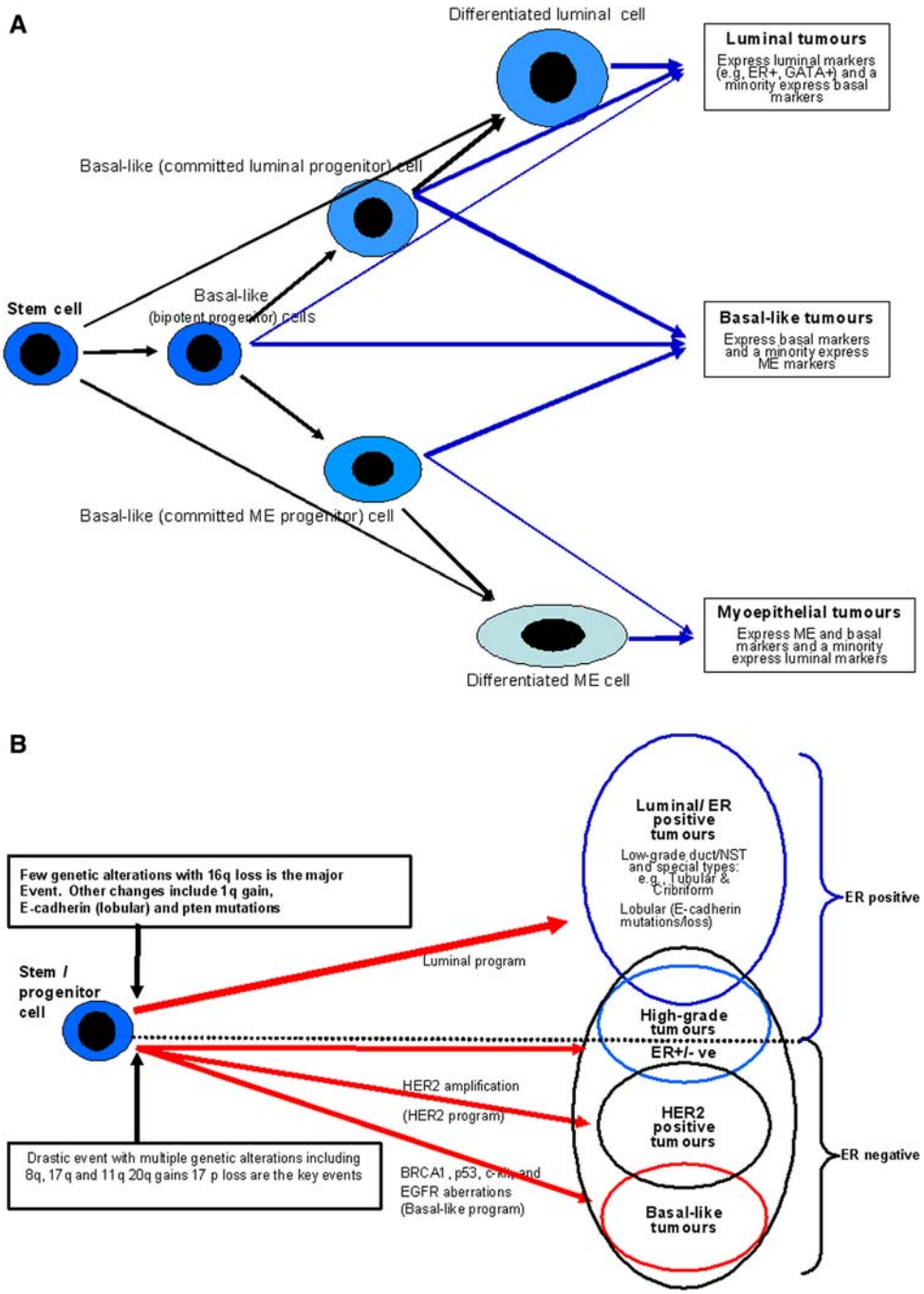

Fig. 1 Hypothetical models for the origin of basal-like, HER2 and luminal breast tumours. (**a**) (Linear cell of origin theory) Stem cells give rise to uncommitted progenitor "basal-like" cells (express luminal and basal markers with or without ME specific markers) which subsequently give rise to committed 'luminal' basal-like (express luminal and basal markers and a minority may express ME markers) and 'ME' basal-like (express basal and ME markers and a minority may express luminal markers) cells that finally differentiate into luminal (express luminal markers and the majority lose their basal markers) and myoepithelial (express ME and basal markers) cells. In this model, basal-like tumours (middle) would mainly stem from uncommitted basal-like cells but a proportion may be derived from committed luminal or ME basal-like cells. Luminal tumours are derived from luminal cells or committed luminal basal-like cells while ME tumours may be derived from ME cells or committed ME basal-like cells. Clonal tumour expansion originates from any cell, whatever its stage of differentiation and the tumour cells acquire a self-renewing capacity but preserve the characteristics of their cell of origin. (**b**) In the alternative 'hierarchy or stem cell' model, transformation occurs in a stem cell, or more likely in a progenitor 'highly proliferating' cell, and expansion proceeds concomitantly to usual maturation until various stages, depending on the identity of genomic alterations. The respective genetic alteration would lead to distinct cellular transcriptomic programmes, including the change of hormone receptors and CKs expression pattern, characterising distinct subgroups of invasive breast cancer

Furthermore, although the expression of some *basal* markers in the associated in situ lesions (DCIS) [37, 69] support the origin of *BLC* invasive cancer from *basal-like* DCIS and the presence of *basal-like* feature early in the process of carcinogenesis, it does not support the origin from *basal-like* cancer stem cell. Furthermore, the majority of basal-like DCIS are of high grade and these have been shown to have remarkably complex patterns of genetic aberrations [134]. We have seen many of HER2 positive DCIS cases associated with HER2 negative invasive cancer and ER positive DCIS with ER negative cancers and vice versa (Rakha and Ellis unpublished observation).

In conclusion, *BLC* breast cancer is a distinct group of tumours that show common but heterogeneous morphologic, genetic and immunophenotypic features. These tumours are associated with poor clinical outcome and specific patterns of distant metastasis, which would be best seen as a spectrum of lesions. The current definition of *BLC* varies widely and further refinement of the criteria for the identification of *BLC*s is required. Although *BLC*s respond to chemotherapy, patients with these tumours still have a poor prognosis. Hence, studies to define more appropriate chemotherapy regimens and to identify specific targeted therapies for *BLC*s are warranted.

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