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Review

Basal-like and triple-negative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists

Sunil Badve[1], David J Dabbs[2], Stuart J Schnitt[3], Frederick L Baehner[4], Thomas Decker[5], Vincenzo Eusebi[6], Stephen B Fox[7], Shu Ichihara[8], Jocelyne Jacquemier[9], Sunil R Lakhani[10], José Palacios[11], Emad A Rakha[12], Andrea L Richardson[13], Fernando C Schmitt[14], Puay-Hoon Tan[15], Gary M Tse[16], Britta Weigelt[17], Ian O Ellis[12] and Jorge S Reis-Filho[18]

[1]*Clarian Pathology Lab, Department of Pathology and Internal Medicine, Indiana University, Indianapolis, IN, USA;* [2]*Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA;* [3]*Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA;* [4]*Department of Anatomic Pathology, University of California, San Francisco, CA, USA;* [5]*Breast-Screening-Pathology, Gerhard Domagk-Institute of Pathology, Reference Centre Münster, University Hospital Münster, Münster, Germany;* [6]*Sezione Anatomia Istologia e Citologia Patologica 'M Malpighi', Università-ASL Ospedale Bellaria, Bologna, Italy;* [7]*Pathology Department, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia;* [8]*Department of Pathology, Nagoya Medical Center, Nagoya, Japan;* [9]*Unité d'Anatomie et de Cytologie Pathologiques, Institut Paoli-Calmettes, Marseille, France;* [10]*Molecular and Cellular Pathology, University of Queensland Centre for Clinical Research, School of Medicine and Pathology Queensland and The Royal Brisbane and Women's Hospital, Brisbane, Australia;* [11]*Servicio de Anatomía Patológica, Hospital Universitario Virgen del Rocío, Sevilla, Spain;* [12]*Department of Histopathology, Nottingham City Hospital NHS Trust, Nottingham University, Nottingham, UK;* [13]*Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA;* [14]*Medical Faculty, Institute of Molecular Pathology and Immunology (IPATIMUP), University of Porto, Porto, Portugal;* [15]*Department of Pathology, Singapore General Hospital, Singapore, Singapore;* [16]*Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China;* [17]*Signal Transduction Laboratory, Cancer Research UK London Research Institute, London, UK and* [18]*The Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, London, UK*

Breast cancer is a heterogeneous disease encompassing a variety of entities with distinct morphological features and clinical behaviors. Although morphology is often associated with the pattern of molecular aberrations in breast cancers, it is also clear that tumors of the same histological type show remarkably different clinical behavior. This is particularly true for 'basal-like cancer', which is an entity defined using gene expression analysis. The purpose of this article was to review the current state of knowledge of basal-like breast cancers, to discuss the relationship between basal-like and triple-negative breast cancers, and to clarify practical implications of these diagnoses for pathologists and oncologists.
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Correspondence: Professor S Badve, MD, FRCPath, Department of Pathology and Internal Medicine, Indiana University, 350 W 11th Street, Indianapolis, IN 4010, USA or Professor Jorge S Reis-Filho, MD, PhD, FRCPath, The Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, UK.
E-mail: sbadve@iupui.edu or jorge.reis-filho@icr.ac.uk
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Breast cancer is a heterogeneous disease, and this term encompasses a variety of entities with distinct morphological features and clinical behaviors. In recent years, it has become apparent that this diversity is the result of distinct genetic, epigenetic, and transcriptomic alterations.[1–5] Although morphology is often associated with the pattern of molecular aberrations in breast cancers,[5] it is also

clear that tumors of the same histological type show remarkably different clinical behavior. This is most evident in invasive ductal carcinomas of no special type (IDC-NST), where even tumors of the same histological grade may have distinct outcomes and dramatically different responses to systemic therapy.[2,3]

Using high-throughput technologies, particularly microarray analysis, several groups have proposed a new taxonomy for breast cancer based on their molecular features. The gene expression microarray-based class discovery studies pioneered by the Stanford group have led to the identification of at least five molecular breast cancer subtypes: luminal A, luminal B, normal breast-like, HER2, and basal-like.[6–11] Although based on the analysis of a limited number of samples and with somewhat different definitions for the various molecular groups in these studies, this approach to the classification of breast cancer has captured the attention of oncologists, pathologists, and scientists alike.

It should be noted, however, that this taxonomy has identified subgroups of breast cancer that were to some extent already known, and that the stability of the assignments of molecular subtypes by microarray-based methods has been called into question.[12–14] Indeed, the most robust distinction observed by microarray analysis is between the transcriptome of estrogen receptor-positive (ER+) and ER-negative (ER−) breast cancers.

Among the molecular subtypes of breast cancer identified through gene expression profiling studies, none has generated as much interest or controversy as the basal-like group. The purpose of this article was to review the current state of knowledge of basal-like breast cancers, to discuss the relationship between basal-like and triple-negative breast cancers, and to clarify practical implications of these diagnoses for pathologists and oncologists.

What is a basal-like breast cancer?

The characteristics of basal-like breast cancer have been extensively reviewed in the past 18 months.[10,14–16] It should be noted that there is still no internationally accepted definition for basal-like breast cancers and how best to define these tumors is a matter of controversy and ongoing debate. Some groups have used microarray-based expression profiling to define basal-like breast cancers, whereas others have used panels of immunohistochemical markers as surrogates. However, direct comparisons between the proposed immunohistochemical markers and the microarray-defined molecular subtypes are scarce.[17,18] Immunohistochemical marker panels that have been proposed to define basal-like breast cancers include: (1) lack of ER, PR, and HER2 expression ('triple-negative' immunophenotype); (2) expression of one or more high-molecular-weight/basal cytokeratins (CK5/6, CK14, and CK17); (3) lack of expression of ER and HER2 in conjunction with expression of CK5/6 and/or epidermal growth factor receptor (EGFR);[17] and (4) lack of expression of ER, PR, and HER2 in conjunction with expression of CK5/6 and/or EGFR.[19]

Despite the different definitions for basal-like breast cancers, it has been demonstrated that these tumors have distinctive clinical presentations,[20] histological features,[18,21] response to chemotherapy,[22–28] sites of distant relapse, and outcome.[7,9,29–31] In brief, basal-like tumors comprise a heterogeneous group that accounts for up to 15% of all breast cancers, affect younger patients, are more prevalent in African-American women, and often present as interval cancers. Histologically, the majority of basal-like breast cancers is of IDC-NST type, high histological grade, and characterized by exceptionally high mitotic indices, the presence of central necrotic or fibrotic zones, pushing borders, conspicuous lymphocytic infiltrate, and typical/atypical medullary features (Figure 1).[18,21,32] The similarity of these features with those of human papilloma virus-induced squamous cell carcinoma of the head and neck has led to the identification of the role of retinoblastoma gene (*RB1*) in these tumors.[33] However, not all basal-like cancers are of the IDC-NST type; the majority of medullary and atypical medullary,[4,34–36] metaplastic,[4,37,38] secretory,[39] myoepithelial, and adenoid cystic carcinomas[4,40] of the breast also show a basal-like phenotype.[5] More recently, a subgroup of lobular carcinomas has been shown to express high-molecular-weight cytokeratins,[41] however it remains to be determined whether these cases truly show a basal-like transcriptome. The majority of basal-like breast cancers lack or show low levels of ER and PR, lack HER2 protein overexpression and *HER2* gene amplification, whereas they express genes and proteins usually found in 'basal'/myoepithelial cells of the normal breast including high-molecular-weight cytokeratins (5/6, 14 and 17),[17,19,21,42] P-cadherin,[43] caveolins 1 and 2,[44,45] nestin,[46] αB crystallin,[47,48] CD109,[49,50] and EGFR[17] and, in a minority of cases, harbor *EGFR* gene amplification[51] or aneusomy.[52] p53 immunohistochemical expression or *TP53* gene mutations is observed in up to 85% of cases,[53,54] and alterations of the pRB and p16 G1/S cell-cycle checkpoint are remarkably prevalent in these cancers.[33,55] A recent study demonstrated that approximately 30% of basal-like breast cancers concurrently show lack of pRB expression, overexpression of p16 and p53 immunoreactivity (pRB−/p16+/p53+), whereas this profile was rarely seen in tumors of other molecular subtypes.[33] Basal-like cancers show remarkably high proliferation indices as defined by mitotic counting or by Ki67 labeling index.[26,33,56]

Of interest, basal-like breast cancers, unlike 'basal'/myoepithelial cells of normal breast, almost uniformly express cytokeratins 8 and/or 18, calling into question the initial histogenetic implications of the microarray-based taxonomy of breast cancers

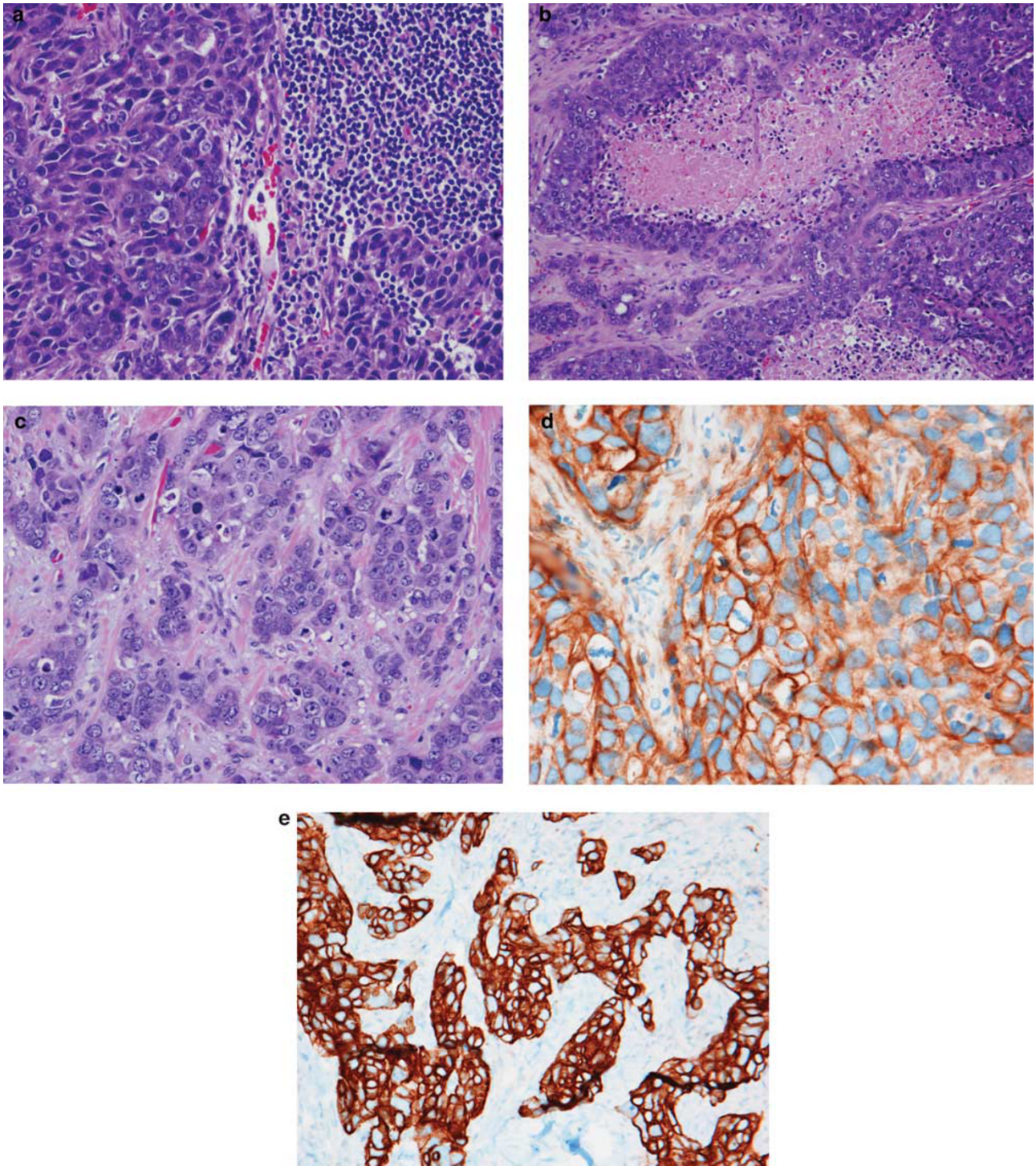

Figure 1 The typical morphological features of triple-negative/basal-like cancer are those of a high-grade ductal carcinoma (Nottingham grade 3) associated with prominent lymphoid aggregates (**a**). It is not uncommon to observe extensive areas of necrosis (**b**) or central fibrosis. Cytologically, the tumor cells show marked nuclear pleomorphism and conspicuous mitotic activity (**c**). Prominent membranous expression of EGFR (**d**) and CK5 (**e**) is frequently noted.

that suggested that basal-like cancers would arise from basal/myoepithelial cells.[5,14] This has been emphasized in a recent study, which suggested that at least a subgroup of basal-like breast cancers may originate from luminal progenitors rather than basal/myoepithelial cells of the breast,[57] and confirmed by the results of conditional mouse models.[58] In this context, it is important to note that histogenesis and differentiation are two distinct processes although often mistakenly used as synonyms.

What is a triple-negative breast cancer?

In contrast to the controversy regarding the definition of basal-like breast cancers, there is uniform agreement that triple-negative cancers are defined as tumors that lack ER, PR, and HER2 expression. These tumors account for 10–17% of all breast carcinomas,[1,24,28,59–65] depending on the thresholds used to define ER and PR positivity and the methods used for HER2 assessment. Future studies are likely to produce slightly different prevalence rates for triple-negative breast cancers given the change in the definition of HER2 and hormone receptor positivity according to the ASCO/CAP guidelines.[66,67] Despite these definitional issues, the clinical interest in these tumors stems from the lack of tailored therapies for this group of breast cancer patients and the overlap with the profiles of basal-like cancers.

The main characteristics of triple-negative cancers that have emerged from the literature illustrate their similarities to basal-like cancers, including the fact that they more frequently affect younger patients (<50 years),[24,30,31,59,61,62] are more prevalent in African-American women,[62–64] often present as interval cancers, and are significantly more aggressive than tumors of other molecular subtypes.[24,28,59,61–63] This aggressiveness is best exemplified by the fact that the peak risk of recurrence is between the first and third years and the majority of deaths occur in the first 5 years following therapy.[59,61] Patients with triple-negative cancers,[59,63] similar to those with basal-like cancers,[42] have a significantly shorter survival following the first metastatic event when compared with those with non-basal-like/non-triple-negative controls.

Are basal-like and triple-negative cancers synonymous?

As should be evident from the foregoing discussion, although there are numerous similarities between basal-like and triple-negative breast cancers, these two terms are not synonymous, despite the fact that some have previously used these terms interchangeably.[10,15,53,68,69] It is true that the majority of triple-negative cancers are of basal-like phenotype[22,60,68] and the majority of tumors expressing 'basal' markers are triple-negative.[16,17,19,53,60,70] However, not all basal-like cancers determined by gene expression profiling lack ER, PR and HER2,[10,12,15,16,68,70–74] and conversely not all triple-negative cancers show a basal-like phenotype by expression array analysis. For example, Bertucci *et al*[70] showed that only 71% of triple-negative cancers were of basal-like subtype by gene expression profiling and that only 77% of molecular basal-like tumors were triple-negative. Similar results were observed by de Ronde *et al*[74] and Parker *et al* (Supplementary Table 1 of Parker *et al*[11]), where 8–29% of triple-negative cancers did not show a basal-like subtype by expression array analysis and 18–40% of basal-like breast cancers defined by gene expression profiling did not harbor a triple-negative phenotype. Further, there is a significant number of triple-negative cancers that do not express basal markers and are classified as normal breast-like (probably an artifact of gene expression profiling due to samples with disproportionately high content of stromal and normal breast epithelial cells),[11,75,76] molecular apocrine[77,78] (tumors with androgen receptor pathway activation, although a substantial proportion of these tumors may be classified as of HER2 subtype[78] using other molecular classification systems) or claudin-low[79,80] (cancers with transcriptomic features suggestive of epithelial to mesenchymal transition and reported to be enriched for the so-called 'cancer stem cells') subtype by gene expression profiling (for review, see Weigelt *et al*[12]). Apart from the more heterogeneous transcriptome, triple-negative cancers also show more varied histological features. Indeed, up to 10% of triple-negative tumors were reported to be of grade I in one study.[59] However, numerous other studies have failed to identify any grade I breast cancers with a triple-negative phenotype. Furthermore, other histological special types of breast cancer that do not show a basal-like phenotype by transcriptomic analysis have been shown to occasionally express a triple-negative phenotype, including apocrine carcinomas, pleomorphic lobular carcinomas, and some mixed duct-lobular cancers.[1,15,69] Taken together, these results are in accord with the concept that the triple-negative phenotype is not an ideal surrogate marker for basal-like breast cancers.[60,70,81]

Relationship between basal-like breast cancer and *BRCA1* germ-line mutations

There is increasing evidence to suggest a link between BRCA1 pathway and basal-like breast cancers.[82,83] The majority of tumors arising in *BRCA1* germ-line mutation carriers, in particular those diagnosed before 50 years of age, have morphological features similar to those described in basal-like cancers[84,85] and show a basal-like phenotype as defined by immunohistochemistry[86,87] or expression arrays.[8]

Both basal-like breast cancers and tumors arising in *BRCA1* germ-line mutation carriers show a peculiar pattern of cell-cycle protein expression;[54,84,88,89] both rarely harbor *CCND1* gene amplification;[54,88] however, they express significantly lower levels of p27,[84,89] and higher levels of Skp2,[84,89] cyclin E,[84,89] and caspase-3,[89] when compared with sporadic breast carcinomas and *BRCA2* mutation tumors.

Although they lack *BRCA1* somatic mutations, sporadic basal-like cancers show similar molecular genetic profiles to tumors arising in *BRCA1*

mutation carriers.[90–94] This may be in part due to the presence of a dysfunctional BRCA1 pathway in these tumors.[32,82,83] *BRCA1* gene promoter is methylated in >60% of medullary[95,96] and metaplastic[32] breast cancers of basal-like phenotype. Sporadic invasive ductal carcinomas with basal-like phenotype express ID4, a negative regulator of *BRCA1*,[97,98] at significantly higher levels than grade-matched controls.[32] This mechanism may account for the low levels of BRCA1 expression in sporadic basal-like carcinomas of ductal morphology. Importantly, recent studies have demonstrated that *BRCA1* gene silencing leads to downregulation of ER[99] and upregulation of genes considered to be markers of basal-like cancers,[100] including CK5, CK17, and P-cadherin. In contrast, reconstitution of BRCA1 in ER− BRCA1 mutant cell lines has been shown to lead to upregulation of ER and downregulation of CK5, CK17, and P-cadherin.[99,100] Taken together, BRCA1 dysfunction appears to be one of the drivers of basal-like breast cancers and of a subgroup of triple-negative tumors.

Precursors of basal-like and triple-negative cancers

A group of high-grade DCIS lacking ER, PR and HER2, and expressing 'basal' markers has been identified.[101–107] However, it should be noted that its prevalence is lower than that of invasive triple-negative and basal-like breast cancers and that triple-negative and basal-like cancers often lack an overt *in situ* component. Whether this is the result of basal-like and triple-negative breast cancers progressing rapidly from DCIS to invasive cancer and/or obliterating the DCIS precursor from which they arose remains a matter of speculation.

The majority of invasive cancers developing in microglandular adenosis is of triple-negative phenotype[108–112] and show metaplastic elements or is of adenoid cystic morphology.[109–112] It has been recently shown that microglandular adenosis may be a nonobligate precursor of triple-negative and basal-like breast cancers.[108,113] A stepwise progression in the number of gross chromosomal changes from microglandular adenosis to invasive carcinoma has been observed.[108] However, given the rarity of microglandular adenosis, it is unlikely to be the precursor lesion for most triple-negative cancers.

Clinical behavior of basal-like and triple-negative breast cancers

Basal-like and triple-negative breast cancers, as defined by microarrays or by immunohistochemical surrogates, have been shown to have a more aggressive clinical behavior.[17,114,115] In fact, some studies have demonstrated that expression of basal keratins is a prognostic factor independent of tumor size, grade, and lymph node status.[114] However, when compared with either ER− non-basal-like cancers[72] or grade-matched non-basal-like cancers,[42] carcinomas with a basal-like phenotype are not associated with a poorer outcome in some studies, whereas a more adverse prognosis is observed in others.[19,116] The pattern of metastatic spread of tumors with a basal-like phenotype seems to be different from that of non-basal-like cancers: they are reported to less frequently disseminate to axillary nodes and bones[42,117] and to favor a hematogenous spread,[42,117–119] with a peculiar proclivity to develop metastatic deposits in the brain and lungs.[120] It should be noted that patients with triple-negative and basal-like cancers tend to develop adverse events and die due to disease within the first 5–8 years after diagnosis. After the 8-year mark, the hazard rate for patients with grade 2 or ER-positive cancers is actually higher than that of patients with basal-like cancers. Finally, some tumors in the 'basal' group have a favorable prognosis, eg, adenoid cystic carcinomas[40,121] and secretory carcinomas.[39] This emphasizes that basal phenotype and bad behavior are not inextricably linked and serves to highlight the heterogeneous nature of basal-like carcinomas. It is controversial as to whether these tumors should be classified as the basal-like carcinomas or should represent a distinct group by themselves.

As to treatment response, 17–58% of patients with triple-negative breast cancers have been shown to have a pathological complete response after anthracycline- or anthracycline + taxane-based neoadjuvant chemotherapy[25,28,122,123] and 17% of triple-negative cancers have been shown to have a pathological complete response after neoadjuvant platinum-based chemotherapy.[124] However, those who fail to achieve pathological complete response have a dismal outcome.[25,28] It should be noted, however, that markers for the identification of patients with triple-negative and basal-like cancers that benefit most from chemotherapy remain to be defined. Recently, several groups have identified a subgroup of good prognosis ER− cancers, encompassing a subgroup of triple-negative and basal-like tumors, which is characterized by the expression of an immune response module.[125–128] This transcriptomic profile may prove helpful for the identification of patients with triple-negative and basal-like cancers that have a better outcome. In this context, the finding of higher expression of CT-X antigens (in particular MAGE and NY-ESO) in this subgroup opens up another potential avenue for therapy as vaccines against these antigens are already in clinical trial for lung cancer.[129]

Finally, as mentioned earlier, a group of basal-like and triple-negative breast carcinomas have been shown to have a dysfunctional BRCA1 pathway.[32,65,81–83] A significant number of these cases lack competent homologous recombination DNA repair. This subgroup may be amenable to specific therapeutic strategies such as inhibitors of the PARP

enzyme.[32,81–83,130,131] Consistent with this hypothesis, results of PARP inhibitor phase I and phase II clinical trials that have included patients with BRCA-deficient tumors have been encouraging[132–134] and sustained responses in patients with BRCA1/2-deficient breast or ovarian metastatic cancers have been observed. Furthermore, preliminary results of a phase II clinical trial revealed that addition of BSI-201, a PARP inhibitor, to gemcitabine/carboplatin chemotherapy led to a significantly increased clinical benefit and longer progression-free survival.[135] However, the specificity of this compound for PARP has yet to be fully established.

Given these exciting results, several clinical trials testing cross-linking agents (eg carboplatin and cisplatin) and PARP inhibitors in patients with *BRCA1* germ-line mutations and sporadic basal-like breast cancers are currently ongoing (for a list of clinical trials, please see clinicaltrials.gov). If positive, these studies may render the identification of tumors lacking competent homologous recombination compulsory in our diagnostic practice.[130]

Practical implications of basal-like and triple-negative breast cancers

As outlined above, a diagnosis of triple-negative breast cancer has direct clinical implications. Given that these tumors lack expression of hormone receptors and lack HER2 protein overexpression and gene amplification, chemotherapy is the only modality of adjuvant systemic therapy currently available for patients with triple-negative disease. Furthermore, the current prognostic algorithms to define which patients should receive chemotherapy may not work optimally for patients with triple-negative breast cancer, given that the impact of size on the outcome of these patients appears to be significantly attenuated.[136,137]

At present, use of the term 'basal-like breast cancer' in diagnostic surgical pathology reports does not appear to be justified, as it does not lead to any direct clinical action. In fact, given the variations in definition of basal-like breast cancers, such a diagnosis may cause clinical confusion. For instance, according to some definitions, a breast cancer showing ER expression and expression of CK 5/6 or CK 14 would be classified as being of basal-like phenotype. However, there are currently no data to indicate that patients with ER+ breast cancers that show basal cytokeratin expression should be managed any differently than ER+, basal cytokeratin-negative breast cancers of equivalent size and stage (ie, with hormonal therapy, with or without chemotherapy). Likewise, patients with an HER2+ breast cancer showing a basal-like phenotype would still receive trastuzumab and chemotherapy, similar to other patients with HER2+ breast cancer. Thus, given that the term basal-like *per se* does not impact on clinical decision making, the inclusion of the term 'basal-like breast cancer' in pathology reports at present would be best avoided. However, it might be argued that subclassification of triple-negative tumors into subtypes using the Nielsen definition[17] is of prognostic significance and is associated with specific patterns of metastatic dissemination. If one were to use such an approach, to ensure consistency it is recommended that tumors that express more than 1% CK5/6 or EGFR should be considered positive for these markers. There are also data to suggest that the CK5 antibody is superior to the CK5/6 antibody for identification of this type of basal cytokeratin.[138] The role of CK14 in the subclassification of triple-negative cancers into basal-like and non-basal-like phenotypes is uncertain.

Perhaps more important than identifying the basal-like subgroup within triple-negative breast cancers is the identification of subgroups of triple-negative disease that are sensitive to specific systemic therapy regimens. Several groups are currently developing biomarkers for the identification of the subgroup of triple-negative cancers with dysfunctional homologous recombination DNA repair, given that these tumors are likely to show an exquisite sensitivity to PARP inhibitors. Furthermore, other promising targets for subgroups of basal-like cancers have recently emerged (eg, FGFR2, TRAIL, antiangiogenic agents). Therefore, the question that is germane for the management of breast cancer patients is the identification of predictive biomarkers to substratify patients with triple-negative cancers into groups that can be managed more efficaciously with specific systemic therapies.

It is also important to remember that the lack of overlap between categories identified by gene expression and immunohistochemistry methods is not restricted to basal-like and triple-negative tumors. Up to 25% of clinically ER+ tumors are classified as of nonluminal subtype by gene expression methods.[11] Similarly, nearly a third of the clinically HER2+ (FISH and/or IHC) are not classified as belonging to HER2-enriched category.[11] At least for now, treatment decisions are made on the basis of clinical (and not gene expression) assays.

Conclusions

Basal-like breast cancer is a heterogeneous group of tumors that is more prevalent in young and African-American patients and is generally associated with a poor outcome. Currently, although it is clearly important that triple-negative cancers be accurately identified in clinical practice for the purposes of management, there is no internationally accepted definition for basal-like cancers and still no clear clinical indication for the routine identification of these tumors as such.[14]

Given that basal-like breast cancers are heterogeneous regardless of the definition used, it is possible that in the next few years, markers that identify subgroups of basal-like or triple-negative cancers that respond to specific agents will become part of our diagnostic armamentarium. With the advent of massively parallel sequencing,[139] which allows for the genome-wide quantitative and qualitative genomic and transcriptomic characterization of cancers, and the imminent death of microarrays,[140,141] it is likely that the taxonomy of breast cancers will be revisited again.[14,56] At that time, it is quite possible that more homogeneous molecular subgroups, their biological drivers, and therapeutic targets will be identified. Until then, it is essential that pathologists continue to strive toward providing optimal assessment of the histological features of breast cancers (including histological grade), as well as accurate determination of ER, PR, and HER2 status according to published guidelines[66,67] as these factors remain the primary determinants of the use and type of systemic therapy for patients with invasive breast cancer.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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