

REVIEW

Luminal-B breast cancer and novel therapeutic targets

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Abstract

Gene expression profiling has led to a new molecular classification of breast cancer characterized by four intrinsic subtypes: basal-like, HER2-positive, luminal A, and luminal B. Despite expressing estrogen receptor, the luminal-B subtype confers increased risk of early relapse with endocrine therapy compared with the luminal-A subtype. Although luminal-B definitions vary, the hallmark appears to be increased expression of proliferation-related genes. Several biological pathways are identified as possible contributors to the poor outcomes, and novel agents targeting these pathways are being developed with aims to improve survival. We review the definition of luminal-B breast cancer, its pathological and clinical features, and potential targets for treatment.

Introduction

The National Cancer Institute defines personalized medicine as 'a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease' [1]. Personalized cancer medicine has existed in breast cancer since the late 1980s when benefits of tamoxifen were found to be limited to patients with tumors expressing estrogen receptors (ERs) [2]. This personalized treatment has advanced further in recent times through the discovery of *erbB2/HER2* gene amplification and its subsequent targeted treatments such as trastuzumab and lapatinib [3,4].

Until very recently, personalized cancer medicine in breast cancer relied on only two predictive markers, ER and *erbB2/HER2*. The advent of gene expression profiling, however, has led to a paradigm shift in breast cancer medicine. Breast cancer is now recognized not as a single disease with variable morphology, but as at least four molecularly distinct neoplastic disorders: basal-like

breast cancer, HER2-positive breast cancer, luminal-A breast cancer, and luminal-B breast cancer [5-8]. Although the immediate additional clinical value of this molecular classification is limited by its close correlation to traditional methods of testing for ER and HER2, the identification of genetic aberrations that underlie molecularly distinct subclasses of breast cancer has revealed new therapeutic targets and has reshaped breast cancer clinical trial design.

The subtypes most in need of therapeutic advances are basal-like breast cancer and luminal-B breast cancer, where therapeutic resistance is common and where advances in molecular profiling have identified promising new therapeutic targets. In the present review article, we discuss the definition of luminal-B breast cancer, the clinical behavior and pathological features of luminal-B breast cancer, and emerging molecular targets for improved therapy (see Table 1 for a summary).

Defining luminal-B breast cancer

Microarray technology has enabled better understanding of cancer biology at a molecular level through the interrogation of tens of thousands of expressed genes simultaneously. In breast cancer, hierarchical clustering of a series of breast cancers based upon a set of differently expressed intrinsic genes between individual patients led to the identification of a novel molecular classification of breast cancer [7]. The so-called intrinsic molecular classification of human breast cancer includes basal-like, HER2-positive, luminal-A and luminal-B subtypes. These subtypes have been associated with distinct pathological features and clinical outcome: basal-like breast cancer is predominantly triple-negative, with absent expression of ER, progesterone receptor (PR) and normal *erbB2/HER2* gene copy number; HER2-positive breast cancer is *erbB2/HER2* gene amplified and is associated with poorer outcomes when untreated; and both luminal-A and luminal-B breast cancers are ER-positive, although luminal-B cancers have poorer outcomes [9].

The seminal work of Perou and colleagues initially identified molecular portraits of breast cancer based upon gene expression profiling of 65 breast cancer samples from 42 individual patients using cDNA

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Table 1. Luminal-B breast cancer

Genes overexpressed in gene expression profiling
ER and ER-regulated genes
Proliferation-related genes
Cell cycle genes
Histopathological features
ER-positive
High grade
High Ki-67
Clinical features
Poorer disease-free survival
Increased risk of early relapse
Predisposition to relapse in bone and pleura
Relative insensitivity to endocrine therapy compared with luminal-A subtype
Relative insensitivity to chemotherapy compared with basal-like and HER2-positive subtypes

ER, estrogen receptor.

microarrays [7]. Their classification was based upon the premise that individual differences in gene expression should be greater than differences in gene expression from paired tumor samples derived from the same patient. They identified a set of 496 genes that demonstrated significantly greater variation between individual tumors than within paired tumor samples from the same individual. When this intrinsic gene set was used to perform hierarchical clustering of their tumor samples, four subgroups were identified: basal-like, based upon similarities in gene expression to basal epithelial cells in the normal breast; Erb-B2 positive, based upon increased expression of genes in the *erbB2/HER2* gene amplicon on chromosome 17q12; luminal, based upon similarities in gene expression to luminal epithelial cells in the normal breast; and normal breast-like, based upon the inclusion of three normal, nonmalignant breast samples. In this initial study, no distinction between luminal-A and luminal-B breast cancers was identified.

A subsequent study from the same group extended the sample size to 78 breast cancers (including 40 from the original publication) using hierarchical clustering with an intrinsic gene set of 456 cDNA clones. Extension of the sample size allowed for the identification of subsets within the luminal cluster (47 tumors): luminal A (32 tumors), luminal B (five tumors), and luminal C (10 tumors) [8]. Luminal B and luminal C demonstrated lower expression of ER-related genes compared with luminal-A tumors, while luminal C was further distinguished from luminal A and luminal B by high expression of a set of genes shared with basal-like and

HER2-positive subtypes, but of unknown function [8]. Compared with luminal-A tumors, poorer outcomes were observed in luminal-B and luminal-C tumors. It is well recognized that hierarchical clustering based on a small sample number can result in unstable molecular classifications. Later studies failed to reproduce the luminal-C subtype and the luminal classification was collapsed into two subtypes: luminal-A with high expression of ER-regulated genes and favorable long-term outcome, and luminal-B with lower expression of ER-regulated genes and poorer long-term outcome.

Multiple gene expression studies have reproduced luminal-A and luminal-B subtypes. Both subtypes have expression patterns reminiscent of the luminal epithelial component of the breast, including expression of luminal cytokeratins 8/18, ER and genes associated with ER activation such as *CCND1* (cyclin D1). The major molecular distinction between the two luminal subtypes is that, in general, luminal B has lower expression of ER-related genes and higher expression of proliferative genes [6,8,10]. Luminal-B tumors also demonstrate increased expression of growth receptor signaling genes, although only 10% of tumors were HER2-positive by immunohistochemistry [11]. A review of several gene expression studies noted that approximately 20% of luminal-B breast cancers were HER2-positive by immunohistochemistry [5]. Since HER2-positive breast cancers are treated very differently from HER2-negative breast cancers, a clinically meaningful classifier of luminal-B breast cancer should not include HER2-positive breast cancers [9]. Approximately 30% of HER2-positive tumors defined by immunohistochemistry are assigned to the luminal-B subtype. Most of the tumors are also ER-positive by immunohistochemistry or *ESR1* gene expression [6,9]. The clinical relevance of whether an ER-positive breast cancer with overexpression of HER2 is classified as HER2-positive or as luminal B by the intrinsic molecular classification remains to be determined.

In many subsequent studies, luminal-B breast cancer has been defined as ER-positive breast cancer with increased proliferation [5]. In gene expression studies, proliferation genes such as *CCNB1*, *MKI67* and *MYBL2* are more highly expressed in luminal-B compared with luminal-A subtypes [12], correlating with a higher proportion of histological grade III also observed in luminal-B cancers [9].

Since the seminal paper of Perou and colleagues first identified the intrinsic molecular subtypes of breast cancer, there have been various single subtype predictors (SSPs) that have been developed to identify the molecular subtype of an individual breast cancer [6,13,14]. These SSPs differ in the intrinsic gene list that is used to define molecular classification. Recently, the reproducibility of subtype assignment across these three SSPs was

evaluated by retrieving expression data from three publicly available datasets involving nearly 800 patients and performing two-way average-linkage hierarchical cluster analysis using five distinct intrinsic gene lists. Whilst the basal-like and HER2 subtypes could be reproducibly identified by independent observers, none of the classification systems could produce substantial agreement in subdividing luminal cancers [15]. A similar study by Weigelt and colleagues produced similar conclusions [16]. Although this lack of agreement is troublesome, it is perhaps not surprising as the initial molecular classification was based upon only 42 individuals with breast cancer [7].

Proliferation has been consistently identified as the most important feature of several prognostic multigene signatures, including the intrinsic molecular classification [5,17]. In ER-positive/HER2-negative tumors, proliferation is the strongest predictor of early relapse risk that differentiates high-risk luminal-B tumors from low-risk luminal-A tumors [5,18]. Whilst ER is bimodally expressed (meaning the overwhelming majority of cases are either completely ER-positive or unambiguously ER-negative) in breast cancer, thus allowing a meaningful cut-off point to be applied [19], proliferation-related genes are expressed along a unimodal continuum. This makes it extremely difficult to apply any meaningful cut-off point that differentiates between high and low proliferative tumors in a reproducible manner. This is evident in the differences in subtype assignment between luminal-B and luminal-A tumors across SSPs, where tumors with a level of proliferation around the median value may be inconsistently classified by SSPs that use different proliferation-driven intrinsic gene lists.

Clinical features of luminal-B breast cancer

Since the earliest studies of the intrinsic molecular subtypes in breast cancer, the defining feature of luminal-B breast cancer has been its poor outcome compared with the luminal-A subtype [7]. Overall survival in untreated luminal-B breast cancer is similar to the basal-like and HER2-positive subgroups, which are widely recognized as high risk. One study used a 50-gene classifier to assign intrinsic subtypes to 761 untreated breast cancer patients, and correlated subtype with outcome. In a multivariate analysis of untreated early breast cancer, using the luminal-A subtype as a reference, luminal-B breast cancers were demonstrated to have a hazard ratio of 2.43 ($P < 0.0001$) for relapse-free survival (RFS), similar to hazard ratios for *erbB2/HER2* amplified (2.53, $P = 0.00012$) tumors [13].

The increased relapse risk associated with the luminal-B phenotype appears to be limited to the early period after surgery. Since increased proliferation is the hallmark of luminal-B cancer [20], it is not surprising that

increased relapse rates observed in luminal-B tumors are limited to the first 5 years after diagnosis, with no difference in distant relapse beyond 5 years [21]. In a series of 831 untreated node-negative breast cancers, curated from five publicly available gene expression datasets, we found the hazard ratio for distant metastases of luminal-B subtype compared with luminal-A subtype to be 2.86 ($P < 0.01$) for early metastases (<5 years) and 0.65 ($P =$ nonsignificant) for late metastases (≥ 5 years) (Table 2).

There are differences in the anatomic sites of relapse according to molecular subtypes. The increased incidence of brain metastases in HER2-positive and basal-like breast cancer is well recognized [22,23]. Luminal breast cancers appear to have a predilection for metastasis to bone and pleura. In a small study of 81 patients with metastatic breast cancer, no differences in sites of metastasis were observed between luminal-B and luminal-A breast cancers [24].

Several studies have suggested luminal-B breast cancer is relatively insensitive to endocrine therapy compared with luminal-A breast cancer, and to chemotherapy compared with HER2-enriched and basal-like breast cancers. Five studies examined the pathological complete response (pCR) rate following preoperative chemotherapy according to molecular subtype. Table 3 compares the pCR for each molecular subtype in each study and demonstrates that the pCR rate is consistently lower in luminal-B breast cancer when compared with HER2 and basal-like subtypes [25-29]. There were important methodological differences in these studies, including the method of subtype definition of the luminal-B subgroup (particularly the inclusion of ER-positive and HER2-positive breast cancer in some studies), and differences in chemotherapy received.

Although luminal-B tumors are characterized by high proliferation, the likelihood of achieving pCR with preoperative chemotherapy is exceedingly low. In other high-risk breast cancer subtypes, pCR is a robust surrogate endpoint for disease-free survival and overall survival [30,31]. It is not clear whether pCR is a meaningful surrogate endpoint in luminal tumors. Paradoxically, large, low proliferative ER-positive tumors categorized with a low recurrence score by the OncotypeDx™ assay that fail to achieve pCR with preoperative chemotherapy experience excellent long-term survival [32]. In this study, there was no difference in long-term outcome for low recurrence score tumors that achieved pCR with preoperative chemotherapy compared with tumors in which there is residual invasive disease, although there were few low recurrence score tumors in this study that achieved pCR.

Response to endocrine therapy in the preoperative setting has also been explored as a surrogate marker for

Table 2. Risk of early versus late relapse in molecular subtypes of breast cancer

	Early (<5 years) distant metastases (n = 831)			Late (≥5 years) distant metastases (n = 652)		
	HR	95% CI	P value	HR	95% CI	P value
Age						
(<50 years vs. ≥50 years)	0.77	(0.56, 1.06)	NS	1.65	(0.97, 2.81)	NS
Tumor size						
(≤2 cm vs. >2 cm)	1.31	(0.91, 1.86)	NS	1.18	(0.69, 2.01)	NS
Histological grade						
(2 vs. 1)	5.02	(1.80, 14.0)	<0.01	0.92	(0.48, 1.76)	NS
(3 vs. 1)	7.22	(2.59, 20.2)	<0.01	0.70	(0.31, 1.60)	NS
Molecular subtype						
Luminal-A	1	–	–	1	–	–
Luminal-B	2.86	(1.70, 4.80)	<0.01	0.65	(0.24, 1.72)	NS
HER2-positive	2.62	(1.50, 4.60)	<0.01	1.41	(0.64, 3.12)	NS
Basal-like	2.83	(1.92, 4.82)	<0.01	0.96	(0.54, 1.70)	NS

Data from five publicly available datasets from patients with node-negative tumors who did not receive adjuvant systemic therapy. Molecular subtype assignment according to the subtype clustering method [17]. CI, confidence interval; HR, hazard ratio; NS, nonsignificant.

Table 3. Pathological complete response rates post neoadjuvant chemotherapy in molecular subtypes of breast cancer

Author	n	Method of molecular classification	Defining luminal B	Pathological complete response rate (%)			
				Luminal A	Luminal B	HER2-positive	Basal-like
Esserman and colleagues [25]	144	Microarray	Intrinsic gene set and hierarchical clustering (included some HER2 ⁺)	–5	13	55	34
De Ronde and colleagues [26]	191	Microarray	Intrinsic gene set and hierarchical clustering (included some HER2 ⁺)	7	7	44	44
Bhargava and colleagues [27]	359	IHC surrogate markers	ER ⁺ , HER2 ⁻	2	1	33	30
Carey and colleagues [28]	107	IHC surrogate markers	ER ⁺ , HER2 ⁺	0	15	36	27
Rouzier and colleagues [29]	82	Microarray	Intrinsic gene set and hierarchical clustering (included some HER2 ⁺)	7 ^a	7 ^a	45	45

ER, estrogen receptor; IHC, immunohistochemistry. ^aIn Rouzier and colleagues [29], luminal-A and luminal-B subtypes were grouped together as the luminal subtype.

long-term outcomes. In ER-positive tumors, the level of residual proliferation after 10 to 14 days of preoperative endocrine therapy is prognostic for long-term RFS [33]. A correlative substudy of the IMPACT trial analyzed 158 patients with paired biopsies (baseline and 2 weeks after endocrine therapy), and found that the absolute value of residual proliferation after short-term endocrine therapy, as assessed by the percentage of Ki-67 immunostaining, was strongly predictive of RFS; Ki-67 index <2.7% was associated with favorable RFS. Interestingly, the Ki-67 index measured after 10 to 14 days of endocrine therapy was more predictive of long-term RFS than the pretreatment Ki-67 index [34]. pCR after preoperative endocrine therapy is rare [33,35-37]. Whether clinical or radiographic response to preoperative endocrine therapy is predictive of long-term outcome in ER-positive disease is not firmly established.

Despite the problems with subtype classification, the luminal-B subtype remains a clinically important classification of breast cancer with prognostic and potential predictive implications. Weigelt and colleagues suggest that standardized methods and definitions for identification of breast cancer molecular subtypes are necessary to incorporate molecular subtype classification into routine clinical practice [16]. HER2 and basal-like subtypes can already be identified using fluorescence *in situ* hybridization and immunostaining for ER, PR and HER2. With regard to differentiating between luminal-A and luminal-B subtypes, various authors have tried to define more pragmatic criteria that can broadly be applied to clinical practice. Some studies have used the level of ER expression to differentiate luminal-B from luminal-A subtypes [27], but this does not take into account the level of proliferation.

One study explored the use of the Ki-67 index as a potential unidimensional proliferation marker that could successfully differentiate luminal-B tumors from luminal-A tumors in a clinically practical way [12]. Subtypes were assigned for a cohort of 357 breast cancers using microarray-based gene expression profiling, and the Ki-67 status, hormone receptor status and HER2 status were concurrently determined by immunohistochemistry. The authors used receiver operating characteristic curves to determine the Ki-67 cut-off point that distinguished luminal-A from luminal-B tumors, then applied it to an independent microarray series of 4,046 breast cancers. They were able to successfully demonstrate using immunohistochemistry that determining the Ki-67 index can distinguish between the two subtypes [12]. However, arbitrarily applying a clinically relevant cut-off point to a continuous variable such as Ki-67 that is unimodally distributed is problematic. Ki-67 immunohistochemistry is also limited by low reproducibility between laboratories, ongoing debate over both the optimal antibody for testing and the method for cell counting (manual versus automated), in addition to potential problems resulting from tumor heterogeneity [38]. Multigene prognostic assays, such as OncotypeDx™, are currently used to assess proliferation in providing independent prognostic information in early breast cancer [39]. Given their level of reproducibility and less potential for influence by tumor heterogeneity, these assays may have potential advantages over a unidimensional marker such as Ki-67 in assigning subtype classification.

Potential targets in luminal-B breast cancer

Insulin-like growth factor signaling

In cancer, ligand activation of the insulin-like growth factor 1 receptor (IGF-1R) and its downstream pathways (phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and Ras/Raf/MEK/ERK) stimulates tumor proliferation, survival, transformation, metastasis and angiogenesis [40]. Laboratory and epidemiological studies have demonstrated a link between cancer and insulin-like growth factor 1 (IGF-1) signaling [41]. IGF-1R is expressed in the majority of breast cancer (90 to 95%) and is often co-expressed with ER [42]. Cross-talk between ER and IGF-1R plays a critical role in tamoxifen resistance. Increased circulating plasma levels of IGF-1, a ligand for IGF-1R, identify women at increased risk of relapse on adjuvant tamoxifen [41]. Activation of IGF-1R signaling is associated with loss of PR expression, which itself is associated with high proliferative luminal-B breast cancer, and with resistance to tamoxifen-induced apoptosis [43]. Creighton and colleagues derived a signature of more than 800 genes whose expression was significantly altered after exogenous IGF-1 stimulation in ER-positive MCF7 cells [44]. Activation of this IGF-1

signature was seen in approximately 25% of ER-positive breast cancers and was associated with an increased risk of recurrence. Similar findings were reported by Ignatiadis and colleagues with their 142-gene *in silico* signature of IGF-1 activation that was more commonly found in luminal-B tumors compared with luminal-A tumors [45].

Inhibition of IGF-1R signaling demonstrates synergistic activity in combination with endocrine therapy in preclinical models of ER-positive breast cancer [43,46]. Various approaches to interrupting the IGF-1 signaling axis have been developed. Although potential targets include growth hormone and growth-hormone-releasing hormone, the most advanced therapeutic approach has been the development of antibodies against IGF-1R that block IGF-1 ligand-mediated activation and small-molecule inhibitors of the IGF-1R tyrosine kinase domain [47]. Table 4 outlines IGF-1R-targeted therapies that are being investigated in ER-positive breast cancer and other solid tumors. The first preliminary report of a randomized phase II trial of exemestane or fulvestrant and AMG-479, a fully human monoclonal antibody against IGF-1R, or matching placebo was presented at the 2010 San Antonio Breast Cancer Symposium [48]. This study involved 156 patients with ER-positive metastatic breast cancer who had progressed following first-line endocrine therapy for advanced disease or who had relapsed within 12 months of completing adjuvant endocrine therapy. This study failed to meet its primary endpoint, as the addition of AMG-479 did not improve progression-free survival. The median progression-free survival for AMG-479 + endocrine therapy was 3.9 months, versus 5.7 months for placebo + endocrine therapy (hazard ratio = 1.17, $P = 0.44$). Correlative studies of this trial and other ongoing studies will be essential to determine whether there is a signal of activity for IGF-1R inhibition in patients with luminal-B-like features, such as increased proliferation measured by Ki-67 immunostaining.

Fibroblast growth factor signaling

The fibroblast growth factor (FGF) signaling system includes 22 ligands and four receptors [49], and is a highly complex growth factor signaling pathway that is responsible for many functions, including cell proliferation, survival and migration, through differing downstream molecules or pathways [49]. Multiple studies indicate that FGF may also be involved in angiogenesis. One study demonstrated that the ligand FGF2 stimulates migration and proliferation of endothelial cells, whilst another study demonstrated that, under anti-vascular endothelial growth factor therapy, tumor angiogenesis can switch from vascular endothelial growth factor receptor dependence to fibroblast growth factor receptor (FGFR) dependence via upregulating FGF2, possibly explaining resistance to vascular endothelial growth

Table 4. Targeted treatment in luminal-B breast cancer

Pathway	Agent	Supplier	Class	Phase	Study design	Eligible population
IGF	BMS-754807	BristolMyersSquibb	IGF-1R/IR TKI	II	BMS-754807 ± letrozole	ER-positive locally advanced/metastatic breast cancer, progressed on prior nonsteroidal aromatase inhibitors
	Cixutumumab	ImClone	IGF-1R mAb	I/II	Cixutumumab and temsirolimus	Locally advanced/metastatic breast cancer progressed on one or two chemotherapy lines
	MK-0646	Merck	IGF-1R mAb	I/II	MK-0646 and fulvestrant and dasatinib	Locally advanced/metastatic ER-positive breast cancer with no previous treatment in metastatic setting
	Dalotuzumab	Merck	IGF-1R mAb	II	Dalotuzumab and ridaforolimus versus standard care	ER-positive locally advanced/metastatic breast cancer, progressed on at least one line of endocrine therapy
	OSI-906	OSI	IGF-1R/IR TKI	II	OSI-906 and endocrine therapy ± erlotinib	ER-positive metastatic breast cancer, treated with ≤4 chemotherapy regimens
	CP-758171	Pfizer	IGF-1R TKI	I	CP-758171 for two cycles prior to curative surgery	Operable early breast cancer
FGF	TKI-258	Novartis	FGFR/VEGFR TKI	II	TKI-259 single agent	HER2-negative, <i>FGFR1</i> amplified and <i>FGFR1</i> normal metastatic breast cancer
	AZD-4547	Astra Zeneca	FGFR TKI	II	Exemestane ± AZD-4547	ER-positive locally advanced/metastatic breast cancer with high levels of <i>FGFR1</i> expression
PI3K/AKT	MK-2206	Merck	AKT inhibitor	II	MK-2206 single agent	Metastatic breast cancer with <i>PIK3CA</i> mutation and/or <i>PTEN</i> loss, progressed on at least one line of therapy
	MK-2206	Merck	AKT inhibitor	II	MK-2206 and endocrine therapy	ER-positive metastatic breast cancer progressed on endocrine therapy
	XL-147	Exelixis	PI3K inhibitor	II	XL-147 and letrozole	ER-positive metastatic breast cancer refractory to nonsteroidal aromatase inhibitors
	XL-765	Exelixis	PI3K/mTOR inhibitor	II	XL-765 and letrozole	ER-positive metastatic breast cancer refractory to nonsteroidal aromatase inhibitors

ER, estrogen receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; IGF, insulin-like growth factor; IGF-1R, insulin-like growth factor 1 receptor; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor.

factor-targeted agents [50,51]. Whether it is through cell proliferation, survival, migration or angiogenesis, the FGF pathway clearly has oncogenic roles in many cancers. These roles occur through various genetic aberrations that include amplifications, activating mutations, chromosomal translocations, SNPs and aberrant splicing at the post-transcriptional level.

In breast cancer, changes to FGF signaling are considered important for oncogenesis, mainly through amplification of *FGFR1* and *FGFR2*. Following *erbB2/HER2*, *FGFR1* is amongst the most commonly amplified genes in breast cancer, present in up to 10% of all breast cancers [52]. Various reports have shown that *FGFR1* amplification is most commonly associated with ER expression, the absence of HER2 overexpression and lobular histology [53,54]. Additionally, the *FGFR2* gene is amplified in approximately 1 to 2% of breast cancers [52]. Genome-wide association studies have also shown that inherited SNPs in the *FGFR2* gene are associated with an increased risk of developing ER-positive breast cancer,

probably through an increase in *FGFR2* transcription [52]. Although activating mutations in *FGFR3* and *FGFR4* occur in many types of human tumors, they seem to be rare in breast cancer [49].

Recent data suggest that the luminal-B subtype is enriched for *FGFR1* gene amplification [52]. One study examined tumors from two independent series of breast cancer for *FGFR1* amplification, demonstrating that *FGFR1*-amplified cancers are frequently PR-negative, have a high proliferative rate assessed by Ki-67 immunostaining and are present in 16 to 27% of luminal-B breast cancer [53]. Furthermore, the same study demonstrated that *FGFR1*-amplified breast cancer cell lines have both enhanced ligand-dependent and ligand-independent signaling, and are dependent upon FGFR signaling for anchorage-independent growth [53]. These authors also demonstrated that *FGFR1*-amplified cells were resistant to endocrine therapy, but this could be reversed by knockdown of *FGFR1* [53]. Other studies have also observed that resistance to endocrine therapy can be

reversed through both knockdown of *FGFR1* expression and the use of a small molecule FGFR tyrosine kinase inhibitor [55]. These findings all suggest that the FGF pathway, and more specifically *FGFR1* gene amplification, may be a major contributor to the poor prognosis observed in luminal-B breast cancer, through increased proliferation and resistance to endocrine therapy.

Preclinical models of breast cancer cells amplified for *FGFR1* or *FGFR2* have demonstrated sensitivity to inhibition of FGFR [49]. This has led to several proof-of-concept early-phase clinical trials using FGFR inhibitors. Several antibodies and small-molecule inhibitors of FGFR are currently in clinical testing. First-generation tyrosine kinase inhibitors also inhibit *VEGFR2* due to structural similarity between the two tyrosine kinase domains [52]. Table 4 lists some of the current agents targeting the FGF pathway in breast cancer clinical trials. An important challenge for all of these studies is the identification of patients whose tumors harbor genetic amplification of *FGFR1* or *FGFR2*. Like *erbB2/HER2*, chromosome *in situ* hybridization and fluorescence *in situ* hybridization are the dominant methods used to identify gene amplification in paraffin-embedded tumor samples.

Phosphoinositide 3-kinase signaling

Deregulated *PI3K* signaling has been implicated in many aspects of carcinogenesis [56]. Genetic aberrations along the pathway can occur anywhere from the upstream growth factor receptors to downstream target molecules, regulatory molecules and *PI3K* itself [56]. These genetic aberrations have the potential to change a number of cell functions that contribute to the transformed phenotype, including cell growth and proliferation, differentiation, cell survival, adhesion and cell motility [56]. Subsequently, the *PI3K* pathway – including its enzymes, targets and regulators – is considered an important potential therapeutic target in cancer.

In breast cancer, the *PI3K* pathway is frequently activated. Amplification of upstream receptors such as *erbB2/HER2*, loss of negative regulators such as *PTEN*, amplification of downstream targets such as *Akt*, and activating mutations or genetic amplification of the α -catalytic subunit of *PI3K* (*PIK3CA*) have all been described in breast cancer. *PIK3CA* somatic mutations occur in approximately 25% of breast cancer [57,58]. In luminal-B breast cancer, the role of *PI3K* signaling is being defined. There appear to be no differences in the frequency of *PIK3CA* mutation between luminal-A and luminal-B breast cancers [58]. A recent preclinical study has demonstrated that increased expression of *PI3K* pathway genes is a feature of luminal-B breast cancer [59]. Growth inhibition induced by endocrine therapy in luminal-B breast cancer cell lines could be significantly

increased by adding a selective *PI3K* inhibitor, suggesting that *PI3K* inhibitors may have a role in luminal-B breast cancer [59].

In breast cancer, the initial studies targeting the *PI3K* pathway involved rapamycin analogs or mTOR inhibitors. A phase II study of ER-positive breast cancer in the neoadjuvant setting compared 4 months of letrozole treatment with 4 months of letrozole and everolimus treatment, an oral mTOR inhibitor [36]. Although the rate of sonographic response was only marginally improved with the addition of everolimus to letrozole (68% vs. 59%, $P = 0.062$), there was a much greater improvement in antiproliferative response, defined as day 15 Ki-67 immunostaining <2.7% (57% vs. 30%, $P < 0.01$). The authors also noted that the rate of anti-proliferative response in the everolimus and letrozole arm was higher in tumors with *PIK3CA* mutations [36].

Recently, a negative intracellular signaling feedback loop between the mTOR complex 1 and the IGF-1 signaling axis has been discovered [60]. Intracellular levels of IRS1, a key mediator of IGF-1R signaling, are increased when mTOR complex 1 is inhibited by everolimus and other similar mTOR inhibitors, leading to paradoxical activation of Akt [61]. Preclinical models suggest robust activity for dual IGF-1R and mTOR inhibition [62,63]. A recent phase I study demonstrated that this combined therapy may be effective in breast cancer, where five out of 23 breast cancer patients had either partial response, prolonged stable disease or partial metabolic response [64]. The combination appeared particularly active in luminal-B like breast cancer – defined as ER-positive with Ki-67 immunostaining $\geq 15\%$ – as three out of 10 patients in this trial, all of whom were heavily pretreated, achieved a partial response by the Response Evaluation Criteria in Solid Tumors.

There is great enthusiasm for highly specific *PI3K* inhibitors that are currently in early development. They range from pure pan-*PI3K* inhibitors to isoform-specific *PI3K* inhibitors, to dual inhibitors of both *PI3K* and mTOR, to Akt inhibitors. Currently, most early-phase studies using these agents attempt to select patients with genetic aberrations in this pathway. A recent preclinical study, however, suggested that *PIK3CA* mutation, but not *PTEN* loss, confers sensitivity to mTOR inhibitors [65]. In the clinical setting, one study retrospectively correlated the *PIK3CA* mutation status of patients with response rates from *PI3K*/Akt/mTOR inhibition. These authors observed higher responses in the *PIK3CA* mutant population (35% partial responses) compared with the *PIK3CA* wild-type population (6% partial responses) [66]. Targeting the *PI3K* pathway appears very promising, although more extensive study is required – particularly in identifying patients who will benefit. Novel agents targeting this pathway are listed in Table 4.

Other potential targets

Cyclin D1 is amplified in approximately 10% of breast cancer and is known to have a role in driving proliferation through its interaction with cyclin-dependent kinases such as CDK4 [67]; subsequently, it has been suggested that cyclin-directed therapies may have a role in luminal-B subtypes, where proliferation is an important factor [67]. Cyclin inhibitors are currently in early-phase development.

Recent preclinical research has identified a potential breast cancer oncogene, *ZNF703*, implicated in the luminal-B subtype [68]. In this study *ZNF703* was significantly amplified in luminal-B tumors, and its overexpression was associated with poor clinical outcome [68]. In cell lines, overexpression of *ZNF703* induced cell proliferation independent of estradiol stimulation [68]. The investigators also observed that *ZNF703* is ER regulated and may have a role in cancer stem cell self-renewal [68], suggesting a potential role for *ZNF703* inhibition in luminal-B breast cancer.

Another recent study has indicated an association between luminal-B tumors and overexpression of the scaffold protein *NHERF1* (sodium–hydrogen exchanger regulatory factor 1). *NHERF1* expression is associated with poorer survival and resistance to endocrine therapy in ER-positive breast cancer [69]. Further study is required to determine whether *NHERF1* is an appropriate candidate for targeted therapy.

Conclusion

Gene expression studies have led to the identification of luminal-B breast cancer, a subtype of ER-positive breast cancer defined by increased proliferation, relative resistance to chemotherapy compared with other highly proliferative breast cancers, and poor outcome with endocrine therapy. Assigning the luminal-B subtype to individual breast cancers has been problematic, however, as the robustness of single subtype classifiers is sub-optimal. Rather than approaching luminal-B cancer as a fixed biological entity, it is more clinically useful to consider the luminal-B phenotype as a conceptual framework, recognizing that proliferation in ER-positive/HER2-negative tumors exists along a continuum. Identification of highly proliferative ER-positive/HER2-negative tumors – whether through histological grading, the Ki-67 labeling index, or a multigene signature – is useful to separate aggressive luminal-B-like tumors with a risk of early relapse from more indolent luminal-A-like tumors that are adequately treated with endocrine therapy alone. In an effort to improve survival in luminal-B breast cancer, there has been a recent focus on particular molecular pathways where development of efficacious therapeutic agents may alter the natural history of the disease. For these novel treatments to have

their desired effect, however, additional work is needed to characterize the drivers of aggressive biology, and future trials should acknowledge the molecular heterogeneity of ER-positive breast cancer and separate the more indolent luminal-A breast cancers from their more proliferative luminal-B-like counterparts.

Abbreviations

cDNA, complementary DNA; ER, estrogen receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; mTOR, mammalian target of rapamycin; pCR, pathological complete response; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphoinositide 3-kinase catalytic alpha; PR, progesterone receptor; RFS, relapse-free survival; SNP, single nucleotide polymorphism; SSP, single sample predictor.

Competing interests

BT declares that he has no competing interests. PLB declares research funding from Novartis, BristolMyersSquibb, and GlaxoSmithKline, and consultancy funding from Roche, Sanofi-Aventis and Johnson and Johnson.

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