

REVIEW

# The Met oncogene and basal-like breast cancer: another culprit to watch out for?

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## Abstract

Recent findings suggest the involvement of the MET oncogene, encoding the tyrosine kinase receptor for hepatocyte growth factor, in the onset and progression of basal-like breast carcinoma. The expression profiles of basal-like tumors – but not those of other breast cancer subtypes – are enriched for gene sets that are coordinately over-represented in transcriptional signatures regulated by Met. Consistently, tissue microarray analyses have revealed that Met immunoreactivity is much higher in basal-like cases of human breast cancer than in other tumor types. Finally, mouse models expressing mutationally activated forms of Met develop a high incidence of mammary tumors, some of which exhibit basal characteristics. The present review summarizes current knowledge on the role and activity of Met in basal-like breast cancer, with a special emphasis on the correlation between this tumor subtype and the cellular hierarchy of the normal mammary gland.

## The Met receptor in normal physiology and disease

The Met tyrosine kinase receptor for hepatocyte growth factor (HGF) fosters invasive growth, a complex physiological program that implies the concerted activation of cell proliferation, survival, invasion and angiogenesis [1-4] (Figure 1). Met-regulated invasive growth plays important roles under physiological conditions – during development and tissue regeneration – and controls cancer invasion and metastasis [3,5].

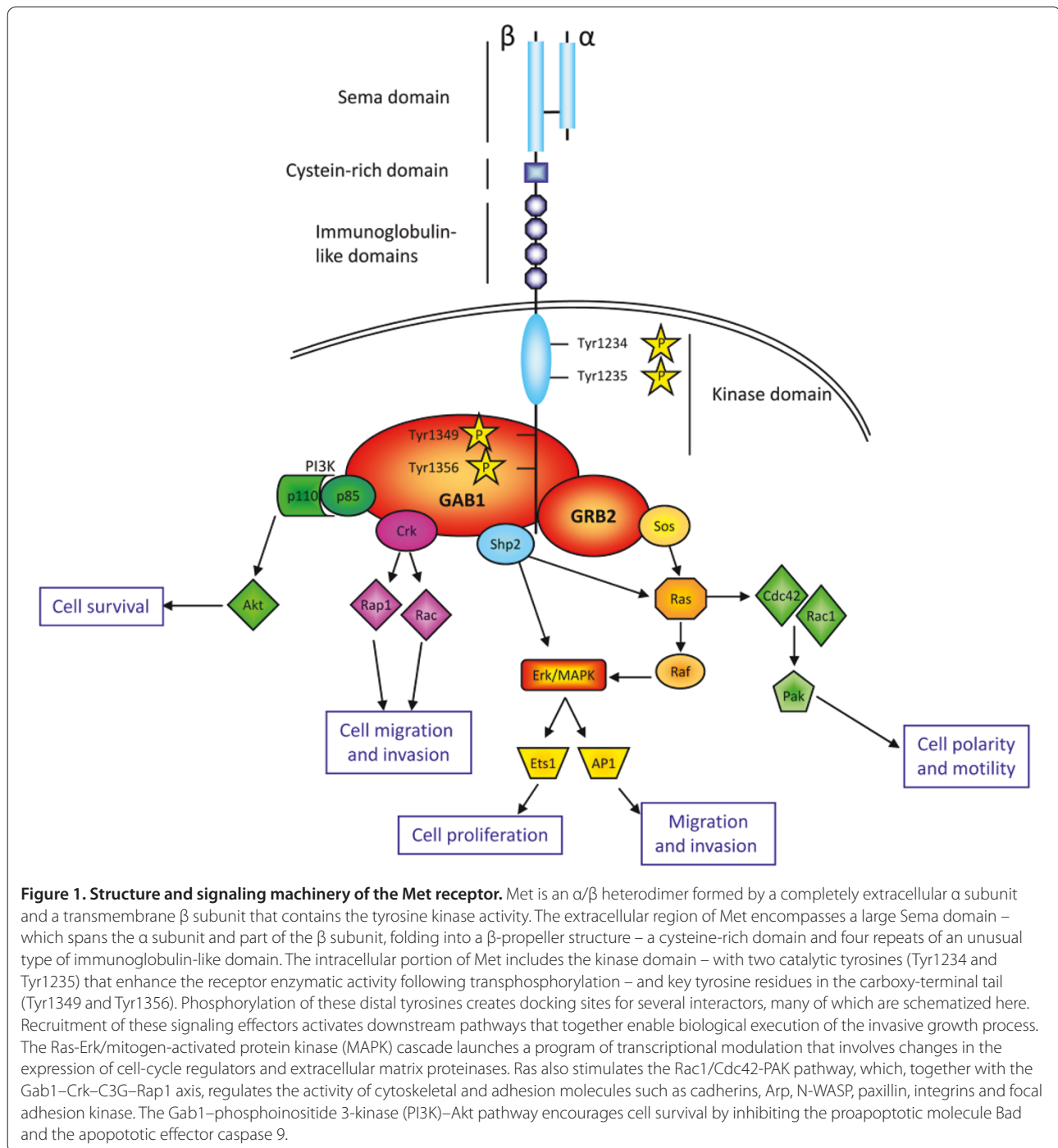
In embryonic life, Met is expressed by epithelial and myoblast progenitors, whereas HGF is secreted by mesenchymal cells [6,7]. The paracrine stimulation of Met by HGF is essential for placenta and liver development and for migration of myoblast precursors [8-10]. In

adulthood, the invasive growth program triggered by Met activation, when reversibly executed in space and time, is commonly associated with organ repair [11,12]. In contrast, derailment of Met-dependent signals promotes the progression and invasiveness of a large number of human cancers. In this context, Met hyperactivation is usually due to transcriptional upregulation, which is in turn induced by oncogenic alterations or micro-environmental stimuli. In a fraction of cases, constitutive firing of Met can be caused by genomic amplification, by point mutations, or by the presence of ligand autocrine loops [13-16]. High levels of HGF and/or Met over-expression correlate with the aggressive phenotype of different carcinomas, including those of the prostate, stomach, pancreas, thyroid and breast [17-20].

## The Met receptor in breast cancer

In past years, a large number of clinical studies have described Met-receptor overexpression and pathway hyperactivation in tissues derived from breast cancer patients, and have found a strong relationship between high HGF/Met signaling and tumor progression (Table 1). Indeed, the HGF content in breast tumor tissue correlates with the aggressive phenotype, being higher in invasive ductal carcinomas than in ductal carcinomas *in situ* and benign hyperplasia [21,22]. In normal mammary tissue HGF is expressed by stromal cells surrounding the epithelial compartment, whereas in cancer the ligand can be produced *de novo* by carcinoma cells that also express the receptor, thus generating an autocrine loop that predicts poor prognosis [16]. Moreover, in many cases HGF and Met are co-expressed in correspondence of the advancing margins of mammary tumors, a finding that goes along with high histological grade and high proliferative index [23]. In axillary lymph node-negative patients, Met overexpression is significantly associated with reduced survival, with a 5-year survival rate of 62% compared with 97% of Met low-expressing patients. The follow-up of these patients revealed that in many cases Met expression was negligible at the time of diagnosis but increased in late recurrences, thus suggesting a possible selection of Met-overexpressing clones in relapse and metastasis [24].

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Clinical data are supported by animal models of Met-driven mammary tumorigenesis: transgenic mice in which HGF has been specifically targeted to the mammary epithelium using the Whey-acidic-protein promoter display a hyperplastic ductal tree with multifocal invasive tumors [25]. Similarly, primary cultures of mammary cells overexpressing Met develop nonprogressive neoplasms upon orthotopic implantation in recipient mice; such lesions are able to progress to adenocarcinomas when the

proto-oncogene Myc is ectopically overexpressed together with Met [26].

### Molecular classification of human breast cancer recalls the cellular hierarchy of the normal mammary gland

Human breast cancer is a heterogeneous disease that comprises a variety of pathologies with different histological features and clinical outcomes. On the basis of

**Table 1. Summary of HGF/Met alterations in breast cancer**

Reference	Observations/lesions	Clinical/biological aspects
Yao and colleagues [21]	High levels of HGF in breast tumor tissue	Invasive ductal carcinomas
Tuck and colleagues [16]	HGF/Met autocrine loop in tumor cells	Co-localization at the advancing margins of the tumors
Jin and colleagues [22]	High levels of HGF and c-Met overexpression in breast tissue	Invasive ductal carcinomas
Camp and colleagues [24]	Met overexpression	Reduced survival, relapse and metastatic dissemination
Edakuni and colleagues [23]	Met overexpression	High histological grade, proliferative index, advancing margins
Kang and colleagues [82]	High levels of Met and HGF in node-negative breast cancer	Tumor progression and poor patient outcome
Lengyel and colleagues [83]	Met overexpression in node-positive breast cancer	Disease progression and decrease in disease-free survival
Charafe-Jauffre and colleagues [43]	Met overexpression in breast cancer cell lines	Basal-like phenotype
Lindemann and colleagues [84]	Imbalance in Met expression between tumor and normal tissue	Aggressive ductal carcinoma <i>in situ</i>
Eichbaum and colleagues [85]	High HGF serum levels	Liver metastatic colonization from breast cancer
Garcia and colleagues [45]	Met overexpression in tissue microarrays	Poor prognosis, basal-like phenotype
Finkbeiner and colleagues [49]	Transcriptional upregulation of Met	Anchorage-independent growth of basal-like breast cancer cells
Smolen and colleagues [65]	Met amplification in a Brca1-p53 mouse model of breast cancer	Mouse mammary tumor progression
Ponzo and colleagues [53]	MMTV-Met mutant transgenic mice	Heterogeneous mammary tumors, basal-like phenotype
Graveel and colleagues [52]	Met mutant knock-in mice	Mammary tumors associated with basal-like phenotype

HGF, hepatocyte growth factor; MMTV, mouse mammary tumor virus promoter.

gene expression profiles obtained from cDNA microarray analysis of a large set of tumor samples, Sorlie and colleagues defined a new molecular classification of human breast cancers [27]. According to this classification, breast tumors have been clustered into five different subtypes: luminal A, luminal B, Her2-overexpressing, normal-like and basal-like. This classification reflects the characteristics of the cell populations that are present in the normal epithelium of the mammary gland. In fact, besides highlighting the molecular heterogeneity of breast tumor subtypes, the transcriptional profiles revealed a molecular/phenotypic connection between the transformed cells and the normal epithelial counterpart. Based on this observation, it has been proposed that the different types of breast cancer have their cell of origin in the different subpopulations that constitute the normal mammary gland under physiological conditions.

#### The cell hierarchy of the normal mammary gland

The mature mammary epithelium is composed of three main epithelial cell types: the basal/myoepithelial cells, which line the outer side of the ducts; and the luminal cells, which are further distinguished into ductal and alveolar elements and form the inner side of the ducts and the alveoli, respectively. According to molecular profiling, it is assumed that the luminal subtype arises from cells belonging to the luminal lineage, whilst the

basal subtype is supposed to derive from less differentiated cells of the gland – such as stem/progenitor cells – that are normally located within the basal/myoepithelial compartment and exhibit basal phenotypic markers.

The epithelial cells of the mammary gland are organized in a hierarchical manner, with stem cells and progenitor cells giving rise to all the different lineages that are present in the mature gland. The stem cells, also called mammary repopulating units, are capable of self-renewal and generate all of the cellular types that make up the mammary gland [28]. The existence of a stem cell population has been postulated for a long time because of the ability of the mammary gland to go through several cycles of proliferation and involution during pregnancies, and due to the fact that the transplantation of mammary fragments into the fat pad of receiving animals is sufficient to form a mature mammary tree [29,30]. The immediate progeny of stem cells identifies the compartment of progenitors, which is composed of actively proliferating cells endowed with a limited differentiation potential. Progenitor cells are also called mammary colony-forming units because of their ability to efficiently generate clonal aggregates when cultured *in vitro* [31].

The recent identification of surface markers characteristic of the distinct subpopulations, from undifferentiated cells to mature cells, allowed their prospective isolation and biological characterization. Two independent

groups were able to isolate mouse mammary repopulating units and progenitor cells on the basis of the differential expression of the surface markers CD24, CD49f and CD29. Stingl and colleagues identified mammary repopulating units on the basis of a CD24<sup>+</sup>CD49f<sup>high</sup> phenotype, while Shackleton and coworkers defined the stem cell subpopulation as Lin<sup>-</sup>CD24<sup>+</sup>CD29<sup>high</sup> [31,32]. Both groups demonstrated the ability of these cells to self-renew and to generate a completely functional mammary gland even after transplantation of one single cell. A subset of progenitors committed to the luminal lineage was isolated based on the expression of CD61 and low levels of CD133 and Sca1. These cells can terminally differentiate into mature luminal cells, which lose CD61 expression and increase expression of CD133 and Sca1 [33,34].

### **Mammary epithelial subpopulations and types of breast cancer**

As mentioned before, the different types of breast cancer probably reflect a distinct cell of origin present along the hierarchical organization of the normal mammary gland. Indeed, the luminal subtype is characterized by high expression of genes of the luminal compartment, including estrogen receptor alpha (ER $\alpha$ ), cytokeratin 18, the transcription factor GATA3 and estrogen-regulated genes; this group is further subdivided into type A and type B, which differ for the level of expression of ER $\alpha$ , the proliferation index (assessed by Ki67 staining), and the clinical outcome [35]. The Her2 subtype is characterized by overexpression of the Her2 protein on the cell membrane, due to genomic amplification of the region 17q22.24 that includes the genes coding for Her2 and growth factor receptor-bound protein 7. The normal breast signature defines a group of tumors with high expression of genes of adipose cells and other non-epithelial cell types, as well as low levels of luminal markers. Finally, tumors belonging to the basal-like subgroup express high levels of basal markers, such as cytokeratins 5/14/17 and laminin, and do not express ER $\alpha$ , progesterone receptor and Her2. Notably, it was initially assumed that the cell of origin of this tumor subtype was to be found in the stem cells of the basal compartment. Recent gene expression profiling of the different subpopulations in the human normal mammary gland and analysis of tumors with basal-like features, however, showed that this tumor phenotype appears to be more similar to the gene signature derived from the luminal progenitor population [36].

The molecular classification of breast cancer has an important prognostic value: the single subtypes have different prognosis and show different responsiveness to specific therapies. The luminal tumors are those with a better outcome and a wider possibility of treatment: ER $\alpha$  is preferentially expressed in terminally differentiated

luminal cells and, accordingly, luminal tumors exhibit a differentiated morphology with almost benign features. More importantly, the mitogenic activity of estrogen can be counteracted by endocrine agents such as tamoxifene and aromatase inhibitors [37,38]. In the case of the Her2 group, tumors are endowed with a more aggressive phenotype, but overexpression of Her2 makes the majority of such tumors highly responsive to Her2 inhibition obtained with the specific monoclonal antibody trastuzumab (Herceptin) [39].

Among the different subgroups, the basal-like breast cancers (BLBCs) are those that have the worst clinical outcome: they represent 15 to 20% of human breast cancer and are characterized by an aggressive phenotype with high histological grade, pushing borders, large areas of necrosis and high mitotic indexes. The majority of BLBCs does not express hormone receptors (ER $\alpha$  and progesterone receptor) and is negative for Her2; they are therefore called triple-negative tumors [40,41]. Their molecular features render these tumors especially difficult to treat with anti-hormonal approaches; moreover, the lack of understanding of the genes and processes involved in transformation and progression of this tumor subtype makes it difficult to target with last-generation tailored therapies. As for conventional chemotherapeutics, BLBCs appear to be more sensitive than luminal subtypes to neoadjuvant anthracycline-based regimens, which could be explained by the fact that anthracyclines work efficiently on hyperproliferating cells and that the proliferation-related gene set is highly represented in this subtype; yet BLBCs have poor survival due to higher relapse rate following incomplete pathologic response [42]. In this scenario, the identification of causative, targetable biomarkers for the basal subtype, which could be challenged for prospective therapies, remains an unmet clinical need.

### **Met and basal-like breast cancer**

Together with patient-derived material, breast cancer cell lines have been utilized as tools to identify new markers for the study of breast tumor subtypes. Both genome-wide expression profiling and proteomic approaches led to the classification of cell lines in two major clusters: the luminal group and the basal group. Similar to data obtained from surgical specimens, genes overexpressed in the luminal cluster include ER $\alpha$ , GATA3, cytokeratin 19 and genes associated with ER-positive status, such as cytokeratin 8, cytokeratin 18 and mucin 1. The basal cluster is typified by high expression of cytokeratins 5/14/17, integrin  $\alpha_6$ , integrin  $\beta_4$ , CD44, CD10 and caveolin 1. Interestingly, these large-scale analyses allowed the identification of new basal markers: together with other tyrosine kinases, including the epidermal growth factor receptor (EGFR) and c-Kit, Met emerged as one of

the most differentially regulated genes in the basal cluster versus the luminal cluster [43,44].

These results have been confirmed in tissue microarray-based clinical studies on a large number of breast carcinomas [44-47]. A cohort of 930 tumor samples, subdivided according to patient survival and lymph node status, was screened for expression of Met together with proteins known to be representative of the basal phenotype (cytokeratin 5, cytokeratin 6, caveolin 1, c-Kit, p63). High Met staining was found in tumors from deceased patients with highly invasive malignancies. Importantly, Met overexpression was consistently associated with co-expression of basal markers, thus pinpointing Met as an additional constituent of the basal phenotype [45]. Similar findings were obtained in an independent tissue microarray containing 1,600 specimens from 547 patients with early breast cancer [44] and in a more limited subset of metastatic tumors [46].

#### **Mechanistic insights**

A mechanistic link between Met and BLBCs is highlighted by the observation that receptor overexpression correlates with high expression levels of the transcription factor Y-box binding protein-1 (YB-1). An oncogenic transcriptional/translational factor, YB-1 was originally identified by screening an expression library for DNA-binding proteins able to interact with the EGFR enhancer and with the Her2 promoter region [48]. A recent survey of candidate DNA-binding regions showed that YB-1 can bind to more than 6,000 promoters, among which promoters of kinases and growth factor receptors are highly represented [49]. YB-1 is highly expressed in more than 70% of basal-like cancers, and its expression correlates with poor survival and high risk of relapse [50]. YB-1 is also expressed in normal mammary bipotent progenitor cells, but the level of the protein is much lower than that observed in tumors. This differential expression is in line with a functional role for this transcription factor in tumor onset and progression.

Among the transcriptional targets of YB-1 there are several genes representative of the basal-like signature, including Met [49,51]. Chromatine immunoprecipitation analysis indicated that YB-1 binds directly to the Met promoter in a region that resides -1,080 bp from the translational starting site, thus driving Met expression. YB-1 and Met are both highly expressed in cell lines belonging to the basal cluster, and the downmodulation of YB-1 produces a reduction in the levels of Met, together with an impairment of cell proliferation and anchorage-independent growth. Neither YB-1 nor the Met gene appeared to be amplified in basal cell lines, indicating that the main mechanism leading to overexpression of both molecules is probably based on transcriptional/translational regulation [49].

#### **Met and mouse models of basal-like breast cancer**

Recently, two different mouse models of conditional expression of oncogenic Met variants in the mammary gland demonstrated a causal role for Met in the onset of diverse types of mammary tumors, including BLBCs. In the first model, the oncogenic mutant of Met, containing activating missense mutations within the tyrosine kinase domain, was knocked-in downstream from the Met endogenous promoter [52]; in the second model, transforming isoforms of Met were transgenically expressed in the mammary epithelium under the control of the mouse mammary tumor virus promoter [53]. Oncogenic Met knock-in mice developed a spectrum of mammary cancers (solid adenocarcinomas, adenosquamous carcinomas, and myoepitheliomas), with some of them displaying histological, cytogenetic, and phenotypic characteristics typical of basal-like cancers, such as cytokeratin 5 expression and absence of progesterone receptor and Her2 expression. Similarly, transgenic mice with mouse mammary tumor virus promoter-driven expression of mutant Met developed tumors with a high degree of morphological heterogeneity, including solid/luminal features and lesions with papillary, scirrhous, adenosquamous, or spindle-cell phenotypes. Gene expression profiling for this latter mixed-pathology group revealed that such tumors have an enrichment of basal markers as well as genes associated with epithelial-mesenchymal transition; for instance, Snail [53].

Analysis of Met expression in a cohort of human breast cancer samples showed that tumors with the highest levels of Met correlate with the basal subtypes, and breast cancers with a transcriptional signature indicative of Met activation mainly fall within the basal cluster. Among these tumors, those with active Met expression profiling had a worse prognosis and a shorter disease-free survival [52]. These transcriptional data have been recently corroborated by genome-wide copy number analysis in BLBC cell lines: although focal amplification of MET was not detected, specific enrichment of the HGF/Met pathway was reflected in frequent copy number gains and overexpression of key adapter molecules and downstream signal transducers [54].

In sum, studies performed in cell lines, in patient-derived material, and in animal models provide a clear indication that Met is preferentially expressed (or is mainly active) in BLBCs with respect to other subtypes of breast cancer. While this is certainly true, it should be noted that Met overexpression can be observed sporadically also in nonbasal-like tumors: for example, increased levels of Met are detectable in some cases of Her2-positive and ER-positive mammary carcinomas [52,53]. Something similar also applies to other tyrosine kinase receptors, including EGFR and c-Kit: their expression strongly correlates with BLBCs, but these

oncogenes are not uniquely expressed in this tumor subtype [40]. Indeed, when taken individually, none of the markers of the basal cluster can function as independent predictors. These markers do, however, comprehensively define an algorithm that significantly segregates BLBCs versus other breast cancer entities.

### **Met, BRCA1 mutated cancer and the basal phenotype**

The basal-like group also includes a type of familial breast cancer that arises in BRCA1 mutation carriers. The presence of germline BRCA1 mutations increases the risk of developing breast cancer and ovarian cancer in young women [55]. The pathologic and molecular features of breast cancers arising in BRCA1 mutation carriers resemble those observed in the basal-like subtype: such tumors have a high histological grade, high proliferation indexes and pushing borders, and lack ER $\alpha$ , progesterone receptor and Her2 expression [56,57].

### **The molecular function of BRCA1**

One of the main activities of BRCA1 involves the regulation of DNA double-strand break repair through the process of homologous recombination. Tumor cells that lack BRCA1 expression are hence relatively sensitive to DNA-damaging agents [58]. These cells are particularly responsive to chemical inhibition of poly(ADP-ribose) polymerase, which leads to the accumulation of DNA single-strand breaks that are then converted into DNA double-strand breaks during replication [59-61]. In normal cells, the DNA double-strand breaks are fixed by repair mechanisms involving BRCA1; in cells lacking BRCA1, these lesions are repaired by error-prone systems, such as nonhomologous end joining, with the consequent accumulation of mutations and complex chromosomal rearrangements that ultimately lead to cell death [62].

Tumors arising in BRCA1-mutated patients are characterized by the presence of somatic inactivating mutations of p53 [63,64]. Genomic instability caused by BRCA1 loss would normally lead to cell-cycle arrest through the p53-mediated DNA damage checkpoint, and eventually to apoptosis. The concomitant loss of function of p53 affords cells the ability to bypass this checkpoint block and to continue unscheduled proliferation in the face of severe chromosomal instability. In this condition, the ensuing occurrence of secondary lesions is likely to contribute to full-blown neoplastic transformation [65].

### **Met, BRCA1 and mouse models of basal-like breast cancer**

Met overexpression has been associated with experimental tumors arising in a BRCA1 mutated context, specifically in a mouse model in which BRCA1 and p53 were conditionally deleted in the mammary epithelium

[65]. A genome-wide screening of tumors developed in these mice revealed that the most common genetic alteration was amplification of the Met locus (73% of cases). As a consequence, these tumors expressed high levels of Met mRNA and protein. The amplification was associated with extra-chromosomal double minutes; these are unstable genomic elements that were detected *in vivo* by fluorescence *in situ* hybridization analysis of mouse-derived tumors but were rapidly lost in primary cultures, probably because double minutes are maintained only in the presence of *in vivo* selection pressures within the breast microenvironment.

It is noteworthy that Met amplification in the form of extrachromosomal double minutes is also a primary alteration in the mutant Met knock-in mice that develop basal-like breast tumors [52]. Together, these findings suggest that Met amplification may be a common event in murine mammary tumorigenesis. Focal amplification of the MET gene, however, is not a common finding in human breast cancer: interphase fluorescence *in situ* hybridization performed on a human breast cancer tissue microarray did not reveal any amplification of the Met genomic locus [65], and this genetic alteration has not so far been reported for BRCA1 mutation carriers. A more frequent occurrence is low-grade polysomy (three to five copies) of chromosome 7 – where the MET locus resides – which is detected in approximately 25% of human ductal infiltrating carcinomas [66].

### **Met and epidermal growth factor receptor in basal-like breast cancer**

Another tyrosine kinase that phenotypically marks basal-like breast tumors is EGFR. Similar to Met, EGFR is highly expressed in the majority of BLBCs *in vivo* and exerts proliferative and anti-apoptotic functions in cultured basal-like breast cancer cells [43]. In preclinical studies, EGFR inhibition can potentiate cisplatin-induced apoptosis in cultured basal-like breast cells [67].

### **Clinical trials with epidermal growth factor receptor inhibitors**

Based on these observations, clinical trials have been designed to study the effect of EGFR inhibition in patients with BLBC. Two studies completed to date have provided interlocutory results. TBCRC 001 was a randomized phase II trial evaluating the role of EGFR inhibition for triple-negative metastatic breast cancer. In this study, eligible women received the anti-EGFR monoclonal antibody cetuximab combined with carboplatin, or received cetuximab alone with a planned crossover to carboplatin at progression. Cetuximab alone showed a low response rate and this trial arm was closed before time; response to the combination of cetuximab plus carboplatin was 17%, with clinical benefit seen in 29% of a pretreated population [68]. A similar study examining

**Table 2. Summary of HGF/Met inhibitors currently in clinical trials**

Agent	Type	Targets	Phase of development	Comments
AMG102 (Amgen)	Antibody	Human HGF	Phase 1/2	Tested in small-cell lung cancer, metastatic colorectal carcinoma, malignant glioma, prostate cancer, renal cell carcinoma, gastric or esophagogastric junction cancer, mesothelioma, ovarian cancer or peritoneal cancer
SCH900105 (Aveo Pharmaceuticals)	Antibody	Human HGF	Phase 1/2	Tested in nonsmall-cell lung cancer
MetMab (Genentech)	Monovalent antibody	Human Met	Phase 1/2	Tested in nonsmall-cell lung cancer
ARQ197 (ArQule)	Selective small-molecule inhibitor, non-ATP competitive	Met	Phase 1/2	Tested in nonsmall-cell lung cancer, metastatic colorectal carcinoma, pancreatic adenocarcinoma, hepatocellular carcinoma, gastric carcinoma, germ cell tumors, renal cell carcinoma, alveolar soft part sarcoma, clear cell sarcoma
JNJ-38877605 (Johnson and Johnson)	Selective small-molecule inhibitor, ATP competitive	Met	Phase 1	
EMD-1214063 (EMD Serono)	Selective small-molecule inhibitor, ATP competitive	Met	Phase 1	
INCB-028060 (Incyte)	Selective small-molecule inhibitor, ATP competitive	Met	Phase 1	
MK-8033 (Merck)	Selective small-molecule inhibitor, ATP competitive	Met, Ron (10-fold less active)	Phase 1	
PF-02341066 (Pfizer)	Multikinase inhibitor, ATP competitive	Met, ALK	Phase 1/2	Tested in nonsmall-cell lung cancer
GSK-1363089/XL880 (Exelixis)	Broad-spectrum kinase inhibitor, ATP competitive	Met, Ron, VEGFR1 to VEGFR3, PDGFR, Kit, Flt-3, Tie-2	Phase 1/2	Tested in gastric cancer, nonsmall-cell lung cancer, papillary renal-cell carcinoma
BMS-907351/XL184 (Exelixis)	Broad-spectrum kinase inhibitor, ATP competitive	Met, VEGFR2, Ret, Kit, Flt-3, Tie-2	Phase 1/2/3	Tested in medullary thyroid cancer, nonsmall-cell lung carcinoma, glioblastoma, astrocytic tumors
MP470 (SuperGen)	Broad-spectrum kinase inhibitor, ATP competitive	Met, Ret, Rad51, mutant forms of Kit, PDGFR, Flt-3	Phase 1b	Tested in neuroendocrine tumors, lung cancer, triple-negative breast cancer
MGCD265 (Methylgene)	Broad-spectrum kinase inhibitor, ATP competitive	Met, Ron, VEGFR1 to VEGFR3, Kit, Flt-3, Tie-2	Phase 1	
MK-2461	Broad-spectrum kinase inhibitor, ATP competitive	Met, KDR, FGFR1 to FGFR3, Flt-1, Flt-3, Flt-4	Phase 1 completed	

FGFR, fibroblast growth factor receptor; HGF, hepatocyte growth factor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

irinotecan plus carboplatin with or without cetuximab showed a modestly higher response rate (from 30 to 49%) with the cetuximab combination [68].

These interim data together indicate that targeted therapies against EGFR in breast tumors appear to be poorly effective with respect to other types of cancer in which EGFR deregulation has been documented, such as lung cancer and colon cancer [69-71]. This lack of effect could be due, at least in principle, to the presence of concomitantly active signal transduction pathways emanating from other tyrosine kinase receptors, including Met.

#### The Met-epidermal growth factor receptor connection

Several pieces of evidence point to an intimate relationship between EGFR and Met signaling, both in

physiological settings, such as mammary gland morphogenesis [72], and in pathologic conditions, including cancer progression and resistance to targeted therapies. In nonsmall-cell lung carcinomas, for example, the onset of secondary resistance to EGFR inhibition relies, among other things, on the acquisition of MET gene amplification and consequent protein overexpression, which leads to activation of signal transduction cascades that compensate for EGFR blockade and sustain tumor maintenance [73-75]. Something similar might also occur in mammary tumors. Met and EGFR are both overexpressed in breast cancer cell lines endowed with a basal-like subtype molecular profile [42]. In this context, resistance to the EGFR inhibitor gefitinib occurs because EGFR is trans-phosphorylated via a Met/Src-mediated

signaling pathway. Accordingly, cancer cell proliferation can be impaired by combined neutralization of EGFR and Met signals [76].

Together with Met and EGFR, other tyrosine kinase receptors have been reported to be overexpressed in basal-like breast carcinoma: among these prominent druggable targets are c-Kit and the fibroblast growth factor receptor. High levels of c-Kit are preferentially found in BRCA1-associated basal-like tumors; of note, c-Kit mRNA expression appears to be already twofold higher in preneoplastic BRCA1 mutation-associated breast tissue versus non-BRCA1/2 breast tissue, suggesting that c-Kit upregulation may be an early event in BRCA1-driven tumorigenesis [36]. Fibroblast growth factor receptor has been shown to be amplified at the genomic level in two BLBC cell lines; both lines undergo apoptosis following pharmacologic or RNA interference-mediated inactivation of the kinase [54].

## Conclusions

Some of the genes described as belonging to the different subtypes of breast cancer have been reported to play important roles in the definition of a specific cell lineage in normal mammary development and to be deregulated in the tumors that recapitulate the characteristics of that specific lineage. For example, the transcription factor GATA3 mediates luminal differentiation in gland development and GATA3 deficiency leads to a block in luminal terminal differentiation, with an expansion of the progenitor compartment [34,77]. Consistently, in the tumor counterpart, GATA3 is highly expressed in the luminal subtypes [27,78].

When applying this line of thinking to the HGF/Met system, one could speculate that the correlation between Met expression and basal markers reflects a precise Met function in physiological gland development; namely, in the definition of a poorly differentiated basal compartment and/or in the negative regulation of luminal terminal differentiation. Future work is needed to address the role of Met in mammary lineage determination and to analyze whether Met activation can trigger a genetic/molecular program that dictates commitment to one specific mammary subpopulation with respect to the others.

While the association between high Met expression and human basal cancers is now well defined, the causative role for Met in the onset and/or maintenance of BLBCs is less clear: mice in which active forms of Met are specifically expressed in the mammary epithelium develop breast carcinomas with basal-like features, but they are also prone to tumors with phenotypic and molecular characteristics other than those of BLBCs [52,53]. To tackle this issue at the clinical level, it will be interesting to explore whether targeting of Met in basal-like cancer will have therapeutic value. Several anti-Met

antibodies and small-molecule Met inhibitors have been recently developed, and many of them are now being tested in phase 1 and phase 2 clinical trials [79-81] (Table 2). These agents will probably prove useful in combination with other therapies, including EGFR, c-Kit, and fibroblast growth factor receptor inhibitors. At present, the availability of mouse models that develop Met-driven basal-like breast tumors provides a useful experimental platform to assay the efficacy of Met inhibition in the preclinical setting and to guide future intervention in human patients.

## Abbreviations

BLBC, basal-like breast cancer; EGFR, epidermal growth factor receptor; ER $\alpha$ , estrogen receptor alpha; HGF, hepatocyte growth factor; YB-1, Y-box binding protein-1.

## Competing interests

The authors declare that they have no competing interests.

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