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# The met receptor tyrosine kinase and basal breast cancer

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**Breast cancer is a complex disease that comprises cancers of distinct biologies and responses to treatment. Clinical management relies on traditional clinicopathological parameters, involving lymph node status, histological grade, as well as expression of the estrogen receptor or human epidermal growth factor receptor 2. Molecular pathology as well as protein and gene expression profiling have divided breast tumors into molecular subtypes associated with different clinical outcomes. One of these, defined as basal breast cancer, is associated with poor prognosis. Molecular mechanisms involved in the induction of basal breast cancer are poorly understood and targeted therapies for this subtype are lacking. Recent evidence using murine models identified a role for the Met receptor tyrosine kinase in the induction of murine mammary tumors with characteristics of human basal breast cancers. Moreover, elevated Met protein and RNA is associated with human basal tumors and poor outcome. These studies identify a link between the Met receptor tyrosine kinase, epithelial mesenchymal transition, and basal breast cancer. In this review, we provide an overview of murine Met models in relation to the spectrum of mouse models of breast cancer and a role for the Met receptor in basal breast cancer tumorigenesis.**

**Key words:** transgenic mouse model, basal breast cancer, gene expression profiling, met receptor tyrosine kinase, epithelial to mesenchymal transition

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## Breast Cancers can be Divided into Molecular Subtypes

The majority of human breast cancers (60%) are Estrogen receptor (ESR1) positive and through gene expression profiling these fall into two predominant subtypes, Luminal A and B.[1-5] The luminal subtype is named as such to reflect a similarity in gene expression profiling to morphologically normal luminal epithelial cells which line mammary ducts and lobules, and typical luminal markers include keratins 8/18, transcription factor GATA binding protein 3 (GATA3) and XBP1. Luminal A tumors tend to have relatively good prognosis and respond to hormonal therapies, whereas luminal B tumors have lower ESR1 protein levels, a higher proliferative index and are more resistant to therapy.[6] The remaining breast cancers are ESR1-negative and fall in two distinct subgroups that are associated with poor prognosis; the human epidermal growth factor receptor 2 (ERBB2)-positive and the basal-like subtypes. The ERBB2-positive class is immunopositive for ERBB2 as well as other genes in the *ERBB2* amplicon located on chromosome 17q21.[7,8] These tumors are treated with a regimen that involves humanized monoclonal anti-ERBB2 antibodies or small molecule kinase inhibitors, and significantly, about 50% of patients respond to treatment.[9,10] The term "basal" reflects the epithelial layer surrounding the luminal layer, lying closest to the basement membrane in the morphologically normal mammary gland, and includes mammary stem cells as well as myoepithelial cells. Basal breast cancers are named as such as they share gene expression similarities to cells within the basal layer of the mammary gland and markers include keratins 5/6, 14, 17 and others. The basal subtype represents between 15–25% of all breast cancers, as defined by immunohistochemistry or gene expression profiling, and this subtype generally lacks expression of ESR1 and

ERBB2.[1,2,11-15] Thus, targeted therapies are not available for tumors falling within this molecular subtype and systemic therapies are the main therapeutic option for basal-like breast tumors. However, their efficacy is currently under investigation in clinical trials.[16]

## Met Coordinates a Program of Invasive and Regenerative Growth

The Met receptor tyrosine kinase (RTK), which is the receptor for Hepatocyte Growth Factor/Scatter Factor (HGF), is expressed in tissues of epithelial and endothelial origin during development and at maturity, including breast epithelium.[17,18] HGF is produced by fibroblasts and other mesenchymal cells and activates the Met receptor in a paracrine manner. In both embryos and adults, Met activation by HGF initiates a morphogenic program of invasive growth that promotes disruption and remodeling of intracellular contacts, cell migration and invasion. During embryogenesis, the Met/HGF axis is required for development of the placenta, liver, kidney, and skeletal muscle.[19-21] Met and HGF expression are coordinately regulated in the mammary gland during development and blocking HGF from excised mammary fat pads using an antisense oligonucleotide approach inhibited ductal branching,[22] supporting a role for Met/HGF in mammary gland development. However, embryonic lethality of $Met^{-/-}$ and $HGF^{-/-}$ mice has precluded the study of mammary development postnatally. In the adult, Met is required for wound healing and liver regeneration.[23,24] Both Met and HGF are expressed by mesenchymal stem cells and are involved in hematopoeisis,[23,24] promoting cellular migration and proliferation required during tissue remodeling and wound healing.[25,26]

## Met and Human Cancer

Perturbation of the HGF/Met axis that leads to enhanced signaling, occurs in a wide range of human cancers, although with variable frequency, and elevated Met signals are in general characteristic of aggressive tumors with poor prognosis (www.vai.org/met). Various mechanisms of Met/HGF-mediated tumorigenesis have been investigated. Establishment of an HGF/Met autocrine loop is associated with many types of cancers including melanomas, osteosarcomas, breast carcinomas, and gliomas and may play a role in driving cell motility, thereby supporting a role in cellular metastasis.[18] Amplification of the Met receptor occurs frequently in gastric cancer,[27] has been observed at low levels in lung cancers,[28-30] and in general, the growth of these tumors is dependent on Met catalytic activity. Elevated expression of Met in the absence of amplification occurs in multiple human cancers and can be induced under hypoxic conditions.[31]

Various Met germline and somatic mutations have been identified and associated with human cancers. Activating mutations in the Met kinase domain are infrequently found, but are associated with both inherited and sporadic renal cell carcinoma (www.vai.org/met). Mutations of the juxtamembrane domain have been identified in gastric and lung cancers.[32,33] These mutations specifically uncouple the recruitment of Cbl and act to delay Met trafficking and subsequent degradation.[34,35] Extracellular domain mutations have been found in a panel of solid tumors (lung, melanoma, renal), though their functional consequences are unknown.[36] Interestingly, Met knock-in mice expressing kinase-activating mutations found in renal cancers develop carcinomas from multiple organs, as well as lymphomas,[37] thus highlighting the involvement of dysregulated Met signaling in tumorigenesis.

Cross-talk between Met and other RTKs as well as with other cell surface protein families such as integrins, plexins, CD44 and G protein-coupled receptors is an additional mechanism through which Met contributes to tumorigenesis.[38] These associations enhance Met signaling and contribute to biological responses downstream from Met. Notably, amplification of Met has been recently identified as a mechanism of resistance to EGFR inhibitors (erlotinib, gefitinib) in non-small cell lung cancer (NSCLC) implicating Met as an additional target in this disease.[28,39-41]

Increasing evidence associates elevated levels of Met RTK protein in breast cancer with poor outcome. Met protein is elevated in 15–20% of human breast cancers[42] and alone,[43,44] or together with downstream signal transduction proteins FAK and PI3K, correlates with decreased patient survival and with metastases.[45] Similarly, elevated levels of the Met ligand, HGF, found in the serum of breast cancer patients, is associated with a shorter disease-free interval following surgery[46] and a higher tumor/lymph node/metastasis score.[47]

## Met/HGF Mouse Models of Breast Cancer

Several different mouse models with deregulation of the Met receptor and HGF have produced mammary tumors (**Table 1**). These models have been examined to a limited extent, however, from the data available, general consistencies can be found. Several transgenic models use the ubiquitously expressed metallothionein (MT) promoter to express HGF, HGF variants (MT/HGF, MT/NK1) or oncogenic mutants of Met (MT/Tpr-Met, MT/M1248T) (**Table 1**).[48-50] Others use the hormonally regulated promoters, whey acidic protein (WAP/HGF)[51] or mouse mammary tumor virus (MMTV).[52] These generally require multiple rounds of pregnancy and lactation to induce tumor formation (**Table 1**).[53] Data from these models demonstrates that the mammary epithelium is susceptible to tumorigenesis by disruption of the Met/HGF pathway. However, mammary tumors form with long latency and low penetrance when compared to those of MMTV/ErbB2 or MMTV/PyMT models (**Table 1**).[54,55]

Although these studies supported the oncogenic potential for the Met-signaling axis in mammary epithelia, models targeting expression of oncogenic forms of the Met RTK specifically to the mammary epithelium, had not been developed. The recent development of transgenic lines carrying wild type and oncogenic variants of the Met receptor under the control of the MMTV promoter, allowed for Met transgene expression in mammary epithelia in a hormone-dependent manner, following multiple rounds of pregnancy.[52] To study involvement of the Met RTK in tumor initiation and progression, several activating

**Table 1.** Met/HGF signaling-induced mouse models of mammary tumorigenesis

| Transgene | Promoter | Genetic background | Pregnancy required | Latency (days) | Penetrance (%) | Mammary tumor histology | References |
|---|---|---|---|---|---|---|---|
| Tpr-Met | MT | FVB/N | yes | 381 | 42 (11/26) | Scirrhous, papillary and solid nodular | Liang TJ, et al. J Clin Inv 1996 |
| HGF | MT | FVB/N | yes and no | ~450 | 41 (11/27) | Adenosquamous and adenocarcinoma | Takayama H, et al. PNAS 1997 |
| NK1 | MT | FVB/N | NA | ~630 | 5 (1/19) | NA | Jakubczak JL, et al. MCB 1998 |
| M1248T | MT | C57BL/6NCR x C3H/ HeNCR F2 | Yes | ~300 | 5 (1/21) | Adenocarcinoma | Jeffers M, et al. PNAS 1998 |
| HGF | WAP | FVB/N | Yes | ~300 | 89 (49/55) | Glandular adenocarcinoma and squamous metaplasia | Gallego MI, et al. Oncogene 2003 |
| M1248T/ L1193V | endogenous | FVB/N | Yes | ~300 | 86 (13/15) | Adenosquamous, scirrhous and solid nodular, myoepithelial, spindle cell tumors | Graveel CR, et al. PNAS 2009 |
| M1248T/ L1193V | endogenous | FVB/N | No | ~338 | 65 (10/16) | Adenosquamous, scirrhous and solid nodular, myoepithelial, spindle cell tumors | Graveel CR, et al. PNAS 2009 |
| Met | MMTV | FVB/N | Yes | 475 | 9 (2/22) | Squamous, adenomyoepithelial, secretory, papillary, spindle cell, glandular tumors | Ponzo MG, et al. PNAS 2009 |
| M1248T | MMTV | FVB/N | Yes | 478 | 12 (2/17) | Adenosquamous, adenocarcinoma | Ponzo MG, et al. PNAS 2009 |
| Y1003F/ M1248T | MMTV | FVB/N | Yes | 381 | 40 (14/35) | Solid nodular, scirrhous, papillary, secretory, microacinar, glandular adenosquamous, spindle cell tumors | Ponzo MG, et al. PNAS 2009 |

NA, data not available.

variants of the Met receptor were tested. These included a mutation in the kinase domain (M1248T) originally identified in hereditary papillary renal cell carcinoma,[56] and a juxtamembrane domain mutation (Y1003F), which results in a loss of receptor ubiquitination, receptor degradation and thus prolonged signaling[34,35] similar to Met mutants found in lung cancers.[57] In this model, mammary tumors were generated with long latency and low penetrance, however the latency was significantly reduced (381 days), and penetrance was significantly increased (40%), in the Met Y1003F/M1248T model (termed MMTV/Met$^{mt}$, **Table 1**).[52] An alternative model expressing a similar oncogenic variant of the Met receptor (M1248T/L1193V) following knock in to the endogenous *Met* locus, (Met$^{mut}$, **Table 1**) developed mammary tumors with high penetrance, and long latency when backcrossed with FVB animals.[58]

## Met Induces Mammary Tumors with Multiple Pathologies Including Basal-Like Breast Cancer

Traditionally, transgenic models where expression of RTKs, or their surrogates, are regulated by the MMTV promoter, such as the MMTV/ErbB2 and MMTV/PyMT models respectively, are known to produce tumors consisting of solid nodules with a scarce stroma component.[59] In addition to generating tumors with solid pathologies, we were intrigued that 50% of tumors in the MMTV/Met$^{mt}$ mouse model as well as the Met$^{mut}$ model of Graveel et al. showed mixed pathologies, including adenosquamous, spindle cell, papillary, myoepithelial and scirrhous pathologies.[52,58] To gain an understanding of the multiple pathologies induced by the MMTV/Met transgene, we performed gene expression profiling. Interestingly, the MMTV/Met$^{mt}$ tumors with mixed pathologies shared a similar gene expression profile and clustered together. Notably, these were distinct from MMTV/Met$^{mt}$ tumors with solid adenocarcinoma pathology (**Fig. 1**). Comparing the gene expression profile of this model to other established models of breast cancer using the intrinsic gene set of Herschkowitz et al. revealed that the Met$^{mt}$ mixed pathology tumors clustered in a group of mouse models with heterogeneous pathologies such as p53$^{-/-}$ transplants, p53$^{+/-}$ irradiated, C(3)/Tag and WAP/$T_{121}$ all of which have an enrichment in basal and mesenchymal genes.[52,60] By contrast, the Met$^{mt}$ solid tumors were homogeneous in their clustering, and stratified to a group of mouse models also exhibiting solid histopathologies such as MMTV/ErbB2 and MMTV/PyMT.[52,60]

These data suggest that a mutationally activated Met transgene may initiate tumorigenesis from a bipotential cell population of the mammary gland. This is supported by expression of the basal lineage marker, p63 and keratin 14 as well as co-staining of MMTV/Met$^{mt}$ transgene with the basal marker keratin 5 and luminal marker keratins 8/18

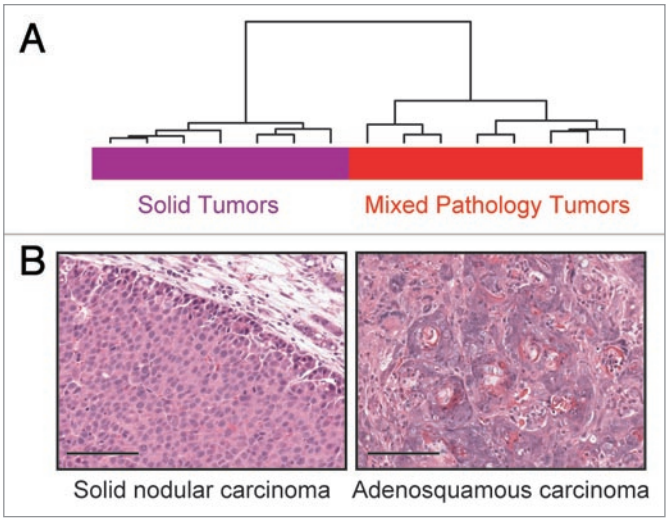


**Figure 1.** MMTV/Met$^{mt}$ mice develop mammary tumors that cluster into two distinct groups by microarray analysis. (A) MMTV/Met$^{mt}$ tumors segregate into two main clusters: solid (purple group) and mixed pathology tumors (red group).[52] (B) MMTV/Met$^{mt}$ transgenic mice induce mammary tumors with solid/luminal and mixed pathology/basal phenotypes. Representative images shown. Scale bars represent 100 μm.

in pockets of cells within Met$^{mt}$ basal-like tumors,[52] in addition to keratin 14 positive cells. In contrast, all MMTV/Met$^{mt}$-induced mammary tumors with solid pathologies were uniquely positive for keratin 8/18, consistent with the MMTV/ErbB2 model or MMTV/PyMT models that induce mammary tumors with solid pathologies. Interestingly, the Met Y1003F and Y1003F/M1248T mutants uncouple Met from the ubiquitin ligases, c-Cbl and Cbl-b and result in delayed degradation of this Met mutant and sustained signaling through the Ras pathway.[35,61,62] Ras-dependent signals are known to promote mammary tumors with a solid pathology in MMTV-transgene driven animal models.[59] Consistent with this, the majority of tumors with solid pathologies arose in mice where the MMTV/Met Y1003F/M1248T transgene was expressed at mid-high levels, whereas mice with tumors with mixed pathologies predominantly arose in mice expressing the MMTV/Met M1248T transgene. Notably, the Met$^{mut}$-induced mammary tumors were also immunopositive for keratin 5 except for tumors with solid pathologies[58] indicating that this is a common phenotype of Met-induced mammary tumors.

Where described in detail, another common feature among Met/HGF mouse models of breast cancer is the production of tumors with multiple pathologies including a squamous component (**Table 1**). The MT/Tpr-Met model (where Tpr-Met is a cytosolic fusion protein product generated from gene rearrangement of the translocated promoter region, Tpr, on chromosome 1q25 and Met locus on chromosome 7q31) induced tumors with papillary, scirrhous and solid nodular pathologies.[48] Similarly, mammary tumors in WAP/HGF transgenic mice showed features of squamous metaplasia and stained positively for basal marker keratin 6,[51] as did the MMTV/Met$^{mt}$ mixed pathology tumors with keratin 5, 6, 14 staining.[52] Expression of Myc using a modified stem cell retrovirus in mammary epithelia of a Met transgenic model resulted in mammary tumors that displayed both keratin 14 and keratin 6 positive cells.[63] Additionally, the Met$^{mut}$ model exhibited positive staining for basal/stem cell markers.[58] Another consistency among mouse models exhibiting Met/HGF deregulation is a tendency for animals to produce multiple tumor foci per animal. This is the case for both the Met$^{mut}$ and MMTV/Met$^{mt}$ models.[52,58] Altogether, this data demonstrates a direct role for the Met/HGF pathway in mammary tumorigenesis and a causative role in the induction of tumors with a basal-like phenotype.

Other transgenic mouse models of breast cancer have been reported to have basal-like features either by gene expression analyses (WAP/$T_{121}$, MMTV/Wnt, Brca1$^{co/co}$; MMTV/Cre; Trp53$^{+/-}$, K14/Cre; Trp53$^{fl/fl}$, Brca1$^{fl/fl}$), and/or by comparative pathology (BLG/Cre; Brca1$^{F22-24/F22-24}$; Trp53$^{+/-}$).[60,64-67] It is intriguing that mice containing diverse genetic alterations produce mammary tumors with a similar phenotype. Although sporadic basal breast cancers, and *BRCA1*-associated basal tumors were initially thought to originate from a bipotential precursor cell population,[68] a recent study suggests that an aberrant luminal progenitor cell population may be the target of tumorigenesis in these cancers.[69] However, there are likely multiple genetic events implicated in the generation of a basal-like tumor phenotype, and it is necessary to identify novel animal models of basal breast cancer to further study the molecular mechanisms of tumorigenesis.

## Met Induced Mammary Tumors Share Similarities with Human Basal Breast Cancer

Clustering the differentially expressed gene profiles of the MMTV/Met$^{mt}$ tumors with human breast cancers,[60] revealed that tumors with Met$^{mt}$ mixed pathology clustered among human basal breast cancers, whereas tumors with solid pathology clustered among luminal breast cancers, therefore illustrating that overall, Met$^{mt}$ tumors share features representative of the spectrum of tumors seen in human breast cancer.[52] In addition to sharing gene signatures with human basal breast cancers, the MMTV/Met$^{mt}$ mixed pathology tumors also exhibited morphological features resembling human basal breast cancer such as squamous metaplasia, central necrosis, pushing margins, high grade, lymphocytic infiltration, nuclear atypia and pleomorphism.[52,70] Some of these histological features are similar to those of medullary (lymphocytic infiltrate and pushing margins) or metaplastic (spindle cells or squamous metaplasia) breast carcinomas, two rare types of breast cancer with a basal-like immunohistochemistry profile.[71,72] These tumors are also known as carcinosarcomas, which are thought to

contain features of epithelial to mesenchymal transitions (EMT).[73,74] Gene expression studies of medullary and metaplastic breast tumors have identified an EMT-signature and they cluster among sporadic basal-like or "claudin-low" tumors.[74-76] In vitro, HGF induces cell scattering and dispersal, which reflects a transient EMT, coinciding with transient upregulation of transcription factors involved in EMT such as Snail.[52] Interestingly, the Met$^{mt}$ basal-like tumors showed an enrichment for EMT-associated genes, including transcription factors *Snai1* (Snail), *Snai2* (Slug), Twist1 and Zeb1, as well as markers of mesenchymal transition such as vimentin, and smooth muscle actin.[52] This provides direct evidence for a deregulated Met/HGF pathway inducing a sustained EMT program in vivo and producing tumors resembling human basal breast cancer with features of EMT.

A strong link between a Met-induced gene expression signature and elevated Met mRNA and protein with human basal breast cancer was further supported by large cohort studies.[52,58] In a cohort of 668 axillary lymph node negative patients, elevated Met protein was significantly correlated with the basal subtype, where 65% of tumors were Met positive,[52] within a similar range (60%) for an established basal marker, the epidermal growth factor receptor (EGFR).[13] A significant correlation to the human basal subtype was also observed with Met RNA in an independent cohort, and using a Met gene expression signature.[52] In agreement with this, Graveel et al. used a Met gene expression signature generated from mouse embryonic fibroblasts to show that the Met gene expression signature most strongly correlated with the human basal subtype.[58] Furthermore, co-expression of the EMT marker SNAIL with MET resulted in worse clinical outcome than either marker alone among human breast cancers.[52] Previous studies had also associated elevated levels of Met protein with breast cancers of the basal subtype. Gene expression profiling of human breast cancer cell lines, identified Met among a group of genes elevated and differentially expressed between basal and luminal breast cancer cell lines.[77] Similarly, elevated levels of Met protein were identified in basal-like primary tumors,[4] as well as corresponding metastases.[78] Interestingly, in inflammatory breast cancers, which are rare but highly aggressive tumors with a 5-year survival rate of 30–50%, all 41 cases were Met positive when compared to 480 non-inflammatory breast tumor tissues.[79] Additionally, inflammatory breast cancers were found to stratify into basal and ErbB2-positive groups as determined by gene expression profiling[80] and immunohistochemistry (where basal tumors were defined as ESR1/ERBB2 negative).[81] Together these data support a role for the Met receptor in aggressive basal, and other poor outcome breast tumors.

## Mechanisms of Basal Breast Cancer: A Role for Met

Gene expression profiling has aided our understanding of the molecular mechanisms implicated in breast cancers by highlighting groups of genes upregulated or downregulated for each molecular subtype. For instance, Luminal A subtype tumors express ESR1, and a panel of ESR1-response genes. The dependence of these tumors on estrogen is demonstrated by their response to hormonal therapy, such as tamoxifen. Expression profiling of basal breast tumors revealed elevation of genes involved in cell proliferation, migration and invasion, and inhibition of apoptosis, however the genes responsible for the aggressive nature of basal breast cancers are still poorly understood and hinders the development of therapy.[1,82,83]

Other models for the genesis of basal breast cancers, include loss of function of BRCA1.[64-67,84] In the normal mammary gland and breast tissue, BRCA1 plays a critical role in the differentiation of ESR1-negative stem/progenitor cells to ESR1-positive luminal cells and BRCA1 loss of function abrogates this transition.[85] This may be sufficient to halt differentiation and together with increased genomic instability due to DNA-repair defects, lead to expansion of a precursor population that gives rise to basal-like tumors.[69,82] Subsequent events are proposed to involve loss of p53, activation of RAS, and EGFR to initiate PI3K/Akt and MAPK signals which are consistent with genes elevated in expression studies of basal-like tumors.[82] The Met RTK also activates RAS, MAPK and PI3K/Akt signals.[86] Notably, a phenotypic similarity between sporadic basal-like tumors and breast cancers harboring a *BRCA1* germline mutation has been identified. About 80–90% of *BRCA1* germline mutation breast cancers share pathological features with basal tumors raising the possibility of a similar mechanism of tumorigenesis between these tumors and sporadic basal breast cancers.[87] Although somatic mutations in the *BRCA1* locus have not been found in sporadic basal tumors, defects in the BRCA1-DNA repair pathway and methylation of the *BRCA1*-promoter, accompanied by loss of heterozygosity of the other *BRCA1* allele results in reduced or undetectable levels of BRCA1 or reduced nuclear localization of BRCA1 in 11–30% of sporadic basal breast cancers.[14,88-90] *BRCA1* mRNA transcription is negatively regulated by the helix-loop-helix transcription factor, ID4.[91] Interestingly, ID4 is elevated in sporadic basal tumors as well as in MMTV/Met$^{mt}$ basal-like tumors.[1,2,52,91] However, these mechanisms remain to be validated and tested experimentally.

Cooperation between Met and the tumor suppressor p53 may also contribute to basal breast cancer. In support of this, amplification of the *Met* locus was observed in 73% of basal-like mammary tumors that develop in a conditional Brca1/p53-deficient mouse model.[92] Met and p53 are also thought to cooperate in Li-Fraumeni syndrome.[93] Under physiological conditions, p53 protein levels are low due to rapid turnover of p53 within the cell, but in response to various stressful stimuli such as DNA damage or hypoxia, p53 protein is stabilized and activated to perform its various functions.[94] In human basal breast cancers, p53 is frequently mutated and positive p53 immunostaining, typically indicative of p53 mutation and loss of function, is elevated in human basal breast cancers.[95,96] The Met receptor is a transcriptional target of the miR-34 family which is negatively regulated by p53.[97] Overall, these results support genetic cooperation between Met and p53, and should be evaluated further for its implication in human basal breast cancer.

Interestingly, subpopulations of cells in the MMTV/Met$^{mt}$ mixed pathology

tumors expressed the basal lineage marker p63, as well as keratin 14 and vimentin, although subsets of cells also expressed luminal lineage markers including keratins 8/18.[52] Notably, in MMTV/Met$^{mt}$ basal-like tumors, keratins 5/6 was co-expressed in keratin 8/18 and keratin 14 positive cells, supporting the presence of both basal as well as luminal or bipotential progenitor cells within MMTV/Met$^{mt}$ tumors.

## Conclusions and Future Perspectives

Altogether, the Met$^{mt}$ and Met$^{mut}$ murine models mimic several of the pathological features and gene expression changes of poor outcome, Met-elevated human breast cancers. These represent mouse models whereby the deregulation of the Met RTK signaling axis induces tumors of solid/luminal-like, mixed/basal-like and EMT pathologies. Since there are a lack of animal and cell-based tools to study mechanisms involved in basal breast cancer, the Met$^{mt}$ and Met$^{mut}$ models are valuable tools to begin to define this subtype at the molecular level. Further work is necessary to uncover the molecular mechanisms implicated in basal breast cancer. This will allow for better identification of poor outcome basal tumors, as well as better treatment options for these patients. Currently, a combination of gene expression profiling, and immunohistochemistry staining are used to identify basal breast cancers, however these methods have their flaws. Gene expression is costly to perform in a population-based setting, and as described, the immunohistochemical definition on basal breast cancer is largely based on negative staining (ESR1/PGR/ERBB2-negative, or "triple-negative") raising the potential for false negative results. Most likely, a combination of basal keratins, and EGFR staining will be used, as these have been shown to have a sensitivity of 73% and specificity of 100%.[13] The Met receptor may be added to the growing list of biomarkers, however the specificity and sensitivity of Met in combination with other basal markers will need to be evaluated. Met inhibitors are currently under investigation in clinical trials.[98] In addition to breast cancer, Met positivity is also emerging as a marker of poor outcome and drug resistance in other tumor types where a role for the Met RTK in collaboration with other RTKs, and as a mechanism for acquired resistance to EGFR inhibitors is now established in NSCLC and glioblastoma.[28,39-41,99,100] Therefore, Met inhibitors could prove useful in combination with other therapies targeting basal breast cancers. Studies will be needed to examine the role of Met and Met inhibitors in these contexts, however the Met$^{mut}$ and MMTV/Met$^{mt}$ mouse model will undoubtedly aid in testing and validating these hypotheses and discoveries.


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