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REVIEW OPEN ACCESS

Mouse Models of HER2+ Human Breast Cancer: A Literature Review

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Abstract

Introduction: HER2+ breast cancer (BC) makes up 15-20% of BC cases, where HER2 overexpression drives BC progression via proliferative signals. Targeted therapies inhibit HER2's activity but face challenges like resistance and metastasis. Thus, HER2+ BC is a developing research area where many preclinical studies are being conducted, and mice are often used due to their genetic and physiological similarities to humans. This study aims to review and compare existing mouse models to determine the best model of HER2+ BC.

Methods: A literature search on PubMed in February 2024 using search terms including HER2, neu, neuNT, MMTV, and mammary tumors identified 16 primary research articles that used Neu-overexpressing mice. The papers were categorized under five models: MMTV-Neu, MMTV-NeuNT, FloxNeo-NeuNT, MMTV-NIC, and MMTV-HER2.

Results: Among examined studies, Andrechek et al.'s FloxNeo-NeuNT model had the longest average tumor onset at 447 days, while Kuang et al.'s MMTV-NIC had the shortest at 126 days. Ursini-Segal et al.'s MMTV-NIC mice showed 100% mammary tumor incidence. Most models resulted in mammary adenocarcinomas, with lung metastases commonly observed, especially in papers that used MMTV-NIC.

Discussion: Human HER2+ BC is commonly adenocarcinoma and often metastasizes to lungs, bones, liver, and brain. The mouse models were also found to be adenocarcinomas, but they primarily showed lung metastasis, possibly due to insufficient tumor detection methods for brain and bone metastasis. Neu copy numbers in Andrechek et al.'s FloxNeo-NeuNT model also align with findings on HER2 copy number amplification in human HER2+ BC.

Conclusion: We have found that MMTV-NIC is the optimal mouse model for HER2+ BC research due to its short latency, 100% tumor incidence, and high rate of lung metastasis.

Keywords: HER2; Neu; mouse; models; breast; cancer; MMTV; NeuNT

Introduction

Breast cancer (BC) is the most common cancer among women in Canada, and the most common neoplasia globally [1]. Despite this, BC incidence has continued to steadily rise in the past four decades by 0.5% per year worldwide, highlighting the ever-growing national and global burden of BC on our societies and healthcare systems [2]. There are several levels for classifying BC, one of which is at the molecular level. Molecular classification identifies the presence of specific proteins on the cancerous cells, which allows for targeted and individualized treatment plans [3]. As such, four molecular subtypes have been identified: luminal A, luminal B, HER2, and basal-like. In an estimated 15-20% of BC cases, the cancerous cells demonstrate higher than normal levels of HER2 [4]. Human Epidermal Growth Factor Receptor 2 (HER2), also known as ErbB2 or by its mouse analog *Neu*, is a tyrosine receptor kinase and oncogene located on human chromosome 17q12 and part of the epidermal growth factor receptor (EGFR) family [5]. HER2 is a monomeric glycoprotein composed of a cysteine-rich extracellular ligand-binding domain, a transmembrane lipophilic domain, and an intracellular kinase domain [6]. Unlike other EGFR proteins, HER2 has no known ligand but is activated upon dimerization into a homo- or heterodimer [7]. The phosphorylated HER2 then activates downstream signaling pathways, like the Ras/mitogen-activated protein kinase (MAPK), the phosphatidylinositol 3 kinase (PI3K)/Akt, and the phospholipase C pathways, which are involved in cell growth and hence implicated in tumorigenesis [6]. Thus, activated HER2 provides proliferative and anti-apoptotic signals, and is an important factor in the progression and growth of BC when dysregulated (Figure 1) [8].

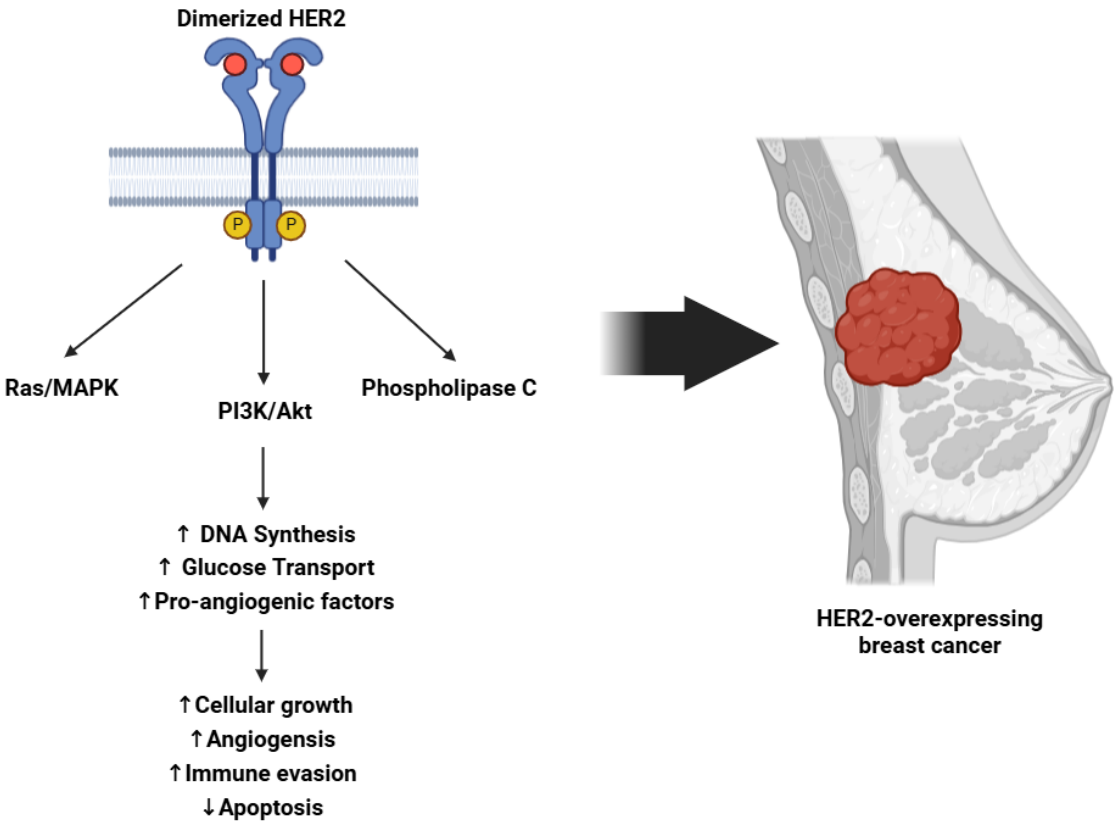

Figure 1. Signal transduction by HER2 in HER2-overexpressing breast cancer. The molecular pathways by which overexpressed dimerized HER2 causes neoplastic growth, including Ras/MAPK, PI3K/Akt, and phospholipase C pathways. Figure created with Biorender.com.

As such, HER2 has become an important marker and immunotherapeutic target in the diagnosis, treatment, and management of HER2+ BC. Such therapies work by binding to either the extracellular or intracellular tyrosine kinase domain of HER2, thus inhibiting its activity. However, while HER2+ cases are eligible for and benefit from HER2-targeted therapies, it is still unclear if HER2-equivocal cases would see a similar advantage [9]. Treatment failure is also common in these therapies, with many cases failing to respond or initially responding and developing subsequent resistance. Additionally, metastases frequently develop from HER2+ BC to sites like the bones, liver, lungs, and brain, where an estimated 40-50% of patients with HER2+ BC go on to develop brain metastasis even in the setting of prior or ongoing HER2-targeted therapy [10]. Thus, due to their unconfirmed mechanism of action, tendency for development of resistance, and low efficacy in metastatic HER2+ BC, these targeted therapies are a developing area of research. Such research requires the use of preclinical models as a stepping stone for clinical trials. The animals of choice for most preclinical studies are rodents, where approximately 85% of animal research is thought to involve rodents including mice [11]. Mice are the preferred animal due to their similar physiology to that of humans, where humans and mice share 95% of their approximate 30,000 genes [12]. In addition, mice require relatively few resources compared to other animal options, reproduce quickly due to their short gestation period of 21 days, and reach sexual maturity within six weeks [12]. Thus, the need for mouse models of HER2+ BC is clear. While several mouse models of HER2+ disease exist, no study to date has comprehensively examined all such existing transgenic models. Additionally, while there have been studies of the various transgenic mouse models for different breast cancer subtypes, including basal-like and luminal, little information was found comparing mouse models for the HER2+ subtype in particular [13]. Thus, the objective of this study is to describe the various mouse models that can be used in HER2+ BC research and compare their translatability to human research. This examination has important implications for researchers who require insight about the optimal mouse model for studying HER2+ BC.

Methods

To conduct this review, a literature search was conducted on February 7, 2024 using the medical database PubMed. Multiple individual searches were conducted to account for the different mouse models, using common

search terms like HER2, MMTV, and mammary tumors. Sixteen primary research articles were identified in total that used *Neu*-overexpressing mice, of which two, four, one, four, and five used MMTV-Neu, MMTV-NeuNT, FloxNeo-NeuNT, MMTV-NIC, and MMTV-HER2 mice, respectively.

Results

In many *Neu*-overexpressing transgenic mouse models, expression of transgenes (HER2/Neu and/or Cre recombinase) in the mammary gland may be driven by the murine mammary tumor virus (MMTV) long-terminal repeat (LTR) promoter. The MMTV LTR promoter is the prototypical hormone-responsive promoter with a hormone-response element that is selectively induced by the glucocorticoids, progesterone and dihydrotestosterone [14]. There are five main mouse models that will be the focus of this paper: MMTV-Neu, MMTV-NeuNT, FloxNeo-NeuNT, MMTV-NIC, and MMTV-HER2 (Table 1). Figure 2 summarizes the models in order of the published papers. These models overexpress one of either mouse Neu, human Neu (also known as HER2), or NeuNT (Table 2). NeuNT is an activated form of the mouse Neu which contains a single point acid mutation at residue 664 (V664E) in the Neu receptor's transmembrane tyrosine kinase domain that leads to constitutive activation of Neu [15].

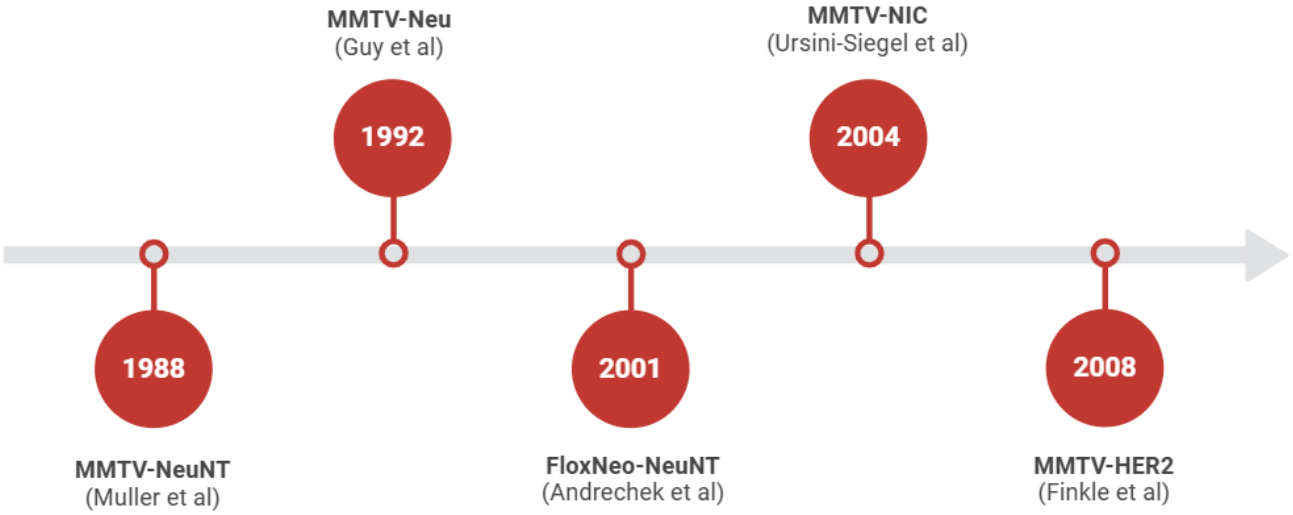

Figure 2. Timeline schematic of the main mouse models for modeling HER2+ BC. MMTV-Neu, MMTV-NeuNT, FloxNeo-NeuNT, MMTV-NIC, and MMTV-HER2, in order of first breeding. Figure created with Biorender.com.

Table 1. Overview of the features of the mouse models extracted from the originating articles

Model	Originating article	Construct description	Tumor incidence	Tumor location	Average latency	Transgene expression	Histology	Metastasis
MMTV-Neu	Guy et al, 1992	Wildtype Neu under the control of MMTV LTR promoter	50% by 204 days	Hyperplastic/dysplastic mammary glands	205 days	Low levels in normal mammary epithelium, higher in tumors	High grade, type not reported	72% to lungs
MMTV-NeuNT	Muller et al, 1988	Activated Neu (V664E) under the control of MMTV LTR promoter	50% by age 1 year	Mammary gland only	Not reported	Nonuniform in mammary epithelia	Adenocarcinomas	Several to lungs
FloxNeo-NeuNT	Andrechek et al, 2001	Activated Neu (V664E) under the control of the endogenous Neu promoter	Not reported	Mammary gland only	14.7 months	Mammary glands, spleen, and salivary glands	Comedo-adenocarcinomas	Not reported
MMTV-NIC	Ursini-Siegel et al, 2008	Activated Neu (NDL2-5) under the control of the endogenous Neu promoter	100%	Mammary gland only	146 days	High in mammary gland, low in adrenal gland, lung, ovary, pancreas, and salivary gland	Solid/nodular adenocarcinomas	91% to lungs
MMTV-HER2	Finkle et al, 2004	Human HER2 under the control of MMTV LTR promoter	73% in treatment control group	Mammary gland or Harderian gland	28.2 weeks	High levels in mammary epithelia and Harderian gland	Adenocarcinomas	40% to lungs

Table 2. Overview of the features of the mouse models

Model	Paper	Neu gene	Promoter controlling Neu	Other construct features	Age of mice until tumor formation (days)
MMTV-Neu	Guy et al., 1992	Wildtype Neu	MMTV	None	205
	Muller et al., 1996	Wildtype Neu	MMTV	TGF-alpha	Not reported
MMTV-NeuNT	Muller et al., 1988	NeuNT	MMTV	None	78-95
	Wang et al., 2005	NeuNT	MMTV	None	140
	Rodrigues et al., 2012	NeuNT	MMTV	None	126-140
	Arpel et al., 2014	NeuNT	MMTV	None	214
FloxNeo-NeuNT	Andrechek et al., 2001	NeuNT	Endogenous Neu promoter	Cre recombinase under MMTV promoter	447
MMTV-NIC	Ursini-Siegel et al., 2008	NDL2-5	MMTV	Cre recombinase, IRES element	146
	Schade et al., 2009	Neu	MMTV	Cre recombinase, IRES element, Pten	198
	Creedon et al., 2016	Neu	MMTV	Cre recombinase, IRES element	Not reported
	Kuang et al., 2024	Neu	MMTV	Cre recombinase, IRES element, Lox-Stop-Lox Usp22 allele	126
MMTV-HER2	Suda et al., 1990	huHER2	MMTV	None	Not reported
	Finkle et al., 2004	huHER2	MMTV	P53	197.4
	Hanker et al., 2013	huHER2	MMTV	PI3K-alpha	368
	De Giovanni et al., 2014	huHER2	MMTV	None	315
	Park et al., 2017	huHER2	MMTV	None	183-365

MMTV-NeuNT

The first Neu-overexpressing mouse model was prepared by Muller et al. in 1988 [16]. Hereafter, Muller et al.'s 1988 model will be referred to as 'MMTV-NeuNT'. In this model, the Neu oncogene is under control of the MMTV LTR promoter [16]. Transformation was accomplished by microinjecting the digested transgene into the male pronucleus in the ova of fertilized FVB/NHd mice. The transformed offspring were found to uniformly express high levels of transgenic Neu in their mammary epithelium [16]. At eight weeks of age, histological evaluation of mammary tissue from the virgin female transgenic mice revealed hyperplastic and dysplastic nodules infiltrating the mammary fat pad [16]. Timepoint 78 days was the youngest age at which a mammary tumor was observed, and by 95 days, all female mice developed 2+ mammary tumors with a non-stochastic pattern [16].

In 2000, Andrechek et al. built on Muller et al.'s work in aims of creating a Neu-expressing mouse model under the control of the endogenous Neu promoter [17]. Hereafter, Andrechek et al.'s model will be referred to as 'FloxNeo-NeuNT' as it was created with Cre recombinase with the MMTV promoter, and a loxP-flanked Neo cassette to prevent expression of the transgene prior to recombination, followed by NeuNT cDNA under the endogenous Neu promoter [17]. Of the 9 transgenic mice generated, NeuNT copy number within tumors ranged from 1.7 to 21.6 with an average of 8.0, and the age at tumor detection ranged from 8 to 17.3 months with an average detection age of 14.7 [17]. Genomic DNA analysis from tumor tissue confirmed the mice expressed very high levels of the activated Neu transcript and protein, with a 2- to 22- fold amplification of the activated Neu allele compared to wildtype [17]. When examining the mammary epithelium at 9 months, an abnormal pattern of lobulo-alveolar development was observed where numerous lobular side buds formed acinar structures instead of solid dysplasia and did not stain positive for Neu. However, older female mice developed focal comedo-adenocarcinomas (n=9, 45% penetrant in mice over age of 12 months). Immunohistochemical analysis of these tumors found both membrane and cytoplasmic localization of activated Neu.

Rodrigues et al. (2012) also used female MMTV-NeuNT mice to investigate the role of the HSP90 inhibitor, 17-AAG [18]. HSP-90 (Heat Shock Protein 90) is a molecular chaperone of HER2/Neu and an important player in the function of many oncoproteins. Thus, inhibition of HSP90 by 17-AAG results in depletion of Neu expression. The authors found that female MMTV-NeuNT mice developed multiple mammary gland tumors between 18 and 20 weeks of age. Western blot analysis on tumor samples showed that Neu was overexpressed. Treatment of cells from the MMTV-NeuNT tumor with 17-AAG caused a significant dose-dependent decrease in Neu expression, in addition to a significant decrease in viable cells relative to control conditions.

Wang et al. (2005) then developed a vaccine using MMTV-NeuNT mice that could induce T-cell and humoral immunity for treatment of human HER2+ BC [19]. The vaccine prototype consisted of virus-like replicon particles (VRP) from the Venezuelan equine encephalitis virus containing the Neu gene [19]. Eight of the 10 mice in the control group were euthanized within 140 days due to mammary gland tumors, while none of the mice in the VPR-Neu group showed signs of tumors upon palpation or pathologic examination of the mammary tissue at 240 days.

Arpel et al. (2014) used the MMTV-NeuNT model to demonstrate that the binding of small peptides with the ErbB2 transmembrane domain results in anticancer effects [20]. The group used a membrane targeting peptide (MTP) that mimics the transmembrane domain of NeuNT (NeuNT-MTP). The MTPs were injected intraperitoneally into immune-competent MMTV-NeuNT mice after they had developed mammary adenocarcinomas. The time frame needed to reach 200 mm^3 in tumor volume was 214 and 218 days, in the control and experimental groups, respectively. All mice in the experimental group responded to treatment, with a median survival increase of 22% (73.5 days versus 90 days in the control and MTP treated mice, respectively). Time to tumor recurrence was also found to double in the MTP-NeuNT treated mice.

MMTV-Neu

The MMTV-*Neu* model was first prepared by Guy et al. in 1992 where the wildtype Neu cDNA was expressed under the transcriptional control of the MMTV LTR to test the oncogenic and metastatic potential of wildtype Neu in mammary epithelium [21]. Transgene expression was reported in mammary glands, and in lower amounts in the salivary glands, spleen, thymus, and lungs. Focal mammary tumors were first observed at 4 months of age and were histologically determined to be mammary adenocarcinomas surrounded by hyperplastic mammary epithelium. By 205 days, 50% of female carriers were found to have mammary tumors, which were found to be composed of solid nests of intermediately dysplastic cells that were morphologically identical to tumors arising from activated Neu. Most tumors were found to have 10- to 50-fold higher levels of transgene RNA compared to adjacent mammary epithelial tissue, while about 30% had equivalent amounts. However, all tumors had elevated levels of Neu protein. It was also found that 72% of tumor-bearing mice that lived to 8 months or older developed metastases from the primary mammary adenocarcinomas to the lungs which were found to also express high levels of the Neu transgene.

The MMTV-Neu strain was later used by Muller et al. (1996) to study the synergistic role of TGFα (transforming growth factor) and Neu in the neoplastic transformation of mammary epithelium [22]. Only 35% of the MMTV-Neu mice were found to have developed mammary tumors via palpation by 250 days. However, 95% of the mice expressing both TGFα (transforming growth factor) and transgenic Neu

developed tumors within the same timeframe. The MMTV-Neu mice developed focal mammary tumors, while the bigenic mice developed multifocal tumors that spanned the entire mammary epithelium. Additionally, the MMTV-Neu mice were found to have normal mammary trees when compared to virgin FVB mice.

MMTV-NIC

Ursini-Siegel et al. (2008) created a construct encoding a bicistronic transcript containing the activated Neu allele, NDL2-5, followed by an IRES element and Cre recombinase. This bicistronic transcript was placed under translational control of the MMTV promoter [23]. This model, hereafter referred to as MMTV-NIC, allows activated Neu and Cre recombinase to be expressed within the same mammary epithelial cells. The NDL2-5 allele used in generating this mouse line is characterized by the Neu8342 oncogene, created by deletion mutations in the extracellular domain of rat neu. MMTV-NIC mice developed tumors with an average latency of 146 days, and only mammary tumors were observed. The tumors were characterized as solid nodular adenocarcinoma and expressed elevated levels of the NIC transgene in the mammary glands, but decreased levels in the adrenal gland, lung, ovary, pancreas, and salivary glands.

In 2009, Schade et al. used the MMTV-NIC model to determine the effect of Pten (phosphatase and tensin homolog) deficiency on mammary tumorigenesis and metastasis [24]. Bigenic mice that were either MMTV-NIC;$Pten^{+/-}$ or MMTV-NIC;$Pten^{-/-}$ were used, where activated Neu, Cre recombinase, and loss of Pten occurred simultaneously in the mammary epithelium. The authors found homozygous inactivation of Pten dramatically accelerated time to tumor initiation and had increased capacity for lung metastasis. All three groups developed multifocal solid nodular tumors with 100% penetrance. Additionally, the MMTV-NIC $Pten^{-/-}$ group developed more frequent but smaller tumor nodules compared to MMTV-NIC controls, which had a higher average tumor volume. In 2016, Creedon et al. confirmed these findings when the MMTV/NIC model was used to define mechanisms of resistance to the HER family inhibitor, AZD8931 [25]. The authors found that the median latency was 102 in the MMTV-NIC $Pten^{+/-}$ group versus 150 days in the MMTV-NIC $Pten^{+/+}$ group.

In 2024, Kuang et al. used MMTV-NIC mice to elucidate how USP22, a component of the histone modifying complex that is overexpressed in human cancers, impacts tumorigenesis in breast cancer [26]. USP22 overexpression did not decrease survival or alter tumor kinetics in MMTV-NIC mice, and USP22 deletion additionally did not affect neu levels [26].

MMTV-HER2

Finkle et al. reported using an MMTV-HER2 model in 2004, which consisted of the full-length wildtype human HER2 gene under the control of the MMTV LTR promoter [27]. The aim of the study was to examine the effectiveness of murine trastuzumab treatment in transgenic mice overexpressing HER2. There are distinct differences between the human HER2 and mouse Neu gene, with the trastuzumab binding epitope not being conserved between the two species. Of the female transgenic mice on a p53 wildtype background, 76% were found to develop asynchronous mammary tumors with an average latency of 28.2 weeks, whereas 78% of those on a p53 heterozygous background developed tumors by 28.6 weeks [27].

This was not the first time that an MMTV-HER2 model was attempted. Suda et al [28]. generated MMTV-HER2 mice in 1990 and tumors were observed but were not limited to the mammary gland. Adenocarcinomas of the lungs and Harderian glands were also observed, in addition to T- and B-cell lymphomas [28]. Additionally, the tumors had late onset, but the average latency was not reported. The HER2 gene was found to be expressed only in tumor tissues and not in the mammary epithelium surrounding the tumors.

In 2013, Hanker et al. used these mice to test the role of PIK3CA mutations in HER2+ BC [29]. The group found that the MMTV-HER2 mice formed tumors within 368 days, compared to the HER2+ PIK3CA mice which did so in 76 days. Additionally, EMT markers Snai1 (Snail), Snai2 (Slug), Twist1, Twist2, Vimentin, and N-cadherin; and the cancer stem cell markers Bmi1, Itgb1, and Thy1 were elevated in the MMTV-HER2 PIK3CA+ group.

In 2014, De Giovanni et al. used MMTV-HER2 mice to study the effect of the cell vaccine IL-12-adjuvanted human HER2+ BC cells or DNA vaccine of chimeric human-rat HER2 on the onset and number of mammary tumors [30]. The control group developed mammary tumors at a median latency time of 45 weeks, compared to the DNA vaccinated group where 65% were tumor-free by 90 weeks. The median time from tumor onset to death was 11.5, 16, and 14.5 weeks for the control, cell vaccinated, and DNA vaccinated groups, respectively.

In 2017, Park et al. used this model to establish cell lines from primary tumors and lung metastases [30]. Hematoxylin and eosin staining showed that the malignant tumors were adenocarcinomas that invaded the stroma and muscle. Strong membranous staining for HER2 compared to normal liver tissue.

Discussion

Of all the studies examined, Andrechek et al.'s FloxNeo-NeuNT model had the oldest average age until onset of tumor formation at 447 days (range: 243 - 526). Meanwhile, the shortest average time was at 126 days reported by Kuang et al's MMTV-NIC model. Additionally, of the originating studies, only Ursini-Segal et al's MMTV-NIC mice developed mammary tumors with 100% incidence. Upwards of 90% of human breast cancers are adenocarcinomas that begin in the milk ducts within the mammary glands. This is paralleled by the mouse tumors,

where almost all models resulted in adenocarcinomas in the mammary glands (Table 1). The only exceptions are Guy et al.'s MMTV-Neu model which did not report the tumors' histology. Additionally, almost all mouse models reported metastasis of the primary mammary tumors to the lungs, with the highest incidence of lung metastases reported by Ursini-Segal et al.'s MMTV-NIC model with 91% of mice displaying lung metastases, and the lowest incidence by the MMTV-HER2 model where only 40% of primary mammary tumors metastasized (Table 1). Thus, the MMTV-NIC model is the model of choice for studying lung metastasis from HER2+ BC. This finding is also in line with human HER2+ BC. Human HER2+ subtypes are associated with higher overall rates of metastases compared to HER2- subtypes, the most common metastatic sites for HER2+ BC being the lungs, bone, liver and brain [31]. However, one study involving more than 400,000 patients found that the most common metastatic site of both the luminal B subtype, which is defined as HR-/HER2+, as well as the double positive subtype, defined as HR+/HER2+, was to the bone, which is not reflective of the mouse models [31]. It is possible that the tumors metastasized to bone but were not reported considering that detection of bone metastasis requires additional imaging and radioactive tracing, while most studies detected lung metastases through dissection [32]. Similarly, brain metastases might have existed but were not checked for. However, there are some steps that researchers who are interested in studying bone metastases of HER2+ BC. These include injection of cancerous cells through the caudal vein in the mouse tail, or alternatively by using breast cancer cell lines more likely to give rise to osteoblastic bone metastasis, including ZR-75-1 and MCF-7[33, 34]. Moreover, Andrechek et al. found that the copy number of transgenic Neu relative to wildtype Neu was 8.0 (range: 1.7-21.6). This is also in line with HER2+ BC, where one study quantified that the median copy number of HER2 in HER2+ tumor tissue was 7.02 (IQR: 3.36-16.34) compared to the non-cancer tissue median copy number of 1.99 [35]. Additionally, immunohistochemical analysis of these tumors found both membrane and cytoplasmic localization of activated Neu, which is unlike the membrane-specific localization of Neu in MMTV-Neu induced tumors. The elevated level of Neu transcript suggests selective amplification of the activated Neu during tumorigenesis, which is analogous to the amplification and overexpression patterns of HER2 in human breast cancer. Despite these findings, it is important to acknowledge that mouse models generally have limitations in their ability to model cancer. One limitation is the relatively low heterogeneity within the mouse tumor mass as compared to human tumors, in addition to a less diverse tumor microenvironment and anti-cancer immune response [36]. Additionally, some signaling pathways that are central to cancer growth are notably different between humans and mice, including the often-mutated tumor suppressor gene p53 [37]. However, while p53 pathway regulation differs between mouse and human samples, humanized mice injected with human hematopoietic cells showed more similar regulation patterns [38].

Conclusions

Despite the limited data, our literature review elucidated that MMTV-NIC is the best model for studying HER2+ BC due to its shortest time to latency as demonstrated by Kuang et al., 100% mammary tumor incidence as demonstrated by Ursini-Segal et al., and highest rate of lung metastasis as demonstrated by Ursini-Segal et al. Future directions in this research domain may involve developing a novel mouse model akin to MMTV-NIC but incorporating human HER2 to enhance translational relevance. Additionally, a comparative study across the identified models within a single laboratory setting would offer valuable insights into how the models compare in regard to parameters like average latency, metastatic patterns, and histological features, allowing for the conclusive determination of the best model.

List of Abbreviations Used

BC: breast cancer
EGFR: epidermal growth factor receptor
HER2: human epidermal growth factor 2
IRES: internal ribosomal entry site
LTR: long terminal repeat
MMTV: murine mammary tumor virus
MTP: membrane targeting protein
PI3K: phosphatidylinositol 3 kinase
Pten: phosphatase and tensin homolog
TGFα: transforming growth factor α

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This review article did not require ethics approval and/or participant consent as it did not involve direct data collection and analysis but rather obtained data from published primary research.

Authors' Contributions

TA: Made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, wrote the manuscript, and revised the manuscript critically.

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