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Assessing estrogen signaling aberrations in breast cancer risk using genetically engineered mouse models

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Abstract

Aberrations in estrogen signaling increase breast cancer risk. Molecular mechanisms impacting breast cancer initiation, promotion, and progression can be investigated using genetically engineered mouse models. Increasing estrogen receptor alpha (ER α) expression levels two-fold is sufficient to initiate and promote breast cancer progression. Initiation and promotion can be increased by p53 haploinsufficiency and by coexpressing the nuclear coactivators amplified in breast cancer1 or amplified in breast cancer1 Δ 3. Progression to invasive cancer is found with coexpression of these nuclear coactivators as well as following a single dose of 7,12-dimethylbenz(a)anthracene. Loss of signal transducer and activator of transcription 5a reduces the prevalence of initiation and promotion but does not protect from invasive cancer development. Cyclin D1 loss completely interrupts mammary epithelial proliferation and survival when ER α is overexpressed. Loss of breast cancer gene 1 increases estrogen signaling and cooperates with ER α overexpression in initiation, promotion, and progression of mammary cancer.

Keywords

breast cancer; mouse models; estrogen signaling; ER α ; BRCA1

Introduction to estrogen signaling

The estrogen signaling pathway starts with ligands—the estrogens—and receptors for these ligands—the estrogen receptors (ERs).^{1–3} Estrogens are steroid hormones involved in normal development of the mammary gland,⁴ but they also contribute to breast cancer growth.^{5,6} The ovary is the main organ responsible for estrogen production in women during reproductive life.^{1,7} With menopause, ovarian estrogen production falls, and other tissues become the primary sources.⁸ Estrogens are synthesized from androgens by aromatization.¹ Increased aromatase expression in breast tissue is associated with breast cancer.⁹

Both ER alpha (α) and ER beta (β) are expressed in mammary tissue.¹⁰ ER α is most closely linked to increasing mammary epithelial cell proliferation with the balance between ER α

and ER β regulating this activity.^{11,12} When estrogen binds to ER, the complex translocates to the nucleus, binds to DNA target sequences called estrogen response elements (EREs),¹³ and regulates expression of a number of downstream genes including progesterone receptor (PR), the receptor for the steroid hormone progesterone.^{14–17} Breast cancers that express ER α are termed ER α positive.¹⁸ Antiestrogens such as tamoxifen, fulvestrant, and aromatase inhibitors are used as endocrine therapy to minimize or even eliminate the growth of ER α -positive breast cancers. Tamoxifen is also approved as a preventative for women at high risk for breast cancer development.¹⁹

The estrogen pathway is subject to inhibitory and growth-promoting feedback at both RNA and protein levels through regulation of ER α gene promoter transcriptional activity, micro RNA expression, epigenetic mechanisms, ubiquitination, and acetylation.^{20–24} In normal mammary gland growth, estrogen pathway activity is naturally inhibited; in breast cancer cells, this inhibitory regulation is lost.¹¹ Downstream genes including Cyclin D1 mediate the proliferative effects of ER α signaling.²⁵ Illustrating the complexity of intracellular molecular interactions, overexpressed Cyclin D1 also activates ER α transcriptional activity independent of estrogen binding and is subject to regulation by other cellular molecules.^{26,27} Nuclear hormone receptor coactivators including amplified in breast cancer 1 (AIB1) and steroid receptor coactivator (SRC)-3 can modulate estrogen signaling.^{28,29} Signal transducer and activator of transcription (STAT) 5 influences estrogen signaling.³⁰ Known tumor suppressor genes p53 and breast cancer gene 1 (BRCA1) also impact the estrogen signaling pathway.^{31,32} The studies in the genetically engineered mouse models reviewed below were initiated to take observations from human breast tissue and cell lines into mechanistic investigations of breast cancer pathophysiology to determine where in the process of breast carcinogenesis³³ specific aberrations in estrogen signaling impact breast cancer risk and how this might happen.

Increased ER α expression as cancer risk factor

Since increased expression levels of ER α in breast epithelial cells are associated with increased risk of breast cancer,¹⁰ a genetically engineered conditional mouse model of increased ER α expression targeted to mammary epithelial cells was generated.³⁴ ER α expression is increased approximately two-fold in mammary epithelial cells in the model and, unlike endogenous ER α , is not down-regulated through inhibitory feedback following estrogen exposure, resulting in an overall increase in ER α and persistent ER α expression throughout the cell cycle. The model has tested at which stage(s) during cancer progression increased ER α expression acts (initiation, promotion, and/or progression)³³ by determining if gain of ER α promotes development and progression of mammary cancer initiated by expression of an oncoprotein³⁵ as well as testing if simply increasing ER α expression levels can initiate as well as promote progression to mammary cancer.³⁴ The model has determined that ER α overexpression can lead to the development of both ER α -positive and -negative mammary cancers and explored the collaborating roles of proteins that directly and indirectly interact with ER α (AIB1, STAT5, p53, and BRCA1).^{36–39}

This genetically engineered mouse model was constructed utilizing the tetracycline responsive gene expression system to temporally and spatially regulate expression of mouse ER α cDNA. The system consists of one of the tetracyclines (usually doxycycline) and two transgenes: one directing expression of a transgene encoding either tetracycline transactivator (tTA) sequences⁴⁰ or reverse tetracycline transactivator (rtTA) sequences⁴¹, and the other encoding the ER α coding sequences.⁴² A FLAG tag was genetically engineered at the 5' end of the ER α coding sequences to facilitate identification of the transgenic RNA and protein.^{35,42} The FLAG-tagged mouse ER α coding sequences were cloned downstream of a genetically engineered tetracycline-operator (tet-op) promoter

containing tetracycline response elements (TREs) to generate the ER α transgene.^{42,43} Spatial regulation is through the use of the mouse mammary tumor virus–long terminal repeat (MMTV) to direct expression of either tTA or rtTA to epithelial cells.^{40,41} Expression of the ER α coding sequence is temporally regulated through the administration or withdrawal of exogenously administered tetracycline.⁴³ The compound bitransgenic model carrying the tet-op-ER α transgene under spatial regulation of MMTV is called the conditional ER α in mammary tissue (CERM model).

A triple transgenic model carrying the MMTV-tTA and tet-op-ER α transgenes in combination with a third tet-op-simian virus 40 T antigen (TAg) transgene was generated to test if increasing ER α expression levels could promote mammary cancer development initiated by the TAg oncoprotein.³⁵ This model coexpresses ER α and TAg in the same cells under the spatial control of the MMTV-tTA transgene. Mammary cancer development in the absence and presence of ER α overexpression was compared. In the absence of ER α overexpression, bigenic mice that carry only the MMTV-tTA and tet-op-TAg transgenes do not develop mammary cancer.^{44,45} In contrast, 37% of the triple transgenic MMTV-tTA/tet-op-ER α /tet-op-TAg female mice develop mammary cancer by 12 months of age. Promotion of cancer progression by ER α in this model results in ER α -positive adenocarcinomas that demonstrate ER–steroid binding to estrogen and show estrogen-dependent growth.

To test if ER α overexpression by itself can initiate mammary cancer progression, double transgenic MMTV-rtTA/tet-op-ER α CERM mice were followed through 12 months of age for development of mammary hyperplasia indicative of the promotion stage of cancer development as well as progression to non-invasive and invasive mammary cancer.^{34,36–38} ER α overexpression induces increased mammary epithelial cell proliferation, and by four months of age, between 20–30% of CERM mice demonstrate ductal hyperplasia and 17% show ductal carcinoma *in situ* (DCIS), a non-invasive cancer.^{34,38} Progression to invasive cancer development by 12 months of age is less than 5% in the CERM model but does occur and may be increased by exposure to a single dose of DMBA or by coexpression of AIB1 or its splice variant AIB Δ 3.^{36,37} Significantly, both ER α -positive and ER α -negative invasive adenocarcinomas develop in CERM mice, and both show increased levels of cyclin D1 expression that is also found in the mammary hyperplasias.^{34,36,37}

To test if cyclin D1 plays an essential role in the development of mammary hyperplasia and cancer initiated by ER α overexpression, ER α -overexpressing mice were crossed with germ-line cyclin D1 knockout mice.⁴⁶ These studies unexpectedly revealed an essential role for cyclin D1 in mammary epithelial cells when ER α is overexpressed. In contrast to germ-line cyclin D1 knockout mice and CERM mice, both of which show normal pubertal mammary gland development, pubertal development of the mammary gland in compound CERM/cyclin D1 knockout mice is completely abnormal. The mammary epithelial cells cannot proliferate and undergo apoptosis due to a DNA damage response associated with an abnormal up-regulation of cyclin E expression. The surrounding mammary fat pad undergoes a transition to an almost purely collagenous stroma. The phenotype cannot be rescued upon transplantation of CERM/cyclin D1 knockout mammary epithelium into a cleared fat pad of wild-type mice, indicating that the defect is intrinsic to the mammary epithelial cells, demonstrating that a modest increase in ER α induces a requirement for cyclin D1 for puberty-associated mammary cell proliferation. Cyclin D1 inhibitors could act as anticancer agents in the breast by preferentially targeting cells with abnormally high ER α expression levels that might exhibit increased sensitivity to interrupting cyclin D1 pathways.⁴⁷

Comparing CERM mouse and ACI rat models

The CERM model is unique in that activating the estrogen signaling pathway through ER α overexpression results in the generation of both ER α -positive and -negative invasive cancers and, significantly, while estrogen is required for disease development, exposure to exogenous 17 β -estradiol (E2) does not provoke progression to invasive cancer, at least when given at four months of age.^{34,37} In contrast, in the ACI rat model, mammary cancer development is increased following chronic administration of E2, and these cancers reproducibly express ER α and PR.⁴⁸ Normally in rats, like mice and humans, chronic administration of exogenous estrogen does not induce mammary cancer. However, the ACI rat is genetically predisposed to estrogen-induced mammary cancer with a median latency of approximately 20 weeks and close to 100% penetration. Administration of E2 results promotes lobuloalveolar hyperplasia, focal regions of atypical epithelial hyperplasia, and, ultimately, progression to numerous independently arising mammary cancers with ER α and PR overexpression. These mammary cancers are estrogen dependent, exhibit genomic instability, and are inhibited by ovariectomy and tamoxifen.^{49,50} The majority of epithelial cells in the mammary carcinomas as well as the atypical hyperplasia exhibit a drastic down-regulation of Cdkn2a and increased PR expression, suggesting that the atypical hyperplasias may be a precursor lesion to carcinoma. Tamoxifen not only decreases tumor prevalence but also restores normal mammary epithelial architecture.⁵⁰ Two genetic determinants of susceptibility to E2-induced mammary cancer have been mapped in this model, *Emca1* (estrogen-induced mammary cancer) and *Emca2* (mapped to rat chromosomes 5 and 18, respectively). The region of RNO5 containing *Emca1* is homologous to human chromosomes 1p and 9p, two regions of the human genome that have been implicated in breast cancer etiology.⁵¹

Effect of STAT5a loss on ER α -induced cancer promotion and progression

STAT5a/b is a signal transducer and activator of transcription that mediates the prolactin/JAK2 pathway contributing to differentiation and survival of normal mammary lobuloalveolar cells.^{52,53} Nuclear-localized STAT5a is found in 40% of human ductal carcinoma *in situ* lesions and 76% of invasive breast cancers.^{54,55} In CERM mice, the impact of germ-line Stat5a deficiency on mammary carcinogenesis is context dependent.³⁶ Absence of STAT5a on the background of ER α overexpression reduces the prevalence of preneoplasia; however, this effect does not extend to protection cancers developing after a single dose of 7,12-dimethylbenz(a)anthracene (DMBA) as a cancer initiator.

AIB1 or AIB1 Δ 3 with ER α in oncogenesis

AIB1 is a nuclear receptor coactivator expressed in human breast cancers.⁵⁶ AIB1 Δ 3 is a splice variant of AIB1 that also is expressed in human breast cancers and has higher transcriptional activity in tissue culture cells as compared to AIB1.^{57,58} To test the effect of combining AIB1 or AIB1 Δ 3 overexpression with ER α overexpression, a series of tetracycline-responsive conditional transgenic mouse models were developed in which either AIB1 or AIB1 Δ 3 coding sequences were placed under the control of the tet-op promoter.³⁷ The outcome of either AIB1 or AIB1 Δ 3 overexpression was then tested and compared in both the absence and presence of ER α overexpression. Similar to *in vitro* results, AIB1 Δ 3 is more transcriptionally active than AIB1 *in vivo* and significantly increases expression levels of both ER α and PR downstream genes. This is associated with increased progression to a multi-layered mammary epithelium. However, both AIB1 and AIB1 Δ 3 overexpression are sufficient to increase mammary hyperplasia and more modestly increase invasive cancer development in CERM mice. Unexpectedly, targeting AIB1 or AIB1 Δ 3 overexpression to mammary epithelial cells with ER α also significantly increased stromal collagen content.

This experiment illustrates how genetic manipulations targeted to mammary epithelial cells can impact not only the mammary epithelial cells themselves but also the surrounding stroma, analogous to what was found in the compound CERM/cyclin D1 knockout mice.⁴⁶ The experiments are consistent with the notion that both AIB1 and AIB1Δ3 can work in combination with ERα to increase breast cancer risk.

p53 modulates impact of ERα overexpression

The tumor suppressor p53 plays a role in mediating cell response to various stresses by inducing or repressing genes that regulate cell cycle arrest, senescence, apoptosis, and DNA repair.⁵⁹ Alterations to p53 are the most common changes so far detected in primary human breast tumors,⁶⁰ reported in up to 40% of human breast cancers.⁶¹ p53 detection in benign lesions, indicative of possible mutation, has been associated with elevated cancer risk.⁶² Human breast cancers with p53 mutations are frequently ERα-negative.⁶³ Serial transplant studies have shown that the absence of p53 in mammary epithelium is associated with ductal carcinoma *in situ* lesions and invasive cancer that progress from an ERα-positive to ERα-negative state.⁶⁴ In addition to the frequent somatic mutation of p53 in sporadic cancers, germline mutation of one allele of this gene in humans causes an inborn predisposition to cancer known as Li-Fraumeni syndrome. In families with Li-Fraumeni syndrome, early-onset female breast cancer is the most prevalent type of tumor.⁶⁵

While both up-regulation of ERα³⁴ and loss of p53 function^{62,64,65} are implicated in the development of breast cancer independently, they also can collaborate to increase the prevalence of age-dependent mammary preneoplasia.³⁸ The combination of both genetic lesions results in an altered balance in the apoptosis/proliferation ratio of mammary epithelial cells with increased rates of cell proliferation and reduced rates of apoptosis. Changes in specific signaling pathways are associated with specific genetic lesions. Increased levels of extracellular signal-regulated kinase 1/2 (ERK1/2) activation are associated with both p53 haploinsufficient and ERα-overexpressing mice. In contrast, changes in AKT activation are limited to mice with p53 haploinsufficiency either alone or in combination with ERα overexpression. The cell cycle inhibitor p27 has been shown to have tumor suppressor activity,⁶⁶ and its expression is documented in human ductal carcinoma *in situ* lesions.⁶⁷ Decreased levels of p27 protein are found in the p53 haploinsufficient mice independent of ERα overexpression. The combination of ERα deregulation and p53 haploinsufficiency results in a significant decrease in the percentage of mammary epithelial cells with nuclear-localized ERα, although ERα mRNA levels remain increased by two-fold and PR expression levels are unchanged. c-Src phosphorylation has been shown to stimulate ERα ubiquitination and proteasome-dependent degradation,⁶⁸ and p53 has been reported to down-regulate some Src functions.⁶⁹ The p53 haploinsufficient mice with ERα overexpression show high expression levels of activated p-Src (Tyr416) in mammary epithelial cells. It is possible that p-Src plays a role in the observed reduction in ERα protein expression in this genotype.

ERα and p53 as breast cancer risk factors in parity protection

Reproductive history is the strongest and most consistent risk factor outside of genetic background and age in breast cancer risk.⁷⁰ Early age at first pregnancy (20 years of age) confers a 50% reduction in lifetime risk compared with the lifetime risk of breast cancer in nulliparous women.⁷¹ Studies in mice have shown that treatment with estrogen and progesterone to mimic pregnancy and parity enhance p53-dependent responses and suppress mammary tumors in BALB/c-Trp53^{+/-} mice.⁷² Significantly, parity results in a noticeable decrease in mammary preneoplasia development in comparison to nulliparous mice in p53 haploinsufficient mice but not in mice with ERα overexpression alone or control wild-type

mice, suggesting a possible protective effect of pregnancy in mice with disease due to loss of p53 function.³⁸ This parity protection effect may be due to an increased activation of p53 signaling through pregnancy that compensates for its reduced expression levels.

BRCA1, estrogen signaling, and breast cancer risk

Human breast cancer development secondary to BRCA1 mutation is successfully modeled in mice.⁷³ The BRCA1-deficient mouse model described below is one of several independently derived models, all of which demonstrate significant similarities in their propensity to develop triple negative mammary cancer and cooperativity with p53 haploinsufficiency in cancer promotion and progression.

The model originally developed by Xu *et al.* is the one that has been used most extensively to investigate how loss of BRCA1 function impacts estrogen signaling in the mammary gland.^{39,74,75} In this model, conditional deletion of exon 11 of the *Brcal* gene in mammary epithelial cells is effected using Cre recombinase (Cre)-LoxP (Lox) technology.⁴³ Exon 11 was selected for deletion due to the large number of proteins that interact with BRCA1 at domains mapping to exon 11.^{76,77} LoxP sites were inserted into intron sequences flanking exon 11 of the *Brcal* gene. At these loxP sites, Cre recombinase binds to the LoxP DNA recognition sites and mediates DNA recombination between the sites deleting the intervening *Brcal* exon 11 sequences. Expression of Cre is targeted to mammary epithelial cells using a MMTV-Cre transgene.⁷⁸

The incidence of mammary cancer development in this and other BRCA1 mutation models is significantly accelerated by simultaneously deleting one or more copies of the *p53* gene.^{73,74} This genetic intervention is hypothesized to promote survival of mammary epithelial cells that do not have functional full-length BRCA1.⁷⁹ Consistent with this notion, *p53* mutations are frequently found in human breast cancers that develop secondary to BRCA1 mutation.⁸⁰ In the BRCA1 mutation model reviewed here, loss of full-length BRCA1 function results in the development of mammary hyperplasia in 19% and cancer in less than 5% of the mice by 12 months of age.^{39,74} The addition of *p53* haploinsufficiency increases the prevalence of hyperplasia to 45% and invasive cancer to 53% by 12 months of age.^{39,74}

BRCA1 mutation carriers have an increased risk of developing basal or triple-negative breast cancers (ER, PR, and human epidermal growth factor receptor 2 [HER2] negative).⁸¹ This predisposition for developing triple-negative breast cancer is found across the different genetically engineered mouse models of BRCA1 mutation.⁷³ In the model reviewed here, approximately 50% of the adenocarcinomas demonstrate a triple negative or basal phenotype by gene expression profiling.⁸²

Estrogen signaling plays a role in the progression of BRCA1 mutation-related breast cancers, even though most cancers are ER α and PR negative.^{83–87} *In vitro* BRCA1 can act as a repressor for ER α -mediated gene transcription, estrogen signaling, and reduces cell proliferation and modulates ER α acetylation and ubiquitination through a direct physical interaction.^{24,32,88–91} This interaction of BRCA1 with ER α can be modulated by p300⁹² and growth factor signaling⁹³ and antagonized by cyclin D1.⁹⁴ *In vivo*, decreasing estrogen signaling through ovariectomy decreases the risk of breast cancer development due to BRCA1 mutation in both human mutation carriers⁹⁵ and the mouse model reviewed here.⁹⁶

Evidence of increased activity of an estrogen-stimulated proliferative pathway can be found *in vivo* during puberty in mice without full-length BRCA1 expression and in post-pubertal mice in which activity of the estrogen signaling pathway is increased either by exogenous estrogen or introduction of increased ER α expression targeted to mammary epithelial cells.

During puberty, mammary ductal extension through the fat pad is faster and estrogen-induced mammary cell differentiation is delayed as compared to wild-type mice.³⁹ When treated with exogenous estrogen post-puberty, these mice demonstrate accelerated promotion to mammary hyperplasia.³⁹ When full-length BRCA1 deficiency is combined with p53 haploinsufficiency and exogenous estrogen treatment, there is a further significant increase in the prevalence of hyperplasia³⁹ and cancer.⁷⁵ On a molecular level increased ERK1/2 phosphorylation and cyclin D1 expression is associated with this estrogen induced abnormal growth.⁷⁵ While introduction of ER α overexpression into BRCA1-deficient mice does not significantly increase cancer promotion or progression, the addition of p53 haploinsufficiency to this model results in a significant increase in both promotion and progression with 100% of the mice demonstrating hyperplasia and invasive cancers by 12 months of age.³⁹ In contrast to the impact of ER α overexpression with TAG oncoprotein where all of the cancers are ER α positive,³⁵ in the setting of BRCA1 deficiency only half of the cancers are ER α positive,³⁹ reminiscent of the increased distribution of ER α -negative (80%) as compared to ER α -positive (20%) breast cancers in women who carry BRCA1 mutations.⁹⁷

Surprisingly, while cancer progression is impeded by ovariectomy in this model,⁹⁶ administration of tamoxifen increases breast cancer promotion and progression.⁹⁸ This is due to the fact that the relative agonist activity of the mixed ER α antagonist/agonist tamoxifen is increased by loss of BRCA1 expression.^{98,99}

Significantly, BRCA1 also interacts with the ER α downstream gene PR to impede its activity, and loss of full-length BRCA1 results in an increased growth response to exogenous progesterone with the most abnormal response following combined estrogen and progesterone treatment.¹⁰⁰

Summary

These studies illustrate that genetically engineered mouse models can be used to explore aberrations in estrogen signaling and investigate the impact of specific signaling pathways through genetic, endocrinological, and pharmacological methods. The investigations synergize with *in vitro* tissue culture cell-based, human tissue-based, and clinical investigations to increase our understanding of the molecular determinants of breast cancer risk.

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