



Estrogen signaling and the DNA damage response in hormone dependent breast cancers

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Estrogen is necessary for the normal growth and development of breast tissue, but high levels of estrogen are a major risk factor for breast cancer. One mechanism by which estrogen could contribute to breast cancer is via the induction of DNA damage. This perspective discusses the mechanisms by which estrogen alters the DNA damage response (DDR) and DNA repair through the regulation of key effector proteins including ATM, ATR, CHK1, BRCA1, and p53 and the feedback on estrogen receptor signaling from these proteins. We put forward the hypothesis that estrogen receptor signaling converges to suppress effective DNA repair and apoptosis in favor of proliferation. This is important in hormone-dependent breast cancer as it will affect processing of estrogen-induced DNA damage, as well as other genotoxic insults. DDR and DNA repair proteins are frequently mutated or altered in estrogen responsive breast cancer, which will further change the processing of DNA damage. Finally, the action of estrogen signaling on DNA damage is also relevant to the therapeutic setting as the suppression of a DDR by estrogen has the potential to alter the response of cancers to anti-hormone treatment or chemotherapy that induces DNA damage.

Keywords: estrogen receptor, DNA damage response, breast cancer, p53, BRCA1, DNA repair, tamoxifen, DDR

DNA DAMAGE INDUCED BY ESTROGEN

Lifetime exposure to estrogen is a major risk factor for breast cancer. Elevated serum levels of estrogen are associated with a 2–2.5× greater risk of breast cancer development (1) and high levels of estrogen in the breast of postmenopausal women are associated with increased cancer risk (2). Estrogen signaling drives proliferation in the 60–70% of breast cancers that express the estrogen receptor, and adjuvant anti-estrogen therapy is prescribed to the majority of these patients to prevent breast cancer recurrence.

Estrogen signals through its two receptors, estrogen receptor α (ER α) and estrogen receptor β (ER β). Only ER α is essential for breast development and activates pro-proliferative signaling in the normal breast and breast cancer, whereas ER β generally antagonizes ER α in the breast (3). Upon estrogen binding ER α acts by parallel pathways to alter gene expression. ER α translocates to the nucleus to activate gene targets directly or in cooperation with co-activator proteins, or it can transactivate growth receptors to boost receptor tyrosine kinase signaling. These pathways converge to promote growth and proliferation and suppress apoptosis (3).

Despite the risks associated with estrogen exposure the exact mechanisms by which estrogen contributes to the initiation and progression of breast cancer remains elusive. However, a major mechanism is potentially the induction of DNA damage as estrogen treatment leads to double stranded DNA breaks and genomic instability (1, 4, 5). Early breast cancer lesions exhibit chromosomal instability and aneuploidy (6), and in rat models this is linked to estrogen exposure (7). Estrogen can induce DNA damage via the production of oxidative metabolites that cause DNA adducts, or

other oxidative DNA damage, and this is supported by *in vitro* and animal model studies (1). The second explanation for estrogen-induced DNA damage is that hyperactivated estrogen signaling provokes excessive proliferation when pathways become dysregulated, and this theory has strong support from *in vitro* modeling and gene signatures in breast cancer (3). Excessive proliferation promotes DNA damage accumulation due to insufficient timely repair leading to replication fork stalling and possibly even double stranded DNA breaks (8). It is likely that both carcinogenic estrogen metabolites and deregulated estrogen signaling contribute to estrogen-induced DNA damage. In this perspective a third possibility is raised, that estrogen signaling suppresses the DNA damage response and DNA repair to allow the accumulation of genomic change conducive to tumorigenesis.

DNA DAMAGE RESPONSE AND DNA REPAIR PATHWAYS ALTERED BY ESTROGEN SIGNALING

DNA damage is recognized and processed by series of pathways called the “DNA damage response (DDR)”. The DDR assesses the scope and severity of DNA damage to initiate cell cycle arrest, senescence, repair, or in the case of irreparable damage, apoptosis. If repair is activated then a number of different repair mechanisms can be engaged [reviewed in Ref. (9)]. Small lesions of damaged or incorrectly inserted nucleotides are repaired by base excision repair (BER), nucleotide excision repair (NER), or mismatch repair (MMR). The more catastrophic double stranded breaks are repaired via non-homologous end-joining (NHEJ) or homologous recombination (HR). Small distorting lesions are extremely common so the pathways that repair these defects (BER, NER, and

MMR) are also activated by constant genome surveillance, and repair is coupled to transcription and DNA replication.

The DDR signals through three main effector kinases, ATM, ATR, and DNA-PK. ATM and DNA-PK recognize double stranded breaks whereas ATR responds to single stranded regions that occur at stalled replication forks and double stranded break overhangs. The signaling pathways downstream of ATM, ATR, and DNA-PK involve a myriad of proteins, however there are a number of key effector proteins that include CHK1, CHK2, BRCA1, 53BP1, and MDC1 which signal to DNA repair coordinators such as BRCA2, PALB2 and to cell cycle checkpoints and the apoptotic machinery. The major tumor suppressor protein, p53, is activated downstream of ATM/ATR, and acts as a genome guardian to determine whether cells should arrest or apoptose. There is significant cross-talk between the various pathways depending on the nature and severity of the DNA damage.

The DDR is important to estrogen carcinogenesis as it dictates how estrogen-mediated damage is processed by breast cells. In prior genome wide studies of estrogen action, the major regulatory nodes of the ER α transcriptional program have included proliferation, growth, and apoptosis, but not the DDR or DNA repair (3). However, there is a growing body of literature, which identifies estrogen signaling as regulating key effector DDR proteins such as ATM, ATR, p53, BRCA1, and BRCA2, as well as direct interactions with the DNA repair machinery. This is significant not only for estrogen carcinogenesis, but also for the processing of any genotoxic insults by estrogen-responsive tissues. Described below are the most important interactions between ER α , the DDR, and DNA repair pathways (**Figure 1**). ER β is not discussed in this perspective, but it should be noted that ER β has opposing effects to ER α in many contexts (10), and this is also true of regulation of the DDR and DNA repair (11–13).

REGULATION OF EFFECTOR KINASES ATM, ATR, AND DNA-PK

ATM and ATR are key initiators of the DDR, and both are negatively regulated by ER α . ER α downregulates transcription of ATM via the activation of *miR-18a* and *miR-106a* (11). The ATR/CHK1 signal transduction cascade is suppressed by ER α -transactivated AKT phosphorylation of TOPBP1 to prevent an interaction with ATR at sites of DNA damage (15). AKT also phosphorylates CHK1 to prevent its interaction with co-activator CLASPIN (15). The downregulation of ATM and ATR by ER α interferes with the induction of cell cycle checkpoints so that cells continue to progress through the cell cycle after DNA damage, and DNA repair is delayed or not engaged (15, 16). Estrogen activity does not, however, preclude activation of the DDR. γ -H2A χ foci form in response to estrogen-induced DNA damage, and the co-localization of Rad51 to these foci suggests the activation of HR (4).

While ER α negatively regulates both ATM and ATR, it is possible that ER α positively regulates DNA-PK mediated repair based on recent findings of DNA-PK regulation by the androgen receptor (AR). AR regulation of DNA-PK catalytic subunit (DNA-PKcs) promotes the repair of DNA double stranded breaks and resistance to DNA damage and DNA-PKcs likewise potentiates the function of AR (17). Like AR, ER α is in a complex with DNA-PK (18) and ER α is stabilized and its transcriptional function

potentiated by DNA-PK (19), and by analogy to AR, ER α may also transactivate DNA-PK.

If ER α does positively regulate DNA-PK, ER α may suppress DNA repair processes of higher fidelity (ATM- and ATR-mediated) in preference for DNA-PK-mediated NHEJ. This is consistent with observations of ER α activity leading to the accumulation of DNA damage (1) as it would sustain proliferation by not engaging the ATM/ATR pathways, while promoting DNA-PK-mediated NHEJ to maintain genome integrity. Toillon et al. found that estrogen treatment of irradiated breast cancer cells led to their sustained proliferation without any increase in p53 activation or apoptosis (20). This is consistent with a failure to activate ATM or ATR but the repair of DNA by DNA-PK mediated NHEJ.

BRCA1

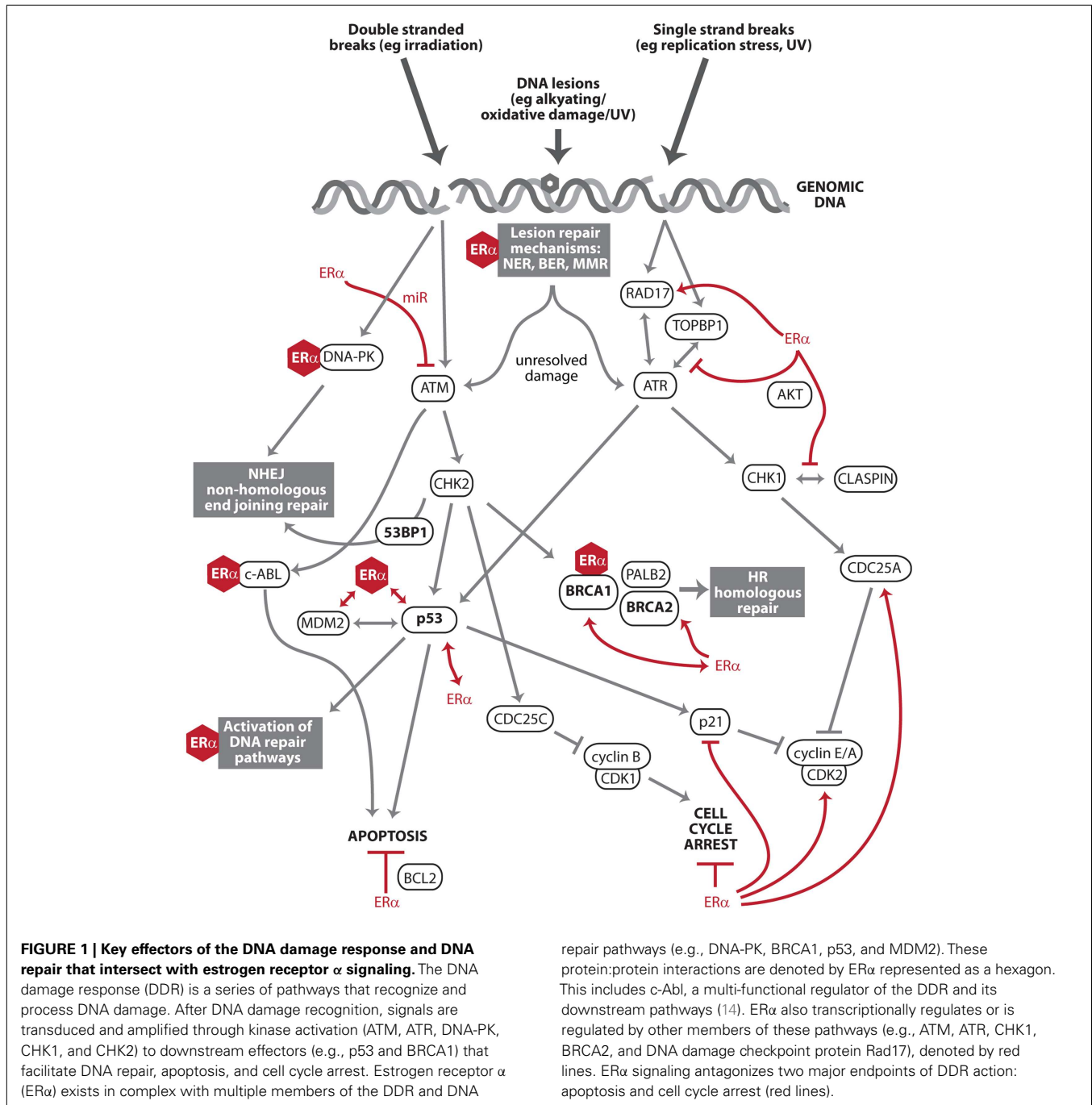
BRCA1 is a downstream effector of the DDR that is recruited to sites of DNA damage, functions directly in HR, but also influences cell cycle arrest and other DNA repair pathways. There is strong evidence that BRCA1 limits estrogen-mediated tumorigenesis: *Brca1* knockout mice show an enhanced proliferative response to estrogen treatment and accelerated development of preneoplastic mammary lesions (21), and the reduction of serum estrogen levels by oophorectomy protects carriers of the *BRCA1* mutation against breast cancer (22). Indeed, BRCA1 has a negative effect on ER α , through direct binding to inhibit ER α -mediated gene transcription (23, 24), downregulation of ER α co-activator, p300 (25), reduced cross-talk from growth factor signaling (26), and potentially monoubiquitination (25, 27). These effects are antagonized by cyclin D1, a direct transcriptional target of ER α that is instrumental in estrogen-induced proliferation (28).

While BRCA1 suppresses ER α , ER α regulation of BRCA1 enhances BRCA1 function. Estrogen promotes transcription of *BRCA1* via binding of an ER α /p300 complex (29), and stimulates the formation of a complex between ER α , CBP, and BRCA1 that facilitates double stranded break repair (30). Surprisingly, BRCA1 induces the transcription of *ESR1* which encodes ER α , and the positive feedback between BRCA1 and ER α provides a rational explanation for why many BRCA1 negative cancers are ER α negative (31).

p53

Estrogen receptor α and p53 have a bi-directional relationship affecting both expression and function. The *TP53* gene is transcriptionally activated by ER α (32, 33) and downstream of ER α -target, c-MYC (34), and ER α stabilizes the p53 protein (35). Despite ER α inducing higher levels of p53 it may not be active: in breast cancer cell lines estrogen induces cytoplasmic redistribution of p53 to reduce its transcriptional function (12, 36). ER α alters the p53 transcriptional program to reverse transcriptional activation and repression by p53, including downregulation of the p53-mediated apoptotic response induced by DNA damage (37). ER α represses p53-mediated transcription either through the recruitment of co-repressors (38) or via independent targeting and repression of p53 target gene sets (39). A separate subset of target genes for p53 activation is enhanced by ER α activity (37).

p53 and ER α exist in complex with MDM2, and this complex modulates the activity of p53 and ER α . MDM2 is a negative



feedback regulator of p53 (40), whereas MDM2 positively regulates $ER\alpha$ transcriptional activity, most probably through direct MDM2: $ER\alpha$ interaction (41, 42). Conversely, the MDM2/p53/ $ER\alpha$ ternary complex downregulates the activity of $ER\alpha$ by monoubiquitination, probably via the ubiquitin ligase activity of MDM2 (43). MDM2 may also downregulate $ER\alpha$ independently of p53 (43). In the presence of cellular stress, including UV-mediated DNA damage, p53 dissociates from MDM2 and this is associated with an increase in $ER\alpha$ levels and block of the estrogen-dependent downregulation of $ER\alpha$ (43). Paradoxically, while $ER\alpha$ represses

p53-mediated transcription, $ER\alpha$ also protects p53 from repression by MDM2 (40), and estrogen treatment is necessary for a p53 response to be mounted in the mouse mammary gland against ionizing radiation (44).

p53 upregulates the expression of *ESR1*, but alters the transcriptional functions of $ER\alpha$. p53 induction of *ESR1* occurs following DNA damage such as irradiation (45). Like $ER\alpha$ modulation of p53 function, p53 alters the transcriptional program of $ER\alpha$ to repress certain estrogen responsive genes such as *BRCA2*, *c-JUN*, and *BCL2* (37, 46). Indeed it appears that the combination of $ER\alpha$

and p53 induces a distinct transcriptional program compared to either ER α or p53 alone (47).

Overall this body of work suggests that estrogen and ER α upregulate but sequester p53, such that the DDR and DNA repair are suppressed in the presence of active estrogen signaling, but there is still some safeguard via p53. When estrogen treated breast cancer cells are irradiated there is partial activation of p53 and its downstream pathways, but the pro-proliferative effects of estrogen override any checkpoint-mediated cell cycle arrest (20). Conversely, in mouse models, p53 provides protection from lymph node hyperplasia and ductal carcinoma *in situ* (DCIS) induced by deregulated estrogen signaling (48).

DNA REPAIR MACHINERY

Estrogen receptor α interacts directly with DNA repair proteins with varying impact on DNA repair mechanisms and ER α function. This includes FEN1, MPG, APE1, and TDG of the BER pathway (49, 50), O(6)-methylguanine-DNA methyltransferase, which corrects mutagenic DNA lesion O(6)-methylguanine back to guanine (51), NHEJ repair proteins Ku70 and Ku86 in the context of gene transcription (18) and MSH2 of the MMR pathway (52). The binding of ER α to MPG enhances BER (53), while estrogen treatment upregulates or downregulates NER, depending on cell type (54, 55). The binding of repair proteins has different outcomes on ER α : MPG inhibits ER α -induced transcription and transactivation of signaling pathways (53), MSH2 and TDG transactivate ER α (50, 52), and the binding of FEN1 and APE1 to ER α has distinct effects on different ER α target genes (56, 57).

Estrogen receptor α interacts with other core DNA damage processing proteins, although the consequence for DNA repair or ER α action is unknown. Estrogen treatment upregulates BRCA2 (58) of the HR pathway, and through phosphorylation protects BRCA2 from degradation (59). ER α also directly interacts with DNA repair signaling and processing protein PARP-1 in the context of ER α -mediated gene transcription (18), which potentially affects ER α -regulated gene networks.

CELL CYCLE CHECKPOINTS AND APOPTOSIS

One of the most important functions of the DDR is to halt proliferation via the activation of cell cycle checkpoints or induce apoptosis. The effector proteins of these responses are not only targets of the DDR but as a set are antagonized by pro-proliferative ER α signaling. The DDR induces a G₁/S phase arrest downstream of ATR via CDC25A inhibition of cyclin A/E/CDK2 complexes, and downstream of p53 via p21 inhibition of cyclin D/CDK4/6 and cyclin E/CDK2 complexes. A G₂/M arrest is induced downstream of Chk1/Chk2 via activation of CDC25 phosphatases to inhibit cyclin B/Cdk1 complexes (60). ER α antagonizes cell cycle arrest by upregulating CCND1 (cyclin D1), CCNE2 (cyclin E2), and CDC25A, and downregulating CIP1 (p21) downstream of c-MYC (61–63). Likewise, p53 induces apoptosis by induction of FAS-R, BAX, PUMA, and NOXA (64), but ER α induces an anti-apoptotic signal including upregulation of BCL2 (65).

Consequently, active ER α signaling will antagonize the anti-proliferative and pro-apoptotic signals of the DRR. The outcome will be dictated by the strength of each signal, but ER α signaling is able to sustain proliferation in situations where otherwise DNA

damage would have induced a cell cycle arrest and apoptosis (15, 20, 66).

DISRUPTION OF DDR AND DNA REPAIR PATHWAYS IN BREAST CANCER, AND THEIR ASSOCIATION WITH ER α STATUS AND PROGNOSIS

DNA damage pathways are altered in breast cancer by mutation, changes in expression, amplification, and methylation, and as a class the DDR and DNA repair proteins are frequently altered in cancer and associated with poor prognosis. A survey of the literature shows that DDR pathways differ significantly between ER α positive and ER α negative breast cancer (Table 1). At least part of this change may be due to loss of ER α signaling, and certainly changes to p53, ATM, and TIMELESS (which functions in the ATR pathway) are consistent with the loss of ER α regulation of these genes/proteins. However, given that changes to DNA damage processing are a hallmark of cancer that contributes to tumor initiation, some of the changes no doubt precede loss of ER α , and may in fact contribute to its loss. This is exemplified in cancers with low BRCA1 and ER α , and BRCA1 loss is hypothesized to lead to ER α downregulation in breast cancer (31). Nevertheless, the presence or absence of DDR/DNA repair proteins will affect DNA repair in hormone-responsive cancers and the bi-directional regulation of the DDR/DNA repair and ER α . Likewise, the loss of ER α will affect the DDR/DNA repair in ER α negative cancers.

PERSPECTIVES

Estrogen receptor signaling is not typically thought to influence DNA repair as the literature has focused on its classic nodes of action of proliferation, growth, and apoptosis. The evidence, however, is overwhelming that ER α signaling has an impact on DNA damage processing through its regulation of ATM, ATR, DNA-PK, p53, BRCA1, BRCA2, and the DNA repair machinery. Given that estrogen can cause DNA damage, this raises a vital question of how estrogen receptor signaling processes the DNA damage caused by estrogen action. For example, does it dampen damage responses in favor of continuing proliferation, or does it act as a sentinel against DNA damage? Overall, estrogen receptor activity appears to downplay the response to DNA damage while simultaneously promoting proliferation. Consequently sustained ER α signaling may be permissive of the accumulation of genomic change from low level DNA damage that contributes to tumor initiation. Some of the major effectors of the DDR (e.g., p53 and BRCA1) do have negative feedback on the estrogen receptor, as does active DNA repair. Thus in the face of serious DNA damage ER α signaling is downregulated to protect the cell from continuing proliferation, and potentially allow full engagement in the DDR.

Several critical experiments will clarify whether active ER α signaling overrides the DDR. These include co-treatment with estrogen and different DNA damaging agents to determine the extent to which the DDR is activated and how ER α promoter binding is affected by DNA damage. This should incorporate the titration of doses of DNA damage to determine if there is a tipping point between sustained proliferation due to ER α action, and engagement of the DDR and DNA repair. Since ER α has cross-talk with both BRCA1 and p53, the combinatorial effects

Table 1 | DNA damage response and DNA repair genes altered in breast cancer and relationship to ER α status.

Gene/protein	Interaction with ER α	Alteration and relationship to ER α status in breast cancer	Prognosis	Reference
ATM	ER α downregulates <i>miR-18a</i> and <i>miR-106a</i> to downregulate ATM protein expression, and <i>miR-18a</i> directly binds to the ATM-3'-UTR	ATM protein is higher in ER negative breast cancers	High ATM protein is correlated with recurrence in breast cancer	(11, 16, 67)
ATR	ATR is functionally downregulated by ER α transactivated AKT signaling, which suppresses the DNA damage induced association between ATR:TOPBP1	–	–	(15)
BRCA1	The BRCA1:Oct1 complex directly binds the <i>ESR1</i> promoter to drive ER α transcription; BRCA1 suppresses ER α -mediated transcription through direct binding and co-activators; ER α promotes <i>BRCA1</i> transcription via an ER α /p300 transcriptional complex	Low <i>BRCA1</i> /BRCA1 (by mutation, methylation, or low mRNA) is associated with ER negative breast cancers	Oophorectomy (resulting in reduced estrogen levels) is protective against breast cancer in <i>BRCA1</i> familial breast cancers	(22–26, 29, 31)
<i>BRCA2</i>	<i>BRCA2</i> is upregulated by estrogen treatment, possibly as an indirect target rather than via ER α	<i>BRCA2</i> is higher in ER negative breast cancers	High <i>BRCA2</i> predicts poor disease-free survival	(68, 69)
c-ABL	c-ABL enhances estrogen receptor ER α transcriptional activity through its ER α stabilization by phosphorylation	Expression of c-ABL and ER α are not correlated	Co-expression of c-ABL and ER α is associated with advanced tumor stage and lymph node involvement	(70, 71)
<i>CHEK2</i>	–	<i>CHEK2</i> mutated breast cancers tend to be ER α positive	In ER positive breast cancers, <i>CHEK2</i> mutation is associated with increased risk of death and second breast cancers, but not in ER negative cancers	(72, 73)
CHK1	CHK1 is phosphorylated via ER α transactivated AKT signaling, which suppresses the DNA damage induced CLASPIN:CHK1 interaction	<i>CHK1</i> mRNA and protein are highly expressed in ER negative	<i>CHK1</i> not prognostic for outcome metastasis in breast cancer	(15, 74)
CLASPIN	CHK1 is phosphorylated via ER α transactivated AKT signaling, which suppresses the DNA damage induced CLASPIN:CHK1 interaction	<i>CLASPIN</i> mRNA and CLASPIN protein are highly expressed in ER negative breast cancers	<i>CLASPIN</i> mRNA is not prognostic for metastasis	(15, 74)
DNA-PK	The DNA-PK:ER α protein complex increases ER α phosphorylation and reduces ER α turnover. The DNA-PK:ER α complex binds to ER α responsive gene promoters, an effect that is not dependent on DNA damage	–	–	(19)
FANCD2	–	FANCD2 protein is higher in ER negative breast cancers	–	(75)
MDM2	MDM2 interacts with ER α in a ternary complex with p53. MDM2 positively regulates ER α transcriptional activity, but downregulates overall activity through ER α monoubiquitination	High MDM2 protein is correlated with ER positive breast cancers	Low MDM2 protein is correlated with high nuclear grade and lymph node involvement	(41–43, 76)

(Continued)

Table 1 | Continued

Gene/protein	Interaction with ER α	Alteration and relationship to ER α status in breast cancer	Prognosis	Reference
p53	ER α upregulates <i>TP53</i> and stabilizes p53, but generally suppresses p53 transcriptional function. p53 upregulates <i>ESR1</i> , but also modulates ER α induced transcription	p53 is generally wild-type and expressed in ER positive breast cancer	<i>TP53</i> mutation or p53 mutated gene signature is prognostic for poor disease-free survival	(12, 32, 33, 35–39, 45–47, 77)
PCNA	PCNA interacts directly with ER α to modulate its transcriptional function in normally proliferating cells	–	–	(78)
RAD17	<i>RAD17</i> mRNA is upregulated by estrogen in an ER α dependent manner	<i>RAD17</i> mRNA often high in breast cancer; high RAD17 protein correlated with ER negative; <i>RAD17</i> sometimes lost in ER negative, but due to loss of 5q11 locus	High <i>RAD17</i> mRNA prognostic of increased lymph node metastasis	(79–81)
<i>TIMELESS</i>	<i>TIMELESS</i> is upregulated by estrogen, probably via ER α , and downregulated by anti-estrogens	<i>TIMELESS</i> mRNA is high in ER+ patients who have relapsed for endocrine therapy	High levels of <i>TIMELESS</i> mRNA prognostic of poor relapse-free survival for ER+ breast cancers	(82)
TOPBP1	TOPBP1 is regulated downstream of ER α transactivated AKT signaling, which suppresses the DNA damage induced association between ATR:TOPBP1	TOPBP1 expression has no relationship to ER α status	Low <i>TOPBP1</i> mRNA and high TOPBP1 protein are both associated with increased breast cancer grade	(15, 83, 84)

–, no relationship reported.

should be considered by simultaneously activating ER α signaling and treating with DNA damage in the context of BRCA1 and p53 ablation. Finally, it is a priority to investigate the effect of ER α on its binding partners DNA-PK, PCNA, and PARP-1 in the context of DNA damage.

The role of ER α in modulating DNA damage has important clinical implications. Anti-estrogen treatment is the mainstay of adjuvant therapy for breast cancer, but the most common therapy, Tamoxifen, is itself a source of DNA damage (85), and this damage has been detected in patients and is implicated in endometrial cancer (86). Tamoxifen has agonist effects through ER α in the endometrium (87) so it is interesting to speculate that Tamoxifen therapy induces DNA damage and disturbs a balance between estrogen signaling and the DDR in the endometrium to detrimental effect. Chemotherapies and radiation therapy induce DNA damage, so ER α may suppress the DDR to reduce the efficacy of these treatments. Indeed, patients with ER positive breast cancers have significantly lower response rates to chemotherapy than those with ER negative cancers (88), and *in vitro* studies suggest this is dependent on ER α action (89–91). Co-administration of anti-estrogens and radiation therapy or chemotherapy appears to enhance therapy cytotoxicity and a likely explanation is that anti-estrogen treatment prevents pro-proliferative bypass of cytotoxicity by estrogen (66, 90). Conversely, estrogen receptor action is needed for sustained p53 expression to allow the induction of apoptosis by chemotherapeutic doxorubicin (92), and good prognosis ER α positive breast cancers generally express p53.

Consequently, the pro-apoptotic arm of the DDR appears compromised in some circumstances by the complete inhibition of ER α signaling. Further understanding of the cross-talk between ER α and DNA damage processing will provide crucial information to guide drug, radiation therapy, and hormone combination treatment of breast cancer patients.

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