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The p53-Estrogen Receptor Loop in Cancer

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Abstract

Tumor suppressor p53 maintains genome stability by regulating diverse cellular functions including cell cycle arrest, apoptosis, senescence and metabolic homeostasis. Mutations in the p53 gene occur in almost all human cancers with a frequency up to 80%. However, it is only 20% in breast cancers, 18% in endometrial cancers and 1.5% in cervical cancers. Estrogen receptor alpha (ERα) plays a pivotal role in hormonedependent cancer development and the status of ERα is used for designing treatment strategy and for prognosis. A closer look at the cross-talk between p53 and ERα has revealed that their activities are mutually regulated. This review will summarize the current body of knowledge on p53, ERα and ERβ in cancer. Clinical correlations between estrogen receptors and p53 status have also been reported. Thus, this review will discuss the relationship between p53 and ERs at both the molecular and clinical levels.

Keywords

Estrogen receptor; hormone-dependent cancer; p53; transcription factors

INTRODUCTION

Stress signals, such as DNA damage, hypoxia, oncogene activation and ribosomal stress, activate the p53 tumor suppressor mainly through posttranslational modifications. Activated p53 acts as a sequence-specific transcription factor that regulates a plethora of downstream target genes involved in diverse cellular processes including cell cycle arrest, DNA repair, apoptosis, and cellular senescence. For example, in response to DNA damage, p53 induces expression of p21, a cyclin-dependent kinase inhibitor, which binds to and inhibits the activity of cyclinD-CDK4/6 and cyclinE-CDK2 complexes and then arrests cells at G1 phase [1, 2]. Cell cycle arrest allows for the cell to repair the damaged DNA before it is replicated in S phase. If the cell cannot repair the DNA damage, p53 then induces expression of apoptotic target genes, such as PUMA and Bax, for programmed cell death [3]. Therefore, loss of p53 leads to aberrant cell proliferation and cell death and eventually tumor formation. Indeed, p53 inactivation occurs in almost all human tumors with a rate up to 80% depending on the type, stage, and etiology of cancers [4, 5]. Loss of p53 activity causes early onset of multiple tumors in p53-knockout mice and Li-Fraumeni syndrome patients [6, 7]. However, p53 mutation is not common in estrogen-responsive tumors. It is only 20% in breast cancers, 18% in endometrial cancers and 1.5% in cervical cancers [8, 9]. In the case of cervical cancer, loss of p53 activity is due to its inactivation and degradation by human papillomavirus E6 protein [10, 11].

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CONFLICT OF INTEREST
The authors confirm that this article content has no conflicts of interest.

Estrogen is an essential hormone for mammary gland development and reproductive organ function. Estrogen also regulates other diverse physiological functions associated with the cardiovascular, central nervous, immune, and skeletal systems. The estrogen activities are mediated by estrogen receptors (ER), including ERα and ERβ. Both ERα and ERβ are intracellular nuclear hormone receptors and mediate estrogen signaling primarily through transcriptional activation of target genes. Estrogen can also be recognized by G-protein coupled receptor 30 (GPR30), an integral membrane protein. In response to estrogen, GPR30 initiates non-genomic functions such as intracellular calcium mobilization, stimulation of adenylyl cyclase, synthesis of nuclear phosphatidylinositol (3,4,5)-trisphosphate (PIP_3), and activation of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling pathways [13]. GPR30 acts independently of ERα and ERβ and its role in hormone-dependent cancer is not well characterized. Thus, this review will focus on ERα and ERβ.

In estrogen-regulated tissues such as the breast, endometrium and colon, tumors can be induced by deregulated ERα expression and signaling in cell proliferation, survival, and migration [14]. About 70% of breast cancers express ERα and are classified as estrogen receptor positive (ER-positive) and anti-estrogen, such as tamoxifen, has been developed to treat ER-positive breast cancer patients. In addition, chemotherapy is used as adjuvant treatment for anti-estrogen or main treatment for metastatic breast cancers. p53 is a major mediator for chemotherapy, and therefore understanding the crosstalk between p53 and ER signaling will provide important clues to improve current breast cancer treatment strategies. In this review, we provide an overview of the relationship between p53 and ERα in estrogen-responsive tumors at both the molecular and clinical levels.

THE ESTROGEN RECEPTOR SIGNALING PATHWAYS

ERα and ERβ are located on different chromosomes, but share 97% identity in their DNA-binding domains and 55% identity in their ligand-binding domains. ERα and ERβ are divided into six functional domains (Fig. 1A). The N-terminal A/B domains interact with coactivators and contain activation function-1 (AF-1), which is necessary for transcriptional activity. The C domain contains the DNA binding region. The D domain, also called the hinge region, contains a nuclear localization signal. The E domain contains a ligand binding region, a dimerization domain, AF-2, and an additional nuclear localization signal. The F domain is the C-terminal ligand binding region, which is highly regulated by agonists and antagonists [15].

Human ERα is expressed as two main isoforms, ERα and ERα46, the latter of which lacks the N-terminal AF-1. ERα46 can form a heterodimer with full length ERα, resulting in suppression of ERα transactivation activity [16]. A third ERα isoform, ERα36, which lacks both transactivation domains AF-1 and AF-2, has been identified [17]. Unlike full length ERα and ERα46, ERα36 is localized in the cytoplasm and the plasma membrane, where it is thought to mediate non-genomic estrogen signaling [18]. Human ERβ is expressed as more than five isoforms through alternative splicing [19]. ERβ1 is the full length receptor and referred to as ERβ. ERβ2-5 have a truncated AF-2 ligand binding domain and therefore cannot bind ligand. Although ERβ2-5 are unable to form functional homodimers, they can form heterodimers with ERα or ERβ1 and modulate their function [20, 21].

Upon binding to 17β-estradiol (estrogen), ERα and ERβ form homo- and hetero-dimers that function as transcription factors. These nuclear hormone receptors regulate gene expression either by binding directly to an estrogen response element (ERE) in their target gene promoters (Fig. 1B) or through secondary interactions with other transcription factors such as Activator Protein 1 (AP1), NFκB, or Sp1 [22, 23]. EREs can be either a full consensus

sequence of 5'-GGTCAnnnTGACC-3' (where "n" is any nucleotide), a half consensus sequence of 5'-GGTCA-3', or a non-consensus sequence [24, 25]. Interestingly, both estrogen receptors have different tissue expression profiles and regulate common as well as unique sets of genes [26]. ERα is the main estrogen receptor in the female reproductive system, including the mammary gland and uterus [27]. ERβ is the main estrogen receptor in the central nervous system, lung, cardiovascular system, prostate and colon [28].

70% of breast tumors express ERα and are classified as estrogen receptor positive (ER-positive) [29]. ER-positive breast cancer generally is an indication of good patient prognosis and treatment responsiveness with anti-estrogens such as tamoxifen [30]. However, half of tamoxifen responsive tumors develop resistance to treatment [31, 32]. ER-positive breast cancer patients with de novo resistance to tamoxifen are generally responsive to ICI 182,780 as are patients who develop resistance to tamoxifen treatment [33]. ICI 182,780 (Fulvestrant) is a pure ER antagonist and inhibits dimerization following binding to ER [34]. In addition, ICI 182,780 reduces ERα levels by increasing receptor degradation *via* the ubiquitin-proteasome pathway [35]. Treatment resistance can be due to a reduction in the amount of ERα, which leads to an ER-negative tumor status. ER-negative tumors are associated with anti-estrogen treatment resistance, aggressive tumor growth, increased invasiveness and poor patient prognosis [30]. Some evidence suggests that ERα downregulation could be achieved by hypermethylation of CpG islands in the ERα promoter region [36], by hyperactive MAPK (ERK1/2) signaling [37], or by elevated expression of its transcription repressors, such as Her2/neu [38] and TWIST [39]. However, the mechanism for loss of ERα expression in ER-positive breast cancers is poorly defined.

While ERα expression is associated with tumor growth, ERβ expression may play an inhibitory role in tumorigenesis [40]. It has been shown that ERβ expression is low in breast cancer and ectopic expression of ERβ leads to reduced proliferation and/or invasion of several breast cancer cells, including MCF7, T47D, and MDA-MB-231 cells [41-44]. However, reports also showed that ERα-negative invasive breast cancers express ERβ and overexpression ERβ stimulated growth and/or metastasis of MDA-MB-231 and MDA-MB-435 breast cancer cells [45-47]. Thus, it is likely that ERβ is capable of either promoting or inhibiting proliferation/metastasis of breast cancer cells. In future studies, characterization of the role of ERβ in breast tumorigenesis and the correlation between ERβ expression in clinical breast tumor samples and patient prognosis will be of great interest.

EFFECT OF ESTROGEN AND ESTROGEN RECEPTOR ON P53

Estrogen Regulates p53 Expression

An early study showed that in serum starved mouse 3T3 cells, p53 mRNA and protein levels were decreased whereas addition of serum increased p53 mRNA and protein levels [48]. This effect was particularly profound to estrogen compared to other steroids in the serum. Similarly, in T47D ER-positive breast cancer cells, the level of mutant p53 (L194F) was decreased to 10% after 4-5 days of culturing with hormone-free medium. However, normal levels of p53 were restored by 24 hours of treatment with 100 pM estradiol, a level well below the physiological level of estradiol. Conversely, anti-estrogen ICI 164,384 decreased p53 expression in both normal and hormone stripped medium [49, 50]. In addition, ER-positive and p53 wild-type MCF-7 breast cancer cells responded to estrogen treatment with an increase in p53 levels [51]. Moreover, in YAMC cells, addition of estrogen induced p53 downstream targets PUMA, Bcl-2-associated X protein (Bax), and Noxa [52]. Consistently, MCF-7 cells treated with doxorubicin, a chemotherapeutic drug that induces DNA damage and p53 activation, had a significantly lower number of cells undergoing apoptosis in estrogen-free conditions compared to cells treated in complete medium [53]. In addition, mRNA levels of PUMA, 14-3-3σ and especially GADD45 were also significantly reduced

in doxorubicin-treated cells grown in estrogen-free media compared to cells treated with doxorubicin in complete media [53]. Moreover, overexpression of ERα sensitizes, whereas knockdown of ERα desensitizes, MCF-7 cells to DNA damage-induced growth suppression in a p53-dependent manner [54]. These together suggest that the estrogen receptor pathway is implicated in p53 regulation as well as DNA damage-induced p53 activation.

Reports showed that estrogen can regulate p53 transcription (Fig. 2A). For example, estrogen is found to induce p53 gene expression through CCAAT-binding transcription factor-1 and NFκB-binding motifs located between nt −106 and −40 upstream of the p53 transcriptional start site [55]. Because the proximal p53 promoter contains no consensus ERE site, it suggests that estrogen could induce p53 transcription through binding to the p65 subunit of NFκB at its C-terminal transactivation domain [55]. In addition, it showed that estrogen induces c-Myc, which then leads to subsequent activation of p53 through the Myc/Max Ebox response element [56]. A recent report showed that the GC-rich Sp1 site on the proximal p53 promoter is activated by ERα/Sp1 complex [57]. Interestingly, we found that ERα binds to and activates the p53 promoter *via* two distal ERE half-sites [54].

To date, knowledge of the post-transcriptional regulation of p53 by estrogen is limited. One report showed that estrogen prolonged p53 protein half-life from a basal time of 5-30 minutes to 90 minutes in MCF-7 cells, but had no effect on mutant p53 stability in T47D or MDA-MD-231 cells [58]. Another report showed that estrogen promoted nuclear export of p53 in MCF-7 cells cultured in serum-free medium, and thus prevented p53 from inducing target genes, such as p21[59].

ERα Modulates p53 to Regulate its Target Genes

ERα and p53 bind to each other directly (Fig. 2B) [60-62]. Initial observations reported that ERα interacts mainly with the N-terminal 102 amino acids of p53 and some of residues beyond 103 amino acid may be also involved in this protein-protein interaction [62]. However, another report showed that the C-terminal aa 319-393 of p53 is necessary for p53 interaction with the AF-2 domain (aa 283-395) of ERα [60]. Although ERα associates with p53 at the region which is important for interacting with p300 and MDM2 [63, 64], ERα interaction with p53 is not affected by MDM2 or p300 [62, 65]. Indeed, MDM2 exists in the p53- ERα complex and has less ability to downregulate p53 in the presence of increased amounts of ERα, suggesting that ERα has protective properties over p53 [62].

ERα is found to interact with p53 on the promoters of p53 target genes, such as p21 and PCNA, and represses p53 transcriptional activity (Fig. 2C) [60]. In addition, estrogen increases the p53- ERα interaction, consistent with the observation that p21 transcription is decreased following estrogen treatment [66]. Moreover, ERα relieved p53 repression of target genes Survivin and MDR-1 (multidrug resistance gene 1) (Fig. 2C) [67]. In contrast, γ-irradiation, on the other hand, disrupted the p53- ERα interaction while anti-estrogens, tamoxifen and ICI 164,384, had no effect [60]. This result was validated in an animal model by exposing mice with xenografted MCF-7 tumors to ionizing radiation. The tumor growth was significantly reduced and a ChIP assay showed a disrupted p53-ERα interaction on the promoter of Survivin in the xenografted cells [68]. Interestingly, a recent report showed that ERα antagonizes p53-mediated cell death by suppressing several doxorubicin-induced proapoptotic p53 target genes, including ATF3, BTG2, and TRAF4, without altering the access of p53 to these gene promoters [69].

Reports showed that ERα regulates some p53 target genes which contain ERE sites (Fig. 2C). For example, FLT1, an angiogenesis-related gene, contains two ERE half sites which are located 225 nt upstream and 145 nt downstream from a half p53 response element. Synergistic transactivation of FLT1 occured in the presence of increased levels of ERα with

both wild-type p53 and some p53 mutants [70, 71]. Since p53 is a direct target of ERα activation [54], it is possible that ERα is able to modulate p53 target gene expression. Indeed, we showed that knockdown of ERα leads to decreased expression of p53 along with its targets including p21, MDM2, PolH, PUMA, and MIC-1 [54]. However, ERα has little or no effect on the expression of these genes in p53-deficient cells [54]. Taken together, it suggests that ERα modulates p53 target gene expression through multiple mechanisms. For example, ERα reduces p21 expression either by physical association with p53 and hence inhibiting p53 transactivation at the p21 promoter or by regulating p53 expression and consequently controlling p21 expression.

In ER-positive breast cancers, the increase of ERα and subsequent increase of p53 could lead to an abnormal balance between the two proteins. ERα induces Bcl-2, an anti-apoptotic gene, while p53 inhibits Bcl-2 through Noxa [72, 73]. If more ERα is present in tumor cells than activated p53, apoptosis of cancer cells can be avoided. However, ERα can block MDM2 inhibition of p53, thus activating the tumor suppressor and possibly promoting the cancer cells to undergo apoptosis. If this delicate balance of ERα and p53 is disturbed, it may result in deregulated signaling pathways as well as changes in ERα- and/or p53-dependent gene expression that promotes tumor growth and survival.

ERβ and p53

Unlike ERα, ectopic expression of ERβ has no effect on the levels of p53 and p21 regardless of DNA-damage treatment in ERα-knockdown MCF10a cells [74]. Consistently, we found that ERβ does not activate the p53 promoter [54]. These indicate that ERβ has no direct effect on the expression of p53. However, emerging evidence suggested that ERβ may contribute to p53 levels in some circumstances. For examples, ERβ-specific agonists induce p53 and apoptosis in MC4-L2 mouse mammary adenocarcinoma cells, which express both ERα and ERβ [75]. In addition, expression of ERβ led to increased expression of mutant p53 in SW480 cells, but decreased expression of wild-type p53 in HCT116 cells [76]. Moreover, overexpression of ERβ inhibited cell survival by enhancing p53-mediated apoptosis and growth suppression in LoVo cells in an estrogen-dependent manner [77]. Furthermore, it showed that ERβ is able to antagonize estrogen-induced cytoplasmic translocation of p53, and thus increases p53 transcriptional activity in MCF7 cells [78]. Therefore, regulation of p53 by ERβ is achieved through multiple mechanisms which need to be further explored.

REGULATION OF ESTROGEN RECEPTOR BY p53

p53 transcriptionally regulates a vast array of target genes, including ERα and a subset of estrogen-responsive genes. There are two potential mechanisms by which ER target genes are regulated by p53. First, protein-protein interaction between ERα and p53 can lead to alterations in ER target gene expression. To suppress hormone-induced cancer cell growth, p53 interferes with ERα binding to EREs in estrogen-responsive target gene promoters instead of interfering with ERα dimerization (Fig. 1C) [65]. This may explain why some estrogen-responsive genes, such as BRCA2, Bcl2, IL-6 and tissue plasminogen activator [79], are repressed by p53 [80-84]. Second, ERα is a p53 target. In MCF-7 cells, ectopic expression of p53 increased ERα expression whereas knockdown of p53 decreased ERα expression [85]. DNA damage treatment with doxorubicin or ionizing radiation increased p53 and subsequently ERα protein and mRNA levels. Additionally, the effect of DNA damage on ERα expression can be further enhanced by overexpression of p53. Treatment with doxorubicin recruited p53 to the ERα promoter at nt −128 to −40 while at a non-stress condition, p53 was recruited to the ERα promoter at nt −2094 to −1941 and −350 to −298 [86].

A positive feedback regulatory loop between ERα and p53 may explain why tumors with mutated p53 tend to be ER-negative and ER-negative breast cancers lose wild-type p53 expression, and consequently become an aggressive tumor. However, there are still a significant number of ER-positive breast cancer cases with mutant p53 tumor status, which would not be explained by this hypothesis.

ER AND p53 IN HORMONE-DEPENDENT CANCERS

ERα and p53 in Breast Cancer

It is well-known that women whose first full term pregnancy occurs under the age of 18 have one third the lifetime risk of breast cancer than women whose first birth occurs over the age of 30 [87]. Similarly, parous rodents were shown to be less likely to develop cancer after exposure to chemical carcinogens than virgin rodents [88-90]. In addition, short term treatment with ovarian hormones estrogen and progesterone enhanced p53-dependent responses and reduced the incidence of mammary cancer in rats and mice [89, 91-93]. In a study of p53-deficient nulliparous mice, those with deregulated ERα expression had higher mammary epithelial cell proliferation and reduced rates of apoptosis compared to mice with normal ERα expression [94]. Interestingly, p53-null mice with estrogen treatment developed mostly ERα-positive mammary tumors with a short latency, but those without estrogen treatment developed mostly ERα-negative mammary tumors [95]. While these observations of p53 and estrogen interaction in animal models and human clinical cases appear to correlate with results from molecular studies, much is left unexplained in the tumor behavior after treatment with anti-estrogen therapy, chemotherapy or radiation therapy as well as development of resistance to these therapies.

To date, many studies of clinical breast cancer cases have given conflicting results, but overall, a correlation between ERα and p53 is observed: that is, p53 is primarily wild-type in ER-positive breast cancer and mutant in ER-negative breast cancer. Many of the inconsistencies stem from small sample size and method of p53 status determination. Immunohisto-chemistry detects increased amounts of p53, which generally indicates mutant p53 status. Wild-type p53 has a much shorter lifespan than mutant p53 and is not easily detected by immunohistochemistry. Moreover, 30% of tumors with mutant p53 cannot be detected by immunostaining [96].

A consortium study on 1,280 breast carcinomas looking at the allele loss on chromosome 17 found that 52.4% of primary breast carcinomas had loss of heterozygosity [97] on 17p, an area where p53 resides (17p13.1) [98]. Previous studies also reported LOH on 17p in 50-60% of breast cancer cases [99, 100]. Furthermore, abnormalities on chromosome 17 were statistically associated with increased aggressiveness of breast tumors, larger tumor size, ER-negative status, and early age of onset [98]. Studies focusing on the p53 locus found that the rate of p53 mutations is in the range of 16-58% using immunohistochemistry and 14-40% using DNA-based methods [101-105]. In 1,794 breast cancer patients, those with p53 mutations in exons 5-8 had a higher risk of breast cancer-specific death as compared to patients with wild-type p53. For patients with ER-positive tumors, mutant p53 status reduced survival to 60% after 10 years [106].

Tamoxifen is the leading drug for all stages of ER-positive breast cancer in pre- and post-menopausal women. Treatment of ER-positive breast cancer patients with tamoxifen resulted in a 31% reduction in mortality rate compared to patients not treated with tamoxifen. As expected, treatment of ER-negative breast cancer patients with tamoxifen showed little to no benefit [107]. While treatment of ER-negative breast cancers with a combination of chemotherapeutic agents (doxorubicin, cyclophosphamide and paclitaxel) increased disease-free survival by 22.8% after five years, addition of these chemotherapy to

tamoxifen treatment of ER-positive patients only increased disease-free survival by 7% [108].

Tamoxifen is classified as a selective estrogen receptor modulator (SERM) for its ability to act as an antagonist of estrogen in some tissues such as breast and act as an agonist in other tissues including heart and bone [109]. As a prodrug, tamoxifen is metabolized in the liver to form the active metabolite 4-hydroxytamoxifen (OHT), which competes with estrogen for binding at the ligand-binding domain of ERα in the breast tissue. Once bound, OHT induces a conformational change by displacing helix 12 to block the coactivator binding groove in the AF-2 domain. As a result, corepressors, such as nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRT), bind and influence ERα to regulate a different set of genes [109-111]. Treatment with tamoxifen also leads to a rapid decrease of cells in S-phase with a concurrent accumulation of cells in the G1-fraction. Though the mechanism of tamoxifen-induced cell cycle arrest is still uncertain, it is thought to be mediated by ERα based on the observation that ER-negative cells are not as sensitive to tamoxifen as ER-positive cells [112]. Treatment of ER-positive, p53 wild-type cells with tamoxifen resulted in a dose-dependent increase of p53 and p21 proteins suggesting that a p53-dependent G1 cell cycle arrest pathway is activated [1, 113]. Addition of estrogen to tamoxifen-treated G1 arrested cells induced the cells to progress into S phase along with an increase in protein levels of cyclin D1 and the kinase activity of cyclin D1/CDK4 and cyclin D1/CDK2 [114-118]. Together, these observations suggest that p53-mediated cell cycle arrest plays a role in the hormone-therapy targeting ERα.

Patients with node-positive tumors containing mutant p53 had a significantly lower overall survival rate upon treatment with tamoxifen and loco-regional radiotherapy as compared to patients with node-positive wild-type p53 status [114]. A similar study, which examined 243 ER-positive breast cancer cases, found that patients with p53 mutation had a lower response to tamoxifen (31%) as compared to those with wild-type p53 (66%) [119]. ER-negative tumors with p53 mutation had a worse overall response to tamoxifen (22%) than ER-positive tumors with wild-type p53 (73%). These studies suggest that mutant p53 has a negative effect on tamoxifen treatment. However, others have found no such correlation [102, 120].

Breast cancer patients with mutant p53 tend to have worse disease free survival rates regardless of estrogen receptor status [121]. Molecular studies showed that tamoxifen increased levels of p53 and activation of downstream p53 target genes in ER-positive, p53 wild-type cells, but not in ER-positive cells with mutant p53 [111]. Because p53 regulates ERα expression, mutations in p53 would inhibit ERα expression, decreasing the effects of tamoxifen [86]. It is not clear whether direct interaction between p53 and ERα has an effect on treatment or if treatment outcome results from other pathway interactions.

ERα and p53 in Cervical Cancer

A majority of cervical cancer cases are positive in human papilloma virus (HPV). Women infected with HPV16 are 38 times more at risk of developing cervical cancer than uninfected women [122]. High-risk HPVs, such as HPV16 and HPV18, express two oncogenes, E6 and E7, which inactivate p53 and pRb (retinoblastoma protein) tumor suppressor proteins, respectively [10, 11]. Loss of p53 and pRb is known to be responsible for increased cervical tumor cell proliferation. However, many patients infected with HPV alone do not develop cervical cancer [123], indicating the involvement of other cofactors. Indeed, the estrogen signaling contributes to HPV-induced cervical tumorigenesis. Analysis showed that long-term use (five years or more) of oral contraceptives in HPV-infected women resulted in a four-fold increase in cervical cancer risk compared to HPV-infected women not exposed to long-term estrogens [124]. This is confirmed in several mouse models. It has been shown

that HPV16 transgenic mice treated with estrogen for nine months developed larger, more aggressive tumors than mice treated with estrogen for six months [125]. In addition, the expression of E6/E7 was increased by estrogen and thus potentiates cervical cell transformation in HPV18 E6/E7 transgenic mice [126]. Moreover, ERα is thought to mediate this effect as ERα-null HPV transgenic mice failed to develop cervical cancer after exposure to estrogen [127] and blocking ERα by dominant negative ERα inhibits the growth of cervical cancer cells [128]. Furthermore, 88% of conditional p53 knockout mice with 6-month exposure to estrogen developed a wide spectrum of high-grade cervical tumors [95]. However, E6 transgenic mice do not develop tumor in the absence of estrogen or develop low-grade cervical cancers with estrogen treatment for 6 or 9 months [95, 129, 130]. This suggests that E6 is unable to fully inactivate p53.

ERα and p53 in Endometrial Cancer

Studies showed that long-term tamoxifen treatment increases the risk for developing endometrial cancer by 50% in ER-positive breast cancer patients [131-133]. However, much fewer cases and diseased-related death of endometrial cancer occur each year compared to breast cancer [134]. While tamoxifen shows strong anti-estrogenic activity in breast tissue, it has weak proestrogenic effects in endometrial tissue [135]. Indeed, tamoxifen users with endometrial cancer had a less favorable prognosis and worse overall survival compared to endometrial cancer patients not exposed to tamoxifen [136]. In addition, longer exposure to tamoxifen (60 *vs* 30 months) correlated with mutant p53 status. Tumors arising in women previously treated with tamoxifen were also more likely to be ER-negative [137]. Like breast cancer, 60-70% of endometrial cancers express ERα with a favorable prognosis compared to ER-negative endometrial cancers. In addition, the level of ERα is decreased, whereas the level of p53 (likely mutant p53) is increased, as the disease is progressed from stage I to stage II-III and recurrent tumors [138]. However, there has been no significant difference in the abnormality of the p53 pathway between ER-negative and ER-positive patients [139]. Similar to breast cancer cases, ER-negative endometrial tumors with a mutant p53 status strongly correlate with aggressive growth and poor patient prognosis [140].

ERβ and p53 in Cancer

The lifetime risk of developing colon cancer is significantly lower in females than in males [141]. In addition, females with colon cancer have better survival rates than male patients [142]. Similar to breast cancer risks, women who have had multiple children have a lower occurrence of colon cancer than women with no children [143]. Studies also report a correlation between postmenopausal women on estrogen replacement therapy and lower incidences of colon cancer [144, 145]. These indicate that estrogen has been implicated in a protective role against colon cancer. ERβ is predominantly expressed over ERα in the colorectal epithelium and mediates the effects of estrogen in the colon [146]. Therefore, although ERβ may not be a major factor for patient survival in breast cancer, it might be critical in colon cancer. Several studies showed that ERβ protein, but not mRNA, is decreased in colon cancer cells compared to normal colon cells and further decreased in poorly differentiated tumors compared to well-differentiated tumors [147, 148]. In addition, a mouse study showed that ERβ-deficiency leads to an accelerated progression of colitis-associated colorectal cancer and is associated with increased cell proliferation [149]. Consistently, ectopic expression of ERβ not only inhibits cell proliferation in multiple colon cancer cells, such as HCT8, SW480 and HCT116, but also suppresses the growth of SW480 cell transplants in mice [76, 150]. It has been shown that c-Myc expression is decreased whereas p21 and p27 are increased by ectopic expression of ERβ [76, 150]. However, whether p53 is necessary for ERβ to exert its activity in colorectal tumorigenesis is not clear.

CONCLUSION REMARKS

In normal cells, estrogen promotes cell proliferation. The concordant increase of p53 may counter the enhanced level of proliferation following estrogen stimulation. In cells where p53 and ER levels are deregulated, the balance between estrogen-stimulated growth *via* ER and p53-mediated growth suppression is disrupted, leading to uncontrolled tumor growth despite the presence of elevated p53 levels.

While there are many other factors contributing to tumor formation, ER-positive cancers make up the majority of breast, cervical and endometrial cancer cases. It is unknown how ER-positive tumors with wild-type p53 progress to become ER-negative tumors with mutant p53 although it is hypothesized that mutant p53 is able to transcriptionally repress ERα transcription. Furthermore, it is largely unexplained why half of patients with ER-positive tumors initially responding to tamoxifen develop resistance to treatment. Fully characterizing the interaction between p53 and ER and their signaling pathways in normal versus cancer cells will provide an insight into hormone-dependent cancer development and progression. Additional molecular and clinical analysis of how tumors respond to treatment with anti-estrogens in the case of ER-positive cancers or DNA damage-induced chemotherapies in the case of ER-negative cancers is needed to improve patient treatment.

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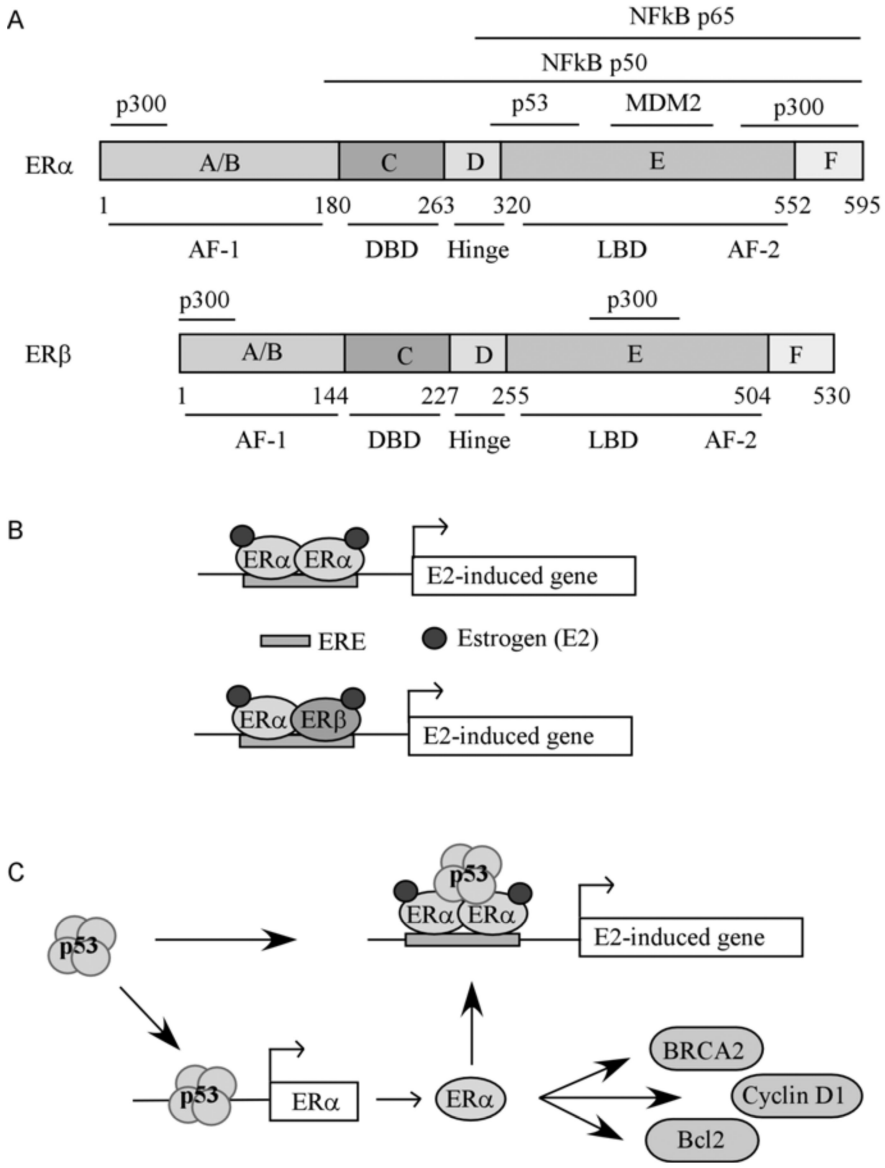

Fig. (1). Regulation of estrogen-induced genes

(**A**) ERα and ERβ functional domains. Top panel: ERα functional domains. A/B, ligand-independent activation function (AF-1: aa 1-180). C, DNA binding domain (DBD: aa 181-263). D, dimerization/hinge domain (Hinge: aa 264-302). E, the ligand binding domain/activation function (LBD/AF-2: aa 303-552). F, the C terminal end of ERα (F: aa 553-595). Marked above ERα functional domains are NFκB p65 binding region (domains E-F), NFκB p50 binding region (domains C-F), p300 binding region (aa 56-72 and aa 534-595), p53 binding region (aa 283-395), and MDM2 binding region (the C-terminal end of the LBD). Bottom panel: ERβ functional domains. A/B, ligand-independent activation function (AF-1: aa 1-144). C, DNA binding domain (DBD; aa 145-227). D, dimerization/hinge domain (Hinge: aa 227-255). E, the ligand binding domain/activation function (LBD/AF-2: aa 256-504). F, the C terminal end of ERα (F: aa 505-530). The location of p300 binding sites (aa 1-72 and aa 432-530) is marked above ERβ functional domains. (**B**) Schematic diagram of how estrogen-induced genes are regulated by ERα homodimers and ERα/ ERβ

heterodimers. (**C**) Schematic diagram of how estrogen-induced genes are regulated by ERα and p53.

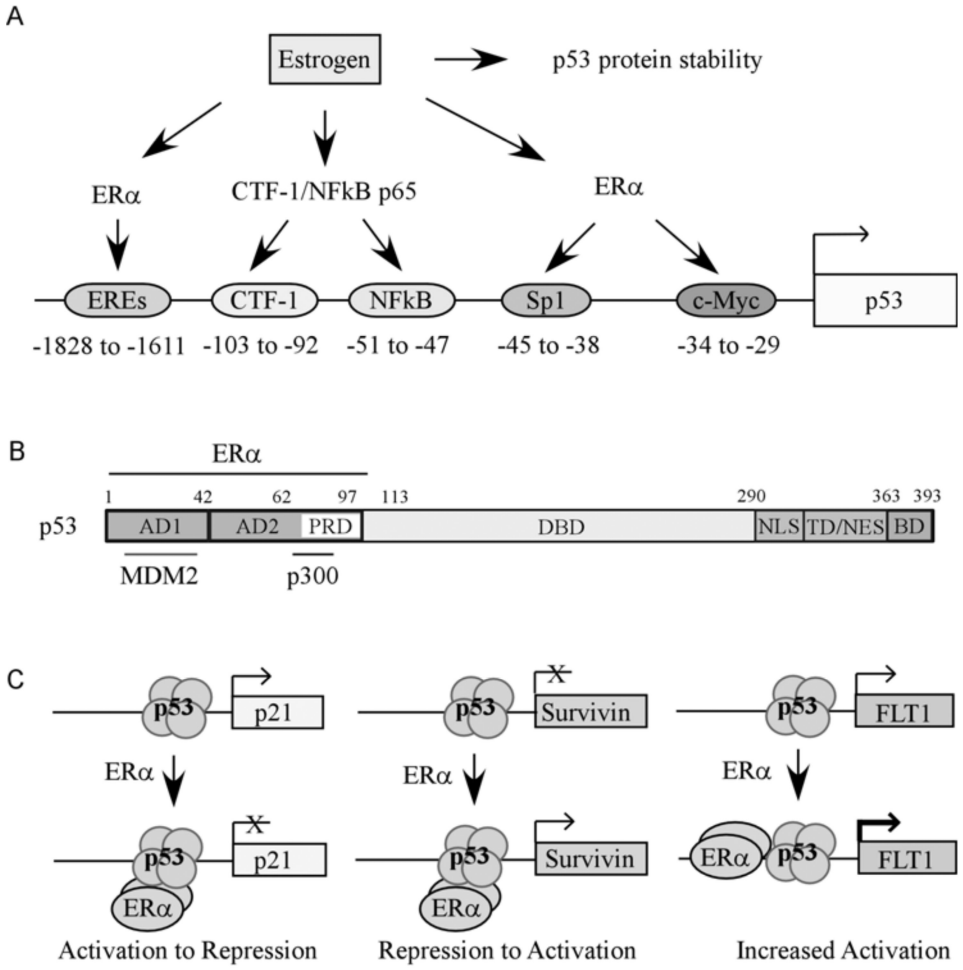

Fig. (2). The effect of estrogen and ER on the p53 pathway

(**A**) Estradiol increases p53 via enhancing p53 protein stability or promoting p53 gene transcription through multiple transcription factors, including ERα and NFκB (see details in the text). (**B**) Schematic presentation of p53 functional domains. AD1, activation domain 1 (aa 1-42); AD2, activation domain 2 (aa 43-92); DBD, DNA binding domain (aa 102-292); NLS, nuclear localization sequence (aa 293-325); TD, tetramerization domain (aa 326-363); BD, C-terminal basic domain (aa 364-393). Marked above p53 functional domains is ERα binding region (aa 1-102). Marked below p53 functional domains is Mdm2 binding region (aa 13-41) and p300 binding region (aa 71-90). ERα binding region overlap with the MDM2 and p300 binding sites. (**C**) ERα modulates p53 target gene expression. ERα binds to p53 on the promoters of p53 target genes, and thus represses p21 expression, relieves the repression of Survivin expression, or cooperatively induces FLT1 expression.