MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Estrogen Receptor Signaling in Breast Cancer

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Abstract

Estrogen receptor alpha (ERα) is expressed in nearly 70% of invasive breast cancers. ERα is a steroid hormone receptor and a transcription factor, its activation by estrogen, stimulates oncogenic growth pathways. Progesterone receptor (PR) expression is another biomarker of ER signalling. Estrogen influences breast cancer cell proliferation and differentiation and can be considered as a risk factor for breast cancer development and progression.

Keywords: Estrogen, MDM2, Breast Cancer.

1. Introduction

Breast cancer-mediated cell proliferation is fuelled by estrogen. ER*α* is a nuclear hormone receptor and oncoprotein that is expressed in approximately 70% of breast cancers **(Karami Fath et al., 2022)**. Estrogen receptor positively regulates growth and development of various tissues **(Wang et al., 2021)**.

Hormone exposure is among the main risk factors for sporadic breast cancer. Estrogen is a breast cancer promoter through its binding to the ER, a ligand-activated transcription factor that is located in the nucleus. Estrogen and progesterone imbalance during menstrual periods boost cell proliferation and could result in DNA damage build up. Each time the process is repeated, there is a chance that the repair mechanism will be damaged resulting in pre-malignant cells which may develop into malignant ones. At this point, oestrogen promotes the growth of these cells as well as the proliferation of stromal cells that support the progression of cancer. The ER interacts with estrogen response elements found in the promoter region of particular genes when it is activated. **(Williams & Lin, 2013)**.

Most breast cancers show positive expression of ER*α* which plays a significant role in tumor progression **(Martín, 2006)**. It was reported that estrogen stimulates cell proliferation (Rodrik et al., 2005) of ERα positive breast cancer cells like MCF7 **(Brekman et al., 2011)** and Ehrlich adenocarcinoma cells **(Ozcan Arican & Ozalpan, 2007)**. The human MDM2 gene is an oncogene that is overexpressed in diverse human cancers **(Momand et al., 1998)**. The primary oncogenic role of MDM2 is to inhibit the p53 tumor suppressor gene, resulting in abnormal cell growth and proliferation **(Haupt et al., 1997)**.

2. Estrogen receptor role in breast cancer pathogenesis

Estrogen controls multiple functions in hormone-responsive breast cancer cells, and ERα plays a major role in the etiology of the disease, serving as a major prognostic marker and therapeutic target in breast cancer management **(Ali et al., 2000)**.

Estrogen receptors α & β are members of the superfamily of nuclear receptors **(Cordera & Jordan, 2006)**. These receptors mediate the effects of the ligand 17h-estradiol (E2) by functioning as transcriptional regulators that access various target gene promoters either by directly binding to specific estrogen response elements within the promoter or indirectly by interacting with other transcriptional regulators bound to the promoter **(Sayeed et al., 2007)**.

Besides its function as a transcriptional regulator, ERα can also mediate several nongenomic effects, including mobilization of intracellular calcium, production of cyclic AMP, activation of mitogen-activated protein kinase signaling pathway, increased phosphatidylinositol 3-kinase activity leading to the activation of protein kinase B/Akt and endothelial nitric oxide synthase, activation of membrane tyrosine kinase receptors and phosphorylation of SRC homology–containing domain **(Singh & Kumar, 2005)**.

High expression of ERα correlates well with high levels of cellular proliferation, whereas high expression of ERβ (Estrogen Receptor beta) is linked to antiproliferative events **(Cordera & Jordan, 2006)**. Estrogen could promote de novo breast cancer though either receptor-dependent or independent mechanisms. It is known that estrogen binds to a specific nuclear receptor and generates a potent stimulus for breast gland cell proliferation and increases the risk of DNA mutation during replication **(Rondón-Lagos et al., 2016)**.

The majority of breast cancers are ERα+ and many of them are resistant to therapies targeting their hormone receptor status **(Jordan & O'Malley, 2007)**. Many ER+ breast cancers have Mouse double minute 2 (MDM2) overexpression suggesting that MDM2 is an ER+ axis driver oncogene that can be targeted for cancer therapy (Hori et al., 2002). MDM2 expression is a negative prognostic marker for breast cancer **(Turbin et al., 2006)**. ER+ cells exposed to estrogen show an increase in their transcription of MDM2 and increased MDM2 protein **(Brekman et al., 2011)**.

3. Breast cancer redemption via anti-estrogens

Inhibit ER signaling is the cornerstone of breast cancer pharmacotherapy for ER-positive/HER2-negative disease **(Ignatiadis & Sotiriou, 2013)**. ERα regulates gene expression of critical genes including cyclin D1, Bcl-2 (B-cell lymphoma 2), and VEGF (Vascular endothelial growth factor), which play a significant role in the cell cycle, cell survival, and angiogenesis **(Elshal et al., 2021)**.

Additionally, the ER can directly interact with proteins, including as growth factor receptors, to promote gene expression linked to cell survival and proliferation **(Levin & Pietras, 2008)**. Tamoxifen and other oestrogen-blocking medications as well as aromatase inhibitors, which stop the production of oestrogen, play important roles in the treatment of hormone-sensitive breast cancer. Aromatase inhibitors can potentially lead to osteoporosis because oestrogen interacts with bone. Tamoxifen, on the other hand, exerts oestrogen-like actions on the bone and prevents osteoporosis **(Santen, 2011)**.

4. Estrogen receptor and its impact on cell cycle progression

Estrogen stimulates cell cycle progression by promoting the G1 to S phase transition and retinoblastoma (Rb) phosphorylation **(Mir & Jan, 2023)**. Rb is a tumor suppressor protein that regulates E2F1 inhibition of DNA replication. RB binds to the activation domain of E2F1 and silences it resulting in S- phase arrest. The key function of Rb relies on its ability to interact with the E2F family of transcription factors to form active repressor complexes and negatively regulate expression of E2F-dependent genes **(Roufayel et al., 2021)**.

It is well established that E2F1 plays an important role in cell cycle control because deregulated expression of the E2F1 protein induces cell entry into S phase and can lead to increased proliferation **(Swetzig et al., 2016)**

Figure 1 reveals a schematic representation of the role of estrogen receptor on the signaling of MDM2 on E2F1 transcription factor and p-RB tumor suppressor protein on cell cycle progression.

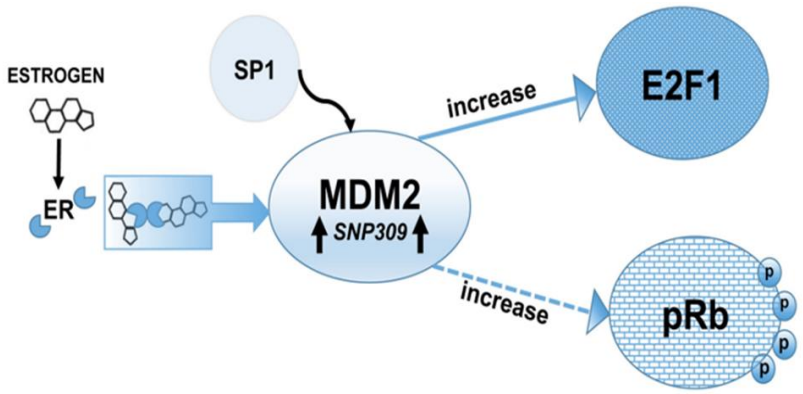

Figure 1: Schematic representation of ERα signaling pathway involving MDM2/E2F1/p-RB axis in breast cancer proliferation **(Kundu et al., 2017)**.

5. MDM2 and its regulatory role towards ER and cell cycle regulators

The oncogenic function of MDM2, as illustrated in **Figure 2**, is due to its ability to interact with wild type p53 and inhibit its ability to activate transcription of its target genes **(Senturk & Manfredi, 2012)**. Proliferative target genes of MDM2 include the stimulation of E2F1 transcriptional activity **(Gnanasundram et al., 2020)**. In addition, MDM2 itself is a transcriptional target of ER. MDM2 protein directly interacts with ER. ER signaling and the MDM2/p53 axis interact in a major way **(Wege et al., 2022)**.

The MDM2 interacts with Rb and E2F-1 to promote cell cycle G1-S transition. MDM2 proliferative targets include the activation of E2F1 transcriptional activity and suppression of tumor suppressive effects of Rb through binding to Rb and inhibiting the function of Rb-E2F repressor **(Wu & Wu, 2021)**. MDM2 knockdown results in a decrease in E2F1 protein (Swetzig et al., 2016). The oncogenic protein MDM2 is frequently expressed in high levels in breast cancer cells with wild-type p53 **(Opoku et al., 2021)**.

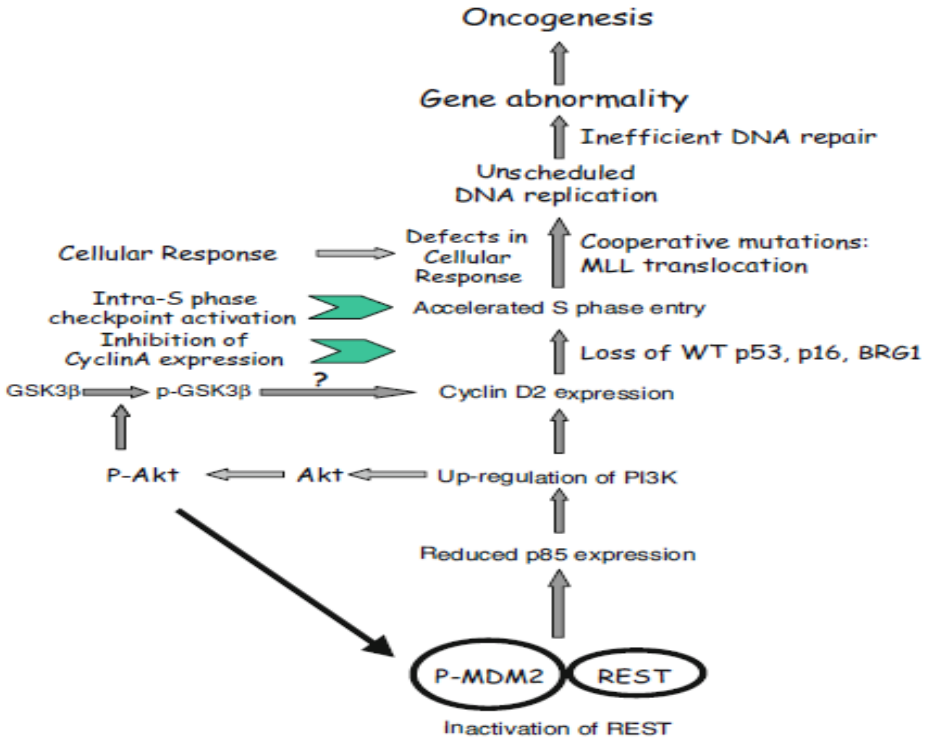

Figure 2: MDM2 proposed mechanism of oncogenesis **(Deb & Deb, 2014)**

6. Correlation between ER, p53 and MDM2

One of the main purposes of active p53 is to induce apoptosis. The p53 tumor suppressor protein binds to specific DNA sequences and regulates the transcription of a number of genes involved in cell-cycle arrest and apoptosis, thus cell cycle arrest is associated with p53 upregulation **(Ghate et al., 2013)**. MDM2 overexpression was observed along with P53 mutation **(Vaughan et al., 2011)**.

Estrogen activation promotes Rb phosphorylation **(Petrossian et al., 2018)**, while MDM2 depletion reduces E2F1 and phosphorylated Rb **(Zhang et al., 2003)**. Additionally, ER inhibits **(Song et al., 2008)** p53 activity when ER is activated by either its corresponding ligand or by specific ER modulators like tamoxifen **(Tang et al., 2006)**.

Conclusion

Estrogen binds to a specific nuclear receptor and generates a potent stimulus for breast gland cell proliferation and increases the risk of DNA mutation during replication. Estrogen signaling increases cell proliferation and cells exposed to estrogen show an increase in their transcription of MDM2. Many ER+ breast cancers have MDM2 overexpression suggesting that MDM2 is an ER+ axis driver oncogene that can be targeted for cancer therapy.

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