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Modulation of Nrf2 by activation of estrogen receptor β as a therapeutic strategy to prevent cancer development and overcome inflammation-related drug resistance in breast cancer

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Running title-Nrf2 modulation by estrogen receptor β in breast cancer

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Abstract

Despite the tremendous progress in breast cancer diagnosis and treatment, the mortality rate is expected to increase due to the emergence of drug resistance. Pro-inflammatory markers are thought to contribute to drug resistance by activation of its naive receptors and its downstream signaling pathways. Elevation of pro-inflammatory markers leads to an increase in the biosynthesis of estrogen which can promote the proliferation of estrogen receptor (ER)+ breast cancer. Inflammation also results in obesity which is one of the key risk factors. Estrogen receptor-beta (ER-β) is an important target that has been widely studied and accepted to possess anti-cancer
activity in a number of cancers including breast cancer. ER-β elicits its action through genomic and non-genomic pathways. The genomic pathway increases the transcription of potent cyclin-dependent kinase inhibitor (p21), and tumor suppressor genes such as melanoma differentiation associated gene 7 and tumor protein (p53). The non-genomic pathway works through protein-protein interaction and phosphorylation. Here, we propose that the activation of ER-β might enhance the activation of nuclear factor-erythroid factor 2-related factor 2 (Nrf2) via estrogen receptor-alpha (ER-α) repression. The activation of Nrf2 increases the transcription of antioxidant genes such as NADH quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), etc., and decreases the expression of pro-inflammatory genes such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), etc. This review hypothesizes and suggests that ER-β agonists could play a beneficial role to overcome inflammation-related drug resistance by modulation of the Nrf2/antioxidant response element (Nrf2/ARE) pathway.

**KEYWORDS:** Breast cancer, drug resistance, ER-α, ER-β, inflammation, Nrf2

**Introduction**

Breast cancer is the most common cancer and the foremost cause of cancer-related deaths in women globally.\(^1\) The 2020 global cancer statistics show that breast cancer (11.7%) is the most frequently diagnosed cancer surpassing lung cancer (11.4%).\(^2\) In India, according to a World Health Organisation 2021 report, breast cancer has overtaken cervix and oral cancers in women. A total of 178,361 new cases of breast cancer were reported in 2020 which constitutes 26.3% of all cancers in women. The incidence of breast cancer is prevalent in all-income countries, however, the overall mortality rate is observed to be higher in lower and medium-income countries.\(^1\) Breast cancer originates in the epithelial cells of the mammary gland and exhibits high heterogeneity at the cellular and the molecular level.\(^3\) Based on molecular classification, breast cancer is categorized into normal-like, luminal A, luminal B, triple-negative or basal-like, and human growth factor receptor2 (HER2) enriched. Additionally, molecular apocrine and claudin-low are other subtypes of breast cancer that are poorly understood. Molecular apocrine is characterized by an estrogen receptor (ER)/androgen receptor (AR)\(^*\) phenotype. Claudin-low is described by low-to-no luminal markers expression but with increased epithelial-mesenchymal transition (EMT).\(^4,5\)
Breast cancer is a multifactorial disease, occurring as a result of genetic mutations, exposure to carcinogens, lifestyle, age, and environmental pollutants. Breast cancer is generally categorized as either genetic and/or sporadic based on the causes of occurrence. Genetic factors include mutations in genes such as breast cancer gene (BRCA)-1 and 2, tumor protein (p53), ataxia telangiectasia mutated, checkpoint kinase-2, phosphatase and tensin homolog (PTEN), cadherin-1, serine/threonine kinase-11, and partner and localizer of BRCA2. Non-genetic factors include chest radiation, diethylstilbestrol, hormone replacement therapy, oral contraceptives, undue alcohol consumption, obesity, nulliparous, etc.1,6–8 Besides the above two factors, epigenetic changes such as hypermethylation of BRCA1, BRCA2, Ras association domain family member 1A genes and elevation of micro RNA (miR)-34a, miR-373, miR-93, miR-21, miR-195 and let7a leads to the development of breast cancer.9 Similarly, pro-inflammatory mediators generated during chronic inflammation are vital in the development and progression of cancer.10–13 Majority of breast cancer patients (70% - 75%) over-express ERs particularly ER-α.14,15 Higher intracrine estrogens have also been reported in breast cancer cells. In those cells, estrogens participate in carcinogenesis by generating reactive oxygen species (ROS) via the formation of 8-hydroxydeoxyguanosine (8-OHdG)16–18 and reactive quinones.19–22 The generation of ROS activates several inflammatory mediators contributing to cancer development23 and drug resistance.23–32

The ER+ breast cancer is considered to be a less aggressive subtype when compared to others. However, the cancer recurrence in ER+ breast cancer is estimated to be 40% after 10 years of initial diagnosis. Additionally, ER+ subtype is linked with poor response to neoadjuvant chemotherapy.33–35 Inhibitors of ER-α sometimes act destructively and produce unwanted outcomes. For example, fulvestrant and tamoxifen mimic estradiol (E2) and activate G-protein coupled estrogen receptor 1. This leads to the progression of cancer via the activation of extracellular signal-regulated protein kinase (ERK1/2) and phosphatidylinositol/protein kinase B (PI3K/AKT) signaling pathways.36 Despite the tremendous advancement in breast cancer diagnosis and treatment the mortality rate is expected to increase due to the emergence of drug resistance and lack of biomarker-driven therapeutic strategy.37–39 Interestingly, in some cases, the emergence of drug resistance occurs due to the off-target effects of anti-cancer drugs.40 This, review projects the critical role of inflammation in the development of drug resistance in breast
cancer and the potential role of ER-β in modulating nuclear factor-erythroid factor 2-related factor 2 (Nrf2) for the treatment of breast cancer.

**Inflammation and estrogen metabolites: their role in breast cancer development and drug resistance**

The role of inflammation in cancer progression was first described by Virchow in 1863. According to Virchow, cancer developed at chronic inflammation sites due to lymphoreticular infiltration. Since then, the implication of chronic inflammation in cancer has been widely studied. Inflammation is a protective response to internal and external injurious stimuli. However, not all inflammatory responses turn out to be positive ones. As mentioned earlier, inflammation could cause cancer development and drug resistance. Few examples of drug resistance caused by inflammation are doxorubicin, docetaxel, trastuzumab, and mitoxantrone in breast cancer, and bicalutamide in prostate cancer. A summary of the role of inflammation and drug resistance in different types of cancer is listed in Table 1. One of the major risk factors for breast cancer is obesity and an increase in body mass index. The increase in body mass index leads to adipose tissue hypertrophy and white adipose tissue inflammation in both mammary and visceral fats. Inflammation in these areas is determined by the presence of macrophages forming crown-like structures that can infiltrate necrotic adipose tissues. Necrosis occurs in adipose tissues at least in part due to hypoxia during adipocytes hypertrophy. Hypertrophic adipocytes undergo elevated lipolysis leading to an increase in the release of free fatty acids. Free fatty acids along with Fetuin-A, activate toll-like receptors in macrophages causing nuclear factor kappa B (NF-κB) activation. Consequently, NF-κB increases the expression of pro-inflammatory markers such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6), cyclooxygenase 2 (COX2), etc., leading to increase in the expression of aromatase enzyme and other genes that participates in cancer initiation and drug resistance.

Aromatase enzyme increases the estrogen biosynthesis and increases the growth of ER+ breast cancer by directly acting on ER-α and/or via generation of ROS through its metabolites. Estrogens that are converted into 4-hydroxyestradiol 2 (4-OHE2), a carcinogenic metabolite by estrogen-4-hydroxylase (CYP1B1), can participate in breast cancer initiation independent of ER. The metabolite 4-OHE2 upregulates specificity protein 1 which can promote cell proliferation and
metastasis via the activation of wingless-related integration β-catenin pathway and epithelial-mesenchymal transition (EMT).\textsuperscript{51} Additionally, 4-OHE2 can also induce carcinogenesis through upregulation of hypoxia-inducible factor α (HIF-α) and vascular endothelial growth factor A (VEGF-A). This is mediated through the activation of the PI3K/mammalian target of rapamycin (mTOR) pathway.\textsuperscript{52} HIF-α and VEGF-A expression could activate the angiogenesis and promotes a stem cell-like population in certain malignant tumors. Here, HIF-α and VEGF-A promote metastasis via SRY-related HMG-box 2-induced expression of snail family transcriptional repressor 2.\textsuperscript{53} Interestingly, according to Okoh \textit{et al.}\textsuperscript{54} the activation of the PI3K/AKT pathway seems to be dependent on ROS such as superoxide anion (\(O_2^-\)), hydroxyl ion (OH\(^-\)), and peroxynitrite (ONOO\(^-\)) generated by the action of 4-OHE2 on mitochondria. The 4-OHE2-induced ROS-PI3K/AKT activation upregulated the nuclear respiratory factor 1, and its targeted genes such as cell-division cycle 2, protein regulatory of cytokinesis 1, and proliferating cell nuclear antigen. These genes are involved in cell growth and malignant cell transformation.\textsuperscript{54} 4-OHE2 is further metabolized to semiquinone and quinone derivatives which could combine with adenine and guanine nucleotides to form DNA adducts.\textsuperscript{55} The reversible reaction of 4-OHE2 to semiquinone and quinone metabolites could also generate ROS suggesting the important role of 4-OHE2 in cancer progression.\textsuperscript{56} Consequently, the generated ROS could induce DNA lesions and mutations. The 8-OHdG and 8-oxo-7, 8-dihydro-2-deoxyguanosine (8-oxodG) serve as a biomarker for ROS-induced DNA damage. This DNA lesion or damage may contribute to mutagenicity and cancer development when overwhelmed.\textsuperscript{57,58} Additionally, ROS can repress tumor suppressor genes and upregulate cancer-promoting genes. One such gene codes for a protein NF-κB,\textsuperscript{59} a transcription factor that increases the transcription of various genes that participate in inflammation, cell survival, proliferation, and metastasis.\textsuperscript{60} ROS, such as hydrogen peroxide can directly activate NF-κB by inducing the phosphorylation and degradation of inhibitor of NF-κB (IκB) alpha (Figure 1).\textsuperscript{61} Activated NF-κB participates in tumorigenesis and drug resistance by stimulating the production of growth factors such as signal transducer and activator of transcription 3 (STAT3), transforming growth factor (TGF)-β, VEGF-A, and other pro-inflammatory mediators. Inflammation has also been linked to oncogenic mutations of genes such as p53, cellular myelocytomatosis (c-Myc), and B-cell lymphoma 6 (Bcl6).\textsuperscript{62}
Table 1: Pro-inflammatory markers, signaling pathways, and drug-associated resistance in different types of cancer.

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<th>Pro-inflammatory markers</th>
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TUBB3-together with class III β-tubulin 3; Smad/ID1-mothers against decapentaplegic/inhibitor of differentiation; SHP2-Src-homology 2 domain-containing phosphatase 2; interleukin 10 receptor (IL-10R).

**Few examples of inflammatory markers and their role in tumorigenesis and drug resistance in different types of cancer**

**TNF-α**

TNF-α was first identified in 1975 but was later cloned in 1984. TNF-α was regarded as an anti-tumor endotoxin because at high concentrations it induced necrosis in mice transplanted with methylcholanthrene-induced sarcomas.\(^{83,84}\) The anti-tumor effect of TNF-α is thought to be mediated upon activation of tumor necrosis factor receptor 1. This is because the anti-tumor activity was more pronounced in tumor necrosis factor receptor 2 knockout mice.\(^{85}\) However, a plethora of research is now in support of TNF-α as a pro-tumor. For instance, TNF-α deficient mice exhibited resistance to developing skin carcinogenesis.\(^{86}\) Mice that are deficient in tumor...
necrosis factor receptor 1−/− mice and tumor necrosis factor receptor 2−/− mice displayed a significant reduction in tumor multiplicity when compared to wild-type.\textsuperscript{87} TNF-α exits in two bioactive forms: i) transmembrane TNF-α (tmTNF-α) and secretory TNF-α (sTNF-α). sTNF-α is generated upon cleavage of tmTNF-α by a metalloproteinase TNF-α-converting enzyme. The elevated expression of TNF-α (tmTNF-α and sTNF-α) and its role in cancer development and chemoresistance is well documented.\textsuperscript{63} sTNF-α-induces the expression of inhibitors of apoptosis proteins (IAPs) through tumor necrosis factor receptor (TNFR)/NF-κB signaling pathway. The IAPs such as IAP-1, IAP-2, and XIAP plays a major role in the sTNF-α induced chemoresistance.\textsuperscript{64} Similarly, tmTNF-α increases the expression of IAP-1, x-linked IAP, Bcl-X\textsubscript{L} and decreases the expression of BAX via the TNFR/NF-κB signaling pathway. Additionally, tmTNF-α increases glutathione-s-transferase (GST) levels via TNFR/ERK signaling pathway.\textsuperscript{63}

TNF-α can also potentiate E2-induce ATP-binding cassette super-family G member 2 (ABCG2) expression possibly by activation of NF-κB. The binding of ER and p65 at the neighboring response elements of ABCG2 promoter increases the expression of the ABCG2 mRNA and protein expression significantly. ABCG2 or breast cancer resistant protein is an ABC transporter that plays a major role in anti-cancer drug resistance by an effluxing number of anti-cancer drugs from breast cancer cells.\textsuperscript{32} In another study it was reported that TNF-α induced drug resistance to sorafenib in hepatocellular carcinoma by inducing EMT. EMT correlates with the upregulation of mesenchymal markers such as snail and vimentin, and downregulation of epithelial marker, E-cadherin upon activation of TNFR/NF-κB signaling pathway. TNF-α-induced sorafenib resistance was rescued upon treatment with ulinastatin. Ulinastatin decreases TNF-α levels, thereby sensitizing tumor cells to sorafenib.\textsuperscript{65} Similarly, TNF-α blockade potentiates anti-programmed cell death protein 1 antibody efficacy and improves cluster of differentiation 8+ (CD8+) tumor-infiltrating T lymphocytes (CD8+ TILs) accumulation. Thereby anti-programmed cell death protein 1 antibody inhibits the expression of PD ligand 1, T cell immunoglobulin and mucin-domain containing-3, and activates cell death of CD8+ T cells in experimental melanoma.\textsuperscript{66}

**IL-1β**

IL-1β is a pleiotropic cytokine that is secreted by stromal, immune, and tumor cells in response to NF-κB activation.\textsuperscript{40,68} NF-κB is a transcriptional factor that increases the gene expression of IL-
1β upon activation. In acute inflammation, IL-1β production and secretion are attributed to beneficial effects. While in chronic inflammation, elevated IL-1β promotes tumorigenesis. In tumor cells, the IL-1β is secreted from the macrophages present in the microenvironment. The secreted IL-1β can reinforce the inflammatory signals through autocrine and paracrine actions. Additionally, IL-1β upregulates the EH-domain containing protein 1, a regulator of endocytosis and vesicle trafficking via the IL-IR1/NF-κB signaling pathway. EH-domain containing protein 1 together with class III β-tubulin 3, a microtubule protein inhibits PTEN and results in PI3K/AKT activation. Activated AKT then phosphorylates and activates the downstream effectors such as proline-rich AKT substrate of 40 kDa, glycogen synthase kinase 3β, and forkhead box O 1/3a, via phosphorylation at Thr246, Ser9, and Thr24/Thr32. The activation of these AKT downstream effectors conferred resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor, gefitinib in lung cancer. IL-1β induced cancer stem cells self-renewal and proliferation by stimulating the expression of the B lymphoma Mo-MLV insertion region 1 homolog (Bmi1) and nestin. It also enhanced EMT by downregulation of E-cadherin and upregulation of Zinc Finger E-Box Binding Homeobox 1 (Zeb1), a mesenchymal marker. Furthermore, it was assumed that Zeb1 could increase the expression of Bmi1 through a double-negative feedback loop on Bmi1 repressor, mRNA-200. In addition, the study also demonstrated the involvement of IL-1β in carboplatin resistance in colon cancer which is in part contributed by Zeb1 and Bmi1 overexpression. Similarly, IL-1β increases paclitaxel and doxorubicin resistance in head and neck cancer by upregulation of stem cell genes such as SRY-related HMG-box 2, octamer-binding transcription factor 4, and Nanog via suppressor of mothers against decapentaplegic (SMAD)/inhibitor of differentiation signaling pathway.

Specifically, in MCF-7 cells, IL-1β promoted cancer growth by triggering the IL-1R1/PI3K/AKT signaling pathway. Activated AKT can directly upregulate the expression of the p53-related p63 isoform (ΔNP63α). ΔNP63α increases the expression of wild-type p53-induced phosphatase. In breast cancer, wild-type p53-induced phosphatase participates in drug resistance via inhibition of ataxia telangiectasia mutated, a DNA damage sensor. Additionally, ΔNP63α activates EGFR via phosphorylation at Tyr1068. In turn, the phosphorylated EGFR activates PI3K/AKT and forms a feedback loop that maintains the signal initiated by IL-1β. Apart from ΔNP63α, β-catenin also conferred resistance to doxorubicin by upregulation of baculoviral IAP Repeat Containing 3, an

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https://ps.tbzmed.ac.ir/
inhibitor of caspase enzymes.\textsuperscript{71} Additionally, IL-1\(\beta\) conferred resistance to tamoxifen by upregulation of transcription factor, twist-related protein 1 (TWIST1).\textsuperscript{72} TWIST1 in turn downregulates the ER-\(\alpha\) expression via recruitment of methyltransferases to the promoter region of the ER-\(\alpha\) gene and represses its expression. Consequently, ER-\(\alpha\) downregulation is associated with tamoxifen resistance in breast cancer.\textsuperscript{72} The emergence of IL-1\(\beta\) in cancer made researchers focus on the use of anti-IL-1\(\beta\) for the treatment of cancer. So far, various studies have shown that the use of anti-IL-1\(\beta\) either alone or in combination with other anti-cancer agents has shown promising results. For example, a randomized, double-blind, and placebo-controlled trial by Paul M Ridker \textit{et al.}\textsuperscript{88} showed that the use of canakinumab, an anti-IL-1\(\beta\) antibodies reduced lung cancer incidence and mortality when compared to the placebo-treated group (NCT01327846). The study included 10061 atherosclerotic patients who had a history of myocardial infarction but were free from cancer. Similarly, other studies for non-small cell lung cancer (NCT03626545), Myelodysplastic Syndrome, Chronic Myelomonocytic Leukemia (NCT04239157), and non-small cell lung cancer (NCT03447769) that employ canakinumab are ongoing.

\textit{TGF-\(\beta\)}

Transforming growth factor-beta (TGF-\(\beta\)) is a multifunctional cytokine that belongs to the transforming growth factor superfamily. TGF-\(\beta\) superfamily consists of more than 30 ligands that have been grouped into two distinct branches. One branch includes activin, nodal, lefty, myostatin, TGF-\(\beta\), etc. The other branch includes bone morphogenetic proteins, anti-muellerian hormone, and various growth and differentiation factors. These ligands play a vital role in cell proliferation, lineage determination, ECM production, immune modulation, and apoptosis.\textsuperscript{75,89} TGF-\(\beta\) ligands (TGF-\(\beta\)1, TGF-\(\beta\)2, TGF-\(\beta\)3) have a high affinity for type 2 TGF-\(\beta\) receptors (TGF-\(\beta\)R2) when compared to type 1 TGF-\(\beta\) receptors (TGF-\(\beta\)R1). They activate TGF-\(\beta\)R2 which then dimerize and activate TGF-\(\beta\)R1 via phosphorylation. The activated TGF-\(\beta\)R2/1 activates the downstream signaling through SMAD as well as non-SMAD mediated signaling pathways. The non-SMAD mediated signaling pathways are mediated through mitogen-activated protein kinase (MAPK)-p38, PI3K/AKT, Rho GTPases, NF-\(\kappa\)B, and c-Jun N-terminal kinase (JNK) pathways.\textsuperscript{74}

In tumorigenesis, TGF-\(\beta\) act as a double-edged sword. It functions as a tumor suppressor by inhibiting epithelial cell growth and preventing EMT. TGF-\(\beta\) prevents tumorigenesis through a
SMAD-mediated increase in the expression of tumor suppressor genes such as maspin and MutS Homolog 2 (MSH2). Nevertheless, mutations that lead to loss of function in TGF-β signaling components could lead to inhibition of cell cycle arrest and increases EMT. TGF-β mediated EMT occurs because of its ability to increase the expression of transcription factors such as snail family transcriptional repressor 1/2, TWIST, Zeb1/2, and transcription factor 3. The above-mentioned transcription factors inhibit the markers of epithelial cells and upregulate the markers for mesenchymal cells. The expression of these transcription factors not only participate in tumor induction but also drug resistance. For example, TGF-β-mediated TWIST expression repressed p53 expression and increased the expression of B-cell lymphoma 2 leading to drug resistance in colon cancer. Low expression of p53, in turn, downregulated the MSH2 expression via SMAD/RNA helicase p38 signaling pathway. Consequently, MSH2 downregulation induced resistance in breast cancer cells treated with cisplatin, methyl methanesulfonate, and doxorubicin. The contribution of TGF-β in tumorigenesis and drug resistance in lung and colon cancer is in part regulated by mediator complex subunit 12 (MED12). MED12 is a component of the transcriptional adaptor complex that functions as a molecular bridge between the basal transcription machinery and its upstream activators. MED12 has been reported to regulate TGF-β signaling by suppression of TGF-βR2 protein expression. A modest increase in TGF-βR2 mRNA and robust expression at protein levels upon MED12 knockdown suggests that TGF-βR2 suppression by MED12 occurs at the post-transcriptional stage.

**IL-6**

IL-6 is a pleiotropic cytokine that plays an important role in cell proliferation, transformation, inflammation, and drug resistance. IL-6 is secreted by cells such as monocytes, macrophages, endothelial, and T cells. IL-6 act through interleukin 6 receptor alpha and dimerize with interleukin 6 receptor beta (IL-6Rβ). Dimerization in turn phosphorylates IL-6Rβ-associated kinases such as janus kinase 1 and 2. This further induces the phosphorylation and nuclear translocation of STAT3. STAT3 is a transcription factor and an oncogene. It regulates several genes which control cell proliferation, survival, angiogenesis, immunosuppression, and drug resistance. Recently, it was shown that the disruption of the IL-6/STAT3 signaling pathway by tocilizumab, an anti-IL-6R monoclonal antibody reversed tamoxifen resistance in ER+ in breast cancer.
involvement of IL-6 in drug resistance has also been linked with the induction of multidrug resistance protein 1 (MDR1) gene expression. This occurs via IL-6Rβ phosphorylation and dimerization, resulting in the recruitment of HER2 to the dimerized IL-6Rβ. Clustering of HER2 molecules to the IL-6Rβ complex accelerates the HER kinase activity and activates MAPK. The activated MAPK could activate the nuclear factor for IL-6 (NFIL-6), which then binds and transactivates the MDR1 gene expression. NFIL-6 is a specific regulatory element that is located between −157 and −126 base pairs of the MDR1 promoter region. 3-CCAAT/enhancer-binding protein delta, another transcription factor from NFIL-6 family has also been reported to facilitate NFIL-6-mediated MDR1 gene expression. In line with this, the involvement of IL-6 in the induction of drug resistance has been demonstrated by Zhi shi et al. in breast cancer cells. The study reported that there was an increased expression of IL-6 in multidrug resistance breast cancer cells when compared to multidrug sensitive cells. Interestingly, inhibition of IL-6 by siRNA technology-enhanced drug sensitivity of the breast cancer cells.

**IL-10**

IL-10 is a pleiotropic cytokine that was first discovered in lymphoid and myeloid cells. It was first reported to act as a cytokine synthesis inhibitory factor. Normally, IL-10 propagates its downstream signaling pathway via binding to interleukin 10 receptor 1/2 and acts as an anti-tumor agent. IL-10 is secreted in large amounts by tumor cells and tumor-activated macrophages (TAMs). TAMs are alternative activated-like macrophages that are activated from monocytes and have been widely accepted to play a major role in cancer development via the production of cytokines and chemokines. Mechanistically, TAMs-secreted IL-10, contribute to tumorigenesis by effectively inhibiting the anti-tumor activity of cytotoxic T cells. Furthermore, elevated IL-10 could activate STAT3 which increases the expression of anti-apoptotic protein leading to drug resistance in breast cancer. However, inhibition of IL-10 activity was not so promising because many studies have reported that inhibition of IL-10 activity alone did not halt the tumor growth. For instance, administration of anti-IL-10 receptor antibody had minimal effect on tumor growth. However, co-administration of cytosine-phosphorothioate-guanine, a toll-like receptor 9 agonist reversed the tumor-infiltrating dendritic cells and suppressed the tumor growth.
Crosstalk among ER-α, ER-β and Nrf2 in breast cancer

ER-α and ER-β play a vital role in mammary growth, development, and homeostasis. These are nuclear receptors and exert their activity through genomic and non-genomic pathways. Stimulation of ER-α has been clinically accepted to contribute to breast cancer development and progression. On the other hand, selective activation of ER-β has shown anti-proliferative effects in breast cancer. Several findings have demonstrated the importance of ER-β and its activation for the suppression of breast cancer and several other cancers. The genomic action of ER-β involves the transcription of genes that are involved in the apoptosis and repression of genes that participate in cancer development and progression. For example, upon transfection of MCF7 cells with ER-β there was an increase in the gene expression of cyclin-dependent kinase inhibitor p21 and tumor suppressor genes such as p53 and melanoma differentiation associated gene 7 (MDA7). Additionally, there is a decrease in the expression of oncogenes such as c-myc, cyclin D1, and cyclin A. The activation of ER-β is also involved in the activation of phase II detoxifying enzyme, NADH quinone oxidoreductase 1 (NQO1). NQO1 is an enzyme that helps to detoxify carcinogenic chemicals. Similarly, the non-genomic action of ER-β involves the activation of proteins that prevents cancer progression and the inactivation of proteins that drive cancer events. For example, ER-β agonists activate PTEN and disrupt the PI3K/ATK signaling cascade. ER-β also downregulates the wingless-related integration β-catenin pathway and decreases the tumor invasion and epithelial-mesenchymal transition. ER-β agonist, Erb-041, increases the ER-β expression and decreases COX2 expression. Erb-041 also decreases the phosphoprotein levels of ERK1/2, p38, and IκB. A decrease in p-IκB subsequently cuts the nuclear accumulation of NFκBp65 and decreases the NFκB mediated transcription of pro-inflammatory mediators such as IL-1β, IL-10, inducible nitric oxide synthase, and IL-6. Interestingly, ellagic acid, a selective estrogen receptor modulator was reported to downregulate inflammation via activation of ER-β/Nrf2 signaling cascade in Parkinson's disorder.

Nrf2 and its dual role in cancer

*Nrf2 promote carcinogenesis*
Nrf2 is a nuclear transcription factor that is kept in an inactive state in the cytoplasm by kelch-like ECH-associated protein-1 (keap-1). Nrf2 is made up of seven domains termed Neh1-Neh7, and two terminals called N-terminal and C-terminal. Neh1 is a basic leucine zipper responsible for DNA binding, and heterodimerization with small musculoaponeurotic fibrosarcoma and other transcription factors. Neh2 also known as the N-terminal domain contains two vital motifs, DLG and EGTE, which are responsible for Nrf2 interaction with the Kelch domain of Keap1. Neh3, also known as the C-terminal domain is critical for the ARE-dependent gene transactivation via its interaction with a transcriptional coactivator chromo-ATPase/helicase DNA-binding protein (CHD6). Neh4 and Neh5 are responsible for Nrf2-targeted gene transactivation via their interactions with another transcriptional coactivator, CREB-binding protein. Neh5 regulates Nrf2 cellular localization via a redox-sensitive nuclear-export signal. Neh6, a serine-rich domain, interacts with β-transducin repeat-containing protein via its two motifs (DSGIS and DSAPGS). The binding of β-transducin repeat-containing protein acts as a substrate receptor for ubiquitin ligase complex which mediates Nrf2 proteasomal degradation. The Neh7 domain inhibits the Nrf2-ARE signaling pathway via its interaction with retinoic X receptor α.\textsuperscript{116–118} Under oxidative stress, Nrf2 translocate into the nucleus and activates the transcription of antioxidant and anti-inflammatory genes. Hence, Nrf2/ARE pathways decrease the production of inflammatory cytokines and ROS (Figure 2).\textsuperscript{119–121} The dual role of Nrf2 as a pro-and anti-tumor target remains a matter of concern.\textsuperscript{19,119,122–125} In fact, in the majority of cancers high expression of Nrf2 had been correlated to poor prognosis.\textsuperscript{122,123} Notably, in breast cancer cell lines it was reported that Nrf2 is positively correlated with cancer cell proliferation and metastasis.\textsuperscript{126} Nuclear translocation and overactivity of Nrf2 in breast cancer are driven by dipeptidyl peptidase 3 (DPP3) overexpression. DPP3 interferes with the Keap1-Nrf2 complex formation in ER+ cells by competitively binding to the Keap1’s ETGE motif. Nrf2 is believed to play a significant part in the DPP3 overexpression-related aggressive breast cancer phenotype.\textsuperscript{127} Molecular insight in relation to nuclear translocation of Nrf2 has also been linked with the modification of Cys 288 in Keap1 by 4-OHE2-derived ortho-quinone.\textsuperscript{19} Clinically, the Nrf2 expression is positively correlated with poor overall survival in breast cancer.\textsuperscript{128} The Nrf2 induced drug resistance to tamoxifen is exclusive of ER signaling. Instead, kinases are involved in the activation of Nrf2 via ERK and p38 MAPK-mediated...
phosphorylation. The Nrf2 mediated chemoresistance is in part contributed by p62 and genetic polymorphisms in Keap1 and Nrf2.\(^{130,130}\)

Lou et al.\(^ {131}\) found that the bioactive compounds from *Aastragali radix* which activate the Nrf2 pathway increases the expression of P-glycoprotein and breast cancer resistance protein (BCRP). Similar study was carried out in HepG2 cell lines and mice (wild and Nrf2\(^{-/-}\)) liver tissues. HepG2 inherently expresses high levels of phase I and II enzymes.\(^ {132}\) The use of HepG2 to study the Nrf2-induced P-gp and BCRP transport mechanisms may not be a suitable one to draw a conclusion on the Nrf2 induced drug resistance in cancer.\(^ {132}\) Furthermore, Nrf2 is a known detoxifier and under normal physiological conditions varieties of detoxifiers are induced by Nrf2 including P-gp and BCRP.\(^ {133,134}\) These transporters are important defense mechanisms and critical for the movement of endogenous molecules, nutrients, hormones, and xenobiotics into and out of cells.\(^ {135,136}\) The mechanism of Nrf2 mediated cancer proliferation has been largely linked to the activation of ras homolog family member A/rho associated protein kinase (RhoA/ROCK) pathway. Nrf2 binds to the promoter area of the estrogen related receptor-\(\alpha\) (ERR-\(\alpha\)) and acts as a suppressor. ERR-\(\alpha\) increases the ubiquitination and degradation of RhoA through road-Complex, Tramtrack and Bric a brac/Pox virus, and Zinc finger domain-containing adapter for Cullin3-mediated RhoA degradation 2 regulation.\(^ {126}\) MCF-7 and MDA-MB-231 breast cancer cells had significantly higher levels of Nrf2 and HIF-\(\alpha\) expression compared to benign breast tumor cells. Nrf2 inhibition slowed the proliferation of MCF7 and MBA-DA-231 breast cancer cells. Here, the proliferative action of Nrf2 in breast cancer was mechanistically linked to the expression of genes involved in the glycolytic pathway. Nrf2 could activate PI3K thereby leading to HIF-\(\alpha\) over-expression one of the key proteins that increase glycolysis.\(^ {128}\) Equally, Nrf2 can also be activated by PI3K in mammary epithelial cells (MECs) setting up a positive loop.\(^ {137}\)

**Nrf2 prevent carcinogenesis**

Numerous studies on breast cancer also illustrated the positive association between Nrf2 expression and survival in ER\(^{+}\) and ER\(^{-}\) breast tumors.\(^ {128,138}\) Improvement in the overall survival rate, disease-specific survival, and disease-free survival are significantly coupled with high Nrf2 expression in ER\(^{+}/HER2^{-}\) breast cancer patients. However, a significant difference was not detected between high and low Nrf2 expression in triple-negative breast cancer patients.\(^ {139}\) Many
studies have also confirmed the beneficial effects of Nrf2 activation in breast cancer.\textsuperscript{20,140,141} In mammary stem cells, the loss of Nrf2 correlates with the overexpression of long non-coding RNA (lncRNA) which is a regulator of reprogramming (lncRNA ROR).\textsuperscript{142} lncRNAs are short RNAs and non-protein coding transcripts with more than 200 nucleotides. They are tissue-specific and independently transcribed. lncRNAs participate in epigenetic, transcriptional, and post-transcriptional regulation of gene expression. Aberrant expression of this gene had been shown to associate with tumor formation and metastasis in various cancers including breast cancer.\textsuperscript{143,144} Recent studies have shown that lncRNA promotes breast cancer by recruitment of mixed lineage leukemia 1 (MLL1) which is a transmethylase enzyme. MLL1 promotes histone 3 lysine 4 methylation and enhances the transcription of tissue inhibitors of metalloproteinase 3 (TIMP3).\textsuperscript{143} TIMP3 is one of the epigenetic markers for BRCA1 breast cancer therapy.\textsuperscript{145} In relation to this, Nrf2 has been reported to silence the expression lncRNA ROR by promoting the trimethylation of histone 3 lysine 27 (H3K27). H3K27 trimethylation prevents mammary stem cell expansion and self-renewal property. Additionally, trimethylation of H3K27 protects the mammary cells against the genotoxic and carcinogenic effects of estrogen metabolites.\textsuperscript{142,146,147}

Recently, it was shown that the dysregulation of the Nrf2-UDP Glucuronosyltransferase Family 1 Member A8 (UGT1A8) axis is a key determinant in the pathophysiology of breast cancer. UGT1A8 is a phase II enzyme and is one of the most dominant isoforms of UDP-glucuronosyltransferase which is responsible for the metabolism of estrogens. UGT1A8 is widely expressed in the liver and participates in hepatic glucuronidation. UGT1A8 was also reported to express in breast and uterine tissues.\textsuperscript{148} In breast tissue, UGT1A8 was present in the cytoplasm of epithelial cells while in the uterus it is present in endometrial glands and stromal cells.\textsuperscript{149} UGT1A8 catalyzes the covalent addition of glucuronic acid to estrogens and its metabolites such as 4-OHE2 and 4-hydroxyestradiol 1 (4-OHE1).\textsuperscript{148–150} Thus, preventing the carcinogenic activity of estrogens. Mutations in UGT1A8 reduce its enzymatic activity and lead to breast cancer development.\textsuperscript{149} 7,12-dimethylbenz[a]anthracene-induced breast cancer animal model shows a significant decrease in the mRNA and protein expressions of UGT1A8. Whereas, activation of Nrf2 rescued the 7,12-dimethylbenz[a]anthracene-induced UGT1A8 downregulation.\textsuperscript{148} In female August Copenhagen Irish (ACI) rats, Nrf2 protects against E2-induced DNA damage and breast initiation by upregulation of 8-Oxoguanine DNA glycosylase (OGG1), an enzyme belonging to the base
excision repair pathway. OGG1 is specific for the removal of 8-OHdG, a metabolite of E2 which is responsible for the formation of DNA adducts. In E2-induced breast cancer, OGG1 hydrolyses the 8-OHdG glycosidic bond, which is followed by the cleavage of the phosphodiester bond leaving an activator protein 1 site. This results in nucleotide pairing by DNA polymerase. Activation of Nrf2 prevents E2-induced DNA damage and breast carcinogenesis by decreasing the expression of miR-93. MiR-93 epigenetically inhibits Nrf2 expression.

Furthermore, Nrf2 has been reported to suppress numerous pro-inflammatory markers such as COX2, TNF-α, inducible nitric oxide synthase, and IL-1β possibly via inhibition of ROS-mediated NF-κB activation. Certain pro-inflammatory mediators can also activate NF-κB nuclear translocation suggesting positive feedback. The anti-inflammatory mechanism of Nrf2 other than that of a redox pathway has been recently unveiled. Nrf2 had shown to directly interfere with the transcriptional activity of pro-inflammatory cytokines via inhibiting the binding of RNA polymerase II to the transcriptional starting sites. This repressing activity of Nrf2 on pro-inflammatory cytokines in turn inhibits their stimulatory effect on the expression of the aromatase enzyme. The significant role of Nrf2 activation against cancer can also be attributed to the fact that its expression is under the regulation of BRCA1, a tumor suppressor gene. Studies on various cell lines representing prostate and breast cancer have demonstrated that BRCA1 elicits its anticancer activity via Nrf2 dependent pathway. Consistently, increased BRCA1 expression correlates with the increased expression of Nrf2 and Nrf2/ARE-driven genes such as GST and NQO1.

**Mechanism of Nrf2 inhibition by ER-α**

Nrf2 regulated enzymes such as superoxide dismutase 3 (SOD3), NQO1, GST, UDP glucuronosyl transferases (UGTs), sulfotransferases, and 8-oxoguanine DNA glycosylase (OGG-1) are considered to be defensive against carcinogenesis. These enzymes participate in the metabolism of carcinogens, removal of ROS, and repair of damaged DNA. Hence, these enzymes reduce the tendency of tissue to develop disease or malignancy. Nrf2 has been reported to elicit cytoprotection against procarcinogenic substances by enhancing the transcription of genes such as NQO1 and heme oxygenase-1 (HO-1) in HEK293 cells. Estrogen-mediated activation of ER-α down-regulates phase II enzymes such as NQO1. Transcriptional repression occurs at the
NQO1 promoter region through the ER-α mediated recruitment of class III histone deacetylase, sirtuin 1 (SIRT1). NQO1 is one of the important enzymes that is responsible for the protective role of Nrf2 against cancer. The ability of NQO1 to exert chemoprotective is attributed to its enzymatic activity. For instance, NQO1 catalyzes the carcinogenic catechol metabolites back to catechol estrogens.

Downregulation of phase II enzymes by ER-α enhances cellular DNA damage and could be one of the reasons for cancer development in estrogen-responsive tissues. The reduction in phase II enzyme as a result of estrogen occurs because Nrf2 expression and transcription activity is repressed by estrogen liganded ER-α mechanisms. Activation of ER-α could repress Nrf2 activity through increasing Keap1. Keap1 is a substrate adapter protein that is involved in the proteasomal degradation of Nrf2. The second potential mechanism is through direct competition for overlapping DNA binding sites. The third mechanism is through direct interaction of ER-α with Nrf2 leading to repression of ARE signaling. The fourth mechanism could be by interfering with the recruitment of p300 and histone acetylation at Nrf2 target genes (Figure 3). In some cases, just like ER-β, selective activation of ER-α has also been reported to increase Nrf2 expression and activity. Importantly, activation and inhibition of ER-α and the regulation of Nrf2 by ER-α seem to be cell-, tissue-, and disease-dependent. For example, silibinin up-regulated ER-α expression and activated the Nrf2/HO-1 pathway in INS-1 cells but decreased ER-α expression in MCF-7 cells. In addition to ER-α, estrogen-related receptor beta, an orphan nuclear receptor that shares a high degree of amino acid sequences with ER-α has also been reported to be a potent inhibitor of Nrf2.

**Mechanism of Nrf2 activation by ER-β**

The involvement of ER-β and Nrf2 in the prevention of breast cancer, and the role of ER-α in dampening Nrf2 activity suggests that a complex but very different interplay exists among these biological targets. Studies, like in the case of Parkinson’s disease, have demonstrated that selective estrogen receptor modulators are involved in the upregulation of Nrf2 expression and activity. In another study where endothelial cells were used, treatment of endothelial cells with ER-β agonist increased the Nrf2 targeted genes and Nrf2 nuclear accumulation. While a study by Jing-Ru Weng *et al.* demonstrated that test ligand OSU-A9 exhibited anti-cancer activity in breast...
cancer cell lines. The OSU-A9 prevented the growth of cancer cells due to the increase in the expression of ER-β and Nrf2. Other than the activation of ER-β, the presence of its interacting protein, the human homolog of xenopus gene which prevents mitotic catastrophe is another critical aspect for the recruitment of transcription factors such as poly (ADP-ribose) polymerase 1, topoisomerase IIβ and steroid receptor coactivator 1. While in the case of Nrf2, recruitment of transcription factors occurs even in the absence of ER-β and human homolog of xenopus gene which prevents mitotic catastrophe.\(^{170}\)

To the best of our knowledge, there is no reported mechanism of ER-β mediated Nrf2 activation. Yet, ER-β and Nrf2 could be linked via ER-α. Studies have demonstrated that ER-β act as a repressor of ER-α. ER-β represses the transcription of ER-α. Mechanistically, ER-β binds to non-classical (activator protein 1 and specific protein 1) and classical estrogen response element motifs, (Figure 4) of ER-α\(^{171}\) and decreases the expression of breast-cancer associated gene 2 (BCA2), a downstream effector of ER-α. BCA2 is associated with enhanced cell proliferation and breast cancer promotion by degradation of p21. Additionally, BCA2 leads to inhibition of epidermal growth factors via disruption of cellular endocytosis and lysosomal pathways.\(^{172}\) At the transcriptional level activation of ER-β represses ER-α expression through downregulation of ER-α promoter activity.\(^{103,171}\) In line with this, dietary tocopherols that are thought to be ER-β agonists are also involved in the downregulation of ER-α expression (both at the protein and mRNA levels). Whereas, dietary tocopherols increased the expression of ER-β, peroxisome proliferator-activated receptor γ (PPARγ), Nrf2, and its targeted genes, leading to suppression of inflammatory markers.\(^{173}\) ER-α downregulation occurs through protein-protein interaction of ER-β with ER-α promoter regions.\(^{103,171}\) This event is accompanied by recruitment of nuclear receptor corepressor 1/silencing mediator for retinoid or thyroid-hormone receptors (a corepressor complex) followed by histone H4 hypoacetylation and RNA polymerase II displacement.\(^{103}\) Hence, from these studies, we postulate that ER-β might modulate Nrf2 by inhibition of ER-α. Apart from this hypothesis, there seems to exist a positive feedback loop between Nrf2 and ER-β. Importantly, Nrf2 seems to exert its anti-inflammatory activity in mouse embryonic fibroblasts by binding to ARE of ER-β and directly regulating its expression. The study shows that ER-β expression was wholly eliminated in the Nrf2 knockout mouse. While ER-β expression was observed in wild-type mice.\(^{174}\) Notably, some drugs and in some cases, Nrf2 activator alone was unable to activate Nrf2 but co-
administration of Nrf2 activator with ER-β agonist result in the activation of Nrf2.\textsuperscript{175} Apart from the above postulation, Nrf2 expression and activity are also under the regulation of the aryl hydrocarbon receptor.\textsuperscript{158}

**Conclusions**

Inflammation is one of the vital factors in the development and progression of breast cancer. Recently, many studies have shown that inflammation is also responsible for the development of chemoresistance in cancer. Hence, finding treatment strategies that can successfully overcome inflammation-related chemoresistance is essential. E2 plays an important role in breast cancer carcinogenesis through the production of reactive quinones, and through the activation of genomic and non-genomic pathways. Selective activation of ER-β has been reported to oppose the carcinogenic effects of ER-α in breast cancer. The activation of ER-β offers an advantage in breast cancer because of its ability to modify the expression of genes that are involved in cancer progression. ER-β increases the expression of genes such as p53, p21, and PTEN that are involved in the suppression of cell growth and division. Additionally, ER-β also decreases the genes such as c-myc, cyclins D1 and A, and PI3K that are involved in cancer growth and development. Most importantly, ER-β can reduce the harmful effects of E2 through suppressing the expression of ER-α. Nrf2’s role in various cancers is debatable. However, several pieces of evidence suggest that it can have a protective role against breast cancer. Further investigations are essential to understand the role of Nrf2 in various cancers. The findings in this review underline the critical role of inflammation in breast cancer, and the therapeutic importance of employing ER-β agonist for the treatment of breast cancer. The beneficial effects of ER-β’s activity in breast cancer could be extended to the modulation of Nrf2. Here, we conclude that further preclinical studies are required to measure the possibility of Nrf2 modulation through selective activation of ER-β in breast cancer and overcome drug resistance.

**Conflicts of interest**

The authors declare that the content in this article have no conflict of interest.

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**Author contributions**

Emdormi initiated the conception and design, data collection, wrote the whole manuscript, and prepared the whole manuscript. Deepa contributed to data collection and manuscript preparation. Divakar, Jubie, and Ram contributed to manuscript suggestions and corrections. Divakar also contributed to proofreading the whole manuscript. All the authors approved the final manuscript for submission and publication.

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Figure legends
Figure 1: Complex interplay of NF-κB, pro-inflammatory markers, and estrogen in the initiation of breast cancer and drug resistance in obese individuals.
Figure 2: Classical mechanism of Nrf2 degradation under basal condition and action under stressed condition.
Figure 3: Proposed mechanism for ER-α inhibition on Nrf2 activity.
Figure 4: Proposed mechanism for ER-β modulation of Nrf2 via the inhibition of ER-α.