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Review Article

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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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.

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,

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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 development[23] 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.[10] 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.[23–32] Few examples of drug resistance caused by inflammation are doxorubicin, docetaxel, trastuzumab, and mitoxantrone in breast cancer,[24–27,30] and bicalutamide in prostate cancer.[29] 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[41] in both mammary and visceral fats.[42] Inflammation in these areas is determined by the presence of macrophages forming crown-like structures that can infiltrate necrotic adipose tissues.[42-44] Necrosis occurs in adipose tissues at least in part due to hypoxia during adipocytes hypertrophy.[45] Hypertrophic adipocytes undergo elevated lipolysis leading to an increase in the release of free fatty acids.[46] Free fatty acids along with Fetuin-A, activate toll-like receptors in macrophages causing nuclear factor kappa B (NF-κB) activation.[47] 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[48,49] and other genes that participates in cancer initiation and drug resistance.[42,43]

Aromatase enzyme increases the estrogen biosynthesis and increases the growth of ER^+ breast cancer[41] by directly acting on ER-α and/or via generation of ROS through its metabolites.[16–22] 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.[50] 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).[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.[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.[53] Interestingly, according to Okoh *et al.*[54] the activation of the PI3K/AKT pathway seems to be dependent on ROS such as superoxide anion ($O_2^{\cdot-}$), 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.[54] 4-OHE2 is further metabolized to semiquinone and quinone derivatives which could combine with adenine and guanine nucleotides to form DNA adducts.[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.[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.[57,58] Additionally, ROS can repress tumor suppressor genes and upregulate cancer-promoting genes. One such gene codes for a protein NF-κB,[59] a transcription factor that increases the transcription of various genes that participate in inflammation, cell survival, proliferation, and metastasis.[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).[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).[62]

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

Table 1. Pro-inflammatory markers, signaling pathways, and drug-associated resistance in different types of cancer.

Pro-inflammatory markers	Signaling pathway	Drug-associated resistance	Cancer type	Ref.
TNF-α	TNFR/ERK and TNFR/NF-κB	Doxorubicin	Breast cancer	63
TNF-α	TNFR/NF-κB	Cisplatin	Pleural mesothelioma	64
TNF-α	TNFR/NF-κB	Sorafenib	Liver cancer	65
TNF-α	TNFR/TIM-3	Anti-PD-1 antibodies	Skin, lung, and breast cancer	66
IL-1β	IL-1R/NF-κB/EDH1 and TUBB3	Gefitinib	Lung cancer	67
IL-1β	IL-1β/Zeb1/Bmi1	Carboplatin	Colon cancer	68
IL-1β	Smad/ID1	Paclitaxel and Doxorubicin	Head and neck, skin cancer	69
IL-1β	ER-α	4-hydroxytamoxifen	Prostate cancer	29
IL-1β	IL-1R/ABCG2 (↑)	Mitoxantrone	Breast cancer	30
IL-1β	IL-1R1/PI3K/AKT/β-catenin	Cisplatin	Breast cancer	70
IL-1β	IL-1R1/PI3K/AKT/β-catenin	Doxorubicin	Breast cancer	71
IL-1β	IL-1R1/PI3K/AKT/β-catenin	Tamoxifen	Breast cancer	72
TGF-β	-	Epirubicin	Breast cancer	73
TGF-β	-	Oxaliplatin, cisplatin, 5-FU	Colon cancer	74
TGF-β	TGF-βR/SMAD/p38	Cisplatin, methyl methanesulfonate and doxorubicin	Breast cancer	75
TGF-β	TGF-βR/SMAD/MEK/ERK	Sorafenib	Lung and colon cancer	76
IL-6	IL-6R/STAT3/AKT/NF-κB	Trastuzumab	Breast cancer	25
IL-6	-	Doxorubicin	Breast cancer	26
IL-6	IL-6R/STAT3	5-Fluorouracil	Gastric cancer	77
IL-6	IL-6R/STAT3	Tamoxifen	Breast cancer	78
IL-6	-	*cis*-diaminedihloroplatinum and etoposide	Prostate cancer	79
IL-6	IL-6R/SHP2/PI3K/AKT	Dexamethasone	Myeloma cancer	80
IL-6	-	Cisplastin	Esophageal cancer	81
IL-10	IL-10R/STAT3/Bcl2	Paclitaxel	Breast cancer	82

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).

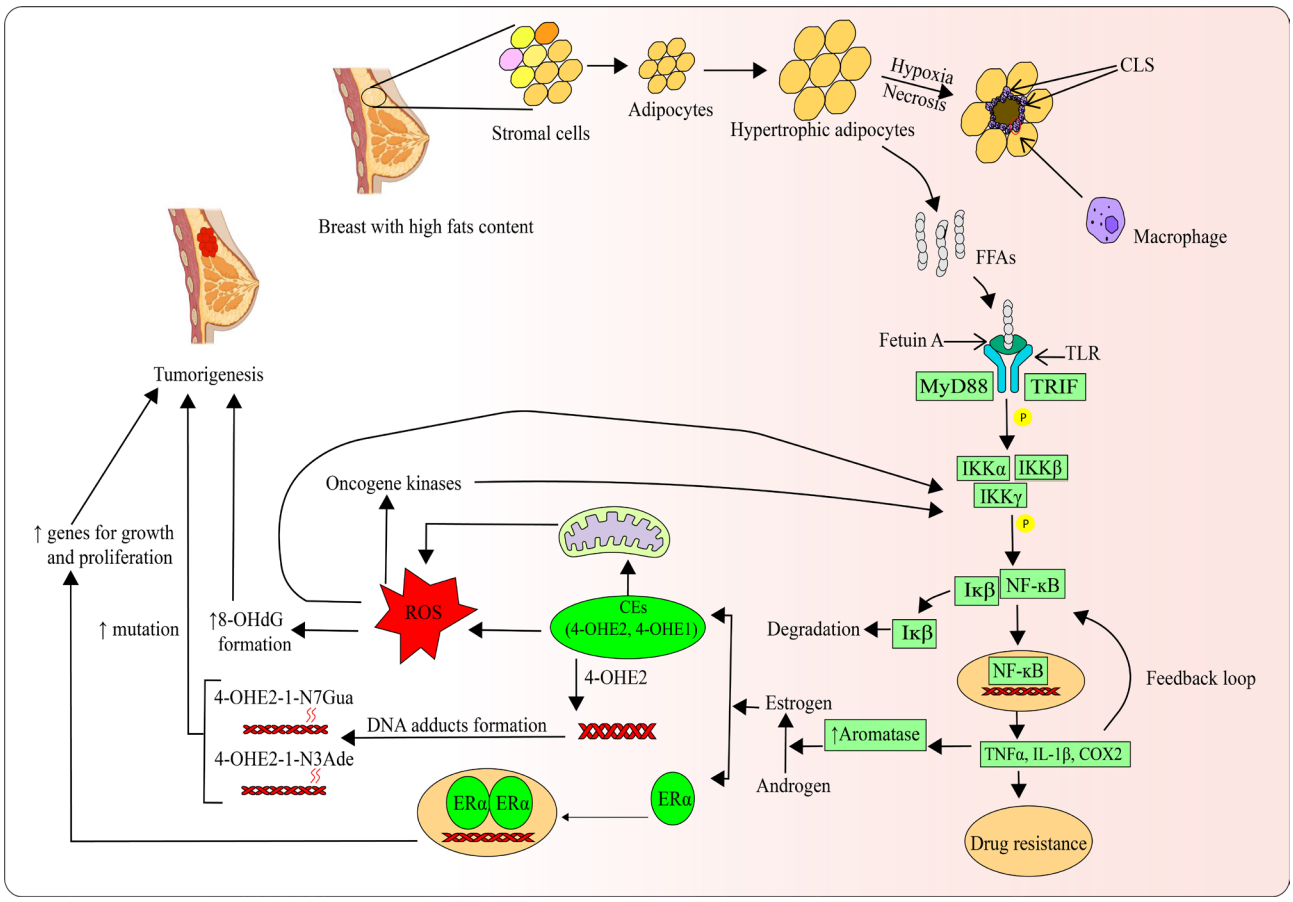

Figure 1. Complex interplay of NF-κB, pro-inflammatory markers, and estrogen in the initiation of breast cancer and drug resistance in obese individuals.

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.[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.[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.[64] Similarly, tmTNF-α increases the expression of IAP-1, x-linked IAP, Bcl-X_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.[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.[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.[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.[66]

IL-1β

IL-1β is a pleiotropic cytokine that is secreted by stromal, immune, and tumor cells in response to NF-κB activation.[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.[40] 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.[67] 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.[68] 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.[69]

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.[70] Apart from ΔNP63α, β-catenin also conferred resistance to doxorubicin by upregulation of baculoviral IAP Repeat Containing 3, an inhibitor of caspase enzymes.[71] Additionally, IL-1β conferred resistance to tamoxifen by upregulation of transcription factor, twist-related protein 1 (TWIST1).[72] TWIST1 in turn downregulates the ER-α expression via recruitment of methyltransferases to the promoter region of the ER-α gene and represses its expression. Consequently, ER-α downregulation is associated with tamoxifen resistance in breast cancer.[72] The emergence of IL-1β in cancer made researchers focus on the use of anti-IL-1β for the treatment of cancer. So far, various studies have shown that the use of anti-IL-1β 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 Ridker *et al.*[88] showed that the use of canakinumab, an anti-IL-1β 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.

TGF-β

Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that belongs to the transforming growth factor superfamily. TGF-β superfamily consists of more than 30 ligands that have been grouped into two distinct branches. One branch includes activin, nodal, lefty, myostatin, TGF-β, 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.[75,89] TGF-β ligands (TGF-β1, TGF-β2, TGF-β3) have a high affinity for type 2 TGF-β receptors (TGF-βR2) when compared to type 1 TGF-β receptors (TGF-βR1). They activate TGF-βR2 which then dimerize and activate TGF-βR1 via phosphorylation. The activated TGF-βR2/1 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-κB, and c-Jun N-terminal kinase (JNK) pathways.[74]

In tumorigenesis, TGF-β act as a double-edged sword. It functions as a tumor suppressor by inhibiting epithelial cell growth and preventing EMT. TGF-β prevents tumorigenesis through a SMAD-mediated increase in the expression of tumor suppressor genes such as maspin and MutS Homolog 2 (MSH2).[75,90] Nevertheless, mutations that lead to loss of function in TGF-β signaling components could lead to inhibition of cell cycle arrest and increases EMT.[73] 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.[74] 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.[74] Low expression of p53, in turn, downregulated the MSH2 espression via SMAD/RNA helicase p38 signaling pathway. Consequently, MSH2 downregulation induced resistance in breast cancer cells treated with cisplatin, methyl methanesulfonate, and doxorubicin.[75,91] 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.[76]

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.[26] STAT3 is a transcription factor and an oncogene. It regulates several genes which control cell proliferation, survival, angiogenesis, immunosuppression, and drug resistance.[26,92–94] 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.[78] The involvement of IL-6 in drug resistance has also been linked with the induction of multidrug resistance protein 1 (MDR1) gene expression.[26] 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.[95] The activated MAPK could activate the nuclear factor for IL-6 (NFIL-6), which then binds and transactivate 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.[26] In line with this, the involvement of IL-6 in the induction of drug resistance has been demonstrated by Shi *et al.*[31] 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.[31]

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.[96,97] 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.[82,98,99] 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.[82] 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.[100–102] 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.[102]

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.[103] Stimulation of ER-α has been clinically accepted to contribute to breast cancer development and progression.[14,15] 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[104–107] and several other cancers.[108,109] 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).[110] Additionally, there is a decrease in the expression of oncogenes such as c-myc, cyclin D1, and cyclin A.[111] 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.[112] 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.[113] ER-β also downregulates the wingless-related integration β-catenin pathway and decreases the tumor invasion and epithelial-mesenchymal transition.[108] 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.[108,109] 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.[114,115]

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.[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).[119–121] The dual role of Nrf2 as a pro-and anti-tumor target remains a matter of concern.[19,119,122–125] In fact, in the majority of cancers high expression of Nrf2 had been correlated to poor prognosis.[122,123] Notably, in breast cancer cell lines it was reported that Nrf2 is positively correlated with cancer cell proliferation and metastasis.[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.[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.[19] Clinically, the Nrf2 expression is positively correlated with poor overall survival in breast cancer.[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.[129] The Nrf2 mediated chemoresistance is in part contributed by p62 and genetic polymorphisms in Keap1 and Nrf2.[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-α (ERR-α) and acts as a suppressor. ERR-α 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-α 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-α 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.

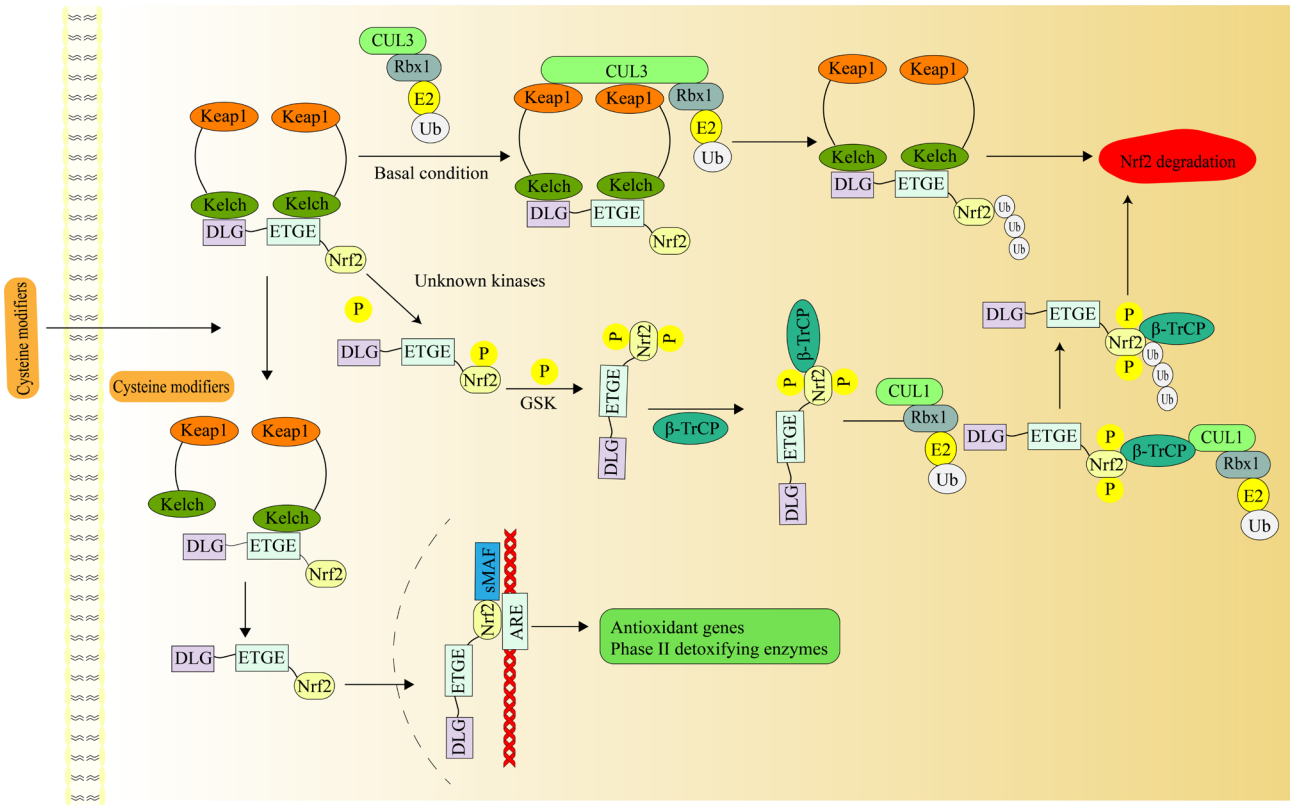

Figure 2. Classical mechanism of Nrf2 degradation under basal condition and action under stressed condition.

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.[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).[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.[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).[143] TIMP3 is one of the epigenetic markers for BRCA1 breast cancer therapy.[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.[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.[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.[149] UGT1A8 catalyzes the covalent addition of glucuronic acid to estrogens and its metabolites such as 4-OHE2 and 4-hydroxyestradiol 1 (4-OHE1).[148–150] Thus, preventing the carcinogenic activity of estrogens. Mutations in UGT1A8 reduce its enzymatic activity and lead to breast cancer development.[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.[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.[20] Activation of Nrf2 prevents E2-induced

DNA damage and breast carcinogenesis by decreasing the expression of miR-93. MiR-93 epigenetically inhibits Nrf2 expression.[21,22]

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.[151–154] Certain pro-inflammatory mediators can also activate NF-κB nuclear translocation suggesting positive feedback.[151] 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.[155] This repressing activity of Nrf2 on pro-inflammatory cytokines in turn inhibits their stimulatory effect on the expression of the aromatase enzyme.[156] 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.[120,157,158]

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.[146] 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.[121] Estrogen-mediated activation of ER-α down-regulates phase II enzymes[159,160] 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).[17] 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.[161]

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.[17,159,160] 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.[160] 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.[160] The second potential mechanism is through direct competition for overlapping DNA binding sites.[160] The third mechanism is through direct interaction of ER-α with Nrf2 leading to repression of ARE signaling.[17,160] The fourth mechanism could be by interfering with the recruitment of p300 and histone acetylation at Nrf2 target genes (Figure 3).[162] In some cases, just like ER-β, selective activation of ER-α has also been reported to increase Nrf2 expression and activity.[163,164] Importantly, activation and inhibition of ER-α and the regulation of Nrf2 by ER-α seem to be cell-,

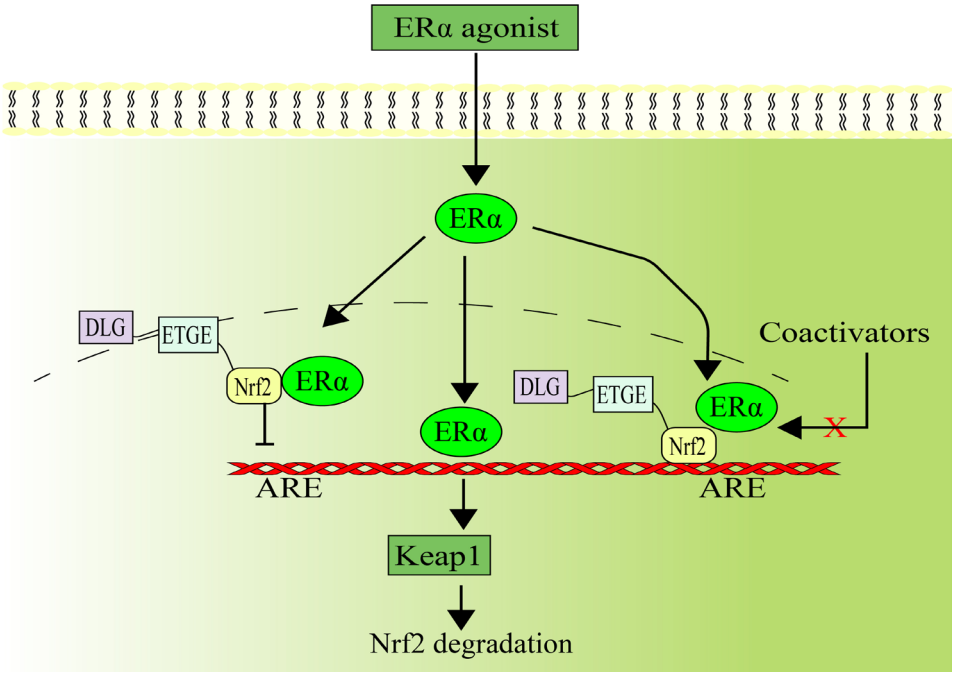

Figure 3. Proposed mechanism for ER-α inhibition on Nrf2 activity.

tissue-, and disease-dependent.[165,166] 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.[165] 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.[167]

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.[115] 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.[168] While a study by Weng *et al.*[169] 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

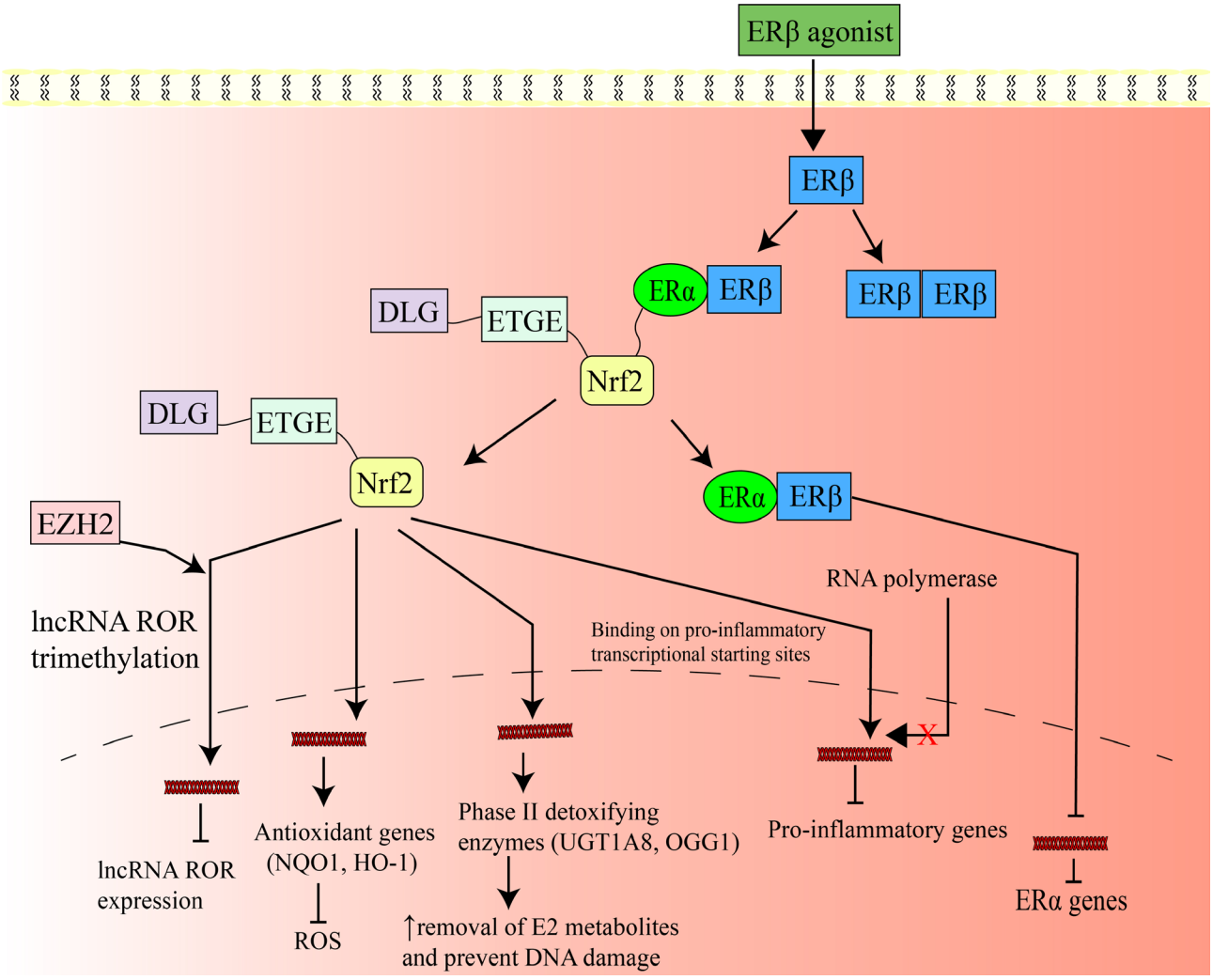

Figure 4. Proposed mechanism for ER-β modulation of Nrf2 via the inhibition of ER-α.

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.[175] Apart from the above postulation, Nrf2 expression and activity are also under the regulation of the aryl hydrocarbon receptor.[158]

Conclusion

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.

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Author Contributions

ER initiated the conception and design, data collection, wrote the whole manuscript, and prepared the whole manuscript. DS[1] contributed to data collection and manuscript preparation. DS[2], JS, and RK contributed to manuscript suggestions and corrections. DS[2] also contributed to proofreading the whole manuscript. All the authors approved the final manuscript for submission and publication.

Conflict of Interest

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

References

1. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global cancer in women: Burden and trends. Cancer Epidemiol Biomarkers Prev. 2017;26(4):444-57. doi:10.1158/1055-9965.EPI-16-0858
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. doi:10.3322/caac.21660
3. Gyamfi J, Eom M, Koo JS, Choi J. Multifaceted Roles of Interleukin-6 in Adipocyte–Breast Cancer Cell Interaction. Transl Oncol. 2018;11(2):275-85. doi:10.1016/j.tranon.2017.12.009
4. Kondov B, Milenkovikj Z, Kondov G, Petrushevska G, Basheska N, Bogdanovska-Todorovska M, et al. Presentation of the molecular subtypes of breast cancer detected by immunohistochemistry in surgically treated patients. Open Access Maced J Med Sci. 2018;6(6):961-67. doi:10.3889/oamjms.2018.231
5. Provenzano E, Ulaner GA, Chin SF. Molecular Classification of Breast Cancer. PET Clin.

2018;13(3):325-38. doi:10.1016/j.cpet.2018.02.004
6. Martin AM, Weber BL. Genetic and hormonal risk factors in breast cancer. J Natl Cancer Inst. 2000;92(14):1126-35. doi:10.1093/jnci/92.14.1126
7. Dieterich M, Stubert J, Reimer T, Erickson N, Berling A. Influence of lifestyle factors on breast cancer risk. Breast Care. 2014;9(6):407-14. doi:10.1159/000369571
8. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018;5(2):77-106. doi:10.1016/j.gendis.2018.05.001
9. Tao ZQ, Shi A, Lu C, Song T, Zhang Z, Zhao J. Breast Cancer: Epidemiology and Etiology. Cell Biochem Biophys. 2015;72(2):333-8. doi:10.1007/s12013-014-0459-6
10. Balkwill F, Mantovani A. Inflammation and cancer: Back to Virchow? Lancet. 2001;357(9255):539-45. doi:10.1016/S0140-6736(00)04046-0
11. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. Mol Cancer Res. 2006;4(4):221-33. doi:10.1158/1541-7786.MCR-05-0261
12. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: Crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer. 2013;13(11):759-71. doi:10.1038/nrc3611
13. Esquivel-Velázquez M, Ostoa-Saloma P, Palacios-Arreola MI, Nava-Castro KE, Castro JI, Morales-Montor J. The role of cytokines in breast cancer development and progression. J Interf Cytokine Res. 2015;35(1):1-16. doi:10.1089/jir.2014.0026
14. Nilsson S, Gustafsson J-Å. Estrogen receptor transcription and transactivation Basic aspects of estrogen action. Breast Cancer Res. 2000;2(5):360-6. doi:10.1186/bcr81
15. Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR. Immunohistochemistry of Estrogen and Progesterone Receptors Reconsidered. Am J Clin Pathol. 2005;123(1):21-7. doi:10.1309/4wv79n2ghj3x1841
16. Musarrat J, Arezina-Wilson J, Wani AA. Prognostic and aetiological relevance of 8-hydroxyguanosine in human breast carcinogenesis. Eur J Cancer Part A. 1996;32(7):1209-14. doi:10.1016/0959-8049(96)00031-7
17. Yao Y, Brodie AMH, Davidson NE, Kensler TW, Zhou Q. Inhibition of estrogen signaling activates the NRF2 pathway in breast cancer. Breast Cancer Res Treat. 2010;124(2):585-91. doi:10.1007/s10549-010-1023-8
18. Karihtala P, Kauppila S, Soini Y, Arja-Jukkola-Vuorinen. Oxidative stress and counteracting mechanisms in hormone receptor positive, triple-negative and basal-like breast carcinomas. BMC Cancer. 2011;11:262. doi:10.1186/1471-2407-11-262
19. Park S-A, Lee M-H, Na H-K, Surh Y-J. 4-Hydroxyestradiol induces mammary epithelial cell transformation through Nrf2-mediated heme oxygenase-1 overexpression. Oncotarget. 2019;10(12):1266. doi:10.18632/oncotarget.26681
20. Singh B, Chatterjee A, Ronghe AM, Bhat NK, Bhat HK. Antioxidant-mediated up-regulation of OGG1 via NRF2 induction is associated with inhibition of oxidative DNA damage in estrogen-induced breast cancer. BMC Cancer. 2013;13:253. doi:10.1186/1471-2407-13-253
21. Singh B, Shoulson R, Chatterjee A, Ronghe A, Bhat NK, Dim DC, et al. Resveratrol inhibits estrogen-induced breast carcinogenesis through induction of NRF2-mediated protective pathways. Carcinogenesis. 2014;35(8):1872-80. doi:10.1093/carcin/bgu120
22. Singh B, Ronghe AM, Chatterjee A, Bhat NK, Bhat HK. MicroRNA-93 regulates NRF2 expression and is associated with breast carcinogenesis. Carcinogenesis. 2013;34(5):1165-72. doi:10.1093/carcin/bgt026
23. Ranneh Y, Ali F, Akim AM, Hamid HA, Khazaai H, Fadel A. Crosstalk between reactive oxygen species and pro-inflammatory markers in developing various chronic diseases: a review. Appl Biol Chem. 2017;60(3):327-38. doi:10.1007/s13765-017-0285-9
24. Deshmukh SK, Srivastava SK, Zubair H, Bhardwaj A, Tyagi N, Al-Ghadhban A, et al. Resistin potentiates chemoresistance and stemness of breast cancer cells: Implications for racially disparate therapeutic outcomes. Cancer Lett. 2017;396:21-9. doi:10.1016/j.canlet.2017.03.010
25. Korkaya H, Kim G Il, Davis A, Malik F, Henry NL, Ithimakin S, et al. Activation of an IL6 inflammatory loop mediates trastuzumab resistance in HER2+ breast cancer by expanding the cancer stem cell population. Mol Cell. 2012;47(4):570-84. doi:10.1016/j.molcel.2012.06.014
26. Conze D, Weiss L, Regen PS, Rincón M, Weaver D, Bhushan A, et al. Autocrine production of interleukin 6 causes multidrug resistance in breast cancer cells. Cancer Res. 2001;61(24):8851-8.
27. Shao N, Chen LH, Ye RY, Lin Y, Wang SM. The depletion of Interleukin-8 causes cell cycle arrest and increases the efficacy of docetaxel in breast cancer cells. Biochem Biophys Res Commun. 2013;431(3):535-41. doi:10.1016/j.bbrc.2013.01.022
28. Teicher BA. Malignant cells, directors of the malignant process: Role of transforming growth factor-beta. Cancer Metastasis Rev. 2001;20(1-2):133-43. doi:10.1023/A:1013177011767
29. Zhu P, Baek SH, Bourk EM, Ohgi KA, Garcia-Bassets I, Sanjo H, et al. Macrophage/cancer cell interactions mediate hormone resistance by a nuclear receptor derepression pathway. Cell. 2006;124(3):615-29. doi:10.1016/j.cell.2005.12.032
30. Mosaffa F, Lage H, Afshari JT, Behravan J. Interleukin-1 beta and tumor necrosis factor-alpha increase ABCG2 expression in MCF-7 breast carcinoma cell line and its mitoxantrone-resistant derivative, MCF-7/MX. Inflamm Res. 2009;58(10):669-76. doi:10.1007/

s00011-009-0034-6
31. Shi Z, Yang WM, Chen LP, Yang DH, Zhou Q, Zhu J, et al. Enhanced chemosensitization in multidrug-resistant human breast cancer cells by inhibition of IL-6 and IL-8 production. Breast Cancer Res Treat. 2012;135(3):737-47. doi:10.1007/s10549-012-2196-0
32. Pradhan M, Bembinster LA, Baumgarten SC, Frasor J. Proinflammatory cytokines enhance estrogen-dependent expression of the multidrug transporter gene ABCG2 through estrogen receptor and NFκB cooperativity at adjacent response elements. J Biol Chem. 2010;285(41):31100-6. doi:10.1074/jbc.M110.155309
33. Takeshita T, Yan L, Asaoka M, Rashid O, Takabe K. Late recurrence of breast cancer is associated with pro-cancerous immune microenvironment in the primary tumor. Sci Rep. 2019;9(1):16942. doi:10.1038/s41598-019-53482-x
34. Bonnefoi H, Litière S, Piccart M, MacGrogan G, Fumoleau P, Brain E, et al. Pathological complete response after neoadjuvant chemotherapy is an independent predictive factor irrespective of simplified breast cancer intrinsic subtypes: A landmark and two-step approach analyses from the EORTC 10994/BIG 1-00 phase III trial. Ann Oncol. 2014;25(6):1128-36. doi:10.1093/annonc/mdu118
35. Berry DA, Cirrincione C, Henderson IC, Citron ML, Budman DR, Goldstein LJ, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. J Am Med Assoc. 2006;295(14):1658-67. doi:10.1001/jama.295.14.1658
36. Segovia-Mendoza M, Morales-Montor J. Immune tumor microenvironment in breast cancer and the participation of estrogens and its receptors into cancer physiopathology. Front Immunol. 2019;10:348. doi:10.3389/fimmu.2019.00348
37. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: An overview. Cancers (Basel). 2014;6(3):1769-92. doi:10.3390/cancers6031769
38. Moiseenko F, Volkov N, Bogdanov A, Dubina M, Moiseyenko V. Resistance mechanisms to drug therapy in breast cancer and other solid tumors: An opinion. F1000Research. 2017;6:288. doi:10.12688/f1000research.10992.1
39. Jardim DL, Groves ES, Breitfeld PP, Kurzrock R. Factors associated with failure of oncology drugs in late-stage clinical development: A systematic review. Cancer Treat Rev. 2017;52:12-21. doi:10.1016/j.ctrv.2016.10.009
40. Bent R, Moll L, Grabbe S, Bros M. Interleukin-1 beta—A friend or foe in malignancies? Int J Mol Sci. 2018;19(8):2155. doi:10.3390/ijms19082155
41. Iyengar NM, Chen IC, Zhou XK, Giri DD, Falcone DJ, Winston LA, et al. Adiposity, inflammation, and breast cancer pathogenesis in Asian Women. Cancer Prev Res. 2018;11(4):227-36. doi:10.1158/1940-6207.CAPR-17-0283
42. Morris PG, Hudis CA, Giri D, Morrow M, Falcone DJ, Zhou XK, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. Cancer Prev Res. 2011;4(7):1021-9. doi:10.1158/1940-6207.CAPR-11-0110
43. Giuliani C, Bucci I, Napolitano G. The role of the transcription factor Nuclear Factor-kappa B in thyroid autoimmunity and cancer. Front Endocrinol (Lausanne). 2018;9:471. doi:10.3389/fendo.2018.00471
44. Maliniak ML, Miller-Kleinhenz J, Cronin-Fenton DP, Lash TL, Gogineni K, Janssen EAM, et al. Crown-like structures in breast adipose tissue: Early evidence and current issues in breast cancer. Cancers (Basel). 2021;13(9):2222. doi:10.3390/cancers13092222
45. Chan P-C, Hsieh P-S. The role of adipocyte hypertrophy and hypoxia in the development of obesity-associated adipose tissue inflammation and insulin resistance. In: Gordeladze JO, editor. Adiposity - Omics and Molecular Understanding. London: IntechOpen; 2017. doi:10.5772/65458
46. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, et al. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci. 2019;20(9):2358. doi:10.3390/ijms20092358
47. Heinrichsdorff J, Olefsky JM. Fetuin-A: The missing link in lipid-induced inflammation. Nat Med. 2012;18(8):1182-3. doi:10.1038/nm.2869
48. Howe LR, Subbaramaiah K, Hudis CA, Dannenberg AJ. Molecular pathways: Adipose inflammation as a mediator of obesity-associated cancer. Clin Cancer Res. 2013;19(22):6074-83. doi:10.1158/1078-0432.CCR-12-2603
49. Libermann TA, Baltimore D. Activation of interleukin-6 gene expression through the NF-kappa B transcription factor. Mol Cell Biol. 1990;10(5):2327-34. doi:10.1128/mcb.10.5.2327-2334.1990
50. Cavalieri E, Chakravarti D, Guttenplan J, Hart E, Ingle J, Jankowiak R, et al. Catechol estrogen quinones as initiators of breast and other human cancers: Implications for biomarkers of susceptibility and cancer prevention. Biochim Biophys Acta - Rev Cancer. 2006;1766(1):63-78. doi:10.1016/j.bbcan.2006.03.001
51. Kwon YJ, Baek HS, Ye DJ, Shin S, Kim D, Chun YJ. CYP1B1 enhances cell proliferation and metastasis through induction of EMT and activation of Wnt/β-catenin signaling via Sp1 upregulation. PLoS One. 2016;11(3):e0151598. doi:10.1371/journal.pone.0151598
52. Gao N, Nester RA, Sarkar MA. 4-Hydroxy estradiol but not 2-hydroxy estradiol induces expression of hypoxia-inducible factor 1α and vascular endothelial growth factor A through phosphatidylinositol 3-kinase/Akt/FRAP pathway in OVCAR-3 and

A2780-CP70 human ovarian carcinoma cells. Toxicol Appl Pharmacol. 2004;196(1):124-35. doi:10.1016/j.taap.2003.12.002
53. Kim M, Jang K, Miller P, Picon-Ruiz M, Yeasky TM, El-Ashry D, et al. VEGFA links self-renewal and metastasis by inducing Sox2 to repress miR-452, driving Slug. Oncogene. 2017;36(36):5199-211. doi:10.1038/onc.2017.4
54. Okoh VO, Felty Q, Parkash J, Poppiti R, Roy D. Reactive oxygen species via redox signaling to PI3K/AKT pathway contribute to the malignant growth of 4-hydroxy estradiol-transformed mammary epithelial cells. PLoS One. 2013;8(2):e54206. doi:10.1371/journal.pone.0054206
55. Mailander PC, Meza JL, Higginbotham S, Chakravarti D. Induction of A·T to G·C mutations by erroneous repair of depurinated DNA following estrogen treatment of the mammary gland of ACI rats. J Steroid Biochem Mol Biol. 2006;101(4-5):204-15. doi:10.1016/j.jsbmb.2006.06.019
56. Fussell KC, Udasin RG, Smith PJS, Gallo MA, Laskin JD. Catechol metabolites of endogenous estrogens induce redox cycling and generate reactive oxygen species in breast epithelial cells. Carcinogenesis. 2011;32(8):1285-93. doi:10.1093/carcin/bgr109
57. Valavanidis A, Vlachogianni T, Fiotakis C. 8-Hydroxy-2′-deoxyguanosine (8-OHdG): A critical biomarker of oxidative stress and carcinogenesis. J Environ Sci Heal - Part C Environ Carcinog Ecotoxicol Rev. 2009;27(2):120-39. doi:10.1080/10590500902885684
58. Cadet J, Delatour T, Douki T, Gasparutto D, Pouget JP, Ravanat JC, et al. Hydroxyl radicals and DNA base damage. Mutat Res - Fundam Mol Mech Mutagen. 1999;424(1-2):9-21. doi:10.1016/S0027-5107(99)00004-4
59. Storz P. Reactive oxygen species in tumor progression. Front Biosci. 2005;10(2):1881-96. doi:10.2741/1667
60. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017;2:17023. doi:10.1038/sigtrans.2017.23
61. Takada Y, Mukhopadhyay A, Kundu GC, Mahabeleshwar GH, Singh S, Aggarwal BB. Hydrogen peroxide activates NF-κB through tyrosine phosphorylation of iκbα and serine phosphorylation of p65. J Biol Chem. 2003;278(26):24233-41. doi:10.1074/jbc.m212389200
62. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883-99. doi:10.1016/j.cell.2010.01.025
63. Zhang Z, Lin G, Yan Y, Li X, Hu Y, Wang J, et al. Transmembrane TNF-alpha promotes chemoresistance in breast cancer cells. Oncogene. 2018;37(25):3456-70. doi:10.1038/s41388-018-0221-4
64. Gordon GJ, Mani M, Mukhopadhyay L, Dong L, Yeap BY, Sugarbaker DJ, et al. Inhibitor of apoptosis proteins are regulated by tumour necrosis factor-α in malignant pleural mesothelioma. J Pathol. 2007;211(4):439-46. doi:10.1002/path.2120
65. Tan W, Luo X, Li W, Zhong J, Cao J, Zhu S, et al. TNF-α is a potential therapeutic target to overcome sorafenib resistance in hepatocellular carcinoma. EBioMedicine. 2019;40:446-56. doi:10.1016/j.ebiom.2018.12.047
66. Bertrand F, Montfort A, Marcheteau E, Imbert C, Gilhodes J, Filleron T, et al. TNFα blockade overcomes resistance to anti-PD-1 in experimental melanoma. Nat Commun. 2017;8(1):2256. doi:10.1038/s41467-017-02358-7
67. Huang J, Lan X, Wang T, Lu H, Cao M, Yan S, et al. Targeting the IL-1β/EHD1/TUBB3 axis overcomes resistance to EGFR-TKI in NSCLC. Oncogene. 2020;39(8):1739-55. doi:10.1038/s41388-019-1099-5
68. Li Y, Wang L, Pappan L, Galliher-Beckley A, Shi J. IL-1β promotes stemness and invasiveness of colon cancer cells through Zeb1 activation. Mol Cancer. 2012;11:87. doi:10.1186/1476-4598-11-87
69. Lu L, Wang P, Zou Y, Zha Z, Huang H, Guan M, et al. Il-1β promotes stemness of tumor cells by activating smad/id1 signaling pathway. Int J Med Sci. 2020;17(9):1257-68. doi:10.7150/ijms.44285
70. Mendoza-Rodríguez MG, Ayala-Sumuano JT, García-Morales L, Zamudio-Meza H, Pérez-Yepez EA, Meza I. IL-1β inflammatory cytokine-induced TP63 isoform ΔNP63α signaling cascade contributes to cisplatin resistance in human breast cancer cells. Int J Mol Sci. 2019;20(2):270. doi:10.3390/ijms20020270
71. Mendoza-Rodríguez M, Arévalo Romero H, Fuentes-Pananá EM, Ayala-Sumuano JT, Meza I. IL-1β induces up-regulation of BIRC3, a gene involved in chemoresistance to doxorubicin in breast cancer cells. Cancer Lett. 2017;390:39-44. doi:10.1016/j.canlet.2017.01.005
72. Jiménez-Garduño AM, Mendoza-Rodríguez MG, Urrutia-Cabrera D, et al. IL-1β induced methylation of the estrogen receptor ERα gene correlates with EMT and chemoresistance in breast cancer cells. Biochem Biophys Res Commun. 2017;490(3):780-85. doi:10.1016/j.bbrc.2017.06.117
73. Xu X, Zhang L, He X, Zhang P, Sun C, Xu X, et al. TGF-β plays a vital role in triple-negative breast cancer (TNBC) drug-resistance through regulating stemness, EMT and apoptosis. Biochem Biophys Res Commun. 2018;502(1):160-65. doi:10.1016/j.bbrc.2018.05.139
74. Brunen D, Willems SM, Kellner U, Midgley R, Simon I, Bernards R. TGF-β: An emerging player in drug resistance. Cell Cycle. 2013;12(18):2960-8. doi:10.4161/cc.26034
75. Yu Y, Wang Y, Ren X, Tsuyada A, Li A, Liu LJ, et al. Context-dependent bidirectional regulation of the muts homolog 2 by transforming growth factor β contributes to chemoresistance in breast cancer cells. Mol Cancer Res. 2010;8(12):1633-42. doi:10.1158/1541-7786.MCR-10-0362
76. Huang S, Hölzel M, Knijnenburg T, Schlicker A, Roepman P, McDermott U, et al. MED12 controls the

response to multiple cancer drugs through regulation of TGF-β receptor signaling. Cell. 2012;151(5):937-50. doi:10.1016/j.cell.2012.10.035
77. Ham IH, Oh HJ, Jin H, Bae CA, Jeon SM, Choi KS, et al. Targeting interleukin-6 as a strategy to overcome stroma-induced resistance to chemotherapy in gastric cancer. Mol Cancer. 2019;18(1):68. doi:10.1186/s12943-019-0972-8
78. Tsoi H, Man EPS, Chau KM, Khoo US. Targeting the IL-6/STAT3 signalling cascade to reverse tamoxifen resistance in estrogen receptor positive breast cancer. Cancers (Basel). 2021;13(7):1511. doi:10.3390/cancers13071511
79. Borsellino N, Bonavida B, Belldegrun A. Endogenous interleukin 6 is a resistance factor for cis-diamminedichloroplatinum and etoposide-mediated cytotoxicity of human prostate carcinoma cell lines. Cancer Res. 1995;55(20):4633-9.
80. Hideshima T, Nakamura N, Chauhan D, Anderson KC. Biologic sequelae of interleukin-6 induced PI3-K/Akt signaling in multiple myeloma. Oncogene. 2001;20(42):5991-6000. doi:10.1038/sj.onc.1204833
81. Suchi K, Fujiwara H, Okamura S, Okamura H, Umehara S, Todo M, et al. Overexpression of interleukin-6 suppresses cisplatin-induced cytotoxicity in esophageal squamous cell carcinoma cells. Anticancer Res. 2011;31(1):67-75.
82. Yang C, He L, He P, Liu Y, Wang W, He Y, et al. Increased drug resistance in breast cancer by tumor-associated macrophages through IL-10/STAT3/bcl-2 signaling pathway. Med Oncol. 2015;32(2):352. doi:10.1007/s12032-014-0352-6
83. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes tumor necrosis. Proc Natl Acad Sci USA. 1975;72:3666-70.
84. Pennica D, Nedwin GE, Hayflick JS, Seeburg PH, Derynck R, Palladino MA, et al. Human tumour necrosis factor: Precursor structure, expression and homology to lymphotoxin. Nature. 1984;312(5996):724-9. doi:10.1038/312724a0
85. Sasi SP, Bae S, Song J, Perepletchikov A, Schneider D, Carrozza J, et al. Therapeutic non-toxic doses of TNF induce significant regression in TNFR2-p75 knockdown Lewis lung carcinoma tumor implants. PLoS One. 2014;9(3):e92373. doi:10.1371/journal.pone.0092373
86. Moore RJ, Owens DM, Stamp G, Arnott C, Burke F, East N, et al. Mice deficient in tumor necrosis factor-α are resistant to skin carcinogenesis. Nat Med. 1999;5(7):828-31. doi:10.1038/10552
87. Arnott CH, Scott KA, Moore RJ, Robinson SC, Thompson RG, Balkwill FR. Expression of both TNF-α receptor subtypes is essential for optimal skin tumour development. Oncogene. 2004;23(10):1902-10. doi:10.1038/sj.onc.1207317
88. Ridker PM, MacFadyen JG, Thuren T, Everett B, Libby P, Glynn R, et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390(10105):1833-42. doi:10.1016/S0140-6736(17)32247-X
89. Massagué J. TGFβ in cancer. Cell. 2008;134(2):215-30. doi:10.1016/j.cell.2008.07.001
90. 90. Zink D, Mayr C, Janz C, Wiesmüller L. Association of p53 and MSH2 with recombinative repair complexes during S phase. Oncogene. 2002;21(31):4788-800. doi:10.1038/sj.onc.1205614
91. Davis BN, Hilyard AC, Lagna G, Hata A. SMAD proteins control DROSHA-mediated microRNA maturation. Nature. 2008;454(7200):56-61. doi:10.1038/nature07086
92. Bromberg JF, Wrzeszczynska MH, Devgan G, Zhao Y, Pestell RG, Albanese C, et al. Stat3 as an oncogene. Cell. 1999;98(3):295-303. doi:10.1016/S0092-8674(00)81959-5
93. Yu H, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: Role of STAT3 in the tumour microenvironment. Nat Rev Immunol. 2007;7(1):41-51. doi:10.1038/nri1995
94. Guo Y, Nemeth J, O'Brien C, Susa M, Liu X, Xhang Z, et al. Effects of siltuximab on the IL-6-induced signaling pathway in ovarian cancer. Clin Cancer Res. 2010;16(23):5759-69. doi:10.1158/1078-0432.CCR-10-1095
95. Qiu Y, Ravi L, Kung HJ. Requirement of ErbB2 for signalling by interleukin-6 in prostate carcinoma cells. Nature. 1998;393(6680):83-5. doi:10.1038/30012
96. Moore KW, O'Garra A, De Waal Malefyt R, Vieira P, Mosmann TR. Interleukin-10. Annu Rev Immunol. 1993;11:165-90. doi:10.1146/annurev.iy.11.040193.001121
97. Moore KW, De Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol. 2001;19:683-765. doi:10.1146/annurev.immunol.19.1.683
98. Solinas G, Germano G, Mantovani A, Allavena P. Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation. J Leukoc Biol. 2009;86(5):1065-73. doi:10.1189/jlb.0609385
99. Kawamura K, Bahar R, Natsume W, Sakiyama S, Tagawa M. Secretion of interleukin-10 from murine colon carcinoma cells suppresses systemic antitumor immunity and impairs protective immunity induced against the tumors. Cancer Gene Ther. 2002;9(1):109-15. doi:10.1038/sj.cgt.7700418
100. Sun Zhaojun, Julien F, Ornella P, Joe-Marc C, Cindy S, Kirkwood JM, et al. IL-10 and PD-1 cooperate to limit the activity of tumor-specific CD8+ T cells. Cancer Res. 2016;75(8):1635-44. doi:10.1158/0008-5472.CAN-14-3016.IL-10
101. Llopiz D, Ruiz M, Infante S, Villanueva L, Silva L, Hervas-Stubbs S, et al. IL-10 expression defines an

immunosuppressive dendritic cell population induced by antitumor therapeutic vaccination. Oncotarget. 2017;8(2):2659-71. doi:10.18632/oncotarget.13736
102. Vicari AP, Chiodoni C, Vaure C, Aït-Yahia S, Dercamp C, Matsos F, et al. Reversal of tumor-induced dendritic cell paralysis by CpG immunostimulatory oligonucleotide and anti-interleukin 10 receptor antibody. J Exp Med. 2002;196(4):541-9. doi:10.1084/jem.20020732
103. Bartella V, Rizza P, Barone I, Zito D, Giordano F, Giordano C, et al. Estrogen receptor beta binds Sp1 and recruits a corepressor complex to the estrogen receptor alpha gene promoter. Breast Cancer Res Treat. 2012;134(2):569-81. doi:10.1007/s10549-012-2090-9
104. Lu W, Katzenellenbogen BS. Estrogen receptor-β modulation of the ERα-p53 loop regulating gene expression, proliferation, and apoptosis in breast cancer. Horm Cancer. 2017;8(4):230-42. doi:10.1007/s12672-017-0298-1
105. Jin W, Chen Y, Di GH, Miron P, Hou YF, Goa H, et al. Estrogen receptor (ER) β or p53 attenuates ERα-mediated transcriptional activation on the BRCA2 promoter. J Biol Chem. 2008;283(44): 29671-80. doi:10.1074/jbc.M802785200
106. Bado I, Nikolos F, Rajapaksa G, Wu W, Castaneda J, Krishnamurthy S, et al. Somatic loss of estrogen receptor beta and p53 synergize to induce breast tumorigenesis. Breast Cancer Res. 2017;19(1):79. doi:10.1186/s13058-017-0872-z
107. Lazennec G, Bresson D, Lucas A, Chauveau C, Vignon F. ERβ inhibits proliferation and invasion of breast cancer cells. Endocrinology. 2001;142(9):4120-30. doi:10.1210/endo.142.9.8395
108. Chaudhary SC, Singh T, Talwelkar SS, Srivastava RK, Arumugam A, Weng Z, et al. Erb-041, an estrogen receptor-β agonist, inhibits skin photocarcinogenesis in SKH-1 hairless mice by downregulating the WNT signaling pathway. Cancer Prev Res. 2014;7(2):186-98. doi:10.1158/1940-6207.CAPR-13-0276
109. Wu WF, Maneix L, Insunza J, Nalvarte I, Antonson P, Kere J, et al. Estrogen receptor β, a regulator of androgen receptor signaling in the mouse ventral prostate. Proc Natl Acad Sci U S A. 2017;114(19):E3816-22. doi:10.1073/pnas.1702211114
110. Yuan B, Cheng L, Chiang HC, Xu X, Han Y, Su H, et al. A phosphotyrosine switch determines the antitumor activity of ERβ. J Clin Invest. 2014;124(8):3378-90. doi:10.1172/JCI74085
111. Paruthiyil S, Parmar H, Kerekatte V, Cunha GR, Firestone GL, Leitmant DC. Estrogen receptor β inhibits human breast cancer cell proliferation and tumor formation by causing a G2 cell cycle arrest. Cancer Res. 2004;64(1):423-8. doi:10.1158/0008-5472.CAN-03-2446
112. Froyen EB, Steinberg FM. Soy isoflavones increase quinone reductase in hepa-1c1c7 cells via estrogen receptor beta and nuclear factor erythroid 2-related factor 2 binding to the antioxidant response element. J Nutr Biochem. 2011;22(9):843-8. doi:10.1016/j.jnutbio.2010.07.008
113. Wang J, Zhang C, Chen K, Tang H, Tang J, Song C, et al. ERβ1 inversely correlates with PTEN/PI3K/AKT pathway and predicts a favorable prognosis in triple-negative breast cancer. Breast Cancer Res Treat. 2015;152(2):255-69. doi:10.1007/s10549-015-3467-3
114. Farbood Y, Sarkaki A, Dolatshahi M, Mansouri SMT, Khodadadi A. Ellagic acid protects the brain against 6-hydroxydopamine induced neuroinflammation in a rat model of parkinson's disease. Basic Clin Neurosci. 2015;6(2):15-22.
115. Baluchnejadmojarad T, Rabiee N, Zabihnejad S, Roghani M. Ellagic acid exerts protective effect in intrastriatal 6-hydroxydopamine rat model of Parkinson's disease: Possible involvement of ERβ/Nrf2/HO-1 signaling. Brain Res. 2017;1662:23-30. doi:10.1016/j.brainres.2017.02.021
116. Chowdhry S, Zhang Y, McMahon M, Sutherland C, Cuadrado A, Hayes JD. Nrf2 is controlled by two distinct β-TrCP recognition motifs in its Neh6 domain, one of which can be modulated by GSK-3 activity. Oncogene. 2013;32(32):3765-81. doi:10.1038/onc.2012.388
117. Hayes JD, Chowdhry S, Dinkova-Kostova AT, Sutherland C. Dual regulation of transcription factor Nrf2 by Keap1 and by the combined actions of β-TrCP and GSK-3. Biochem Soc Trans. 2015;43:611-20. doi:10.1042/BST20150011
118. Chakkittukandiyil A, Sajini DV, Karuppaiah A, Selvaraj D. The principal molecular mechanisms behind the activation of Keap1/Nrf2/ARE pathway leading to neuroprotective action in Parkinson's disease. Neurochem Int. 2022;156:105325. doi:10.1016/j.neuint.2022.105325
119. Ramos-Gomez M, Kwak MK, Dolan PM, Itoh K, Yamamoto M, Talalay P, et al. Sensitivity to carcinogenesis is increased and chemoprotective efficacy of enzyme inducers is lost in nrf2 transcription factor-deficient mice. Proc Natl Acad Sci U S A. 2001;98(6):3410-5. doi:10.1073/pnas.051618798
120. Bae I, Fan S, Meng Q, Jeong KR, Hee JK, Hyo JK, et al. BRCA1 induces antioxidant gene expression and resistance to oxidative stress. Cancer Res. 2004;64(21):7893-909. doi:10.1158/0008-5472.CAN-04-1119
121. Gan FF, Ling H, Ang X, Reddy SA, Lee SSH, Yang H, et al. A novel shogaol analog suppresses cancer cell invasion and inflammation, and displays cytoprotective effects through modulation of NF-κB and Nrf2-Keap1 signaling pathways. Toxicol Appl Pharmacol. 2013;272(3):852-62. doi:10.1016/j.taap.2013.07.011
122. Wang XJ, Sun Z, Villeneuve NF, Zhang S, Zhao F, Li Y, et al. Nrf2 enhances resistance of cancer cells

to chemotherapeutic drugs, the dark side of Nrf2. Carcinogenesis. 2008;29(6):1235-43. doi:10.1093/carcin/bgn095
123. Ohta T, Iijima K, Miyamoto M, Nakahara I, Tanaka H, Ohtsuji M, et al. Loss of Keap1 function activates Nrf2 and provides advantages for lung cancer cell growth. Cancer Res. 2008;68(5):1303-9. doi:10.1158/0008-5472.CAN-07-5003
124. Fahey JW, Haristoy X, Dolan PM, Kensler TW, Scholtus I, Stephenson KK, et al. Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of *Helicobacter pylori* and prevents benzo[a] pyrene-induced stomach tumors. Proc Natl Acad Sci U S A. 2002;99(11):7610-5. doi:10.1073/pnas.112203099
125. Acharya A, Das I, Chandhok D, Saha T. Redox regulation in cancer: A double-edged sword with therapeutic potential. Oxid Med Cell Longev. 2010;3(1):23-34. doi:10.4161/oxim.3.1.10095
126. Zhang C, Wang HJ, Bao QC, Wang L, Guo TK, Chen WL, et al. NRF2 promotes breast cancer cell proliferation and metastasis by increasing RhoA/ROCK pathway signal transduction. Oncotarget. 2016;7(45):73593-606. doi:10.18632/oncotarget.12435
127. Lu K, Alcivar AL, Ma J, Foo TK, Zywea S, Mahdi A, et al. NRF2 induction supporting breast cancer cell survival is enabled by oxidative stress-induced DPP3-KEAP1 interaction. Cancer Res. 2017;77(11):2881-92. doi:10.1158/0008-5472.CAN-16-2204
128. Zhang HS, Du GY, Zhang ZG, Zhou Z, Sun HL, Yu XY, et al. NRF2 facilitates breast cancer cell growth via HIF1α-mediated metabolic reprogramming. Int J Biochem Cell Biol. 2018;95:85-92. doi:10.1016/j.biocel.2017.12.016
129. Kim SK, Yang JW, Kim MR, Roh SH, Kim HG, Lee KY, et al. Increased expression of Nrf2/ARE-dependent anti-oxidant proteins in tamoxifen-resistant breast cancer cells. Free Radic Biol Med. 2008;45(4):537-46. doi:10.1016/j.freeradbiomed.2008.05.011
130. Hartikainen JM, Tengström M, Winqvist R, Jukkola-Vuorinen A, Pylkäs K, Kosma VM, et al. KEAP1 genetic polymorphisms associate with breast cancer risk and survival outcomes. Clin Cancer Res. 2015;21(7):1591-601. doi:10.1158/1078-0432.CCR-14-1887
131. Lou Y, Guo Z, Zhu Y, Zhang G, Wang Y, Qi X, et al. Astragali radix and its main bioactive compounds activate the Nrf2-mediated signaling pathway to induce P-glycoprotein and breast cancer resistance protein. J Ethnopharmacol. 2019;228:82-91. doi:10.1016/j.jep.2018.09.026
132. Wilkening S, Stahl F, Bader A. Comparison of primary human hepatocytes and hepatoma cell line HepG2 with regard to their biotransformation properties. Drug Metab Dispos. 2003;31(8):1035-42. doi:10.1124/dmd.31.8.1035
133. Keum YS. Regulation of Nrf2-mediated phase ii detoxification and anti-oxidant genes. Biomol Ther. 2012;20(2):144-51. doi:10.4062/biomolther.2012.20.2.144
134. Wang X, Campos CR, Peart JC, Smith LK, Boni JL, Cannon RE, et al. Nrf2 upregulates ATP binding cassette transporter expression and activity at the blood-brain and blood-spinal cord barriers. J Neurosci. 2014;34(25):8585-93. doi:10.1523/JNEUROSCI.2935-13.2014
135. Kannan P, John C, Zoghbi SS, Halldin C, Gottesman MM, Innis RB, et al. Imaging the function of P-glycoprotein with radiotracers: Pharmacokinetics and in vivo applications. Clin Pharmacol Ther. 2009;86(4):368-77. doi:10.1038/clpt.2009.138
136. Natarajan K, Xie Y, Baer MR, Ross DD. Role of breast cancer resistance protein (BCRP/ABCG2) in cancer drug resistance. Biochem Pharmacol. 2012;83(8):1084-103. doi:10.1016/j.bcp.2012.01.002
137. Gorrini C, Gang BP, Bassi C, Wakeham A, Baniasadi SP, Hao Z, et al. Estrogen controls the survival of BRCA1-deficient cells via a PI3K-NRF2-regulated pathway. Proc Natl Acad Sci U S A. 2014;111(12):4472-7. doi:10.1073/pnas.1324136111
138. Funes JM, Henderson S, Kaufman R, Flanagan JM, Robson M, Pedley B, et al. Oncogenic transformation of mesenchymal stem cells decreases Nrf2 expression favoring in vivo tumor growth and poorer survival. Mol Cancer. 2014;13:20. doi:10.1186/1476-4598-13-20
139. Oshi M, Angarita FA, Tokumaru Y, Yan L, Matsuyama R, Endo I, et al. High expression of nrf2 is associated with increased tumor-infiltrating lymphocytes and cancer immunity in er-positive/her2-negative breast cancer. Cancers (Basel). 2020;12(12):3856. doi:10.3390/cancers12123856
140. Mandal A, Bhatia D, Bishayee A. Anti-inflammatory mechanism involved in pomegranate-mediated prevention of breast cancer: The role of NF-κB and Nrf2 signaling pathways. Nutrients. 2017;9(5):436. doi:10.3390/nu9050436
141. Katary MA, Abdelsayed R, Alhashim A, Abdelhasib M, Elmarakby AA. Salvianolic acid B slows the progression of breast cancer cell growth via enhancement of apoptosis and reduction of oxidative stress, inflammation, and angiogenesis. Int J Mol Sci. 2019;20(22):5653. doi:10.3390/ijms20225653
142. Zhang Y, Xia J, Li Q, Yao Y, Eades G, Gernapudi R, et al. NRF2/Long noncoding RNA ROR signaling regulates mammary stem cell expansion and protects against estrogen genotoxicity. J Biol Chem. 2014;289(45):31310-8. doi:10.1074/jbc.M114.604868
143. Hu A, Hong F, Li D, Jin Y, Kon L, Xu Z, et al. Long non-coding RNA ROR recruits histone transmethylase MLL1 to up-regulate TIMP3 expression and promote breast cancer progression. J Transl Med. 2021;19:95. doi:10.1186/s12967-020-02682-5
144. Li L, Gu M, You B, Shi S, Shan Y, Bao L, et al. Long non-coding RNA ROR promotes proliferation, migration and chemoresistance of nasopharyngeal carcinoma.

Cancer Sci. 2016;107(9):1215-22. doi:10.1111/cas.12989
145. Maleva Kostovska I, Jakimovska M, Popovska-Jankovic K, Kubelka-Sabit K, Karagjozov M, Plaseska-Karanfilska D. TIMP3 Promoter methylation represents an epigenetic marker of BRCA1ness breast cancer tumours. Pathol Oncol Res. 2018;24(4):937-40. doi:10.1007/s12253-018-0398-4
146. Giudice A, Barbieri A, Bimonte S, Cascella M, Cuomo A, Crispo A, et al. Dissecting the prevention of estrogen-dependent breast carcinogenesis through Nrf2-dependent and independent mechanisms. Onco Targets Ther. 2019;12:4937-53. doi:10.2147/OTT.S183192
147. Liehr JG. Genotoxic effects of estrogens. Mutat Res Genet Toxicol. 1990;238(3):269-76. doi:10.1016/0165-1110(90)90018-7
148. Zhou X, Zhao Y, Wang J, Wang X, Chen, Chunxia C, Yin D, et al. Resveratrol represses estrogen-induced mammary carcinogenesis through NRF2-UGT1A8-estrogen metabolic axis activation. Biochem Pharmacol. 2018;155:252-63. doi:10.1016/j.bcp.2018.07.006
149. Thibaudeau J, Lépine J, Tojcic J, Duguay Y, Pelletier G, Plante M, et al. Characterization of common UGT1A8, UGT1A9, and UGT2B7 variants with different capacities to inactivate mutagenic 4-hydroxylated metabolites of estradiol and estrone. Cancer Res. 2006;66(1):125-33. doi:10.1158/0008-5472.CAN-05-2857
150. Guillemette C, Bélanger A, Lépine J. Metabolic inactivation of estrogens in breast tissue by UDP-glucuronosyltransferase enzymes: An overview. Breast Cancer Res. 2004;6(6):246-54. doi:10.1186/bcr936
151. Wardyn JD, Ponsford AH, Sanderson CM. Dissecting molecular cross-talk between Nrf2 and NF-κB response pathways. Biochem Soc Trans. 2015;43:621-6. doi:10.1042/BST20150014
152. El-Shitany NA, Eid BG. Icariin modulates carrageenan-induced acute inflammation through HO-1/Nrf2 and NF-kB signaling pathways. Biomed Pharmacother. 2019;120:109567. doi:10.1016/j.biopha.2019.109567
153. Pfeilschifter J, Köditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. Endocr Rev. 2002;23(1):90-119. doi:10.1210/edrv.23.1.0456
154. Jayaram S, Krishnamurthy PT. Role of microgliosis, oxidative stress and associated neuroinflammation in the pathogenesis of Parkinson's disease: The therapeutic role of Nrf2 activators. Neurochem Int. 2021;145:105014. doi:10.1016/j.neuint.2021.105014
155. Kobayashi EH, Suzuki T, Funayama R, Nagashima T, Hayashi M, Sekine H, et al. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. Nat Commun. 2016;7:11624. doi:10.1038/ncomms11624
156. Johnston SRD, Dowsett M. Aromatase inhibitors for breast cancer: Lessons from the laboratory. Nat Rev Cancer. 2003;3(11):821-31. doi:10.1038/nrc1211
157. Fan S, Meng Q, Saha T, Sarkar FH, Rosen EM. Low concentrations of diindolylmethane, a metabolite of indole-3-carbinol, protect against oxidative stress in a BRCA1-dependent manner. Cancer Res. 2009;69(15):6083-91. doi:10.1158/0008-5472.CAN-08-3309
158. Szaefer H, Krajka-Kuźniak V, Licznerska B, Bartoszek A, Baer-Dubowska W. Cabbage Juices and Indoles Modulate the Expression Profile of AhR, ERα, and Nrf2 in Human Breast Cell Lines. Nutr Cancer. 2015;67(8):1344-56. doi:10.1080/01635581.2015.1082111
159. Ansell PJ, Espinosa-Nicholas C, Curran EM, Judy BM, Philips BJ, Hannink M, et al. In vitro and in vivo regulation of antioxidant response element-dependent gene expression by estrogens. Endocrinology. 2004;145(1):311-7. doi:10.1210/en.2003-0817
160. Ansell PJ, Lo SC, Newton LG, Espinosa-Nicholas C, Zhang DD, Liu JH, et al. Repression of cancer protective genes by 17β-estradiol: Ligand-dependent interaction between human Nrf2 and estrogen receptor α. Mol Cell Endocrinol. 2005;243(1-2):27-34. doi:10.1016/j.mce.2005.08.002
161. Licznerska B, Szaefer H, Krajka-Kuźniak V. R-sulforaphane modulates the expression profile of AhR, ERα, Nrf2, NQO1, and GSTP in human breast cell lines. Mol Cell Biochem. 2021;476(2):525-33. doi:10.1007/s11010-020-03913-5
162. Lo R, Matthews J. The aryl hydrocarbon receptor and estrogen receptor alpha differentially modulate nuclear factor erythroid-2-related factor 2 transactivation in MCF-7 breast cancer cells. Toxicol Appl Pharmacol. 2013;270(2):139-48. doi:10.1016/j.taap.2013.03.029
163. Sprouse J, Sampath C, Gangula PR. Role of sex hormones and their receptors on gastric Nrf2 and neuronal nitric oxide synthase function in an experimental hyperglycemia model. BMC Gastroenterol. 2020;20(1):313. doi:10.1186/s12876-020-01453-2
164. Wu J, Williams D, Walter GA, Thompson WE, Sidell N. Estrogen increases Nrf2 activity through activation of the PI3K pathway in MCF-7 breast cancer cells. Exp Cell Res. 2014;328(2):351-60. doi:10.1016/j.yexcr.2014.08.030
165. Chu C, Gao X, Li X, Zhang X, Ma R, Jia Y, et al. Involvement of estrogen receptor-α in the activation of Nrf2-antioxidative signaling pathways by silibinin in pancreatic β-cells. Biomol Ther. 2020;28(2):163-71. doi:10.4062/biomolther.2019.071
166. Wang J, Zhang X, Zhang L, Yan T, Wu B, Xu F, et al. Silychristin A activates Nrf2-HO-1/SOD2 pathway to reduce apoptosis and improve GLP-1 production through upregulation of estrogen receptor α in GLUTag cells. Eur J Pharmacol. 2020;881:173236. doi:10.1016/j.ejphar.2020.173236

167. Zhou W, Lo SC, Liu JH, Hannink M, Lubahn DB. ERRβ: A potent inhibitor of Nrf2 transcriptional activity. Mol Cell Endocrinol. 2007;278(1-2):52-62. doi:10.1016/j.mce.2007.08.011
168. Zhang T, Liang X, Shi L, Wang L, Chen J, Kang C, et al. Estrogen receptor and PI3K/Akt signaling pathway involvement in S-(-)equol-induced activation of Nrf2/ARE in endothelial cells. PLoS One. 19;8(11):e79075. doi:10.1371/journal.pone.0079075
169. Weng JR, Tsai CH, Omar HA, Sargeant AM, Wang D, Kulp SM, et al. OSU-A9, a potent indole-3-carbinol derivative, suppresses breast tumor growth by targeting the Akt-NF-κB pathway and stress response signaling. Carcinogenesis. 2009;30(10):1702-9. doi:10.1093/carcin/bgp202
170. Sripathy SP, Chaplin LJ, Gaikwad NW, Rogan EG, Montano MM. hPMC2 is required for recruiting an ERβ coactivator complex to mediate transcriptional upregulation of NQO1 and protection against oxidative DNA damage by tamoxifen. Oncogene. 2008;27(49):6376-84. doi:10.1038/onc.2008.235
171. Trukhacheva E, Lin Z, Reierstad S, Cheng YH, Milad M, Bulun SE. Estrogen receptor (ER) β regulates ERα expression in stromal cells derived from ovarian endometriosis. J Clin Endocrinol Metab. 2009;94(2):615-22. doi:10.1210/jc.2008-1466
172. Lee YH, Sun Y, Gerweck LE, Glickman RD. Regulation of DNA damage response by estrogen receptor β-mediated inhibition of breast cancer associated gene 2. Biomedicines. 2015;3(2):182-200. doi:10.3390/biomedicines3020182
173. Smolarek AK, So JY, Thomas PE, Lee HJ, Paul S, Dombrowski A, et al. Dietary tocopherols inhibit cell proliferation, regulate expression of ERα, PPARγ, and Nrf2, and decrease serum inflammatory markers during the development of mammary hyperplasia. Mol Carcinog. 2013;52(7):514-25. doi:10.1002/mc.21886
174. Song CH, Kim N, Kim DH, Lee HN, Surh YJ. 17-β estradiol exerts anti-inflammatory effects through activation of Nrf2 in mouse embryonic fibroblasts. PLoS One. 2019;14(8):e0221650. doi:10.1371/journal.pone.0221650
175. Kerns ML, Hakim JMC, Zieman A, Lu RG, Coulombe PA. Sexual dimorphism in response to an NRF2 inducer in a model for pachyonychia congenita. J Invest Dermatol. 2018;138(5):1094-100. doi:10.1016/j.jid.2017.09.054