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Review

Potential Mechanisms by which Glucocorticoids Induce Breast Carcinogenesis through Nrf2 Inhibition

Aldo Giudice[1,*,†], Silvana Mirella Aliberti[2,*,†], Antonio Barbieri[1], Paola Pentangelo[2], Ilaria Bisogno[3], Giovanni D'Arena[4], Emidio Cianciola[5], Michele Caraglia[6], Mario Capunzo[2]

[1]Animal Facility, Istituto Nazionale Tumori - "Fondazione G. Pascale" - IRCCS, 80131 Naples, Italy
[2]Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, 84081 Salerno, Italy
[3]Department of Radiological, Oncological and Anatomo-Pathological Science, University of Rome "Sapienza", 00161 Rome, Italy
[4]Hematology Service, San Luca Hospital, ASL Salerno, 84124 Salerno, Italy
[5]Anesthesia and Intensive Care Unit, "Immacolata di Sapri" Hospital– ASL Salerno, 84073 Salerno, Italy
[6]Department of Precision Medicine, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
*Correspondence: a.giudice@istitutotumori.na.it; aldo.giudice@libero.it (Aldo Giudice); sialiberti@unisa.it (Silvana Mirella Aliberti)
†These authors contributed equally.

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Abstract

Breast cancer is the most common malignancy among women worldwide. Several studies indicate that, in addition to established risk factors for breast cancer, other factors such as cortisol release related to psychological stress and drug treatment with high levels of glucocorticoids may also contribute significantly to the initiation of breast cancer. There are several possible mechanisms by which glucocorticoids might promote neoplastic transformation of breast tissue. Among these, the least known and studied is the inhibition of the nuclear erythroid factor 2-related (Nrf2)-antioxidant/electrophile response element (ARE/EpRE) pathway by high levels of glucocorticoids. Specifically, Nrf2 is a potent transcriptional activator that plays a central role in the basal and inducible expression of many cytoprotective genes that effectively protect mammalian cells from various forms of stress and reduce the propensity of tissues and organisms to develop disease or malignancy including breast cancer. Consequently, a loss of Nrf2 in response to high levels of glucocorticoids may lead to a decrease in cellular defense against oxidative stress, which plays an important role in the initiation of human mammary carcinogenesis. In the present review, we provide a comprehensive overview of the current state of knowledge of the cellular mechanisms by which both glucocorticoid pharmacotherapy and endogenous GCs (cortisol in humans and corticosterone in rodents) may contribute to breast cancer development through inhibition of the Nrf2-ARE/EpRE pathway and the protective role of melatonin against glucocorticoid-induced apoptosis in the immune system.

Keywords: breast carcinogenesis; glucocorticoids (GCs); glucocorticoid receptor (GR); glucocor-ticoid response element (GRE); nuclear factor erythroid 2-related factor 2 (Nrf2); antioxidant/electrophile response element (ARE/EpRE); melatonin (MLT)

1. Introduction

Breast cancer is the most common malignancy among women and the second leading cause of cancer death among women worldwide [1,2]. Unlike other malignancies that increase at the end of the fifth decade, breast cancer begins as early as the third decade of life. This may be due not only to the effects of estrogen but also of other ovarian hormones on breast tissue. Physiological and behavioral risk factors for breast cancer include: age, family history, reproductive history, BRCA1 and BRCA2 gene mutations, as well as elevated endogenous estrogen, hormone therapy, and certain types of benign breast disease [3–5]. In addition to these better known factors, other factors are suspected to confer an increased risk of breast cancer. These include alcohol consumption, tobacco abuse, physical activity, and certain aspects of diet such as meat and fat consumption [3–5]. Among the risk factors, prolonged exposure to high levels of estrogen may contribute significantly to the initiation and development of breast cancer. Indeed, recent experimental studies suggest that imbalanced oxidative metabolism of estrogen can generate genotoxic metabolites (e.g., estrogen-reactive quinones, oxygen free radicals) that can react with DNA to form unstable estrogen-DNA adducts in critical genes leading to cancer initiation [6]. In addition, the possible contribution of psychosocial stress on breast cancer initiation has been less studied. However, it is well known that neuroendocrine hormones (e.g., glucocorti-coids and noradrenaline) can significantly influence cancer biology [7,8]. Animals and people are continuously exposed to a wide range of stresses (social or environmental) throughout their lifetime. Prolonged exposure to stressful conditions results in chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent release of glucocorticoids (GCs) from the adrenal cortex, which can lead to an increased risk of breast cancer [7,8]. The HPA axis is linked to the circadian clock, resulting in modulation of GC levels in a diurnal pattern [9]. Evidence of alterations in circadian

cortisol secretion is not a simple epiphenomenon alone but it is one of the most frequent signs of cancer-related desynchronization [10]. There is also evidence that an altered cortisol rhythm is prognostic for early breast cancer mortality because of its association with a more severe immunosuppressive state [11] or deficient pineal gland function that exerts antitumor activity [12,13]. Other neuroendocrine alterations described in patients with breast cancer include progressive decline in nocturnal melatonin production (MLT) by the pineal gland, abnormally high levels of prolactin as well as altered daily patterns in estrogen signaling [14–16]. Several studies link GCs to increased incidence, progression, and recurrence of breast cancer, suggesting a likely link between circadian disruption and breast carcinogenesis [10,17]. Regarding the treatment of human breast cancer, GCs may significantly contribute to decreased apoptosis of cancer cells, while increasing cancer cell survival and re-sistance to chemotherapy [18,19]. An important role in these processes could be played by the transcription factor Nrf2 (NF-E2-related factor 2), which is tightly regulated by Keap1 (Kelch-like ECH-associated protein 1) mediated ubiquitination [6,20,21]. Specifically, Nrf2 is an important basic leucine zipper-containing transcription factor that controls gene expression of an elaborate network of cytoprotective proteins including antioxidant and detoxifying enzymes that defend cells from electrophiles and free radicals, playing a key role in preventing human carcinogenesis [6,20,21].

This review focused on the role of GC signaling in breast cancer biology. In particular, we discussed the potential mechanisms by which both glucocorticoid pharmacotherapy and endogenous GCs (cortisol in humans and corticosterone in rodents) may influence breast cancer initiation through inhibition of the Nrf2-ARE/EpRE pathway. We also examined the role of melatonin in protecting the immune system from apoptosis by reducing nuclear translocation of the glucocorticoid receptor (GR).

2. Breast Carcinogenesis and the Potential Molecular Mechanisms by which Glucocorticoids Suppress the Nrf2-ARE/EpRE Pathway

In addition to estrogen [6], glucocorticoids (GCs), known as stress hormones, may also play an important role in mammary carcinogenesis process [22]. GCs are produced and released from the adrenal cortex following activation of the hypothalamic-pituitary (HP) axis in both a circadian and highly impulsive manner [23]. These hormones exert their effects by binding to the glucocorticoid receptor (GR), which belongs to the nuclear receptor type 1 subfamily 3. Once bound to GR, the GC-GR complex translocates to the nucleus to modulate gene expression through both transactivation and transrepression of several genes implicated in hyperglycemia and immunosuppression. Alternatively, the GC-GR complex may also exert biological effects through direct protein-protein interactions in the cytosol [24]. There are several mechanisms by which glucocorticoids (GCs) may influence the development and progression of breast cancer. Among these, the least known and studied involves the Nrf2-ARE pathway.

As mentioned above, nuclear erythroid 2-related factor 2 (Nrf2) is a major leucine zipper-containing basic transcription factor that plays an important role in protecting cells from neoplastic transformation by increasing the expression of several cytoprotective enzymes including glutathione-S-transferase (GSTs), NAD(P)H: Quinone oxidoreductase 1,2 (NQO1,2), glutamate cysteine ligase, modifier subunit (GClm), superoxide dismutase (SOD1), catalase (CAT), glutathione peroxidase (GPX1) etc. capable of maintaining cellular redox homeostasis [6]. Specifically, when translocated into the nucleus, Nrf2 binds to the antioxidant/electrophile response element (ARE/EpRE) in the promoters of genes encoding endogenous antioxidants and proteins to enhance their transcription and affect particular cellular functions such as cell cycle and apoptosis, inflammation, inflammasome signaling, endoplasmic-reticulum stress (ER stress), and the unfolded protein response (UPR), autophagy and mitochondrial biogenesis [6,21,25–28]. A loss of Nrf2 in response to high levels of glucocorticoids may lead to a significant decrease in the expression of these cyto-protective enzymes and proteins against oxidative stress that may be important for the initiation and development of breast carcinogenesis.

Below, we will summarize the main known molecular mechanisms by which glucocorti-coids inhibit Nrf2-ARE/EpRE signaling by promoting oxidative DNA damage and initiation of the breast carcinogenesis process.

2.1 GCs Repress Nrf2-ARE/EpRE Pathway Using Specific Promoter Regions with Multiple DNA Response Elements

In support of this notion, a previous study by Ki *et al.* [28] suggests that dexamethasone (DEX), a synthetic glucocorticoid (GC) more potent than cortisol, inhibits constitutive and oltipraz or tert-butylhydroquinone (t-BHQ) inducible expression of glutathione-S-transferase A2 (GSTA2) in H4IIE cells, binding to the glucocorticoid receptor (GR) and subsequent activation of the GR without inhibiting nuclear translocation of Nrf2 and CCAAT/enhancer binding protein β (C/EBPβ) and their DNA binding in cells. Notably, the expression of glutathione-S-transferase (GST), a phase 2 detoxifying enzyme capable of exerting cytoprotective and chemopreventive effects in cancer, is mainly modulated by the activation of Nrf2 and C/EBPβ through their binding to their respective response elements in the promoter regions of target genes [29,30]. Specifically, the authors suggest that after GR activation by DEX, the DEX-GR complex migrates to the nucleus where it binds to glucocorticoid response elements (GREs) on the GST promoter region that contains multiple DNA response elements such as the glucocorti-

coid response element (GRE), ARE/EpRE sequences, and the C/EBP response element. This leads to the recruitment of transcription factors such as nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRT) in H4IIE cells. Subsequently, NCoR is incapable of exerting measurable interactions with the DEX-GR complex, Nrf2, or C/EBPβ. In contrast, SMRT recruited to the DEX-GR complex on GRE acts as a corepressor of GST expression not only by reducing histone acetylation through recruitment of histone deacetylases (HDACs) but also by directly binding to the Neh 4/5 domain of Nrf2, a protein motif essential for transactivation of Nrf2 or the TAD domain of C/EBPβ. Because both Nrf2 and C/EBPβ are able to interact with the CBP (CREB binding protein) coactivator [31,32], functional inactivation of Nrf2 or C/EBPβ upon interaction with SMRT also inhibits CBP-dependent gene transcription activated by transcription factors. Importantly, without activation of GR by DEX, SMRT is unable to physically interact with activating Nrf2 or C/EBPβ transcription factors. Therefore, binding of SMRT to the Neh 4/5 domain of Nrf2 or the TAD domain of C/EBPβ can repress the expression of their target genes only after GR activation by GCs. Collectively, these results indicate that repression of Nrf2 or C/EBPβ by GCs is not only restricted to certain promoter regions with multiple DNA response elements (e.g., GREs, ARE/EpRE sequences, and C/EBP response element) in a composite manner, but also that DEX inhibition of GSTA2 induction by oltipraz or t-BHQ results primarily from the ability of SMRT recruited to the steroid-GR (hormone-bound GR) complex to physically interact with Nrf2 and C/EBPβ and repress their transactivation (Fig. 1).

2.2 Cortisol Suppression of Nrf2 Signaling by Increasing 11-Beta-Hydroxysteroid Dehydrogenase-1 (11beta-HSD1) Enzyme Activity in Different Tissues

The study by Kratschmar *et al.* [33] suggests that cortisol can suppress Nrf2 signaling without requiring a GRE sequence in the promoter region. These authors hypothesize that elevated 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) enzyme activity in various tissues may suppress the Nrf2-dependent antioxidant cellular defense pathway through the generation of active cortisol. Specifically, 11β-HSD1 catalyzes the conversion of inactive 11-ketoglucocorticoids (cortisone in humans, 11-dehydrocorticosterone in rodents) to active 11β-hydroxyglucocorticoids (cortisol in humans, corticosterone in rodents) in several metabolically relevant tissues such as liver, adipose, and skeletal muscle. Another enzyme, 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2) on the other hand, catalyzes the reverse reaction or can metabolically inactivate endogenous glucocorticoids in tissues such as cortical collecting ducts of the kidney, placenta and distal colon. In summary, endogenous glucocorticoids can be metabolically inactivated by the enzyme 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2) in tissues such as the kidney and colon and regenerated by 11beta-HSD1 primarily in the liver. Notably, the reducing activity of 11β-HSD1 depends mainly on the availability of NADPH in the endoplasmic reticulum (ER), which is determined by the activity of the luminal enzyme ER hexose-6-phosphate dehydrogenase (H6PDH) that couple's glucose-6-phosphate oxidation to NADP reduction [34,35]. Importantly, under basal conditions, glucocorticoid concentrations vary during circadian and ultradian rhythms. The impact of glucocorticoid fluctuations on Nrf2-dependent signaling *in vivo* should reflect the expression of the respective 11β-HSD enzyme in specific cells or tissues. In addition, previous studies have also reported different genus-related expression of NQO1 enzyme in specific rat strains and for humans [36–38]. These findings collectively suggest that in tissues expressing 11β-HSD2, Nrf2 may be insensitive to glucocorticoids. In contrast, in tissues expressing high levels of 11β-HSD1 (e.g., liver, adipose, hippocampal neurons, and macrophages) that are capable of generating active cortisol, Nrf2-dependent antioxidant cellular defense may be suppressed by glucocorticoids activated by11β-HSD1 and acting through GR. Based on these observations, pharmacological inhibition of 11β-HSD1 and antagonism of GR by reducing the amount of GC available in the tissue, may become capable of enhancing the capacity of Nrf2-modulated detoxification processes. Indeed, recent studies suggest that metformin, a synthetic guanidine derivative isolated from Galega officinalis extracts, not only activates Nrf2 signaling by increasing the expression of several cytoprotective enzymes [39] but can also inhibit 11β-HSD1 expression induced by pro-inflammatory cytokines in human adipocytes by suppressing the NF-kB pathway [40] (Fig. 1).

2.3 Dexamethasone Inhibition of Nrf2 Signaling by Direct GR-Nrf2 Interaction

Recently, Alan *et al.* [41] also suggest that GR activated by DEX antagonizes the acti-vation of Nrf2 target genes through GR-Nrf2 interaction. This study indicates that im-pairment of the Nrf2-dependent defense system against oxidative stress accounts for glucocorticoid side effects, suggesting a new viewpoint for the pathogenesis of hypercortico-steroidism. Specifically, the authors demonstrated that DEX treatment during the antioxidant response increased GR recruitment to ARE/EpREs without affecting Nrf2 binding to ARE/EpREs, resulting in inhibition of histone acetyltransferase CBP (CREB-binding protein) recruitment and histone acetylation at ARE/EpREs that reduces Nrf2-mediated cytoprotection from oxidative stress. Because both CBP and GR share Neh4/Neh5 domains to bind Nrf2, it is expected that GR can not only put CBP away from Nrf2 but also recruit and interact with histone deacetylase 2 (HDAC2) to ARE/EpREs by associating with Nrf2 resulting in a decreased transcriptional activity of Nrf2

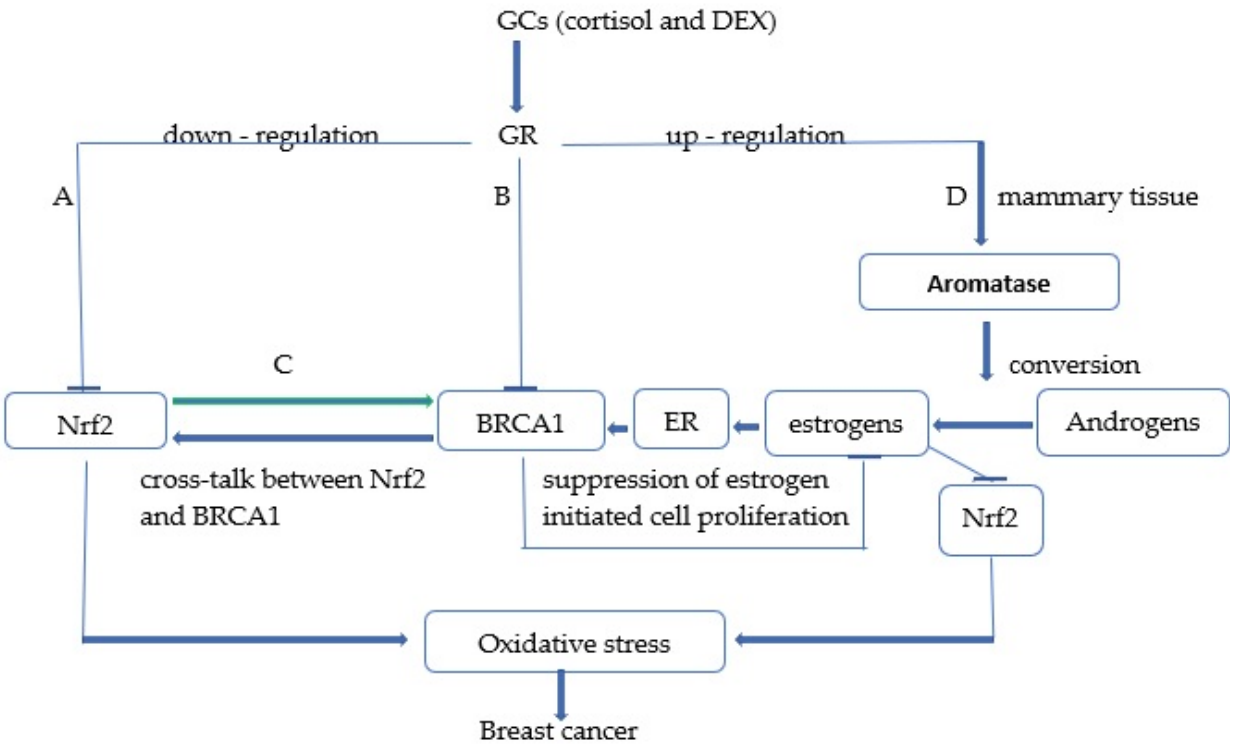

Fig. 1. Schematic representation of potential cellular mechanisms by which both endogenous glucocorticoids (GCs) and dexamethasone (DEX) pharmacotherapy promote breast cancer development through inhibition of Nrf2 signaling. Note: (A) High levels of glucocorticoids (cortisol, DEX) inhibit Nrf2 signaling through several mechanisms exhibited in the report. (B) GCs also inhibit expression of the tumor-suppressor gene breast cancer susceptibility gene 1 (BRCA1) that is involved in both activation of Nrf2 signaling by binding to the Nrf2 promoter and suppression of estrogen-initiated cell proliferation. (C) There is a reciprocal positive cross-talk between Nrf2 and BRCA1, so Nrf2-ARE/EpRE signaling can also stimulate BRCA1 expression, and both the Nrf2 and BRCA1-dependent pathways can be inhibited by high levels of GCs. (D) GCs indirectly inhibit Nrf2 signaling in breast tissue through activation of aromatase, which catalyzes the con-version of androgens to estrone that represses the Nrf2-ARE/EpRE pathway through estrogen receptor (ER)-dependent and -independent mechanisms.

as a consequence of histone deacetylation. In support of this notion, the authors demonstrated that the inhibitory effect of DEX was significantly abrogated by treatment with HDAC inhibitors such as valproic acid (VA) and trichostatin A (TSA), suggesting that GR signaling inhibits the Nrf2-mediated antioxidant response through HDAC recruitment and subsequent histone deacetylation. These results collec-tively support the hypothesis that GR not only reduces Nrf2-dependent transcriptional activation by binding to Nrf2, which is referred to as transrepression, but also that it inhibits the expression of Nrf2 target genes regardless of the presence or absence of glucocorticoid response elements (GREs) (Fig. 1).

2.4 GCs Indirectly Suppress Nrf2 Signaling through Activation of the Aromatase Enzyme and Subsequent Estrogen Generation and Inhibition BRCA1 Gene Expression in Breast Tissue

Glucocorticoids can also indirectly inhibit Nrf2 signaling in breast tissue by activating cytochrome 450 aromatase [42]. This microsomal enzyme catalyzes the conversion of androgen to estrone which is directly involved in the repression of the Nrf2-ARE/EpRE pathway through estrogen receptor (ER)-dependent and independent mechanisms [43–45]. Another important mechanism by which GCs may indirectly promote breast cancer development and progression is through inhibition of BRCA1 gene expression. Specifically, the breast cancer susceptibility gene (BRCA1) is responsible for half of all inherited cases [46]. Mutations in the BRCA1 and BRCA2 genes significantly increase the risk of developing breast and ovarian cancer in women and prostate cancer in men [47–49]. The function of the intact BRCA1 protein has been reported to prevent cancer development through several mechanisms including DNA repair, regulation of cell cycle progression, regulation of transcription, ubiquitination, and maintenance of genomic stability [50]. Importantly, studies by [51] have reported that the BRCA1 promoter contains an estrogen receptor response element (ERE) that can be stimulated by estrogenic activity. Because BRCA1 exerts an important role in suppressing estrogen-initiated cell proliferation and estrogen signaling pathways [52], increased ex-

pression of BRCA1 by estrogen is considered a key feedback mechanism by which rapidly proliferating cells modulate their growth [51]. Accordingly, factors that inhibit this control mechanism are considered essential in inducing dysregulated cell proliferation and breast cancer development. These authors argue that cortisol may act as one of these factors. Indeed, cortisol treatment of breast cells is expected to produce the loss of estrogen-induced stimulation of BRCA1 and the subsequent apoptotic effect by blocking the binding of the transcription factor GABP (GA-binding protein) to promoter regulatory sites (RIBS and UP regulatory elements) that are involved in the regulation of BRCA1 by cortisol [53]. Previous study by Kang *et al*. [54] also suggest that BRCA1 may increase the expression of Nrf2-modulated cytoprotective genes that are involved in the antioxidant and detoxifying cytoprotective response by binding to the Nrf2 promoter and regulating its transcription. In addition, Gorrini *et al*. [55] also reported that the tumor suppressor BRCA1 modulates Nrf2-dependent antioxidant signaling by physically interacting with Nrf2 and promoting its stability and activation. Accordingly, the authors demonstrated not only that mouse mammary cells lacking BRCA1 have increased ROS levels due to an altered Nrf2-dependent antioxidant response, but also that estrogen treatment can partially restore Nrf2 levels in the absence of BRCA1 to promote cell survival. These results collectively indicate that Nrf2 is downstream of BRCA1 and BRCA1 may promote Nrf2 transcriptional activity playing an important role in protecting cells against oxidative stress and carcinogens by Nrf2 [54,56]. Further studies by Wang Q *et al*. [57] also demonstrated that Nrf2, plays an important role in the activation of BRCA1 transcription by binding directly to the BRCA1 promoter, suggesting the existence of a positive regulatory feedback loop between BRCA1 and Nrf2. Specifically, these authors suggest that increased Nrf2 expression significantly promoted not only the recruitment and binding of Nrf2, CBP and p300 active transcription complex to the ARE/EpRE (antioxidant/electrophile response element) site on the BRCA1 promoter but also the acetylation of histone H3 and H4 on the BRCA1 promoter. Both CBP and p300 are histone acetyltransferases (HATs) that act as key transcriptional coactivators [58] by catalyzing histone acetylation, chromatin remodeling, and promoting target gene transcription [59,60]. These experimental results suggest that Nrf2-mediated epigenetic changes involving histone modifications and chromatin remodeling may be responsible for BRCA1 expression. Notably, reduced levels of wild-type BRCA1 expression have been identified in several sporadic breast cancers without BRCA1 gene mutations [61]. Therefore, somatic mutations in the BRCA1 gene may not play a decisive role in breast cancer [62,63]. Decreased BRCA1 expression in sporadic breast cancer could be due to disturbances in gene regulatory mechanisms. For example, UHRF1 (Ubiquitin-like with PHD and ring finger domains 1) might be involved in epigenetic silencing of BRCA1 in sporadic breast cancer by inducing DNA methylation, histone modifications, and recruitment of the transcriptional complex on the BRCA1 promoter [64]. Therefore, elucidating the mechanism of regulation of BRCA1 expression by Nrf2 complexes could lead to a better understanding of breast cancer development. Taken together, these findings clearly indicate that high levels of glucocorticoids as a consequence of stressful life events or drug treatment may significantly contribute to the initi-ation of numerous diseases including breast cancer development and progression through direct and indirect mechanisms involving not only suppression of Nrf2 and BRCA1 expression but also activation of the aromatase enzyme involved in estrogen generation (Fig. 1).

2.5 Persistent Cortisol Production, Increased AGEs Formation and Accumulation, and Breast Cancer

Originally glucocorticoids were so named because of their ability to increase blood glucose concentration. Indeed, adrenalectomized animals or individuals with adrenocortical deficiency (Addison's disease) suffer from persistent hypoglycemia [65]. In humans, glucocorticoids increase circulating glucose levels and lipids metabolites within minutes by acting simultaneously on the liver, skeletal muscles and adipose tissue through the action of the GR [65–70]. Human individuals with higher circulating cortisol levels under resting (non-stressed) conditions also have higher glucose and triglyceride levels and a higher score reflecting insulin resistance and a pre-diabetic state [71]. As mentioned above, chronic psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis and increases circulating levels of cortisol [72]. The HPA axis also stimulates the sympathetic nerves system (SNS) activity, which, in turn, increases catecholamine levels [73]. Increased cortisol concentrations can be considered as an important risk factor for the development and progression of many disease conditions, including type 1 and 2 diabetes, cancer, and metastasis [74,75]. Indeed, elevated cortisol levels associated with stressful life events [7] or diets based on high-glycemic index carbohydrates [76,77] due to their ability to create hyperglycemic conditions such as those found in diabetes, are recognized to be responsible for high rates of protein glycation and the subsequent formation and accumulation of advanced glycation end products (AGEs) [78]. Increased protein glycation and gradual accumulation of AGEs are involved in the pathogenesis and development of numerous chronic and age-related inflammatory diseases, such as diabetes and diabetic complications, cardiovascular diseases, Alzheimer's disease, stroke and various types of cancer, including breast cancer [77–81]. It is important to note that AGEs are a heterogenous group of cross-linked irreversible components (e.g., pentosidine, hydro-imidazolone, carboxymethyllysine) that are formed through nonenzymatic post-translational modifications of macromolecules such as proteins, lipids and nu-

cleic acids by reducing sugars (glucose, fructose and pentose) through the Maillard reaction. AGEs can be generated exogenously in food, particularly through thermal processing, but also endogenously in the body [82]. More commonly, the most potent reactive α-dicarbonyls, such as 3-deoxyglucosone (3-DG), methylglyoxal (MGO) and glyoxal (GO), derived from different pathways, serve as precursors for AGE formation [83,84]. These compounds exert their effects not only by direct damage to protein structures and extracellular matrix alteration but also by binding the receptor for advanced glycation end products (RAGE) [78]. Indeed, numerous studies indicate that AGEs through interaction with RAGE could play an important role in the initiation and progression of different subtypes of breast tumors through NF-kB activation [78,85]. RAGE is a multiligand transmembrane receptor that belongs to the cell surface immunoglobulin superfamily [86]. In addition to binding to AGEs, RAGE can also bind to several other molecules, such as high-mobility group box-1 (HMGB), β-sheet fibrils, β-amyloid peptides, several members of the S100 protein family, and prions [87]. AGE-RAGE interaction activates a multitude of signaling cascades, causing multiple pathological effects associated with oxidative stress and inflammation [88]. For example, studies by Sharaf H *et al*. [89] suggested that AGE treatment of breast cancer cell lines induced the promotion of cell growth, migration, and invasion. In addition, Nankali M *et al*. [90], also showed that the mRNA and protein levels of RAGE were increased in triple-negative, advanced stage breast tumors and node-positive tissues compared with noncancerous tissues, suggesting that RAGE may significantly contribute to the malignant potential of tumors. The authors also reported that RAGE expression and tumor size were well-correlated. Therefore, RAGE could be used as a potential biomarker for prognosis and diagnosis of breast cancer progression. Notably, Nrf2 is a redox-sensitive transcription factor that plays a dual role in both cancer initiation and progression. At early stages, Nrf2 exerts a protective role against cancer development by blocking the ROS-induced mutagenic effects of carcinogens through activating the transcription of several cytoprotective genes responsible for glutathione (GSH) synthesis, redox homeostasis, xenobiotics detoxification and anabolic metabolism, etc. [21,91]. In addition, Nrf2 also induces glyoxalase 1 (GLO-1) expression which is involved in the detoxification of reactive dicarbonyl compounds such as methylglyoxal (MGO), using the glutathione as a cofactor [82]. Indeed, loss of Nrf2 function can promote neoplastic transformation of primary cells [92]. However, once tumors have developed, activation of Nrf2 signaling may protect tumor cells from ROS-mediated cytotoxicity, thereby facilitating their survival, migration, invasion and progression to highly advanced tumors, as well as drug resistance [93,94]. Recent studies from several laboratories suggest that mechanisms of protein glycation and deglycation may play an important role in regulation of oncosuppressive and oncogenic functions of Nrf2 *in vivo*. Specifically, Nrf2 activity primarily depends on deglycating enzyme fructosamine-3-kinase (FN3K), an unique kinase cpable of triggering protein deglycation or removal of attached sugars by directly phosphorylating the attached sugars, leading to their destabilization and spontaneous shedding from the protein surface [85,95]. In normal cells, in its absence, Nrf2 is incapable of triggering transcriptional activation being largely glycated, unstable, and defective in binding to small proteins in musculoaponeurotic fibrosarcoma (MAF). Importantly, glycation significantly increases Keap1 mediated Nrf2 degradation. Moreover, glycation of Nrf2 also alters its interaction with transcription cofactors and sMAF proteins. In contrast, deglycated Nrf2 by FNK3 is stable and binds to small MAF proteins, thereby activating cellular antioxidant mechanisms to protect cells from oxidative stress. Instead, in cancer cells or *in vivo* cancer models, FNK3 deficiency inhibits the pro-oncogenic and drug resistance effects of Nrf2. This indicates that deglycating enzyme FNK3 is required to maintain Nrf2 in its unglycated and active state, despite not being sufficient to active Nrf2. Another important pathway for the detoxification of reactive α-dicarbonyls such as MGO, glyoxal (GO) and other reactive dicarbonyl compounds in eukarjotic cells is the glyoxalase system. It consists of two enzymes: glyoxalase 1 (GLO-1) and glyoxalase 2 (GLO-2) and molecules of reduced glutathione (GSH), a tripeptide involved in the detoxification of xenobiotics, maintenance of the redox state and regulation of the immune response [82,96]. As mentioned above, the expression of GLO-1/GSH is under the control of Nrf2 stress response, so the glyoxalase system and GSH exert dual roles in both normal and cancer cells. Accordingly, several research groups have shown that induction of the glyoxalase detoxification system by Nrf2 signaling represents an important defense mechanism against decarbonyl glycation–induced stress under conditions of chronic hyperglycemic, inflammation, cellular aging and senescence by significantly reducing toxic levels of MGO, GO and other AGEs through catabolization of these two AGE precursors [96–98]. In contrast, increased GSH expression and GLO-1 activity has also been reported in several human cancers, including breast cancer and multidrug resistance. This suggests that increased GLO-1 and GSH activity is favorable for survival and growth of malignancies, including different breast cancer subtypes with high rate of glycolytic and relative high fluxes of MGO formation [99–101]. Taken together, these results suggest that elevated cortisol levels associated with stressful life events, through their ability to generate higher levels of glucose and tryglicerides, play an important role in the induction of the process of breast carcinogenesis through the formation and accumulation of AGEs and the elevated expression of the gene encoding RAGE in breast cancer samples.

3. The Possible Role of Melatonin in Suppressing Glucocorticoid-Induced Apoptosis in the Immune System by Involving Nrf2 Signaling and Breast Carcinogenesis Results

In addition to the functions described above, high cortisol levels may also contribute to the development and progression of breast cancer by altering immune system function and elimination of transformed breast cells [102]. In particular, glucocorticoids at pharmacological levels exert a potent antiinflammatory effect, whereas prolonged exposure to glucocorticoids can lead to a variety of undesirable side effects through several mechanisms, including immunosuppression [102–104]. Indeed, both chronic stress conditions (when endogenous glucocorticoid production is high) and glucocorticoid pharmacotherapy can significantly alter immune cell differentiation, exerting immunosuppressive effects [105–107]. In addition, glucocorticoids may also elicit a state of immunosuppression by inhibiting the Nrf2-dependent antioxidant response and increasing apoptosis in immune cells [28,108,109]. As mentioned above, Nrf2 signaling may protect normal cells against DNA damage, ROS-induced mutagenesis, and carcinogenesis by increasing the expression of several phase 2 detoxification enzymes and oxidative stress-related proteins such as NQO1, heme oxygenase 1 (HO-1), GSTs, UDP-glucuronosyl transferases (UGTs), superoxide dismutase's (SODs) [21,110, 111]. Activation of GRs by glucocorticoids has been reported to increase apoptosis by affecting apoptotic proteins and through downregulation of the Nrf2-dependent antioxidant response [33,112]. Binding of GCs to GRs is known to sensitize GRs for their nuclear translocation [113]. Indeed, many studies suggest that GR transcriptional activity is regulated at every step of its activation, including ligand binding, nuclear translocation, transcriptional cofactor binding, and DNA binding [114,115]. The level of Heat Shock Protein 90 (HSP90), which is an important molecular chaperone of GR, is essential for translocation and transactivation of activated GR [113,116]. It appears that an increase in the HSP90/GR ratio can significantly affect the interaction of GR with its ligand (GC), and excess HSP90 blocks the binding of GR to its DNA response element [117]. In particular, it has been shown that association of HSP90 with GRs is essential to maintain the receptor not only in its steroid-binding conformation but also in an inactive transcriptional state, even when GRs are located in the nucleus [118]. Indeed, dissociation of HSP90 from the receptor allows binding of the receptor to DNA and subsequent modulation of gene transcription [118]. Either chronically stressful conditions or dexamethasone treatment may promote nuclear GR translocation by facilitating dissociation of HSP90 from GR-HSP90 complex, reduce Nrf2/HO-1 dependent antioxidant response and up-regulate apoptosis by reducing Bcl-2 and increasing Bax expression respectively in immune cells [33,112,119–121]. It has also been reported that dexamethasone treatment reduced the proliferative response by down-regulationg IL-2R expression and exerting an inhibitory effect on IL-2 secretion from immune cells [122–124]. In contrast, treatment with melatonin (MLT) alone or in combination with DEX, due to its immunomodulatory property, significantly enhanced proliferative responses [125,126]. In addition, MLT also blocked stress-dependent immunosuppression by increasing IL-2 secretion from immune cells such as T-helper cells and peripheral blood mononuclear cells (PBMCs) [127,128]. Notably, melatonin is a chronobiotic hormone produced primarily by the pineal gland only at night or more precisely in the darkness from the amino acid tryptophan. There is also evidence that melatonin is produced by the mitochondria of many other cells and organs, including immune cells in a non-circadian manner [129]. Melatonin (MLT) exerts considerable functional versatility with antioxidant, oncostatic, anti-aging, antistress, and immunomodulatory properties [130]. In mammals, rhythmic melatonin production, in addition to being controlled by the central biological clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus via nocturnal sympathetic input from noradrenaline, is also influenced by glucocorticoids through modulation of the NF-kB transcriptional program [131]. Indeed, some studies suggest that corticosterone increases nocturnal melatonin synthesis by reducing the activity of NF-kB, a pivotal transcription factor that regulates the expression of the key enzyme arylalkylamine N-acetyltransferase (AANAT) directly involved in melatonin synthesis. Accordingly, the pineal gland is a target of GCs as it expresses many glucocorticoid receptors [132]. In particular, glucocorticoids exert a dual effect on melatonin production. Under stressful conditions, characterized by concomitant $\beta 1{+}\alpha 1$ adrenoceptors stimulation, corticosterone reduces melatonin synthesis in the pineal gland [133,134]. In contrast, nocturnal melatonin production is stimulated by low stress conditions when only $\beta 1$-adrenoceptors are activated [133,134]. Studies by Singh and Haldar [108] have shown that melatonin can also regulate stress condition by modulating antioxidant responses and apoptosis in immune cells such as PBMCs through different mechanisms. For example, previous studies by Sainz *et al*. [135] suggest that melatonin is capable of preventing apoptosis *in vivo* and *in vitro* in Wistar rat thymocytes treated with GCs (DEX) to induce apoptosis. Mechanistically, MLT significantly reduces the percentage of apoptotic cells induced by GCs through several mechanisms. These include the antiox-idant action of MLT, direct interaction of melatonin with GCs in the thymus, induction of interleukin-4 releases, an effect on nitric oxide synthase, and finally a direct genomic ac-tion regulating the expression of apoptosis inhibitory genes. Melatonin has also been proposed to counteract the immunosuppressive effects of GCs by up-regulating the ex-pression of melatonin receptors (MT1, MT2) on the cell surface of lymphoid organs on the one hand and down turning the sensitiv-

ity of immunocompetent cells towards glucocorticoids on the other hand, decreasing corticosterone secretion and attenuating GR expression in lymphocytes [136]. Studies by Pressman *et al*. [119] also indicate that MLT exerts antagonistic activity on GR-mediated effects through inhibition of HSP90 dissociation and cytoplasmic retention of GR in mouse thymocytes. Similar studies published recently by Singh and Haldar [108] also demonstrated that melatonin can regulate GR-mediated suppression of antioxidant responses and apoptosis in other immune cells. For example, melatonin may inhibit apoptosis in PBMCs by blocking nuclear translocation of GR through suppression of HSP90 dissociation from the GR-HSP90 complex and by retaining GR in the cytoplasm. It appears that melatonin treatment also increases HSP90 in the nuclear fraction compared with dexamethasone treatment in PBMCs and that accumulation of HSP90 in the nucleus may dramatically decrease GR binding to its DNA response ele-ment and transactivation [137]. Therefore, increased expression of HSP90 by pineal hormone could significantly attenuate GR-mediated activities and increase Nrf2/HO-1 expression in PBMCs. In addition to HSP90, other factors such as the immunophilins FKBP52, FKBP51, and cyclophilin 40 may also play important roles in the maturation and nuclear translocation of GR, and the stress condition influences their binding to HSP90 in the GR-HSP90 complex [116]. Several studies have also reported that melatonin exerts antiapoptotic effects by down-regulating cleaved Bax and caspase-3 (proteins) [108,138] and up-regulation of Bcl-2 through involvement of the Nrf2-ARE/EpRE pathway [108,139,140]. These results collectively indicate that inhibition of GR nuclear translocation upon melatonin treatment can significantly increase Nrf2/HO-1-dependent antioxidant response and Bcl-2 expression, leading to an increased Bcl-2/Bax ratio in PBMCs that rescued cells from apoptosis under stress conditions [108,112] (Fig. 2).

4. Discussion and Conclusions

Although several genetic factors have been identified in breast cancer, most cases are attributed to environmental factors. At least, it is widely accepted that among risk factors, prolonged exposure to high levels of estrogen plays an important role in the initiation and development of breast cancer [141]. Indeed, studies in experimental animal models and cultured human cells strongly suggest that estradiol (E2), its interconvertible metabolite estrone (E1), and their estrogen quinones exert carcinogenic effects on breast tissue through several mechanisms [142]. There are at least two main mechanisms involved in the development and progression of estrogen-induced breast cancer: (i) estrogen receptor mediated stimulation of abnormal cell proliferation that generates random mutations; (ii) ER-independent mechanisms involving chemical (oxidative pathway) inflammatory, epigenetic, and cancer stem cell pathways [143–145]. In addition, although less well known and studied, either chronic stress conditions (when endogenous glucocorticoid production is high) or dexamethasone treatment to reduce inflammation may also significantly increase breast cancer risk. In our review, we examined potential cellular mechanisms by which (both) glucocorticoid drug treatment and psychological stress-related cortisol release may contribute to breast cancer development through inhibition of the Nrf2-ARE/EpRE dependent antioxidant response. For example, research has shown that cortisol treatment significantly reduced the expression of the gene encoding the tumor suppressor protein BRCA1 involved in the control of estrogen-induced breast cell proliferation and DNA repair capacity. Because BRCA1 is able to influence Nrf2-dependent transcriptional activation and the subsequent antioxidant response, factors that inhibit this mechanism should also contribute to the development of breast cancer in response to stress. There are also other mechanisms by which glucocorticoids may influence breast cancer development and progression by involving the Nrf2-ARE/EpRE pathway. For example, glucocorticoids may antagonize the activation of Nrf2 target genes in a GR-dependent manner. Specifically, dexamethasone (DEX) treatment can increase GR recruitment to ARE/EpREs without altering chromatin binding of Nrf2, resulting in suppression of CBP recruitment and histone acetylation to ARE/EpREs. Thus, GR signaling significantly reduces Nrf2 transcriptional activation by decreasing Nrf2-dependent histone acetylation, consequently impairing the Nrf2-dependent cellular antioxidant response and predisposing to diseases such as immune dysfunction and cancer [41,146]. Studies by Ki *et al*. [28] also indicate that after activation of GR by DEX, the GC-GR complex migrates to the nucleus where it binds to GREs on the promoter region of GST. Subsequently, recruitment of transcriptional repressors NCoR and SMRT to the DEX-GR complex on GRE leads to suppression of the expression of phase II detoxifying enzymes such as glutathione-S-transferase (GST) not only by regulating chromatin structures through histone deacetylation but also by directly binding to the Neh 4/5 domain of Nrf2, a protein motif essential forNrf2 transactivation. Accumulating scientific evidence also indicates that circulating levels of GCs are regulated by the hypothalamic-pituitary-adrenal axis, whereas their tissue levels are controlled by en-zymes such as 11β-HSD1 and 11β-HSD2 [147,148]. In addition, previous studies by Kratschmar *et al*. [33] also reported that cortisol can inhibit Nrf2 signaling without requiring a GRE sequence in the promoter region. Specifically, the authors suggest that, endogenous GCs can be metabolically inactivated by 11β-HSD2 and regenerated by 11β-HSD1 in several tissues. Therefor in tissues expressing high levels of 11β -HSD1 enzyme that generates active cortisol, the Nrf2-dependent antioxidant response can be in-hibited by high levels of GCs whereas in those expressing high levels of 11β-HSD2 en-zyme, Nrf2 can be insensitive to GCs. This

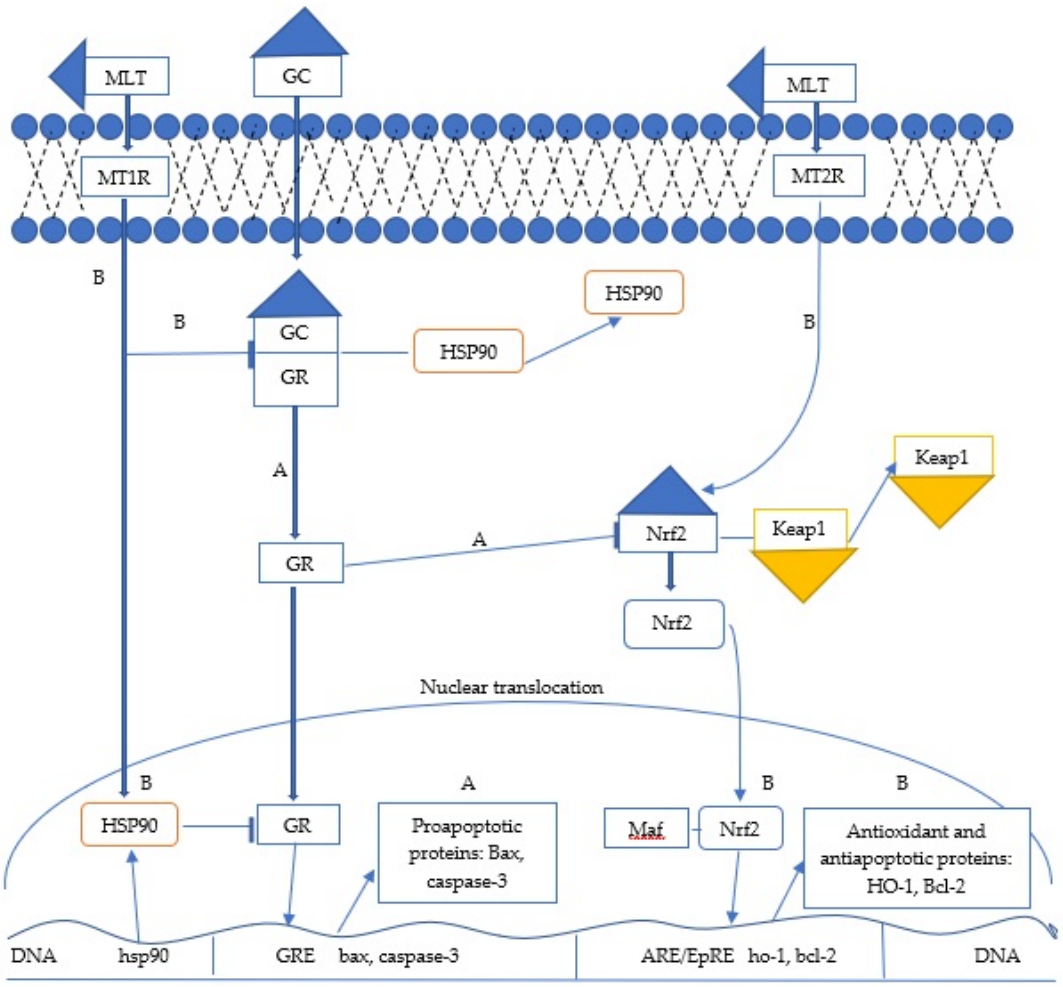

Fig. 2. Potential mechanisms by which melatonin inhibits immunosuppressive effects by either high levels of endogenous glucocorticoids (GCs) or dexamatasone (DEX) pharmacotherapy. Note: (A) Binding of GCs to the glucocorticoid receptor (GR) sensitizes the GR to its nuclear translocation by promoting dissociation of HSP90 from the GR-HSP90 complex, suppression of the Nrf2 signaling-dependent antioxidant response, and subsequent apoptosis in peripheral blood mononuclear cells (PBMCs) by increasing expression of the proapoptotic proteins Bax and cleaved caspase-3. (B) The binding of melatonin to its receptors (MT1,MT2) inhibits the immunosuppressive effects of GCs through several mechanisms such as : (1) blocking the dissociation of HSP90 from the GR-HSP90 complex; (2) increasing the expression of HSP90 protein in the nuclear fraction that attenuates the transcriptional activity of GR involved in the expression of apoptotic proteins; (3) stimulating the Nrf2 signaling-dependent antioxidant response and finally (4) increasing the expression of Bcl-2 and the Bcl-2/Bax ratio in PBMCs to maintain immune homeostasis under stressful conditions.

observation indicates that the effect of GCs on the Nrf2 signaling is highly-tissue and cell-specific, reflecting the expression of the respec-tive 11β-HSD enzyme. Growing evidence also suggests that cortisol may contribute indirectly to breast carcinogenesis by modifying estrogen generation and activity. Indeed, persistent exposure to elevated estrogen levels may play an important role in the etiology of breast cancer. An important mechanism of estrogen production in breast tissue is the expression and activity of the cytochrome P450 aromatase (CYP19) enzyme that converts androgens to estrogens. Many studies also indicate that aromatase activity and mRNA levels are significantly increased in breast tissue and that aromatase is able to stimulate breast cancer cell proliferation *in vitro*. Several factors are responsible for aromatase activation in breast tissue. These include not only cytokines and prostaglandin-E2 (PGE2) released by inflammatory cells or breast cancer cells [149,150] but also cortisol [151]. Thus, the stimulation of breast cancer development by prolonged exposure to elevated cortisol levels during periods of stress may depend primarily on increased estrogen production by the aromatase enzyme. Other limitations of the use of GCs for breast cancer therapy are their undesirable effects such as hyperglycemia and immunosuppression. In addition, glucocorticoids may also promote breast cancer development by increasing RNS/ROS production and interfering in DNA

repair processes in different cell types [8]. Indeed, studies of peripheral blood lymphocytes and spleens from stressed rats showed that levels of a major DNA repair enzyme, O6-methylguanine-methyltransferase (MGMT), were significantly reduced compared with those obtained from control rats [152]. The study by Singh and Haldar [108] have also shown that melatonin can regulate the stress condition by modulating antioxidant responses and apoptosis in immune cells such as PBMCs through several mechanisms. For example, it can inhibit GR nuclear translocation by blocking the dissociation of HSP90 from the GR-HSP90 complex and retaining GR in the cytoplasm. Moreover, under stress conditions, melatonin may also neutralize the immunosuppressive and apoptotic effects of GCs by increasing Nrf2/HO-1-mediated antioxidant response and Bcl-2 expression on the one hand and reducing the expression of Bax and caspase-3 proteins in PBMCs on the other side. In summary, through GR signaling makes a critical contribution to maintenance of systemic energy homeostasis and stress response in collaboration with the sympathetic nervous system, increased activation of GR signaling by high levels of GCs often causes many side effects. These effects can be exacerbated in Nrf2-deficiency conditions that promote oxidative stress enhancing the risk of developing several malignancies. Given the protective role of melatonin in breast cancer development and progression, many researchers are developing strategies to implement daily rhythms of this pineal hormone in women at risk for breast cancer and in those currently fighting cancer. Further studies using *in vivo* animal models and clinical trials are needed to improve our knowledge not only of the role of melatonin in breast cancer, but also of the mechanisms of action by which glucocorticoids promote breast carcinogenesis through inhibition of Nrf2. A better understanding of these processes could significantly contribute to develop novel strategies for the prevention and therapy against diseases including breast cancer.

Author Contributions

AG, AB, GDA, EC, MCar and MCap designed the study. AG wrote the manuscript. SMA provided help and advice on grammar. PP and IB contributed to the literature search. SMA designed the figures and provided review and editing. AB, PP, IB, GDA, EC and MCar critically visualized the manuscript. MCap supervised the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Ethical approval from the Human Research Ethics Committee was not required for this study. This is a retrospective study and is not directly associated with patients.

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Conflict of Interest

The authors declare no conflict of interest.

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