Review Article
Genomic and non-genomic effects of glucocorticoids: implications for breast cancer

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Abstract: Glucocorticoids (GC) are essential steroid hormones for human life. They regulate a series of important processes by binding with three glucocorticoid receptors (GR) and activating genomic and non-genomic pathways. Activated cytoplasmic GR can directly bind DNA and transactivate or transrepress specific genes. Additionally, it can interact with other transcription factors to affect gene expression indirectly. The two membrane GR can interact with mitogen-activated protein (MAP) kinases or activate cAMP and Ca2+-dependent pathways, respectively. Glucocorticoids have been widely used as co-treatment of patients with breast cancer (BC) due to reduction of chemotherapy-induced side effects such as nausea, lack of appetite, and inflammation. However, GC may exert a direct effect on tumor response to chemotherapy. In vitro, GC inhibits chemotherapy, radiation and cytokine-induced apoptosis by upregulating antiapoptotic genes and detoxifying proteins. They also upregulate the proto-oncogene c-fms, tumor suppressor gene Nm23, several members of the epidermal growth factor (EGF) signaling pathway and the estrogen sulfotransferase signaling pathway, thus indirectly inhibiting estrogen receptor activation. They inhibit the proangiogenic gene (vascular endothelial growth factor (VEGF)); Therefore, they could play a role in reducing angiogenesis. Interestingly, the phosphorylation status of ser-211 in the GR is dependent on the expression of the BRCA1 gene, a tumor suppressor gene that is mutated in the majority of patients with triple negative BC. Some clinical randomized trials have also attempted to address the effect of GC on patients with BC. Thus, in this review we summarize GC mechanisms of action and their participation in several facets of BC.

Keywords: Glucocorticoids, breast cancer, genomic, non-genomic, glucocorticoid membrane receptor

Introduction

The main physiological functions of glucocorticoids (GC) include downregulating the immunological function (immunosuppression), increasing the production of glucose [1], changing carbohydrate, protein, and lipid metabolism, regulating vascular tone, regulating bone mineralization, and affecting the central nervous system (CNS) [2, 3]. GC is released in response to stress conditions. Under such conditions, the hypothalamus secretes a corticotrophin-releasing hormone that stimulates the hypophysis gland. In turn, this gland produces the corticotrophin hormone that acts on the cortex of the suprarenal gland. It is here that GC are produced and secreted into the bloodstream, where they bind with globulins and are transported throughout the body [4]. This system is known as the hypothalamic-pituitary-adrenal axis (HPA axis).

GC have genomic and non-genomic effects

Three main mechanisms of action for GC have been described. The first is the genomic mechanism, which involves a classic cytosolic GC receptor (GR), while the remaining two mechanisms are non-genomic. One uses the classic GR but bound to the plasma membrane, and the other is dependent on a non-classic membrane GR.

GR belongs to the family of steroid receptors

GR belong to the superfamily of nuclear receptors of transcription factors [5]. It relates to other steroid receptors, such as those for min-
eralocorticoids, androgens, estrogens, progesterone, thyroid hormones, vitamin D, and retinoic acid [6]. All of these receptors are evolutionarily conserved in mammals and it has been proposed that they originated from the multiple duplication of a common ancestor gene 400 million years ago [7].

**GR is essential for life, tissue-specific GR deletion**

GR are essential for life; this has been proven in various murine models containing the mutated GR. Complete deletion of the second exon of the murine GR gene gives rise to severe anomalies in lung development, which lead to death a few hours after birth [8]. In the liver, the GR has proven to be responsible for gluconeogenesis [9]. In the CNS, GR deficiency causes irregularities in the HPA axis, and the development of a great number of physiological and behavioral changes that mimic depressive disorders [10].

**GR gene and its alternative splicing**

The GR gene in humans is located on the fifth chromosome (5p31q region) and has 9 exons. Its transcription is regulated by at least three promoters, which contain sites for the binding of diverse transcription factors. In mature messenger RNA (mRNA), exon 1 represents the 5' untranslated (UTR) region, exons 2-9 encode for the protein and the 3'UTR [4, 11, 12]. The following five isoforms of the human GR gene are known: GRα; GRβ; GRγ; GR-P, and GR-A [13]. The processing of exon 9 by alternative splicing produces the two most well-known isoforms: human GRα (hGRα), and human GRβ (hGRβ). The latter isoform has only 742 aa, permanently localizes to the nucleus, is transcriptionally inactive, cannot bind with any GC [14], and acts as an antagonistic form (dominant negative regulator) of GRα, but its physiological relevance is poorly understood [15]. Its overexpression has been associated with the development of cardiovascular disease, GC-resistant asthma, ulcerative colitis, and rheumatoid arthritis.

**GRα isoform, the predominant physiological form, and its protein domains**

On the other hand, Glucocorticoid receptor alpha (GRα) is the predominant isoform, and mediates the classic GC effects [16]. It consists of 777 aa and has a molecular weight of 94 kDa (estrogen receptor α has only 66 kDa) [17]. The amino terminal side possesses a domain called the Transcriptional activation (AF-1) that plays a role in gene transcription and is hormone-independent. Near this domain, a leucine zipper has been discovered that is important in GC action [18]. In the central region of the GR lies the DNA binding domain (DBD) that has specificity for GC response elements (GRE). The DBD is composed of two zinc ions complexed with eight cysteines, a motif termed zinc fingers, which interacts with the major groove of the DNA double helix. Additionally, in the central domain lies the dimerization domain, which forms a helix that reacts with a similar domain in an identical receptor in order to dimerize. On the carboxyl terminus side we find the following: the ligand-binding domain; the nuclear importation and exportation sequences; heat shock protein-90 binding zones and, on the very end, the hormone-dependent transcriptional activation domain (AF-2) [19].

**Genomic effect of GC**

The genomic mechanism of GC is that which produces changes in the levels of the specific mRNA. These might result from changes in the transcription or changes of the half-life of the mRNA [20]. It involves the classical cytosolic GRα (cGRα) that, once coupled with the GC, translocates to the nucleus and interacts with DNA directly or indirectly by forming protein-protein complexes.

**GR activation, nuclear translocation, and GRE**

Because GC is lipophilic substances, they can easily go through the cell membrane and bind the cGRα, which is expressed in nearly every human cell. In the absence of its ligand, the cGRα is localized in the cytoplasm, complexed with Heat shock proteins/chaperones of 90 kDa (HSP-90), immunophilin, and other proteins. They block the Nuclear localization sequence (NLS) of the cGRα, thus inhibiting GR nuclear translocation. The GR bound to these proteins presents a three-dimensional (3-D) structure with three exposed domains, the HSP binding domain; the DNA binding domain, and the ligand binding domain. Once the GC binds the cGRα, the latter undergoes conformational changes and is phosphorylated by p38 MAP Kinase.
kinase at serine 211. This serine is crucial for maximal transactivation of GC signaling. Other phosphorylatable serines have been identified at positions 203, 226, and 404; however, they have been associated with the inhibition of GC signaling [13]. After phosphorylation of the GR, an allosteric change is produced in the inhibitory complex of proteins mentioned earlier that promote their dissociation from the cGRα, allowing the NLS and the dimerization domain (DD) to be exposed. Consequently, the cGRα forms a homodimer with an identical cGRα, translocates to the nucleus, and binds GC response elements (GRE) in the promoters of its target genes. The majority of GRE are composed of a palindromic 15 bp conserved sequence 5'-AGAACANNNTGTTCT-3'. However GRE in some genes are one half of that size but have similar transcription activity. The number and localization of GRE in a specific promoter is highly variable. This conformation of the activated cGRα allows physical interaction with a variety of co-regulating factors and with chromatin [21, 22].

**DNA binding-dependent transactivation mechanisms**

Three mechanisms by which the cGRα can directly transactivate gene expression have been described. If the GRE is near a TATA box, the cGRα can recruit the general transcription factors (TAF), such as TAFIID, and promote gene transcription [23]. On the other hand, if the GRE is located far from the TATA box, the cGRα can associate with co-activators that serve as bridges to promote recruitment of basal transcription machinery. Third, the cGRα can recruit chromatin remodeling complexes (CRC) to alter the nucleosomal structure of DNA, creating a favorable environment for gene transcription. These CRC are histone acetyltransferases (HAT), for example CBP, p300, PCAF, and SRC-1, or ATP-dependent CRC-like SWI/SNF. Examples of genes upregulated by GRE are tyrosine-aminotransferase, alanine-aminotransferase, and phosphoenolpyruvate-carboxykinase, all involved in gluconeogenesis of the liver [14, 24, 25]. The immunosuppressive anti-inflammatory effects of GC are mediated through the transrepression function of GR, whereas undesirable side effects, such as GC resistance, are thought to occur mainly through the activation of gene transcription [26].

**Transrepression by direct DNA binding (negative GRE)**

Interestingly, cGRα can also transrepress gene transcription by directly binding negative GRE (nGRE). nGRE are similar to the previously described GRE and are nearly always localized within the proximity of the binding sites of other transcription factors. This binding produces gene silencing by competition and displacement in the DNA of the other transcription factor [27]. An example can be found in the promoter of the osteocalcin gene. It contains an nGRE that overlaps with the TATA box, and the association of cGRα at this site prevents the binding of the transcription machinery. In the human FASL gene, the nGRE is adjacent to the nuclear factor-kappa B (NF-kB) binding site; thus, the binding of cGRα does not allow binding of NF-kB, and induces gene silencing. Even though GC represses one half of the genes that they regulate, it is known, only for some of these, that they are regulated by nGRE. Other genes regulated by nGRE include proopiomelanocortin, CRH, prolactin, and the serotonin neuronal receptor [14, 23]. The concentration of the GR and the specific ligand it encounters, such as Dex or Corticosterone, determines negative feedback on the HPA axis [28]. GC also regulates post-transcriptional events such as protein synthesis and secretion [15].

**Transactivation independent of direct DNA binding (cross-talk with other transcription factors)**

Alternatively, cGRα indirectly modulates gene transcription by interacting with other proteins in the nucleus, such as transcription factors like activated protein complex-1 (AP-1), nuclear factor of activated T-cells (NFAT), NF-kB, and Signal transduction and transcription proteins (STAT). AP-1 is a heterodimer composed of c-jun and c-fos that promotes gene transcription, but activated cGRα inhibits AP-1 action by binding with the c-jun unit, transrepressing the transcription of the target genes such as collagenase, stromelysin, and other metalloproteinases. In the case of STAT, it has been shown that cGRα interacts physically with STAT-5 while it is directly associated with DNA, but cGRα does not bind with DNA, this allows the activation of a variety of genes [14, 29]. It is noteworthy that gene transrepression by cGRα appears to be
attributable essentially to its direct protein-protein interaction with transcription factors of pro-inflammatory genes such as AP-1, NF-κB, and Smad3. Activated cGRα is able to interact with the p65 subunit of NF-κB or to stimulate, in some cells, the synthesis of inhibitors such as members of the IκB protein family, which prevent translocation of NF-κB to the nucleus. IκB also inhibits NF-κB gene transcription effects by directly inhibiting the histone acetylation function of CBP, p300, SRC-1, or by interfering with the phosphorylation of RNA polymerase II. In the case of Smad, cGRα reduces the transcriptional activity of the Smad 3-4 complex by an unknown mechanism [14].

Post-transcriptional regulation by GR, reducing mRNA half-life

GC is able to reduce the half-life of some mRNA, such as that of tumor necrosis factor (TNF), an important pro-inflammatory cytokine. This is due to that cGRα induces the expression of tristetrapoline (TTP), a protein with zinc-finger domain capable of binding mRNA that contain adenylation/uridylate (ARE)-rich 3'UTR sequences [30]. These sequences are considered important cis-elements and are the most relevant and conserved group of functional sequences associated with mRNA stability and translation. The TTP-ARE association produces the rapid degradation of the target mRNA by recruiting specific RNAses. These sequences are heterogenic, but in general form AUUUA pentamers. They can be found in different combinations, and occasionally the pentamer is not present [24, 20, 31, 32].

Non-genomic effects of GC

The wide range of actions of steroids cannot be explained only by their nuclear effects. Therefore, the hypothesis has been postulated that they possess non-genomic effects. These latter effects would include those produced at the level of the plasma membrane and the ion channels. Non-genomic effects were defined by Losel and Wehling as any action that does not affect gene expression initially or directly, but that does induce rapid effects, such as activation of signal transduction pathways. The short time that these take implies that the effects are unaffected by inhibitors of transcription and protein synthesis; they can occur in cells that do not have a nucleus, such as platelets, erythrocytes, and sperm, and they can be triggered by steroid analogs (for example, bovine serum albumin [BSA] conjugated with steroid molecules) that cannot access the intracellular compartment (e.g., bind cGRα) [20, 33, 34]. In 2002, the Working Group at the FASEB Summer Conference on rapid steroid signaling suggested naming these effects Membrane-initiated steroid signaling (MISS), in contrast with genomic or Nuclear-initiated steroid signaling (NISS) [21]. However, in the literature, the former effects are described as non-genomic.

Ca²⁺, the second messenger of non-genomic GC effects

The second messenger most commonly involved in the non-genomic effects of steroid hormones is intracellular Ca²⁺. Its basal levels decrease rapidly in human bronchial epithelial cells treated with dexamethasone (Dex). Additionally, GC also affect actin polymerization, such as in the endometrial adenocarcinoma cells of Ishikawa and human T lymphocytes, where it even increases their migration capacities after treatment with 0.1 µM [20, 35]. Some therapeutic drugs specifically target the non-genomic pathway [36].

Classic membrane GR

To date, the non-genomic effects of GC have been described as involving two types of receptors: the well-known classic GR, but that localizes in the plasma membrane instead of in the cytosol (mGR), and the non-classic GR, also associated with the plasma membrane.

Classic mGR was identified in peripheral blood lymphomas and monocytes as a modified form of the cGRα [37]. It is recognized by antibodies developed against cGRα, has a similar capacity for binding HSP and DNA, and presents similar phosphorylation patterns [38]. However, it presents a different localization, molecular weight, and binding specificity to GC than cGRα [39, 40]. It regulates three signaling pathways. First, it has been shown that it can activate p42 MAPK [41]. Second, it has been demonstrated that it inhibits MAPK ERK1/2 in mice mastocytes, human osteoblasts, and T-cells. This inhibition occurs by different mechanisms; in mastocytes and osteoblasts, it is dependent on MAPK phosphatase-1 (MKP-1), while in human T-cells, it involves phosphorylation of Raf-1.
Moreover, GC generate post-translational modifications on other MAPK, such as JNK/SAPK in smooth muscle cells of the respiratory tract [42, 43] and in murine macrophages. In primary cultures of hippocampal neurons, GC stimulates the PKC signaling pathway. In the heart, GC activates the PI3K/Akt pathway, which activates endothelial nitric oxide synthase (eNOS), and this produces nitric oxide (NO). In endothelial cells, the same pathway is turned on by Dexamethasone (Dex) [20]. In skin cancer, the mGR/PI3K complex possesses an antitumor effect [44]. A third pathway has been described that initiates by the activation of proteins with SH3 domains such as Src and Ras. The latter can activate the MAPK signaling pathway [24, 34, 45].

**Non-classic membrane GR**

The non-classic mGR is an acidic glycoprotein of 63 kDa that was identified in neuronal plasma membranes of the amphibian Taricha granulosa as a functional receptor of GC [14, 46]. It has completely different pharmacological characteristics from those of classic mGR. Additionally, it presents high-affinity binding for corticosterone, but not for hormones that classically bind GR, such as aldosterone and Dex [47]. It has seven alpha helices coupled with G proteins. Upon GC binding the receptor, the G proteins activate adenylate cyclase and phospholipase C (PLC) [45, 48]. The former in turn synthesizes cAMP, which activates PKA, which phosphorylates CREB, and pCREB translocates to the nucleus where it binds DNA elements and promotes gene transcription [49]. PLC induces the production of diacylglycerol (DAG) inositol trisphosphate (IP3). DAG activates PKC and IP3 mobilizes the Ca\(^{2+}\) stored in the endoplasmic reticulum [34, 50, 51]. Other membrane-resident proteins capable of binding GC have been identified in the liver of chickens, rats, and mice. However, in vitro and in vivo experiments suggest that classic and non-classic mGR are the those that play a crucial role in mediating some of the neurophysiologic- and behavior-related non-genomic effects of GC [21, 50].

**GC effect on breast tumor response to chemotherapy**

Before, during, and after chemotherapy in patients with BC, GC, that is, cortisone, methylprednisolone, hydrocortisone, ketoprogesterone, fluorometholone, prednisone, and prednisolone [52] are administered at various doses. These drugs reduce the secondary effects of chemotherapy, such as nausea and vomiting, and protect the normal tissue of patients with cancer against the long-term effects of genotoxic drugs [53]. This effect should not be observed as trivial, because a lack of control of these symptoms can cause the patient to abandon therapy. Additionally, these drugs reduce tumor-dependent effects on the patients' health, such as lack of appetite, electrolyte imbalance, pain, edema, and inflammation [53]. In combination with chemotherapy or another endocrine therapy in BC, Glucocorticoids (GC) increase the Response rate (RR), but do not change survival. Some tumor responses may be a consequence of anti-inflammatory activity rather than anti-tumor activity. GC is commonly administered with monoclonal antibodies used in BC therapy, such as Trastuzumab, which mediates antibody-dependent cellular cytotoxicity. However, there is evidence that GC may inhibit antibody-dependent cellular cytotoxicity [52].

In 1958, an increase in the frequency of metastases upon GC co-treatment was observed in patients with BC [54]. Some authors have associated the likelihood of developing metastases with GC therapy and suggest that patients who have been administered steroids may develop metastases due to the possible influence of immunosuppressive effects [54] that could inhibit immunosurveillance and allow tumor progression.

**In vitro** experiments suggest that Dex protects cancer cells from the cytotoxic effects of several chemotherapy agents, such as ionizing radiation, carboplatin, cisplatin, and actinomycin D [53]. It is noteworthy that the concentrations of GC utilized in these experiments is on the same order of magnitude as the plasma concentration of GC in patients with cancer observed a few hours after they receive a dose of GC. The mechanism by which GC induce chemotherapy resistance depends on the cytotoxic agent in question, but it has been shown that GC increase levels of several known key mediators of gene expression, such as the following: cellular glutathione content; metallothionein synthesis; multidrug resistance efflux pump ABCB1 and ABCG2 activity and gene expression, and O6-methylguanine DNA methyl transferase activity [2], [53].
Moreover, it has been proven that GC-induced expression of the serine/threonine kinase, survival kinase gene (SKG-1) protects BC cells from apoptotic cell death. Therefore, it should be tested whether GC induce resistance to chemotherapy in vivo and in randomized clinical trials. If GC do convey chemotherapy resistance to patients, then the antiemetic effect is not worthwhile, and the need for non-steroidal antiemetic drugs without such secondary effects is urgent [53].

In one study of BC xenografts, Dex pre-treatment significantly reduced paclitaxel-induced apoptosis. Systemic Dex pre-treatment was found to upregulate the anti-apoptotic gene MKP-1 while downregulating pro-apoptotic genes such as Bid and TRAIL in BC tumor cells, an effect that persisted for weeks. More recently, microarray analysis of Dex-induced anti-apoptotic genes in BC cell lines revealed MKP-1 and SGK-1 proteins to be of particular importance in GC-induced chemotherapy resistance in BC, with glucocorticoid treatment upregulating both of these genes [56]. Moreover, RNA interference (RNAi) knockdown of these genes abrogates the anti-apoptotic effects of GC in BC cells. Overall, potential mechanisms of action of GC signaling leading to anti-apoptotic events rather than to cell death include the activation of MKP-1, NF-κB, SGK-1, ACK, and WNT pathways. Clearly, the balance between GC-induced pro- and anti-apoptotic events in specific cell types plays an important role in cell death or survival, and the pros and cons of including GC in cancer treatments should be investigated further [56].

Dex protects MCF7 cells against the cytotoxic effects of TNF-α by inducing expression of Inhibitors of apoptosis (IAP) through an NF-κB-dependent pathway [57].

GC have also been shown to inactivate apoptosis pathways during normal mammary gland development [2].

**GC, menopause, and chemotherapy**

Several randomized clinical trials have addressed the question of whether a patient’s menstrual status may be important with regard to the effectiveness of GC enhancement of the beneficial effects of chemotherapy. In order to do this, the trials have included pre- and post-menopausal women. The trials have concluded that GC enhance chemotherapy more efficiently in post-menopausal than in premenopausal women, that there is no correlation between GC administration and estrogen receptor status, and that GC administration induces adrenocortical inhibition, which might reduce the synthesis of endogenous GC [52].

**Role of endogenous GC in patients with breast cancer**

However, contact with exogenous GC is not the only source to which a cancer is exposed. One’s own body synthesizes endogenous GC as cortisol. This raises the question of what effect does endogenous GC have on non-hematologic malignancy. Therefore, future trials should measure the levels of endogenous GC in patients prior to treatment [52].

**GR expression in human breast tissues**

The presence or absence of GR in BC biopsies is controversial. GR is strongly expressed in metaplastic carcinomas and malignant tumors, but is not expressed in non-metaplastic carcinomas [2]. However, the percentage of positive patients presenting nuclear GR localization decreases significantly with the tumor’s histological grade [26]. Although activated GR is located mainly in the nuclei, cytoplasmic or membrane GR localization does not implicate inactive GR status. Two membrane GRs (mGR) have been discovered that mediate GC non-genomic actions, activating different signaling pathways, and not requiring translocation to the nucleus to mediate these effects. Interestingly, it has been reported that in advanced BC samples, GR is localized within the cytoplasm and the mitochondria; the latter localization could be associated with an apoptotic inhibitory function [13].

**GR and BCRA1**

Interestingly the tumor suppressor BRCA1 protein has recently been implicated in GC signaling upstream of p38. Triple negative BC cells with mutated tumor suppressor BRCA1 possess reduced levels of phosphorylated serine 211 GR. The expression of BRCA1 is crucial in order for GC to exert efficient signaling through GR P-Ser211 phosphorylation in MCF-7, a non-invasive BC cell line. This may be due to that BRCA1 induces the phosphorylated form of p38. Additionally, in the absence of ligand, GR
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increases BRCA1 expression, whereas the addition of hydrocortisone downregulates BRCA1 expression in non-malignant mouse mammary cells [55]. The significance of this finding relates to the controversy of GR nuclear localization at different tumor-progression stages in BC. Perhaps screening for both BRCA1 and GR expression in tumor samples could be helpful, because tumors that do not express GR in the nucleus may not express BCRA1 and vice-versa.

GR and ER

Interestingly, GR activation induced the expression and activity of estrogen sulfotransferase, an important enzyme for the deactivation of estrogens, because sulfonated estrogens fail to activate the estrogen receptor (ER) [26]. The synthetic GC Dex and the GR agonist medroxyprogesterone-acetate (MPA) elevate the breast carcinoma metastasis suppressor Nm23-H1 gene in triple negative BC cells in vitro and reduce their migration capacities [58]. However, Dex treatment also upregulates the c-fms (CSF-1R) proto-oncogene in MDA-MB-231 cells, which is associated with an increase in cancer invasiveness [59].

GC inhibit EGF signaling of breast cancer in vitro

Deregulation of growth signaling pathways and acquired autonomy in growth signals are among the main characteristics that dictate malignant mammary cellular growth. One of the most active growth factors in breast glandular cell proliferation is the epidermal or endothelial growth factor (EGF). It exerts, via binding to the EGF receptor, potent growth-promoting effects in mammary epithelium and is involved in the proliferation and migration of BC cells. GC have been shown to increase EGF binding to its receptor, also accompanied by increases in epidermal growth factor-receptor (EGF-R) mRNA levels in human BC cell lines [2]. However, in MCF-7 cells, Dex treatment inhibits EGF-induced SK-1 mRNA expression and activity in a GR-dependent manner, resulting in reduced EGF-induced proliferation and migration [2].

GR and VEGF

GC has been shown to repress, in cancer cells, the expression of vascular endothelial growth factor (VEGF), a potent pro-angiogenic factor. Because angiogenesis is a recognized tumor-promoting factor, further experiments should be conducted to test the possibility that GC do inhibit angiogenesis. The latter would redeem the GC effect on cancer [53].

Conclusions

For nearly 60 years, GC has been employed for their anti-inflammatory, immunosuppressive response. Despite extensive studies in several organ systems, little is known about the physiological role of GC and its GR.

Additionally, GC has been utilized as antiemetics in breast cancer therapy. The role of glucocorticoids in breast cancer is complex and unpredictable, and many contradictions have been demonstrated. The expression and activation levels of GR (phosphorylation status and localization), in BC tumors depends upon several factors, such as the degree of invasiveness of the tumor cell and the concomitant expression of other tumor markers. The addition of GC to other therapies does not change the long-term outcome. The implications of the use of GC as monotherapy or in combination with anticancer drugs for the clinical management of women with breast cancer needs to be further studied.

GC can activate a range of responses because they may act through genomic and non-genomic mechanisms by involving classic or the non-classic cytosolic receptor or the membrane receptor. This involves activation of signaling pathways and different key molecules in breast cancer that play an important role and that are very promising as therapeutic targets. To our understanding, little is known of the role of the membrane GR in breast cancer; therefore, there is a great opportunity for research in this area. Genomic and non-genomic pathways are currently considered as simultaneous but independent events; it could be that there are more links between them than those that we have described.

Ultimately, the future of the synthesis of novel synthetic GC developed through the application of knowledge obtained in vitro and in vivo offers the hope of a new era in which the adverse effects of glucocorticoids are infinitesimal compared to their benefits.
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