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Review

# Glucocorticoid resistance in chronic diseases

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ABSTRACT

Glucocorticoids are involved in several responses triggered by a variety of environmental and physiological stimuli. These hormones have a wide-range of regulatory effects in organisms. Synthetic glucocorticoids are extensively used to suppress allergic, inflammatory, and immune disorders. Although glucocorticoids are highly effective for therapeutic purposes, some patients chronically treated with glucocorticoids can develop reduced glucocorticoid sensitivity or even resistance, increasing patient vulnerability to exaggerated inflammatory responses. Glucocorticoid resistance can occur in several chronic diseases, including asthma, major depression, and cardiovascular conditions. In this review, we discuss the complexity of the glucocorticoid receptor and the potential role of glucocorticoid resistance in the development of chronic diseases.

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**Contents**



## 1. Introduction

Glucocorticoids (GCs) are steroid hormones involved in several responses triggered by a variety of environmental and physiological stimuli. These hormones have wide-range regulatory effects on development, metabolism, and the immune system, and are synthesized and released into the circulatory system by the adrenal

*Abbreviations:* 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; ACTH, adrenocorticotropic hormone; AP-1, activator protein-1; GC, glucocorticoid; GR, glucocorticoid receptor; HDAC2, histone deacetylase 2; hGR, human glucocorticoid receptor; HPA, hypothalamuspituitaryadrenal; MR, mineralocorticoid receptor; NF-κB, nuclear factor-κB; PBMCs, peripheral blood mononuclear cells.

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cortex through activation of the hypothalamus-pituitaryadrenal (HPA) axis. In stressful situations, the hypothalamus releases the corticotropin-releasing hormone that stimulates the release of the adrenocorticotropic hormone (ACTH). In response to ACTH, the adrenal cortex synthesizes and releases GCs. As part of a feedback response, elevated circulating GCs levels inhibit further ACTH release. Therefore, GCs constitute part of the adaptive stress response mechanism that maintains behavioral homeostasis.

Under stressful conditions, endogenous physiologically active cortisol is released in humans while corticosterone is released in rodents. These steroid hormones act through glucocorticoid receptors (GRs) or mineralocorticoid receptors (MRs). Through the activation of GRs, GCs regulate diverse cellular functions, including development, homeostasis, metabolism, cognition, and inflammation [1].

Chronic psychological stress is associated with high risks for depression, cardiovascular disease, diabetes, autoimmune diseases, upper respiratory infections, and poor healing [2]. Persistent exposure to environmental and psychological stress, concomitant with increased circulating GCs, is a probable risk factor for the current obesity and metabolic syndrome epidemics [3]. Indeed, organ transplant or chronic inflammatory-related illness patients chronically treated with exogenous GCs show features of metabolic syndrome. Over the last decades, these physiological hormones have been complemented by several synthetic GCs developed and provided by the pharmaceutical industry. While used for therapeutic purposes, these compounds are currently among the most commonly prescribed drugs worldwide.

The use of GCs is continuously growing as a result of increased chronic disease prevalence in the ageing segment of the population. Currently, GCs are used in the treatment of asthma, allergic rhinitis, hematologic malignancies, ulcerative colitis, rheumatoid arthritis, eczema, and psychological disorders. Although GCs are highly effective for therapeutic purposes, some patients chronically treated with GCs develop reduced GC sensitivity or resistance [4]. Alterations in the GR could also lead to GC resistance, thus increasing vulnerability to exaggerated inflammatory responses [5]. Specifically, several reports have detected GC resistance in chronic stress or major depressive disorder patients, as well as in elderly individuals and subjects at high risk for cardiovascular conditions [6]. Furthermore, GC resistance may occur as a result of prolonged exposure to inflammatory cytokines [6]. Importantly, synthetic GCs, such as dexamethasone or prednisolone, mainly act through GRs in contrast to cortisol or corticosterone. Therefore, the overall effects of chronic synthetic GC administration could differ from endogenous GCs, which act through both GRs and MRs.

Presently, the idea that the adverse effects of GCs are mainly due to increased circulating GCs levels is controversial, and there is greater focus on GR sensitivity as a highly relevant factor for the GCs response and effects of this process. To shed light onto this debated subject, it is crucial to understand how different tissues respond to GCs. In this review, we discuss the complexity of GR in the contexts of gene expression and regarding genomic and non-genomic actions. We also highlight the impacts of GCs resistance in chronic diseases.

## 2. Glucocorticoid receptors

Glucocorticoid actions are mainly mediated by two nuclear receptors, the GR and the mineralocorticoid receptor (MR). Both are members of the steroid/thyroid hormone receptor superfamily of ligand-inducible transcription factors, which include GCs, vitamin-D, and the thyroid receptor [7–9]. The human GR (hGR, NR3C1) is the product of a gene located in chromosome 5. While the hGR promoter lacks a consensus TATA box and CCAAT motif, it does contain binding sites for transcription factors such as activator protein-1 (AP-1), SP1, AP2 nuclear factor-κB (NF-κB), and the cAMP response element-binding protein. The hGR gene consists of 9 exons; exon 1 encodes the 5′-untranslated region, and exons 2–9 encode for the GR protein. Exon 2 forms the N-terminal domain of the GR; exons 3–4 form the central DNA-binding domain, and exons 5–9 encode for the ligand-binding domain. An alternative splicing in exon 9 encodes two highly homologous mRNA transcripts that result in two GR isoforms known as GRα and GRβ [4].

GRα is the classic receptor that binds to GCs and mediates most of the actions described for GCs. The β isoform differs from GRα in 50 carboxy-terminal amino acids, which are substituted by 15 amino acids retaining the receptor within the nucleus and conferring a different biologic function [4]. GRβ does not bind endogenous GCs but does act as a dominant negative inhibitor of GRα-induced transactivation. Moreover, GRβ has intrinsic and GRα-independent transcriptional activity [10]. The use of alternative start codons from single GRα mRNA transcripts results in several GR proteins (GRα-A, GRα-B, GRα-C1, GRα-C2, GRα-C3, GRα-D1, GRα-D2, and GRα-D3). Several polymorphisms have also been identified in the GR. These polymorphisms result in altered amino acid sequences, thus expanding the possible different cellular responses to GCs [11].

On the other hand, the mineralocorticoid receptor (MR, NR3C2) is the product of a gene located in chromosome 4 and through aldosterone play a critical role in regulating fluid and electrolyte balance [12]. The MR structure contains three functional domains. The N-terminal domain recruit co-regulators for the transcriptional activity of MRs that differ from other steroid receptors [13] possesses functional domains responsible for either ligand-dependent transactivation or transrepression [14]. The central DNA-binding domain that recognizes specific DNA sequences or hormone response elements very similar to GCs, progesterone, and androgen receptors [15]. The C-terminal ligand-binding domain permits selective hormone binding [16].

Mineralocorticoid receptor function is mainly conducted via the stimulation of specific ion transporters on the apical (i.e. epithelial Na channel) [17] and basolateral membranes (i.e. $Na^+$, $K^+$-ATPase pump) [18] of epithelial tissues (e.g. kidney and colon). Importantly, MRs also occur on non-epithelial tissues, including the heart, brain, vasculature, and adipose tissue, thereby evidencing functional importance beyond $Na^+/K^+$ homeostasis.

Glucocorticoids also bind to MR with an affinity similar to aldosterone (nM range). Since GCs are 100- to 1000-fold more abundant in the plasma, GCs could activate MRs [19]. Aldosterone binding in epithelial tissues is facilitated by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) [20], which prevents the cortisol-activation of MRs by metabolizing cortisol into inactive cortisone. Therefore, GCs could activate MRs in tissues that do not express 11β-HSD2, such as in the heart and some areas of the central nervous system [21]. The role of MR in the pathogenesis of cardiovascular diseases is associated with the impairing vascular reactivity to decreased glucose-6-phosphatase dehydrogenase [22]; increasing angiotensin-converting enzyme levels [23]; and increasing collagen in heart and kidney cells [24,25]. In addition, a recently published hypothesis about the role of MRs in obesity highlights that the lipogenic actions of GCs could be related to GC resistance and MR activation by GCs in adipose tissue [26].

## 3. Genomic and non-genomic actions of glucocorticoids

Genomic GCs actions occur through a direct regulation of gene transactivation or transrepression. In the absence of a ligand, GRα mainly resides in the cytoplasm attached to a multisubunit com-

plex that includes multiple molecular chaperones (Hsp90, Hsp70, and p23) and the immunophilins FKBP51 and FKBP52 [27]. These proteins maintain the receptor in a tridimensional structure that allows hormone binding and prevents unbound GR translocation into the nucleus, thereby preventing the modulation of gene expression [27].

When GCs bind to GRs, complex conformation changes, and GRs dissociate from the chaperone complex. Once FBK51 is replaced by FBK52, ligand-bound GRs produce a rapid non-genomic action via cytosolic kinases [28]. Additionally, GRs are driven by dynein proteins to translocate to the nucleus [29]. Once in the nucleus, GRs bind to glucocorticoid-response-elements, specific DNA sequences that are located in the promotor region of target genes [30]. This specific binding to DNA triggers the transcription or repression of several genes.

Interactions with other transcriptional factors are also relevant to consider, GR knockout mice immediately die after birth as a result of severe distress syndrome [10]. However, mice harboring a mutant GR, which is active for protein interaction but inactive for transactivation via glucocorticoid-response-elements, survive and procreate. Furthermore, GCs repress the transcriptional activity of important inflammatory-associated transcription factors, such as AP-1 and NF-κB [31]. Specifically, GCs reduce the DNA binding ability of AP-1 and NFκB, leading to the down-regulation of the transcriptional factors P50/p105 (NFKB1), c-Jun, and c-Fos [32,33] and the up-regulation of the NF-κB inhibitor IκBα [34]. Moreover, GCs inhibit the synthesis of several cytokines involved in different inflammatory processes in several diseases, such as IL-2, IL-6, and TNF-α [35–37].

The non-genomic actions of GCs occur seconds to minutes after stimulation and do not require changes in gene expression. This is in contrast to genomic actions, which are dependent on gene expression modulation and, consequently, occur hours after stimulation [38]. The following three mechanisms for non-genomic GC actions have been proposed: (i) binding of GCs to cytoplasmic GRs and the release of molecular chaperones; (ii) binding of GCs to plasma membrane GRs; and (iii) non-specific physicochemical interactions of GCs with cell membranes [39]. Non-genomic GC actions can affect the cardiovascular, immune, and neuroendocrine systems [40–42].

## 4. Glucocorticoid resistance in chronic diseases

### 4.1. Primary generalized glucocorticoid resistance or Chrousos syndrome

Primary generalized glucocorticoid resistance, or *Chrousos syndrome*, is a familial disorder characterized by primary generalized tissue insensitivity to GCs. The first case of GC resistance in this syndrome was described in 1976 as hypercortisolism without the characteristics of Cushing's syndrome, and the GCs resistance was related to impaired functioning of GRs [43]. To date, 20 hGR mutations have been described, with these mutations principally affecting ligand affinity, nuclear translocation, or gene transactivation [44,45].

Glucocorticoid resistance leads to HPA axis activation, consequently resulting in elevated circulating cortisol and ACTH levels. These increased hormone levels then maintain a chronic stress-like response [46] that does not clinically manifest as hypercortisolism [47]. The chronic release of ACTH causes adrenal hyperplasia, an excess of circulating GCs, mineralocorticoids, and androgens. Abnormal levels of these compounds can lead to clinical manifestations of hypertension, hypokalemia, and menstrual cycle abnormalities [48,49]. Additionally, these clinical manifestations can range from asymptomatic to mild or severe cases, depending on differences in the tissue-specific actions of GCs, mineralocorticoids, and androgens [44].

### 4.2. Asthma

Asthma, chronic inflammation of the airways characterized by lower lung function, smooth muscle bronchoconstriction, and mucous hypersecretion, is widely recognized as a disease involving GC resistance. Indeed, asthma is commonly treated by inhaled or oral GC doses, where the disease grade (low to severe) is dependent on the GC therapy related-response [50]. Two types of GC resistance occur in asthma. Type 1 resistance is cytokine-induced or acquired, the first one is associated with polymorphisms that lead to an overproduction of certain cytokines and the second is the result of chronic exposure to corticosteroids [51]. In turn, type 2 also known as primary cortisol resistance affects all tissues and is associated with mutations in the GR gene.

Changes in the cellular microenvironment play an important role in GC signaling in inflammatory diseases [48]. The overexpression of IL-2 and IL-4 reduces the translocation and binding affinity of GRs in some target cells. However, the impairment of GRs can be rescued by inhibiting p38 MAPK activity, suggesting p38-mediated GR phosphorylation under a condition of cytokine-induced resistance [40]. On the other hand, oxidative stress can impair GR activity by attenuating histone deacetylase 2 (HDAC2), as corroborated for refractory asthma [52,53] and in the lungs of smoking patients [54]. Another proinflammatory cytokine, TNF-a, phosphorylates GRs via JNK, leading to glucocorticoid-response-element binding [55]. Furthermore, the transcription factor AP-1, which binds GRs to inhibit its cellular function, is over activated in GC-resistant asthma patients.

Notably, asthmatic GC resistance differs from primary generalized glucocorticoid resistance, with no cDNA variations existing for the GR between GC-sensitive and asthmatic GC-resistant subjects [56]. Nevertheless, microarray comparisons of peripheral blood mononuclear cells (PBMCs) in GC-sensitive and asthmatic GC-resistant subjects identified 11 genes that could be involved in GR resistance [57]. This approach could be useful for identifying other inflammatory diseases associated with GR resistance, with an ultimate aim of developing a reliable genomic test.

On the other hand, single nucleotide polymorphisms on the GR gene locus have also been correlated with altered GC sensitivity, while a ER22/EK23 mutation within the GR exon 2 is associated with an increased GRβ:GRα ratio, correlating with GC resistance [58]. Another frequent polymorphism is a BclI restriction fragment length polymorphism on intron 2, which results in decreased GC sensitivity in some individuals [59]. Glucocorticoid resistance has also been related to an elevated expression of GRβ in the airway cells of asthma patients [60,61]. Furthermore, GRβ expression is increased by IL-2, IL-4, and IL-17 in the PBMCs of healthy donors [62–64]. Moreover, IL-17 has an additional inhibitory effect by activating the PI3K pathway, with a consequent decrease in HDAC2 activity [65].

Most *in vitro* studies suggest that circulating monocytes and T-lymphocytes show GC resistance in severe asthma patients [66,67]. In addition to this, peripheral monocytes and alveolar macrophages have a diminished response to the inhibitory effects of GCs on cytokine and chemokine production [68,52]. Worth noting, up to 30% of healthy volunteers fail to response to the inhibitory effects of dexamethasone on the proliferation of peripheral lymphocytes [69]. Therefore, GC resistance could be a relatively frequent condition that needs to be considered.

Recent studies have focused on the inflammatory secretory function of airway smooth muscle [70–72]. In asthmatic patients, the expression of inflammatory cell attractant chemokines, such as CCL5, CCL11, and CCL19, are up-regulated in airway smooth

muscle [73–75]. Another proinflammatory factor is thymic stromal lymphopoietin, a TH2 activating cytokine associated with GC resistance in an experimental model of allergic asthma [76]. Another key cytokine related to TH2 activation is IL-33, which is positively correlated with severe steroid-resistant asthma in pediatric patients [77]. Additionally, dexamethasone has reduced effects on the production of TNF-α, CCL11, and CCL18 in airway smooth muscle cells of patients with severe asthma [78,79]. A possible mechanism underlying this response is the impairment of GR nuclear translocation mediated by p38-MAPK phosphorylation [52,80,81]. Therefore, the proinflammatory molecules secreted by airway smooth muscle cells could maintain GC insensitivity in severe asthmatic patients. Moreover, others cytokines, such as IFN-γ and TNF-α, increase the expression of GRβ, thus producing a dominant-negative effect on GR signaling [82].

Glucocorticoids are strongly ineffective in treating virus-induced asthma exacerbations [83,84]. An *in vitro* study showed that rhinovirus infections cause GC resistance through a mechanism that involves the activation of the JNK and NF-κB pathways [85].

### 4.3. Autoimmune diseases

Insensitivity to GCs plays a role in many autoimmune diseases, including in inflammatory bowel syndrome, lupus erythematosus, and rheumatoid arthritis, where IL-17 and TNF-α deter GC sensitivity [86,87]. In fact, approximately 30% of patients with autoimmune conditions have an impaired response to GCs [88]. Additionally, the circulating lymphocytes of patients with autoimmune diseases evidence a higher expression of the multidrug resistance protein 1 [89]. In turn, colon mononuclear cells of patients with ulcerative colitis disease present a high expression of the macrophage migratory inhibitory factor. This factor promotes the systemic inflammatory response by counter-regulating the actions of GCs in inhibiting immune-cell activation and pro-inflammatory cytokine production. Therefore, the use of migratory inhibitory factor antibodies can restore GR sensitivity [90].

It has been also reported that both ulcerative colitis and rheumatoid arthritis patients have a lower expression of GRα [91,92], also in patients with ulcerative colitis the GRα expression in colonic mucosal cells is correlated with GC response [93]. On the other hand, a role for the isoform GRβ also has been reported, the GRβ mRNA levels in PBMC are higher in GC resistant patients with Crohn's disease or ulcerative colitis [94–96]. In addition, in colonic mucosal cells GRβ expression correlated negatively with the response to GCs in ulcerative colitis patients, thus in contrast to GRα expression [93].

Polymorphisms in the GR have a role in GC response in autoimmune diseases. Pediatrics patients with inflammatory bowel disease have a higher prevalence of the BcII genotype in the GC responsive group [97]. Both the 9β polymorphism, which results in an increased GRβ mRNA stability and protein expression, and the ER22/23EK polymorphism, which increased the GRβ:GRα ratio, are associated with risk to develop rheumatoid arthritis [98,99]. By contrast, both the N363S and BcII polymorphisms, which are associated with hypersensitivity to GCs, decrease the risk of develop rheumatoid arthritis [99].

### 4.4. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is a lung condition characterized by a shortness of breath, a cough, and sputum production. Alveolar macrophages originating from monocytes possibly cause the chronic inflammatory response and tissue destruction observed in these patients [100]; particularly when considering that alveolar macrophages are responsible for releasing many cytokines and chemokines [101]. Moreover, elevated reactive oxygen species levels are involved in activating many inflammatory responses [102]. Oxidative stress induced by $H_2O_2$ and lipopolysaccharides promotes the generation of proinflammatory mediators such as cytokines and neutrophil chemotactic mediators in alveolar macrophages, which are correlated with worsened chronic obstructive pulmonary disease [103,104]. Related to this, the alveolar macrophages and peripheral lung cells of chronic obstructive pulmonary disease patients have low HDAC2 expression and activity. The reason might be related to abnormal protein nitrosylation or oxidative stress leading to low HDAC2 function, which in turn results in GC insensitivity, a condition present in 10% of chronic obstructive pulmonary disease patients [68,105]. Accordingly, *in vitro* experiments show that theophylline, a HDAC2 activator, restores alveolar macrophage GC sensitivity [106].

### 4.5. Cancer

Glucocorticoids are widely used in the treatment of blood cancer due to effects on cell cycle progression and apoptosis. These hormones can also be used as a co-medicine against solid tumors, either treating malignancy or the adverse effects of diverse treatments [107]. Other cancer malignancies have variable response to GC therapy. In addition to the use of GCs as adjuvants in decreasing the side effects of chemotherapy [108], preclinical data show that GR activation reduces the proliferation of breast and prostate cancer cells, suggesting an intercommunication with other nuclear hormone receptor, such as estrogen and the androgen receptor [109,110]. In cancer models, GC therapies are associated with diminished cancer migration and invasiveness through the down-regulation of RhoA [111], IL-6, and metalloprotease [112] or the induction of E-cadherin [113]. Moreover, GC treatments reduce the production of new blood vessels by down-regulating vascular endothelial growth factor [114,115].

Specifically in regards to leukemia, apoptosis induced by GCs in lymphoid progenitor cells is essential for treating acute lymphoblastic leukemia [116,117]. However, GC resistance is associated with a poor prognosis in acute lymphoblastic leukemia [118,119]. The first studies in GC resistance were performed in the mouse lymphoma cell line S49.1A, which has been used to describe GC action mechanisms. In this cell line, dexamethasone induces cell death, and a similar response to GCs is achieved in diverse neoplastic lymphoma cells [120]. As some S49.1 clones were dexamethasone-resistant, the nuclei of some clones were normally internalization by dexamethasone, while others did not present nuclear localization [121]. Similar results regarding GCs resistance were obtained with the T-lymphoid cell line, where exposure to 5-azacytidine, which generated DNA demethylation, led to an activation of genes that conferred GCs resistance [122].

Several mechanisms could explain how the oncogenic T-cell transformation signaling pathway induces GC resistance in patients with leukemia [123]. Phosphatase and tensin homolog mutations are associated with GC resistance [124], and a loss of phosphatase and tensin homologs promotes a sustained activation of the AKT1 pathway, inducing PI3K signaling to ensure T-cell transformation [125,126]. Furthermore, AKT1 can directly induce GC resistance by phosphorylating GRs [127], and AKT1-dependent mTOR phosphorylation increases the expression of the myeloid leukemia cell-1 protein, leading to decreased GC-induced apoptosis [128]. Additionally, patients with GC-resistant leukemia express higher levels of the NLRP3-CASP1 inflammasome, with the overexpression of CASP1 consequently resulting in the cleavage of GR and induced GR resistance [129]. Other novel mechanism of GR resistance is the autophagy induction by GCs. In lymphoid malignant cells resistance to GCs, there is an increase in autophagy in response to dexamethasone. Blocking autophagy overcomes GC

**Table 1**
Summary of papers on glucocorticoid (GC) resistance and associated diseases and signaling.

| Tissue/Systemic | Signaling | Disease | Clinical manifestation | References |
|---|---|---|---|---|
| Systemic | Chronic release of ACTH<br>GRα mutations | Chrousos syndrome | Hypertension, hypokalemia and menstrual cycle abnormalities | [43,46–48] |
| Lungs Bronchopulmonary<br>PBMC<br>Monocytes<br>T-Lymphocytes | Overexpression of IL-2 and IL-4/P38-MAPK pathway<br>TNFα-JNK<br>GRα mutations and GRβ overexpression | Asthma | Chronic inflammatory disease of the airways, lower lung function, smooth muscle bronchoconstriction, and mucous hypersecretion | [40,54–56,60–63] |
| Lymphocytes<br>Colon | IL-17 and TNFα<br>MDR1<br>MIF | Autoimmune diseases<br>Inflammatory bowel disease<br>Lupus erythematosus<br>Rheumatoid arthritis | Elevated inflammatory state | [86–87,89–92] |
| Lung<br>Alveolar macrophages | ROS<br>Proinflammatory cytokines<br>HDAC2 | COPD | Breath shortness, cough and sputum production | [68,100,102,105] |
| Blood | Cell cycle progression and apoptosis<br>T-cell transformation<br>PTEN mutations-AKT-PI3K<br>NLRP3-CASP1 inflammasome | Cancer | Tumor progression | [116–119,124–128,136] |
| Arteries | GRα mutations<br>GR-9β polymorphism | Cardiovascular Diseases | Elevated inflammatory state | [146–150] |
| Systemic | Pituitary and Adrenal disorders | Cushing syndrome | Central obesity, purple striae of the skin, buffalo hump, hypertension, osteoporosis, glucose intolerance, overt diabetes mellitus, dyslipidemia, leukocytosis and great risk of severe cardiovascular complications | [151–154] |
| Monocytes/Microglia/Key immune cells | Impaired HPA axis feedback<br>C-reactive protein and IL-1 | Depression | Chronic stress, increased pituitary and adrenal gland volume | [155–156,159–160,169–171] |

*Table abbreviations:* ACTH, adrenocorticotropic hormone; COPD, chronic obstructive pulmonary disease; GR, glucocorticoid receptor; HDAC2, histone deacetylase 2; HPA, hypothalamus-pituitary-adrenal; IL, interleukin; MAPK, mitogen-activated protein kinases; MDR1, multidrug resistance protein 1; MIF, migratory inhibitory factor; PBMC, peripheral blood mononuclear cells; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species.

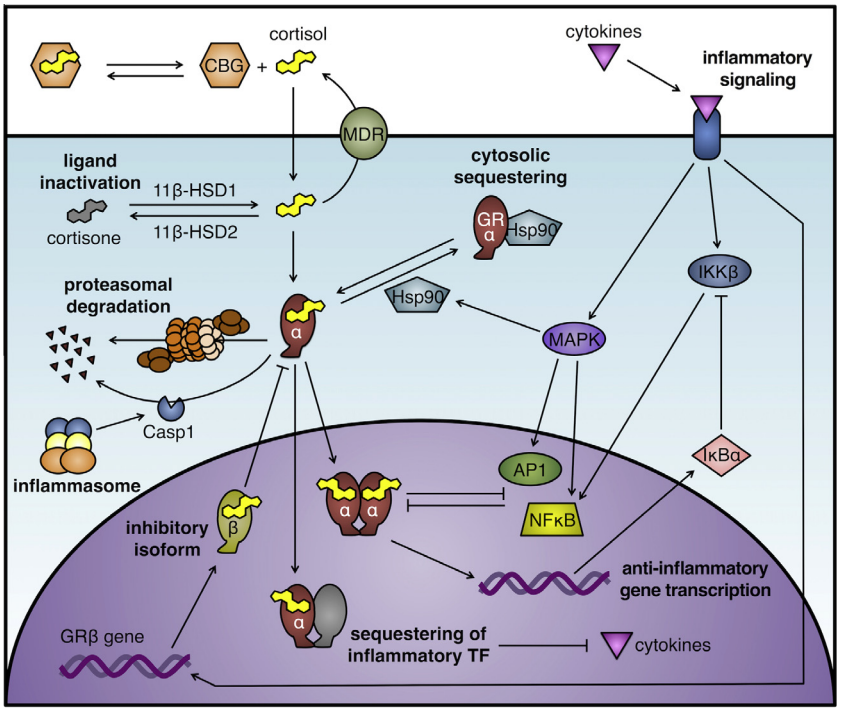


**Fig. 1. Mechanisms of glucocorticoid receptor resistance. a)** Corticosteroid binding globulin, **b)** Multidrug resistance transporter (pump), **c)** 11β-hydroxisteroid dehydrogenase, **d)** GR interaction with others transcription factors (AP-1, NF-κB), **e)** MAPK phosphorylation of receptor or HSP90, **f)** GRα:GRβ ratio, and **G)** Inflammasome-mediated degradation. Figure abbreviations: 11β-HSD, 11β-hydroxisteroid dehydrogenase; CBG, corticosteroid binding globulin; GR, glucocorticoid receptor; HSP, heat shock protein; MAPK kinase, mitogen-activated protein kinase; MDR, multidrug resistance.

resistance and enhances dexamethasone-induced cell death [130]. Therefore, identifying reliable biomarkers for the early diagnosis of GR resistance may help in designing more effective therapies for lymphoblastic leukemia patients.

On the other hand, GCs can have pro-oncogenesis effects. Some clinical and preclinical studies show that GC treatments induce resistance in solid tumors, including in breast, ovarian, and prostate cancers [131]. In healthy human keratinocytes, GCs present anti- and proinflammatory activities that are time- and concentration-dependent [132]. A possible explanation for these mechanisms is that GC hypersecretion reduces peripheral blood lymphocytes, a key cell in killing tumor cells [133]. Moreover, elevated GC levels during stress decrease levels of the tumor inhibitory protein p53 [134]. Dexamethasone, commonly used in tumor treatments, induces proliferation in 9 of 17 cancer cell lines derived of solid tumors, surprisingly only in the tumors cells that are resistant to apoptosis induction by GCs [135].

### 4.6. Cardiovascular diseases

Glucocorticoids are essential for normal functioning of the cardiovascular system, with excess or insufficient GCs affecting the human heart. Exposure to high levels of cortisol increases the risk of cardiovascular disease, particularly in older subjects with atherosclerosis [136] and in patients with Cushing's syndrome [137]. Excess GCs can induce hypertension independent of an exogenous or endogenous origin. Indeed, Cushing's syndrome patients have an 80% incidence of hypertension [138] and a fivefold increase in standard mortality rate [139]. The antagonist of GRs, RU486, can reduce hypertension [140–142].

In cardiomyocytes, 11β-HSD2 is absent. This indicates that most GCs bind to MRs, and that GRs are activated only when GC levels are excessive [143]. With diurnal GC levels, MRs are preferred as a result of greater GC affinity than GRs, but GRs are occupied during the diurnal peak or under stressful conditions [144]. In a rat model, GCs affect eNOS mRNA and protein expression stabilities, thus favoring hypertension [145]. However, tissue-specific GR deletion in cardiomyocyte and vascular smooth muscle results in cardiac hypertrophy and the up-regulation of myosin heavy chain-β [146].

Glucocorticoid receptor gene variants are associated with cardiovascular disease. A large population study revealed that subjects homozygous for haplotype 3 of the GR have an increased risk for myocardial infarctions and coronary artery disease [147]. Additionally, this variation was also associated with an augmented risk of cardiovascular disease in men with familial hypercholesterolemia [148]. Furthermore, the GR gene splice GR-9β, which is associated with reduced GC sensitivity in the immune system, increases the risk of cardiovascular disease [147]. Patients with metabolic syndrome, which is a risk factor for cardiovascular diseases, have decreased HPA sensitivity associated to GRβ overexpression and lower frequency of GG genotype in the BcII polymorphism [149]. Moreover, patients with coronary heart disease and comorbid depression can present GC resistance, leading to insufficient GC signaling that results in an elevated inflammatory state [150].

### 4.7. Cushing syndrome

Cushing syndrome patients present pathologically increased cortisol levels. These patients have central obesity, purple striae of the skin, a buffalo hump, hypertension, osteoporosis, glucose intolerance/overt diabetes mellitus, dyslipidemia, leukocytosis, and a high risk for severe cardiovascular complications [151]. This phenotype could be a result of a perturbed HPA axis produced by pituitary and adrenal disorders or by an ectopic tumor producing ACTH or the corticotropin-releasing hormone [152]. Patients with Cushing syndrome present hypercortisolism, insulin resistance, elevated levels of the C-reactive protein, and an increased leukocyte count in comparison with sex- and aged-matched controls,

thus suggesting dysfunctional GR signaling [153]. Moreover, the PBMCs of these subjects evidence a reversible decrease in receptor affinity to GCs [154].

### 4.8. Depression

The characteristic neuropathology of depression is a dysfunctional monoamine system, impaired neurogenesis, abnormalities in regional brain activity, and alterations in synaptic function [155]. Chronic stress is a predisposing factor for the development of depression. Chronic stress can also lead to increased pituitary and adrenal gland volumes, higher cortisol levels (in 50% of depressed patients), and diminished cortisol reactivity together with impaired stress recovery [156–158]. Glucocorticoid resistance in depression could be caused by impaired HPA axis feedback [159] or/and a lack of GC actions on monocytes, microglia, and other key immune cells [160]. Depressed patients have a dysregulated HPA axis and stronger responses to psychological stressors [161,162]. The hyperactivity of the HPA axis response could be associated with GR problems at the limbic hypothalamic level, including GC resistance [163]. A post-mortem study showed that in the frontal and hippocampal lobes, GR mRNA is reduced in depressed patients [164–166]. Moreover, in human hippocampal progenitor cells, GCs decrease proliferation, suggesting neurogenesis inhibition by GCs in the hippocampus [167].

Animals subjected to wound stressors develop GR resistance in proportion to the number of wounds received [168], and a chronically stressed population presents increased levels of inflammatory molecules such the C-reactive protein and IL-1 receptor antagonist [169]. Indeed, lonely people show a correlation between the degree of loneliness and GC resistance [170]. Currently, the relationship of GC resistance and/or an increased inflammatory response with depression is not completely understood. Animals treated with a GC antagonist or that were adrenalectomized show enhanced sickness and depressive-like behaviors (e.g. lethargy, reduced locomotor activity and food intake, increased sleep) [171,172], possibly favoring a sustained catabolic state to provide a sustained level of energy to the chronic immune response.

## 5. Future perspectives and conclusions

Chronic diseases are the leading causes of global mortality, with incidences increasing with longevity. Chronic inflammation is a common condition in chronic diseases, including in type 2 diabetes, obesity, heart disease, cancer, and allergies. Abundant evidence supports that GC resistance occurs in several diseases that present a chronic inflammatory state (Table 1). Advances in understandings of GC signaling have identified a variety of cellular mechanisms that contribute to GR resistance, such as an altered affinity of GRs to bind DNA elements (e.g. glucocorticoid-response-elements), a reduced affinity of GRs for its ligand, and induced changes in the relative expression of GR isoforms (Fig. 1) [173–175].

To date, determinations of cortisol levels in the serum, hair, and saliva do not discriminate GC resistance. Instead, target-tissue GC responses need to be evaluated. Nevertheless, most studies have assessed GC resistance by evaluating several factors that do not necessarily implicate a deregulated GR response, such as gene polymorphisms and the expression of GR isoforms. The most accurate method for evaluating GC responses is by assessing the effects of dexamethasone on lipopolysaccharide-induced, pro-inflammatory cytokine secretion in isolated monocytes. However, this technique is not completely reliable as a rapid and informative test for use in clinical situations. Recently, Bali et al., reported a methodology to evaluate antagonism of GR though FKBP5 mRNA expression in blood samples of human subject treated with a single dose of prednisone, showing a peak of mRNA expression at 4 h after administration [176], this methodology could be a reliable approach to determine GC sensitivity.

In conclusion, developing a rapid, non-invasive test to assess individual responses to GCs is a remaining challenge for researchers. Such a test would be a highly valuable prognostic tool for inflammatory-related diseases or for determining the outcome of anti-inflammatory therapy. Finally, therapeutic modulators of GC sensitivity need to be identified to improve the outcome of chronic disease patients affected by chronic inflammation.

## Conflict of interests

The authors declare no conflict of interests regarding the publication of this paper.

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