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Immune regulation by glucocorticoids

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Abstract

Endogenous glucocorticoids are crucial to various physiological processes, including metabolism, development and inflammation. Since 1948, synthetic glucocorticoids have been used to treat various immune-related disorders. The mechanisms that underlie the immunosuppressive properties of these hormones have been intensely scrutinized, and it is widely appreciated that glucocorticoids have pleiotropic effects on the immune system. However, a clear picture of the cellular and molecular basis of glucocorticoid action has remained elusive. In this Review, we distil several decades of intense (and often conflicting) research that defines the interface between the endocrine stress response and the immune system.

In 1948 at Mayo Clinic (Minnesota, United States), a patient with rheumatoid arthritis began daily injections of ‘Compound E’, a synthetic version of a steroid hormone that was isolated from animal adrenal glands. Within 3 days, the patient was nearly asymptomatic. In 1950, the Nobel Prize in Physiology or Medicine was awarded to Philip S. Hench, Edward Kendall and Tadeus Reichstein for their discovery of ‘the adrenal cortical hormones’. Much excitement surrounded the miracle drug, Compound E, and it was referred to as a glucocorticoid or corticosteroid, although prolonged clinical use was discouraged upon the realization of adverse side effects (BOX 1). To this day, however, glucocorticoids remain the mainstays in the treatment of inflammatory and autoimmune pathologies, and they are used as immunosuppressants following organ transplantation and as lympholytics in chemotherapeutic regimens.

For decades, the clinical application of glucocorticoids outpaced our mechanistic understanding of their immunosuppressive properties, and research into glucocorticoid-mediated regulation of the immune system continues to be an intense field of investigation for several reasons. First, the modes of glucocorticoid action are manifold. Classically, glucocorticoid binding to glucocorticoid receptors activates or represses gene transcription, and glucocorticoids regulate up to 20% of the genome according to some studies[1]. However, studies in recent years have uncovered other mechanisms that underlie glucocorticoid

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activity, including the non-genomic effects of the liganded glucocorticoid receptors, ‘crosstalk’ of glucocorticoid receptors with other transcription factors, and possibly even receptor-independent effects. Second, glucocorticoid receptors are expressed by nearly all nucleated cells, but the functional effects of glucocorticoids differ by cell type. The physiological outcomes of glucocorticoid signalling therefore reflect a kaleidoscope of cell-specific effects. Cell-depletion studies and lineage-specific glucocorticoid receptor-knockout mice have allowed investigation of the cell-specific contributions to the *in vivo* effects of glucocorticoids (BOX 2). Finally, there is evidence that glucocorticoids promote immune responsiveness under certain conditions, which presents an often overlooked challenge to the clinical dogma of glucocorticoids acting solely as immunosuppressive agents.

A formidable amount of literature exists on the topic of glucocorticoid-mediated regulation of the immune system. Here, we provide an update on the effects of glucocorticoids on canonical immune processes — for example, on the production of inflammatory mediators, leukocyte migration, lymphocyte development and antigen receptor signalling — with the goal of providing a primer for readers who are interested in the interface between the neuroendocrine stress response and the immune system. We begin with a brief overview of steroidogenesis and the glucocorticoid receptor; the following sections are dedicated to discussing glucocorticoid-mediated regulation of innate immunity and inflammation, and adaptive immunity, and we finish with a working model that explains both the immune-potentiating and immunosuppressive actions of glucocorticoids.

Glucocorticoid production

Steroidogenesis.

Endogenous glucocorticoids (cortisol in humans and corticosterone in rodents) are essential for life, and they regulate myriad physiological and developmental processes. Like all steroid hormones, glucocorticoids are synthesized from cholesterol through an enzymatic process called steroidogenesis, which occurs in mitochondria[2]. Glucocorticoid bio-synthesis occurs in the adrenal cortex, although local glucocorticoid production has also been reported in the thymus, intestine and skin[3]. As shown in FIG. 1, adrenal glucocorticoid production is induced upon activation of the hypothalamic–pituitary–adrenal axis (HPA axis), which is a neural–endocrine ‘hub’ that coordinates physiological responses to external stimuli. Glucocorticoids released into the blood exert systemic effects by binding glucocorticoid receptors that are present in cells throughout the body, including cells in the hypothalamus and pituitary gland, which are part of a negative feedback loop that controls glucocorticoid production (FIG. 1). Notably, early clues about the effects of glucocorticoids on the immune system came from patients with Cushing syndrome (which is characterized by glucocorticoid excess; BOX 1) and patients with Addison disease (which is characterized by glucocorticoid deficiency).

Psychological distress, physical strain and tissue trauma activate the HPA axis, which in turn triggers rapid and substantial increases in glucocorticoid production. The hypothalamus is also stimulated by interleukin-1 (IL-1), tumour necrosis factor (TNF) and IL-6 (REF. 4) (FIG. 1). Cytokine-induced HPA activation promotes glucocorticoid secretion, which, as detailed below, potently suppresses pro-inflammatory cytokine expression; thus, a second

feedback loop links the inflammatory response to the HPA axis (FIG. 1). Recent studies have demonstrated that direct ligation of Toll-like receptor 2 (TLR2) and TLR4 in adrenocortical cells induces glucocorticoid production, and this is indicative of an inflammatory pathway of glucocorticoid production that feeds into the HPA axis[5] (FIG. 1).

The HPA axis also couples glucocorticoid production to circadian and ultradian rhythms[6] (FIG. 1). Although the amplitudes of circadian and ultradian fluctuations in steroidogenesis are not as pronounced as those associated with a stress response, these small changes in glucocorticoid concentrations still modulate immune responsiveness and leukocyte trafficking[7]. Fluctuations in blood lymphocyte counts in humans, for example, inversely correlate with diurnal patterns of glucocorticoid secretion, such that there is a 40% decline in the number of circulating T cells from night to morning as a result of altered tissue homing[8].

Local regulation of glucocorticoid activity.

Adrenal steroidogenesis drives systemic changes in glucocorticoid concentrations, but extracellular binding proteins and intracellular enzymes regulate glucocorticoid activity locally. Corticosteroid-binding globulin (CBG) renders cortisol inactive and leaves only ~5% of circulating cortisol in a bioactive form. CBG is important for the systemic distribution of glucocorticoids via the circulation, but it may also have a tissue-specific role in glucocorticoid delivery. For example, neutrophil elastase cleaves CBG, thereby liberating bioactive glucocorticoids at inflammatory sites[9]. Within cells, 11β-hydroxysteroid dehydrogenase enzymes (11βHSD1 and 11βHSD2) regulate the interconversion of bioactive cortisol and inactive cortisone. Inflammatory signals, including TNF and IL-1β, modulate the expression of 11βHSD enzymes, thereby altering cellular sensitivity to endogenous glucocorticoids[10].

Glucocorticoids in the clinic.

The earliest glucocorticoid used in the clinic was synthetic cortisone (Compound E, described above; note that inside cells, cortisone is converted into cortisol by 11βHSD1). Although this treatment was efficacious in treating rheumatoid arthritis, prolonged cortisone therapy causes mineral imbalance and fluid retention through the activation of mineralocorticoid receptors in the kidney. A decades-long pharmaceutical search for synthetic glucocorticoids that have minimal mineralocorticoid effects yielded several analogues that are routinely used in the clinic today, including prednisone, beclomethasone and fluticasone[11]. Each glucocorticoid analogue has distinct pharmacological properties, including fat solubility, half-life and mineralocorticoid activity. In general, synthetic glucocorticoids are more potent immunoregulators than is cortisol because they are not subject to endogenous inhibitors of cortisol activity, including CBG binding and 11βHSD inactivation. Moreover, synthetic glucocorticoids bind the glucocorticoid receptors with higher affinity and mineralocorticoid receptors with lower affinity than do endogenous glucocorticoids, thereby minimizing mineralocorticoid-based side effects.

Glucocorticoid signalling

Lipophilic glucocorticoids diffuse through cell membranes to bind cytosolic glucocorticoid receptors, which are ubiquitously expressed by nucleated cells. The human glucocorticoid receptor is encoded by the nine-exon gene *NR3C1* (see Further information). Similar to other nuclear receptors, the glucocorticoid receptor comprises three domains: first, the amino-terminal domain, which interacts with co-regulators and the transcriptional machinery; second, the DNA-binding domain, which contains two zinc-finger motifs for genomic interactions; and third, the ligand-binding domain, which features a hydrophobic pocket for ligand binding[12]. A flexible hinge region — which promotes receptor dimerization, nuclear translocation and DNA binding — lies between the DNA-binding domain and the ligand-binding domain[12]. Glucocorticoid receptors contain multiple sites for post-translational modifications, including phosphorylation, acetylation, ubiquitylation and sumoylation sites, which have important roles in nuclear import and export, gene regulation and receptor degradation[13].

There is substantial heterogeneity in the proteins that are translated from the *NR3C1* gene. The canonical receptor associated with transcriptional regulation by glucocorticoids is GRα. GRβ, by contrast, is a splice variant that does not bind a ligand but is thought to exert a dominant-negative effect on GRα, although some direct transcriptional activity has been reported[13]. Accumulating evidence indicates that inflammation affects the glucocorticoid receptor isoform expression profile, and enhanced GRβ expression has been associated with glucocorticoid resistance in several pathologies[14]. The repertoire of glucocorticoid receptor proteins is further expanded by the presence of eight alternative translation initiation sites; the resulting N-terminal glucocorticoid receptor isoforms exhibit distinct transcriptional activities, nuclear trafficking properties and tissue distribution patterns[15]. Differential expression of glucocorticoid receptor isoforms may, to some degree, explain cell-specific responses to glucocorticoids.

In the absence of ligand, GRα localizes to the cytoplasm in a multiprotein complex that contains heat-shock proteins, immunophilins and other chaperones, which enhance the affinity of the receptor for ligand and prevent receptor degradation (FIG. 2). Classically, ligand binding was thought to induce a conformational change in the glucocorticoid receptor that disassociates the chaperone complex, thus allowing nuclear translocation. Recent studies, however, provide evidence that glucocorticoid receptor chaperones are important for the nuclear import of the glucocorticoid receptor[16]. Within the nucleus, the glucocorticoid receptor interacts with DNA and with other proteins to exert biological effects (FIG. 2). The withdrawal of ligand results in calreticulin-mediated nuclear export of the glucocorticoid receptor to the cytoplasm, where the glucocorticoid receptor–chaperone complex reforms, poised for another round of ligand binding[17].

As mentioned above, endogenous glucocorticoids also bind with high affinity to mineralocorticoid receptors (encoded by *NR3C2*), which regulate genes involved in sodium reabsorption. The expression pattern of mineralocorticoid receptors is more restricted than that of glucocorticoid receptors; high expression of mineralocorticoid receptors is found in the ducts and tubules of the kidney, in the colon, in the heart and in the hippo

campus, but low expression is found in leukocytes. Blood concentrations of glucocorticoids are typically much higher than are concentrations of the endogenous mineralocorticoid aldosterone, but in classic mineralocorticoid-sensitive tissues, mineralocorticoid receptors specificity for aldosterone is enforced by 11βHSD2, which prevents glucocorticoid occupation of mineralocorticoid receptors through the inactivation of cortisol. There is little information about the roles of mineralocorticoid receptors in immunity, although it is notable that leukocytes do not express 11βHSD2, which raises the possibility that the leukocyte mineralocorticoid receptor is not 'protected' from occupation by endogenous glucocorticoids.

Gene regulation by glucocorticoid receptors.

Glucocorticoid-mediated immune modulation has classically been attributed to glucocorticoid receptor-induced alterations in gene expression. The genomic effects of glucocorticoids are categorized into three general mechanisms (FIG. 2). The first mode of regulation occurs through the function of the glucocorticoid receptor as a transcription factor and involves direct binding of the liganded glucocorticoid receptor to DNA. Glucocorticoid receptor homodimers bind glucocorticoid response elements (GREs; which have the consensus sequence GGAACAnnnTGTTCT, where 'n' is any base) to enhance gene expression[18,19]. The GRE-bound glucocorticoid receptor recruits co-regulators, including steroid receptor co-activator 1 (SRC1; also known as NCOA1), glucocorticoid receptor-interacting protein 1 (GRIP1; also known as NCOA2) and CREB-binding protein (CBP; also known as CREBBP), and then binds transcriptional activator BRG1 of the SWI/SNF chromatin-remodelling complex to form the pre-initiation complex and activate transcription. Glucocorticoid receptor monomers, by contrast, can bind negative GREs (nGREs; which have the consensus sequence CTCC(n)$_{0–2}$GGAGA), and recruit the co-repressors nuclear receptor co-repressor 1 (NCOR1) and SMRT (also known as NCOR2) to inhibit gene transcription[20]. Classically, GREs and nGREs were thought to function as components of gene promoters, but recent genome-wide studies have revealed that most glucocorticoid receptor-binding sites lie in intragenic areas and regions distant from transcription start sites, which indicates that glucocorticoid receptors may exert regulatory effects over considerable genomic distances[21]. Whole-genome studies have also revealed that there is little overlap in glucocorticoid receptor-binding sites among tissues and cell types, which suggests that chromatin accessibility is a pre-requisite for the glucocorticoid receptor–DNA interaction[22]. GRE and nGRE accessibility probably contributes to the cell type-specific activities of glucocorticoids.

The second mode of glucocorticoid receptor-mediated gene regulation occurs when the glucocorticoid receptor physically interacts with, or 'tethers', another transcription factor without contacting DNA[23]. This protein–protein interaction alters the capacity of the partnering transcription factor to bind DNA, or to recruit co-regulators and/or the transcriptional machinery. Tethering has received a considerable amount of attention as a mechanism for glucocorticoid-mediated inhibition of immune responses, as the glucocorticoid receptor interferes with key pro-inflammatory transcription factors, including nuclear factor-κB (NF-κB) and activator protein 1 (AP-1), as well as members of the signal transducer and activator of transcription (STAT), CCAAT/enhancer-binding protein (C/EBP)

and nuclear factor of activated T cells (NFAT) families (BOX 3). Glucocorticoid receptor tethering is not a one-way relationship; numerous studies have revealed that tethering affects the ability of the glucocorticoid receptor to activate its target genes[23].

The third mode of action occurs when glucocorticoids regulate gene expression through glucocorticoid receptor binding to composite elements, which are DNA sequences that contain both a GRE and a response element for a distinct transcription factor[24]. Although it is common for the glucocorticoid receptor to inhibit a partner transcription factor at a composite element or in cases of tethering, it is important to note that glucocorticoid receptor binding can enhance the activity of the partnering transcription factor. For example, AP-1 is a common partner for the glucocorticoid receptor at composite elements throughout the genome[25], but the effects of the glucocorticoid receptor depend on the AP-1 subunit composition; the glucocorticoid receptor robustly inhibits the activity of AP-1 heterodimers comprising JUN and FOS, whereas the function of AP-1 homodimers comprising JUN–JUN is less constrained by interaction with the glucocorticoid receptor and may even be enhanced[26,27]. Similarly, the glucocorticoid receptor differentially affects the activity of various STAT family members[28] (BOX 3).

An attractive but controversial idea posits that glucocorticoids exert immunosuppressive effects primarily through glucocorticoid receptor tethering of transcription factors such as NF-κB and AP-1, which reduces the expression of pro-inflammatory genes (trans repression), whereas adverse side effects occur through gene activation via direct binding of the glucocorticoid receptor to GREs (transactivation). The notion that clinically beneficial and harmful properties of glucocorticoids are dissociable at the molecular level was suggested by observations of glucocorticoid receptor-dimerization mutants that fail to induce the expression of certain GRE-bearing genes yet still repress the activity of AP-1 and NF-κB[29]. These observations fuelled a pharmaceutical search for glucocorticoid receptor-binding compounds that selectively promote the transrepressive properties of the glucocorticoid receptor with minimal induction of transactivation[30]. It is generally appreciated now, however, that the transrepression-versus-transactivation concept is likely to be an oversimplification of the effects of glucocorticoids on immune processes, particularly in light of reports that glucocorticoid receptor-dimerization mutants retain some capacity to promote gene transcription[31]. Moreover, it is unclear whether monomers of glucocorticoid receptor-dimerization mutants retain the ability to bind nGREs and thus repress gene transcription. The degree of immunomodulation that occurs through glucocorticoid receptor-mediated gene regulation as opposed to that occurring through transcription factor inhibition is still unclear, but several genes that are directly targeted by glucocorticoids — as discussed below — exert robust regulatory effects on immune responses.

Non-genomic effects of glucocorticoids.

Whereas the genomic effects of glucocorticoids typically manifest over a period of hours, glucocorticoids also exert biological changes within seconds to minutes of exposure that do not arise from altered gene transcription. Glucocorticoid intercalation into membranes has been implicated as a glucocorticoid receptor-independent mechanism for altering cation transport through plasma membranes and promoting proton leak from mitochondria[32].

By contrast, glucocorticoid receptors are reported to interfere with cytoplasmic signalling complexes[33]. Moreover, ligand-dependent liberation of molecular components of the glucocorticoid receptor–chaperone complex has been implicated in attenuating signal transduction[33]. The ligand-bound glucocorticoid receptor has also been reported to translocate to mitochondria, resulting in apoptosis[34].

Regulation of inflammation

Glucocorticoids are potent regulators of inflammation. The inflammatory response comprises a series of interconnected processes that can be generally divided into three sequential phases: first, the alarm phase, in which ‘danger’ signals trigger the release of inflammatory mediators; second, the mobilization phase, in which leukocytes infiltrate the injured site; and last, the resolution phase, in which the tissue is cleared of cellular debris. The successful progression and resolution of the inflammatory response are crucial to wound healing. As detailed below and in FIG. 3, glucocorticoids regulate processes in each of these phases.

Effects of glucocorticoids on the alarm phase.

The alarm phase of the inflammatory response occurs upon detection of pathogens and/or tissue trauma. Tissue-resident cells express transmembrane and cytoplasmic proteins that function as ‘danger’ sensors; these sensors include pattern recognition receptors (PRRs), complement receptors and Fc receptors (FIG. 3a). PRRs bind pathogen-associated molecular patterns (PAMPs), which are evolutionarily conserved molecular motifs from microbial organisms, and damage-associated molecular patterns (DAMPs), which are endogenous cellular products that are released following tissue injury. Upon PRR activation, tissue macrophages, mast cells and stromal cells secrete inflammatory mediators, including lipid agents, vasoactive amines and cytokines (FIG. 3b). Glucocorticoids attenuate signalling pathways downstream of many danger sensors, thereby suppressing the production of inflammatory mediators. TLR signalling, for example, is subject to regulation by glucocorticoids at several points of signal transduction (FIG. 4). Liganded glucocorticoid receptors tether and inhibit transcription factors downstream of TLR signalling, including NF-κB, AP-1 and interferon-regulatory factor 3 (IRF3) (FIG. 4). Glucocorticoids also activate genes that encode inhibitors of TLR signalling, including dual-specificity protein phosphatase 1 (DUSP1), which attenuates the activity of mitogen-activated protein kinase 1 (MAPK1), and IL-1 receptor-associated kinase 3 (IRAK3), which is a negative regulator of TLR and IL-1 receptor signalling[35] (FIG. 4). Another glucocorticoid gene target is *NFKIA*, which encodes IκBα, a potent cytoplasmic inhibitor of NF-κB[36], although the physiological contribution of this gene to the effects of glucocorticoids is debated[37]. Glucocorticoids also induce the expression of glucocorticoid-induced leucine zipper protein (GILZ; also known as TSC22D3), which further inhibits NF-κB activity[38]. Notably, inflammatory signals can override some inhibitory effects of glucocorticoids; in plasma cytoid dendritic cells (pDCs), sustained signalling through TLR7 and TLR9 disrupts the capacity of the glucocorticoid receptor to inhibit NF-κB activity, which may contribute to autoimmune pathology[39].

Importantly, many of the TLR signalling components that are targeted by glucocorticoids, particularly NF-κB and AP-1, are shared by the signalling pathways of other danger sensors (as well as those of cytokine receptors). For example, glucocorticoids dampen signalling through Fcε receptors, thereby attenuating histamine release by mast cells[40] (FIG. 3b). By inhibiting shared 'modules' of signal transduction, glucocorticoids suppress multiple signalling pathways that are involved in the detection of noxious agents and the propagation of inflammatory signals.

Inflammation is characterized by the dilation of local blood vessels, increased vascular permeability and the leakage of plasma into tissue. Glucocorticoids act on macrophages in inflamed tissue to inhibit the generation of eicosanoids, which are lipid mediators (such as prostaglandins and leukotrienes) that promote vascular dilation and permeability (FIG. 3b). The liganded glucocorticoid receptor activates the expression of annexin A1, which interferes with the phospholipase A2-catalysed release of arachidonic acid[41], a fatty-acid intermediate of eicosanoid biosynthesis. Glucocorticoids further curb prostaglandin generation by inhibiting cyclooxygenase 2 (also known as PTGS2) through the NF-κB-suppressing properties of GILZ[42]. Glucocorticoids reduce blood flow to inflammatory sites by inducing the expression of angiotensin-converting enzyme and endothelin, by sensitizing endothelial cells to vasoconstrictors and by inhibiting the production of vasodilators, including bradykinin[43]. In an animal model of acute lung injury, Vettorazzi *et al.*[44] found that glucocorticoids preserve the barrier function of the endothelium by upregulating macrophage expression of sphingosine kinase 1 (which is encoded by *SPHK1*), which inhibits vascular leakage[44].

Danger signals detected by PRRs are propagated through cytokine induction. Cytokines bind to cognate receptors on neighbouring cells to stimulate biological effects, which often include the expression of more cytokines. Thus, cytokine networks amplify and shape the inflammatory response. Glucocorticoids inhibit the expression of many pro-inflammatory cytokines, including IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-11, IL-12, IL-13, IL-16, IL-17, interferon-γ (IFNγ), TNF and granulocyte–macrophage colony-stimulating factor (GM-CSF) (FIG. 3b). As described above, glucocorticoid-mediated attenuation of cytokine expression occurs downstream of danger sensor and cytokine receptor signalling[45]. In addition, nGREs have been identified in some cytokine genes, including *IL1B* (which encodes IL-1β), *IL6* and *TSLP* (which encodes thymic stromal lymphopoietin)[20]. Glucocorticoids also regulate cytokine production at the post-transcriptional level; glucocorticoid receptor-mediated upregulation of tristetraprolin (also known as ZFP36) decreases the half-life of *TNF* mRNA[46]. In cytokine-responsive cells, glucocorticoids attenuate cytokine receptor signalling via protein–protein inter actions between the liganded glucocorticoid receptor and pro-inflammatory transcription factors (for example, STAT family members and NF-κB), as well as by induction of suppressor of cytokine signalling 1 (SOCS1), an inhibitor of Janus kinase (JAK)–STAT signalling[47,48]. The importance of glucocorticoid receptor signalling in dampening cytokine production is exemplified by mice with conditional glucocorticoid receptor ablation in macro phages or dendritic cells (DCs). These mice produce supranormal levels of IL-1β, IL-6, TNF and IL-12, and exhibit greater mortality during experimentally induced sepsis than do wild-type animals[49–51].

Effects of glucocorticoids on the mobilization phase.

Inflammatory mediators produced in the alarm phase induce the expression of adhesion molecules and chemo attractants that recruit leukocytes from proximal blood vessels into inflammatory foci. The mobilization phase is crucial to the clearance of pathogens and cellular debris. Endothelial expression of E-selectin initiates the tethering of circulating neutrophils and monocytes to blood vessel walls, which facilitates the interaction between chemokines emanating from inflammatory sites and chemokine receptors on leukocytes (FIG. 3c). Chemokine ligand–receptor interactions promote leukocyte rolling on the endothelium and the binding of integrins to integrin ligands, which lead to firm adhesion and leukocyte transmigration through the blood vessel wall[52] (FIG. 3c). Extravasated leukocytes then migrate through the tissue following chemokine gradients to inflammatory sites. Glucocorticoids attenuate leukocyte extravasation by inhibiting endothelial transcription of *SELE* (which encodes E-selectin), as well as the integrin ligands *ICAM1* (intercellular adhesion molecule 1) and *VCAM1* (vascular cell adhesion molecule 1)[53,54]. Glucocorticoids also downregulate the production of several chemokines and chemoattractants, including IL-8 (also known as CXCL8), IL-16, CC-chemokine ligand 2 (CCL2), CCL3, CCL5, CCL11, CCL24 and CCL26, thereby curbing leukocyte migration. Recent studies have also suggested that direct glucocorticoid receptor binding to chemokine-encoding mRNA transcripts, including *CCL2* and *CCL7*, promotes their decay[55]. Glucocorticoids also reduce leukocyte expression of adhesion molecules, including CD44 and the integrins lymphocyte function-associated antigen 1 (LFA1) and very late antigen 4 (VLA4)[56]. Glucocorticoid-mediated induction of annexin A1 also impedes leukocyte recruitment[57]. In experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, glucocorticoids inhibit T cell infiltration into the central nervous system[56].

Roles of glucocorticoids in the resolution phase.

As pathogens and noxious agents are eliminated from inflammatory sites, PRR signalling subsides and the production of inflammatory mediators diminishes. However, inflammation is fully resolved through an active programme of immunoregulation, in which glucocorticoids — along with lipoxins, resolvins, collectins and protectins — have important roles[58]. Important processes in the resolution phase include the clearance of cellular debris and the production of anti-inflammatory factors. Glucocorticoids initiate gene programmes in monocytes and macrophages that promote the phagocytosis of apoptotic cells and debris[59–61]. Indeed, glucocorticoid-mediated programming of macrophages has received enough attention to warrant the classification of an ‘M2c’ subtype of alternatively activated macrophages; macrophages in this state are characterized by high expression of scavenger receptors (CD163 (also known as M130), CD206 (also known as MRC1) and tyrosine-protein kinase MER (MERTK)) and by the secretion of the anti-inflammatory cytokines transforming growth factor-β (TGFβ) and IL-10 (REF. 62) (FIG. 3d). Another function of glucocorticoids during the resolution phase is to sensitize cells to other pro-resolving factors through the upregulation of the lipoxin A4 receptor[63]. Resolution of the inflammatory response is followed by wound healing, which restores tissue integrity and function. Glucocorticoids inhibit many wound-healing processes, including collagen deposition, re-epithelialization and angiogenesis; attenuating glucocorticoid activity may be an important component of the transition from inflammation to wound healing.

Glucocorticoid regulation of cell death

Glucocorticoids exert potent regulatory effects on cellular immunity, and affect the development, activation and polarization of T cells. Discerning the specific role of glucocorticoids in thymocyte development has been perplexing, and there are conflicting reports about glucocorticoid receptor-mediated regulation of thymopoiesis. Thymocytes are exquisitely sensitive to glucocorticoid-induced cell death *in vitro* and *in vivo*; moreover, adrenalectomy results in thymic hyperplasia, which suggests that glucocorticoid insufficiency allows the supranormal expansion of thymocyte populations. These observations are central to a long-standing hypothesis of endogenous glucocorticoids as negative regulators of thymopoiesis. However, the thymomegaly phenotype of adrenalectomized mice is not recapitulated in glucocorticoid receptor-deficient fetal liver chimaeras[64]. Moreover, mice with a T cell-specific ablation of the glucocorticoid receptor still exhibit thymic hyperplasia following adrenalectomy, which indicates that glucocorticoid insufficiency promotes thymocyte expansion independently of glucocorticoid receptor signalling (or the lack thereof) in these cells[65]. The issue of the roles of glucocorticoids in thymopoiesis is further complicated by reports of glucocorticoids having a positive, rather than negative, role in thymocyte survival. According to the ‘mutual antagonism’ hypothesis, crosstalk between glucocorticoid receptor signalling and T cell receptor (TCR) signalling alters the thresholds for positive selection and negative selection during thymocyte development. Supporting this hypothesis, a recent study of a strain of mice with a T cell-specific deletion of the glucocorticoid receptor reported reduced thymic cellularity, an altered TCR repertoire and impaired T cell responsiveness[66]. Although stress and pharmacological levels of glucocorticoids have clear negative effects on thymocyte survival, a role for endogenous glucocorticoids in the steady-state regulation of thymopoiesis is still unclear.

The lympholytic properties of glucocorticoids are routinely exploited for the treatment of certain haemato-logical malignancies. Although glucocorticoids were among the earliest described inducers of cell death in lymphocytes, the molecular mechanisms that induce apoptosis downstream of glucocorticoid receptor activation are still unclear. Thus, there is some irony in the common use of glucocorticoids to benchmark cell death in studies of novel pro-apoptotic and anti-apoptotic factors. The mechanisms of glucocorticoid-induced apoptosis have been comprehensively reviewed elsewhere (REFS. 33, 67). Importantly, the apoptotic mechanisms activated by glucocorticoids differ by activation state, lymphocyte type and even the stage of differentiation[68]. There seems to be considerable redundancy in the apoptotic programmes induced by glucocorticoids, as lymphocytes from many single-gene-knockout mice (for example, knockouts of individual caspase family members) are still sensitive to glucocorticoid receptor-mediated death. It is generally thought that glucocorticoid receptor-mediated apoptosis requires gene activation, although recent studies have also implicated non-genomic mechanisms, particularly glucocorticoid receptor translocation to mitochondria[33]. N-Terminal isoforms of the glucocorticoid receptor exhibit different capacities to induce apoptosis, so the glucocorticoid receptor isoform profile of a cell probably affects sensitivity to glucocorticoid-induced death[69]. Lastly, it is worth noting

that lymphocytes are not the only cells that are sensitive to glucocorticoid-induced death, as DCs[70], eosinophils[71] and osteocytes[72] also undergo apoptosis in response to glucocorticoids.

Effects of glucocorticoids on T cell activation

A crucial component of cellular immunity is TCR-mediated activation of antigen-specific T cells. Antigen-presenting cells (APCs) display peptide antigens complexed with MHC class I or MHC class II molecules to activate $CD8^+$ or $CD4^+$ T cells, respectively. DCs — which are professional APCs that integrate antigens and signals from the innate immune response to stimulate T helper (T_H) cell responses — are cellular targets of glucocorticoids. The effects of glucocorticoids have been investigated for various DC types, including tissue-resident DCs, migratory DCs and pDCs, with the general conclusions being that glucocorticoids attenuate DC activity by inhibiting DC maturation; by downregulating the expression of MHC class II, the lipid-presentation molecule CD1a, co-stimulatory molecules (for example, CD80 and CD86) and pro-inflammatory cytokines (such as IL-12 and TNF); and by promoting the expression of anti-inflammatory cytokines, such as IL-10 (REF. 73) (FIG. 5a). Interestingly, glucocorticoid exposure during monocyte-to-DC maturation enhances the capacity of DCs to take up antigens but inhibits their function as APCs, which has led to the hypothesis that glucocorticoids promote the differentiation of ‘tolerogenic’ DCs[74]. Moreover, in both rodents and humans, pharmacological doses of glucocorticoids decrease DC numbers, and this is probably a result of increased apoptosis and tissue redistribution[75,76].

Glucocorticoids also dampen T cell activation by interfering with TCR signalling. Mechanisms implicated in glucocorticoid receptor-mediated attenuation of TCR signalling include the downregulation of FOS and interference with the activity of AP-1, NF-κB and NFAT[77] (FIG. 5a). A recent study revealed that glucocorticoids also modulate the expression of several kinases that are involved in TCR signalling, including ITK, TXK and LCK[78]. Non-genomic actions of glucocorticoid receptors have been implicated in attenuating TCR signalling by reducing the activity of the kinases LCK and FYN[79] (FIG. 5a). Glucocorticoid receptor-mediated tempering of TCR signalling results in reduced proliferative responses and diminished cytokine production, including reduced secretion of IL-2 (REF. 80).

Although the net effect of glucocorticoid action is diminished T cell activity, numerous studies suggest that glucocorticoids preferentially suppress the responses of T_H1 cells and T_H17 cells, while sparing, or possibly even promoting, the function of T_H2 cells and regulatory T (T_{reg}) cells (FIG. 5b). Mechanisms proposed for glucocorticoid-induced T_H2 cell polarization include downregulation of the production of the T_H1 cell-promoting cytokine IL-12 by APCs, attenuation of IL-12 receptor expression in T cells, inhibition of the T_H1 cell master transcription factor T-bet, and enhanced production of the canonical T_H2-type cytokines IL-4, IL-10 and IL-13 by T_H2 cells[81,82]

Evidence for glucocorticoid-based regulation of T_H17 cell polarization stems from the repressive effects of GILZ on the production of T_H17 cell-promoting factors (that is, IL-1, IL-6 and IL-23) by DCs, and on the expression of genes involved in the differentiation and activity of T_H17 cells (namely IL-17A, IL-23 receptor, RORγt, STAT3, BATF and

IRF4)[83,84]. Studies in mice with a T cell-specific deletion of the glucocorticoid receptor revealed T_H17 cells as crucial targets for glucocorticoid treatment in animal models of multiple sclerosis and rheumatoid arthritis[56,85]. These findings probably explain, at least in part, the capacity of glucocorticoids to ameliorate other auto immune and inflammatory pathologies, including psoriasis and spondyloarthropathy.

Studies in mice and humans have also implicated glucocorticoids in promoting T_{reg} cell differentiation and activity. Glucocorticoid treatment is associated with increased frequencies of T_{reg} cells in the circulation and/or inflamed tissue, and this effect is possibly mediated by glucocorticoid receptor-induced upregulation of the T_{reg} cell master transcription factor forkhead box P3 (FOXP3)[86], which is perhaps a result of the upregulation of GILZ[87].

Glucocorticoids and humoral immunity

Our understanding of the effects of glucocorticoids on humoral immunity is limited. Nonetheless, glucocorticoids are effective in treating autoimmune diseases in which antibody contributes to pathology, such as rheumatoid arthritis. Moreover, recent studies have shown that B cells exhibit potent immunoregulatory functions, most notably through the expression of IL-10 (*IL10* is a known glucocorticoid receptor target gene in macrophages), perhaps warranting a second look at the effects of glucocorticoids on B cells.

Effects on B cell development and survival.

In some ways, the actions of glucocorticoids on thymopoiesis are mirrored in B lymphopoiesis. Immature B cells are more sensitive to glucocorticoid-induced apoptosis than are mature B cells[88,89], and adrenalectomy or treatment with the glucocorticoid receptor antagonist mifepristone results in the expansion of immature B cell populations in the bone marrow[89]. B cells express the glucocorticoid receptor throughout development[90], and the glucocorticoid receptor affects several transcription factors downstream of B cell receptor (BCR) signalling (for example, AP-1, NF-κB and NFAT), which raises the possibility that glucocorticoids have effects on B cell selection. To our knowledge, however, mechanistic studies of crosstalk between glucocorticoid receptor signalling and BCR signalling are lacking.

Clues about the direct effects of glucocorticoids on B cell function may be gleaned from mice that lack the glucocorticoid target gene *Gilz*. In response to BCR stimulation, *Gilz*-deficient B cells exhibit an exaggerated proliferative response and, with age, *Gilz*-knockout mice develop a lupus-like syndrome[91]. Mice with a B cell-specific deficiency of *Gilz* do not recapitulate the autoimmune phenotype of global *Gilz* deficiency, which indicates a B cell-extrinsic role for GILZ in autoantibody production; however, mice that specifically lack GILZ expression in B cells exhibit systemic increases in B cell numbers, which suggests an intrinsic role for glucocorticoid receptor signalling in B cell survival and/or homeostasis[92].

Effects on antibody production.

A consensus on the effects of glucocorticoids on humoral immunity has not been achieved, although, in general, pharmacological treatment with glucocorticoids is associated with

reduced immunoglobulin concentrations. Only a few studies have addressed the effects of long-term glucocorticoid treatment on vaccination of humans, and little impact (if any) on antibody titres has been reported. Nonetheless, the regulation of IgE production by glucocorticoids has garnered some attention, as some clinical and *in vitro* studies suggest that glucocorticoids may, in certain situations, promote the production of this immunoglobulin isotype. In studies of patients with asthma who were undergoing glucocorticoid therapy, the serum concentrations of IgE rose, whereas the concentrations of other immunoglobulin isotypes were unaffected or decreased[93,94]. Proposed mechanisms for glucocorticoid-mediated enhancement of IgE production include direct effects on B cells, whereby glucocorticoids synergize with IL-4 to promote isotype class-switching[95], as well as indirect effects on B cells via the actions of glucocorticoids on T cells and monocytes[96–98]. The efficacy of glucocorticoids in the treatment of asthma and allergies, however, suggests that glucocorticoid-mediated enhancement of IgE production (as well as T_H2 cell activity) does not exacerbate pathology in these diseases. Indeed glucocorticoids exert potent effects on myeloid cells to suppress disease in animal studies of allergic dermatitis[99].

In light of the clinical evidence that pharmacological treatment with glucocorticoids reduces blood concentrations of some non-IgE immunoglobulins, it is puzzling that endogenous glucocorticoids have also been implicated as positive regulators of antibody responses to immunization. For example, adrenalectomized rats mount poor IgM and IgG responses to the T cell-dependent antigen keyhole limpet haemocyanin[100,101]. The induction of T cell-dependent humoral responses involves multiple glucocorticoid receptor-expressing cell types, including DCs, $CD4^+$ T cells and B cells. Determining the glucocorticoid-sensitive cells and processes that enhance antibody responses will provide important insights into the endocrine regulation of humoral immunity. In the next section, we address the enigmatic issue of glucocorticoids as potentiators of immune responses in more detail.

Immune-enhancing effects of glucocorticoids

This Review, like much of the literature on glucocorticoids that has been published in the last 60 years, has focused on the immunosuppressive properties of glucocorticoids. However, there is a considerable amount of work showing that glucocorticoids also enhance inflammation and immunity. In some studies, the potentiating — as opposed to suppressive — effects of glucocorticoids are linked to dose. For example, in macrophages activated by lipopolysaccharide (LPS) and IFNγ, high doses of corticosterone inhibit the transcription of inflammatory genes, whereas low doses of corticosterone enhance inflammatory gene expression[102]. The temporal relationship between a noxious stimulus and glucocorticoid exposure can also affect the directionality of the effects of glucocorticoids on inflammation. In rats, pro-inflammatory cytokine expression is enhanced if glucocorticoids are administered before LPS challenge but are dampened if glucocorticoids are administered following LPS treatment[103]. Similarly, acute low-dose corticosterone treatment before challenge enhances inflammation in a rat model of delayed-type hyper sensitivity, whereas high-dose or prolonged glucocorticoid treatment mitigates the delayed-type hypersensitivity response[104].

Genome-wide expression studies of glucocorticoid-treated cells have yielded surprising results, and suggest that glucocorticoids largely spare or enhance gene pathways that are associated with innate immunity, but selectively suppress pathways that are involved in adaptive immunity (FIG. 6a). For example, the treatment of blood mononuclear cells with glucocorticoids leads to the upregulation of several PRRs, scavenger receptors, cytokine and chemokine receptors, complement components and other factors that are involved in innate immunity, but suppresses the expression of genes that encode TCR components as well as genes involved in T cell activation, including those that encode MHC class II and co-stimulatory molecules[1] (FIG. 6a). Selective enhancement of innate immune gene expression by glucocorticoids at the expense of adaptive immune gene expression has also been observed in human macrophages[105].

Clues about the molecular mechanisms that underlie the immunopotentiating effects of glucocorticoids might be found among glucocorticoid receptor target genes. Glucocorticoids promote the expression of TLR2, TLR4, the inflammasome component NOD-, LRR- and pyrin domain-containing 3 (NLRP3) and the purinergic receptor P2Y2R, which may sensitize cells to PAMPs and DAMPs[106]. Interestingly, although glucocorticoids are well-recognized to decrease cytokine secretion, they are reported to increase the expression of several cytokine receptors, including the receptors for TNF, IL-1, IL-6 and IFNγ[107]. Rapid increases in circulating glucocorticoid concentrations triggered by physiological stress may serve as a systemic warning system, and sensitize cells to DAMPs, PAMPs and inflammatory cytokines. Thus, glucocorticoids (along with catecholamines) are important contributors to altered immune function associated with chronic stress[108,109].

A unified model

As discussed above, glucocorticoids have been shown to have both enhancing and suppressive effects on the immune system. To explain this apparent paradox of glucocorticoid action, Munck and Naray-Fejes-Toth posited that glucocorticoid physiology follows a biphasic dose–response curve, such that glucocorticoids have ‘permissive’ (that is, immunostimulatory) effects at low concentrations and suppressive effects at high concentrations[110,111]. Biphasic effects of glucocorticoids have also been observed in other physiological contexts, including neural plasticity[112]. Wiegers and Reul[107] further hypothesized that the net cellular effect of concurrent glucocorticoid-mediated upregulation of cytokine receptors and downregulation of cognate cytokines is a bio logical response with a more rapid initiation but shorter duration.

We propose a unified model for glucocorticoid-mediated regulation of the immune response that incorporates the hypotheses of a biphasic dose–response proposed by Munck and Naray-Fejes-Toth[110], and the kinetic effects of disparate cytokine–cytokine receptor regulation described by Wiegers and Reul[107]. We propose that in the absence of inflammation, basal levels of glucocorticoid receptor signalling — which are driven by circadian and ultradian rhythms of glucocorticoid production — sensitize cells to harmful stimuli by promoting the expression of PRRs, cytokine receptors and complement factors, which allow for the rapid detection of PAMPs and DAMPs, and promoting the induction of an inflammatory response upon tissue insult. During the inflammatory state, however,

stress-induced (or pharmacological) concentrations of glucocorticoids restrain the immune response, primarily by blunting the propagation of PRR, Fc receptor and cytokine signals, thereby shortening the duration of the immune response (FIG. 6b). This model predicts that in the absence of glucocorticoids (via adrenalectomy or glucocorticoid antagonism), the immune response will be delayed in onset but prolonged in duration (FIG. 6b). Although this is likely to be an oversimplification of the actions of glucocorticoids, we offer this model as a framework for future research. Understanding the mechanisms by which and the conditions in which glucocorticoids shape an immune response, both positively and negatively, will probably provide important insights into optimized glucocorticoid therapies.

Conclusions and perspectives

The clinical efficacy of glucocorticoids in treating inflammatory and autoimmune disease is clear, yet the molecular mechanisms that underlie the immunoregulatory effects of glucocorticoids are still being elucidated. There are substantial gaps in our knowledge of glucocorticoid-mediated regulation of immunity, especially regarding cell lineage-specific functions and disease-specific roles, and possible sexually dimorphic effects. Moreover, the adverse effects of excess glucocorticoids are wide-ranging (BOX 1); a deeper understanding of the actions of glucocorticoids that are shared among physiological systems versus those that are unique to the immune system is necessary to achieve the ‘holy grail’ of safe glucocorticoid therapy.

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Glossary

Lympholytics
Agents that cause the death of lymphocytes.

Steroidogenesis
The enzymatic processing of cholesterol into steroid hormones.

Hypothalamic–pituitary–adrenal axis
(HPA axis). The three-organ system that receives inputs from the endocrine, neural and immune systems, and controls physiological responses to stress.

Sumoylation
A post-translational modification consisting of small ubiquitin-like modifier (SUMO) proteins.

Immunophilins
Members of a family of highly conserved cytosolic isomerases, many of which have unknown cellular functions.

Pattern recognition receptors

(PRRs). Transmembrane and cytosolic host receptors that recognize damage-associated molecular patterns and/or pathogen-associated molecular patterns.

Scavenger receptors
Members of a subclass of pattern recognition receptors that are involved in the identification and removal of unwanted molecules and cellular debris.

Positive selection
The process by which thymocytes expressing T cell receptors that bind self-peptide–MHC complexes are provided with survival signals during T cell development.

Negative selection
The process through which thymocytes expressing highly self-reactive T cell receptors are induced to undergo cell death.

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Box 1 |

Adverse effects of glucocorticoid excess: the CUSHINGOID mnemonic

The term ‘cushingoid’ describes the collection of signs and symptoms that are associated with Cushing syndrome, which results from excess glucocorticoid activity (either endogenous or exogenous). The medical mnemonic below reveals the widespread roles of glucocorticoids in various physiological systems.

Letter of mnemonic	Sign or symptom	Pathophysiology
C	Cataracts	Unknown but may involve perturbed migration of lens epithelial cells[113]
U	Ulcers	Disputed, but may be due to the inhibition of gastric-protective prostaglandins, mucus production and/or bicarbonate secretion[114]
S	Striae and skin thinning	Unclear but may involve decreased fibroblast proliferation and/or altered metabolism of the extracellular matrix[115]
H	Hypertension and hirsutism (in women)	Increased plasma volume, cardiac output and peripheral vascular resistance occur through both mineralocorticoid and glucocorticoid effects[116]; hirsutism occurs due to dysregulated production of adrenal testosterone
I	Immunosuppression and infections	Discussed in the main text
N	Necrosis of femoral heads	Increased bone marrow fat, decreased bone perfusion and osteocyte apoptosis[117]
G	Glucose elevation	Glucose intolerance and insulin insensitivity[118]
O	Osteoporosis and obesity	Inhibition of osteoblast function and survival, decreased bone mass (osteoporosis)[119] and redistribution of adipose tissue (obesity)[118]
I	Impaired wound healing	Reduced proliferation of fibroblasts and epidermal cells, inhibition of collagen synthesis and reduced angiogenesis[120]
D	Depression and mood changes	Psychological, cognitive and behavioural disturbances[121]

Box 2 |

Cellular targets of glucocorticoid action in animal models of disease

Mouse studies have revealed the crucial cellular targets for glucocorticoid treatment of various inflammatory and autoimmune models of human disease. In the studies cited in the table below, glucocorticoid efficacy in the indicated disease model was reduced by genetic ablation of glucocorticoid receptor expression in target cells or by *in vivo* depletion of specific cell types.

Animal model	Human disease modelled	Crucial cellular target of glucocorticoids
Contact hypersensitivity	Allergic contact dermatitis	Myeloid cells[99]
Experimental autoimmune encephalomyelitis	Multiple sclerosis	T_H17 cells[56]
Antigen-induced arthritis	Rheumatoid arthritis	T_H17 cells[85]
LPS-induced endotoxaemia	Sepsis	Myeloid cells[50] and dendritic cells[51]
Experimentally induced thrombocytopenia	Immune thrombocytopenia	$CD8^+$ T cells[122]
Doxorubicin-induced renal injury	Focal segmental glomerulosclerosis	Myeloid-derived suppressor cells[123]

LPS, lipopolysaccharide; T_H17, T helper 17.

Box 3 |

Transcription factors modulated by the glucocorticoid receptor

Glucocorticoid receptors bind other transcription factors to modulate their effects on gene transcription. The table below lists various transcription factors that interact with the glucocorticoid receptor via protein–protein binding. For each partnering transcription factor, the type of protein–protein interaction is shown as either tethering (in which glucocorticoid receptor binds the indicated transcription factor but glucocorticoid receptor binding to DNA is unnecessary) or composite (in which glucocorticoid receptor binding to both the target transcription factor and DNA is required).

Transcription factor	Type of interaction	Effects of interaction with glucocorticoid receptor	Refs
AP-1	Tethering	AP-1 inhibited	124
C/EBPβ	Composite	C/EBPβ inhibited	125
CREB	Composite	Enhanced CREB2 activity	126
ETS2	Composite	Enhanced ETS2 activity	127
GATA1	Composite	GATA1 inhibited	128
NF-κB	Tethering	NF-κB inhibited	129
NR4A1	Tethering	NR4A1 inhibited	130
POU2F1	Tethering	POU2F1 inhibited	131
SMAD3	Tethering	SMAD3 inhibited	132
STAT3	Tethering	Enhanced STAT3 activity	133
STAT5	Tethering	Enhanced STAT5 activity	134
STAT6	Tethering	STAT6 inhibited	135
T-bet	Tethering	T-bet inhibited	82

AP-1, activator protein 1; C/EBPβ, CCAAT/enhancer-binding protein-β; CREB, cAMP-responsive element-binding protein; GATA1, GATA-binding factor 1 (also known as erythroid transcription factor); NF-κB, nuclear factor-κB; NR4A1, nuclear receptor subfamily 4 group A member 1 (also known as NUR77); POU2F1, POU domain class 2 transcription factor 1 (also known as OCT1); SMAD3, mothers against decapentaplegic homologue 3; STAT, signal transducer and activator of transcription.

FURTHER INFORMATION

GeneCards entry for *NR3C1*: http://www.genecards.org/cgi-bin/carddisp.pl?gene=NR3C1

Nuclear Receptor Signaling Atlas entry for *NR3C1*: https://www.nursa.org/nursa/index.jsf

Online Mendelian Inheritance in Man entry for *NR3C1*: http://www.omim.org/entry/138040

The British Pharmacological Society and the International Union of Basic and Clinical Pharmacology (IUPHAR) Guide to PHARMACOLOGY entry for *NR3C1*: http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=625

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

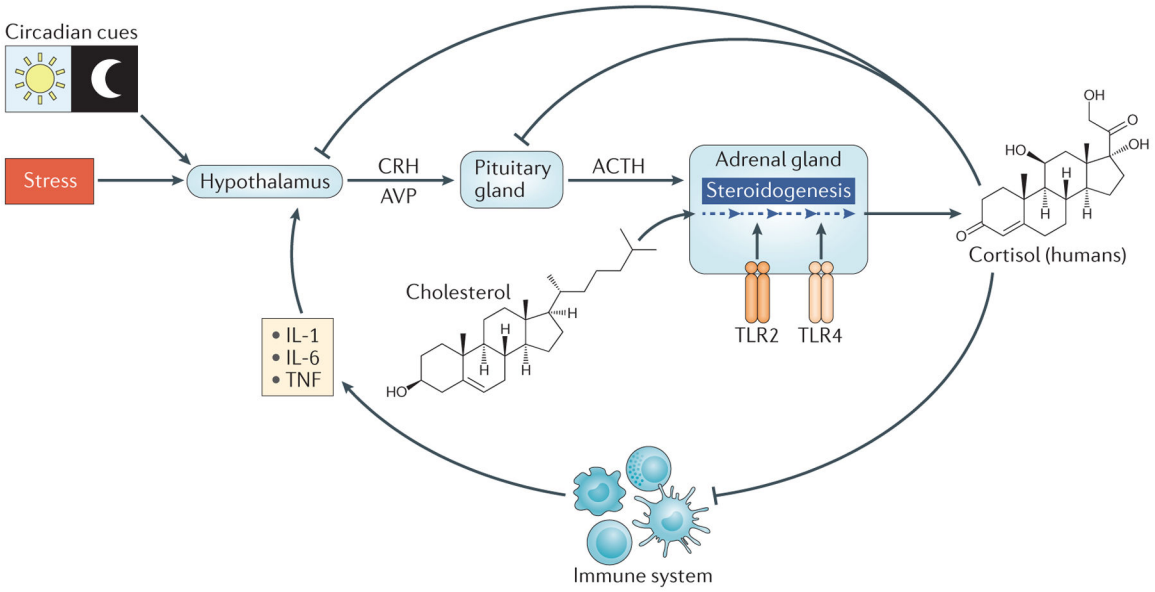

Figure 1 |. Regulation of glucocorticoid production by the hypothalamic–pituitary–adrenal axis. The hypothalamus responds to circadian cues, stress (real or perceived) and inflammatory cytokines by producing corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH and AVP act on the anterior pituitary gland to induce the synthesis and secretion of adrenocorticotropin hormone (ACTH). ACTH enters the circulation and binds receptors on adrenocortical cells to stimulate steroidogenesis (indicated by the dark blue dashed arrows). Activation of Toll-like receptor 2 (TLR2) and TLR4 on adrenocortical cells also triggers steroidogenesis. During steroidogenesis, cholesterol undergoes a series of enzymatic changes that result in the production of glucocorticoids. Cortisol and corticosterone are the primary glucocorticoids in humans and rodents, respectively. Glucocorticoids enter the circulation for distribution throughout the body. Glucocorticoids negatively regulate the hypothalamic–pituitary–adrenal (HPA) axis by feeding back on the hypothalamus and pituitary gland, and by decreasing the expression of pro-inflammatory cytokines. IL, interleukin; TNF, tumour necrosis factor.

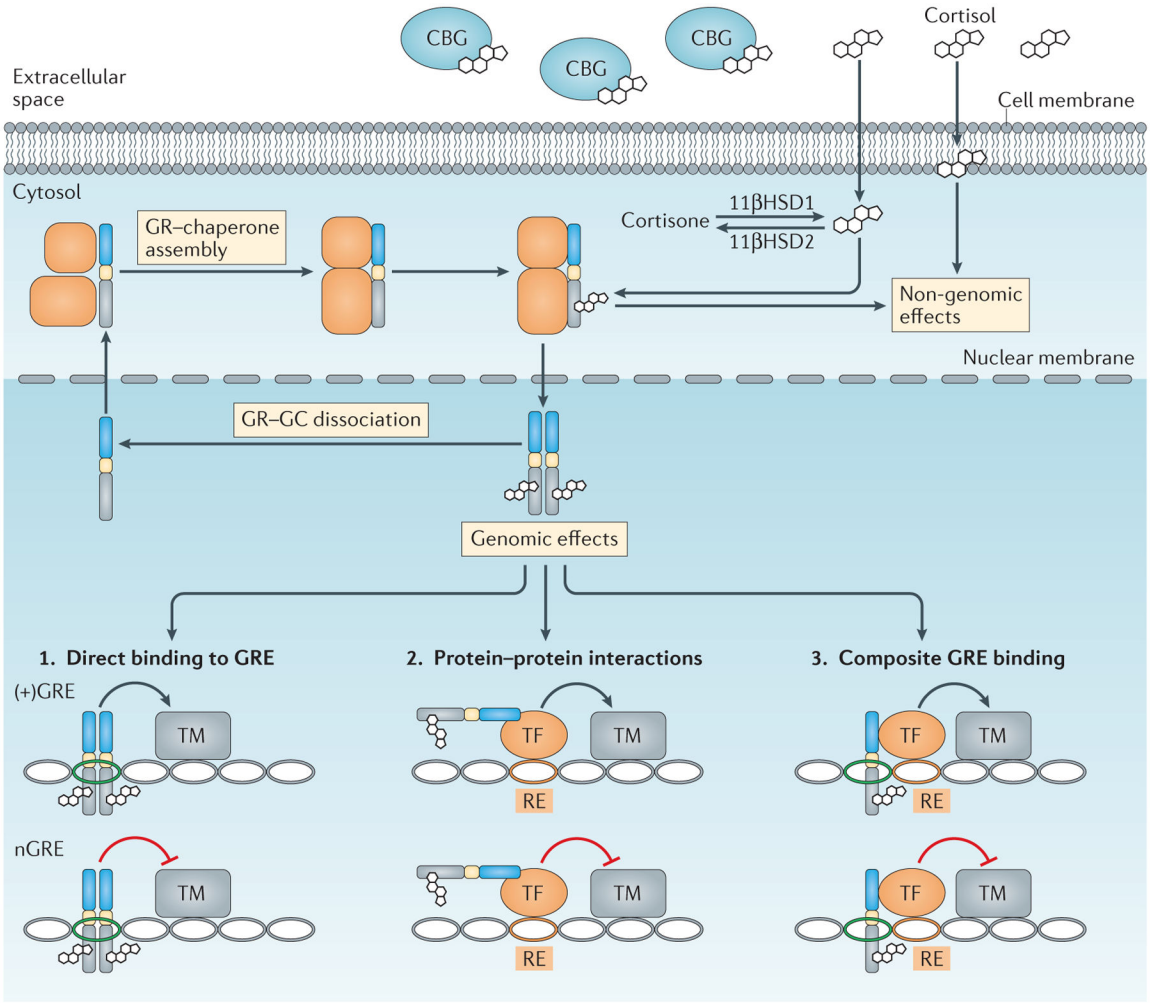

Figure 2 |. Mechanisms of glucocorticoid activity.

In the extracellular space, most endogenous glucocorticoids (GCs) are inactive owing to binding with corticosteroid-binding globulin (CBG). Unbound cortisol is lipid soluble and diffuses through cell membranes. Cortisol that enters the cytoplasm can be converted into inactive cortisone through enzymatic modification by 11β-hydroxysteroid dehydrogenase 2 (11βHSD2), whereas 11βHSD1 favours the reverse reaction. Cortisol intercalation into plasma membranes can exert non-genomic effects. Cytoplasmic cortisol binds the GC receptor (GR) as part of a chaperone complex. The ligand-bound GR translocates to the nucleus to exert genomic effects, or has non-genomic effects in the cytoplasm and mitochondria. Within the nucleus, the liganded GR alters gene expression through three basic mechanisms: direct binding to GC response elements (+GREs) or negative GREs (nGREs); protein–protein interactions with other transcription factors (TFs) that affect their transcriptional activity; and composite binding to DNA and protein substrates. Notably, positive and negative gene regulation is possible for each of these mechanisms. RE, response element; TM, transcriptional machinery.

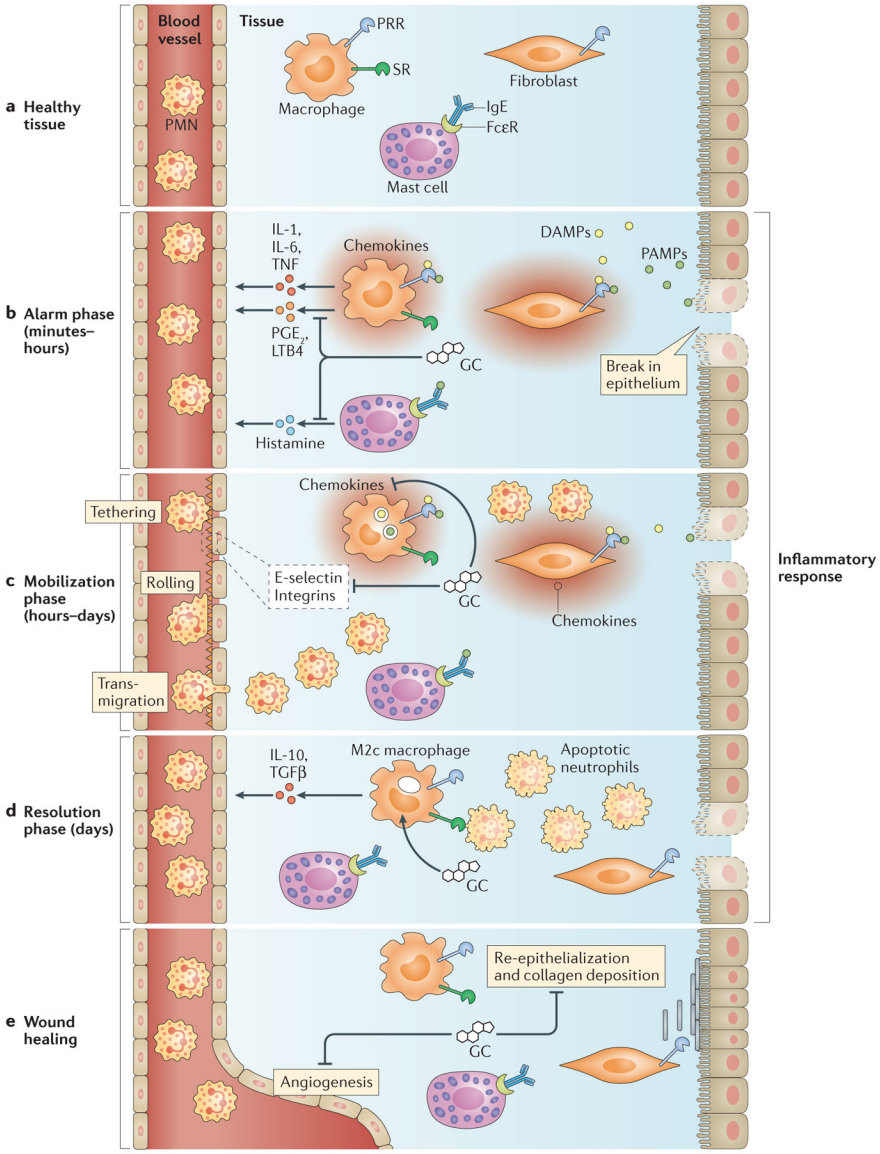

Figure 3 |. Effects of glucocorticoids on inflammation.

a | In healthy tissue, tissue-resident macrophages, fibroblasts and stromal cells express pattern recognition receptors (PRRs) and scavenger receptors (SRs). Mast cells bind soluble IgE via Fcε receptors (FcεRs). **b** | During the alarm phase of inflammation, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) trigger PRR signalling, which induces the production of inflammatory mediators, including cytokines, prostaglandin E_2 (PGE_2) and leukotriene B4 (LTB4). Antigens bind FcεR-bound IgE on mast cells to induce histamine release. Glucocorticoids (GCs) dampen signalling through PRRs, FcεRs and cytokine receptors. **c** | During the mobilization phase of inflammation, inflammatory mediators induce the display of adhesion molecules — including E-selectin, chemokines and integrins — on the vascular endothelium to recruit leukocytes, especially polymorphonuclear leukocytes (PMNs), into the tissue. Extravasating leukocytes follow chemokine gradients towards inflammatory sites. GCs inhibit the

expression of E-selectin, chemokines and integrins to reduce leukocyte recruitment. **d** | During the resolution phase of inflammation, GCs promote the differentiation of alternatively activated ‘M2c’ macrophages, which clear apoptotic PMNs and secrete anti-inflammatory factors. **e** | The resolution of inflammation triggers wound healing, which is characterized by re-epithelialization, collagen deposition and angiogenesis. As GCs inhibit these processes, optimal wound healing probably depends on reduced glucocorticoid production. IL, interleukin; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.

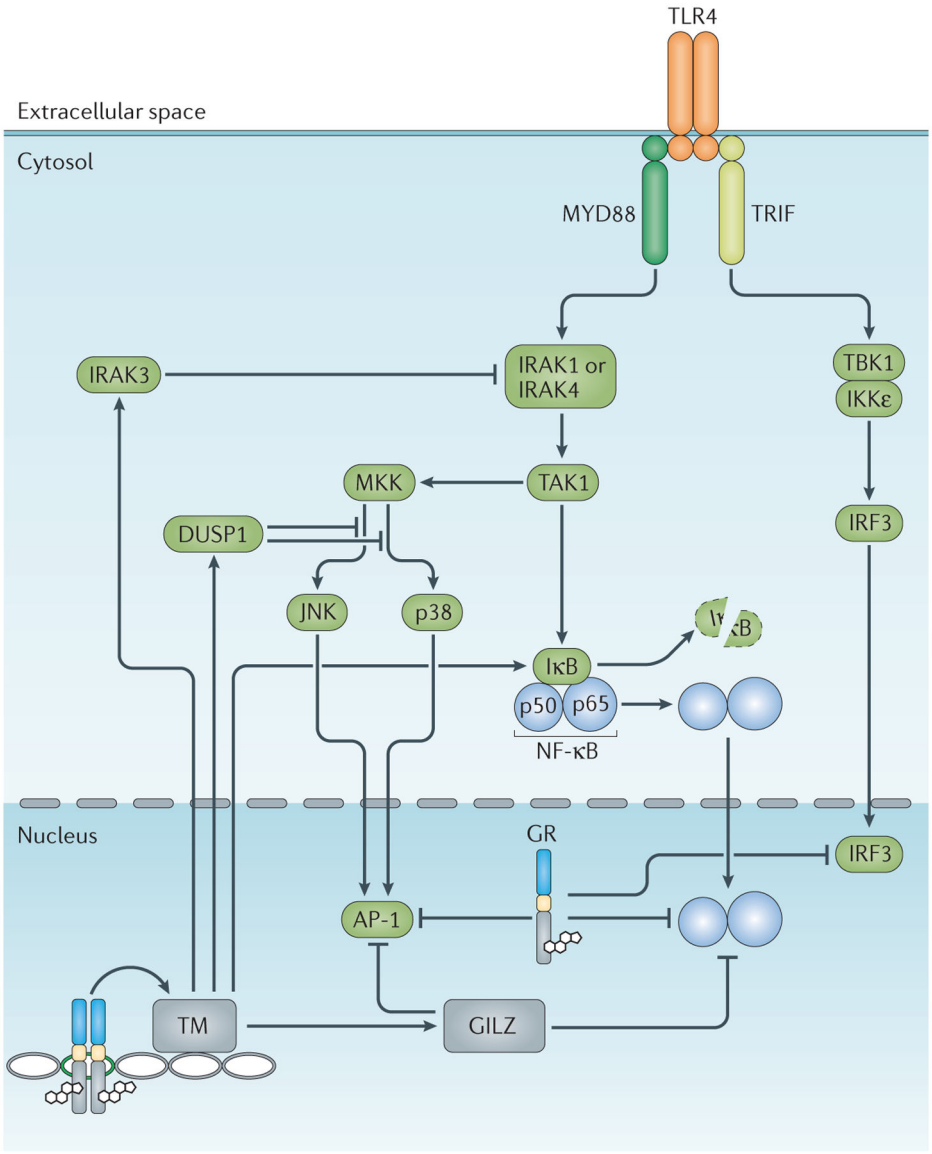

Figure 4 |. Glucocorticoids inhibit signalling through Toll-like receptors.

Glucocorticoid receptors (GRs) regulate various points in the Toll-like receptor (TLR) signalling cascade, and many of these steps are shared with other immune receptors. The activated GR enhances the transcription of genes encoding TLR signalling inhibitors, including interleukin1 receptor-associated kinase 3 (IRAK3), dual-specificity protein phosphatase 1 (DUSP1), inhibitor of nuclear factor-κB (IκB) and glucocorticoid-induced leucine zipper (GILZ). The liganded GR also represses the activity of pro-inflammatory transcription factors — including activator protein 1 (AP-1), nuclear factor-κB (NF-κB) and interferon-regulatory factor 3 (IRF3) — through protein–protein interactions. IKKε, IκB kinase-ε; JNK, JUN N-terminal kinase; MKK, mitogen-activated protein kinase kinase (also known as MAP2K); MYD88, myeloid differentiation primary response protein 88; TAK1, transforming growth factor-β-activated kinase 1 (also known as MAP3K7); TBK1, TANK-

binding kinase 1; TM, transcriptional machinery; TRIF, TIR domain-containing adapter protein inducing IFNβ (also known as TICAM1).

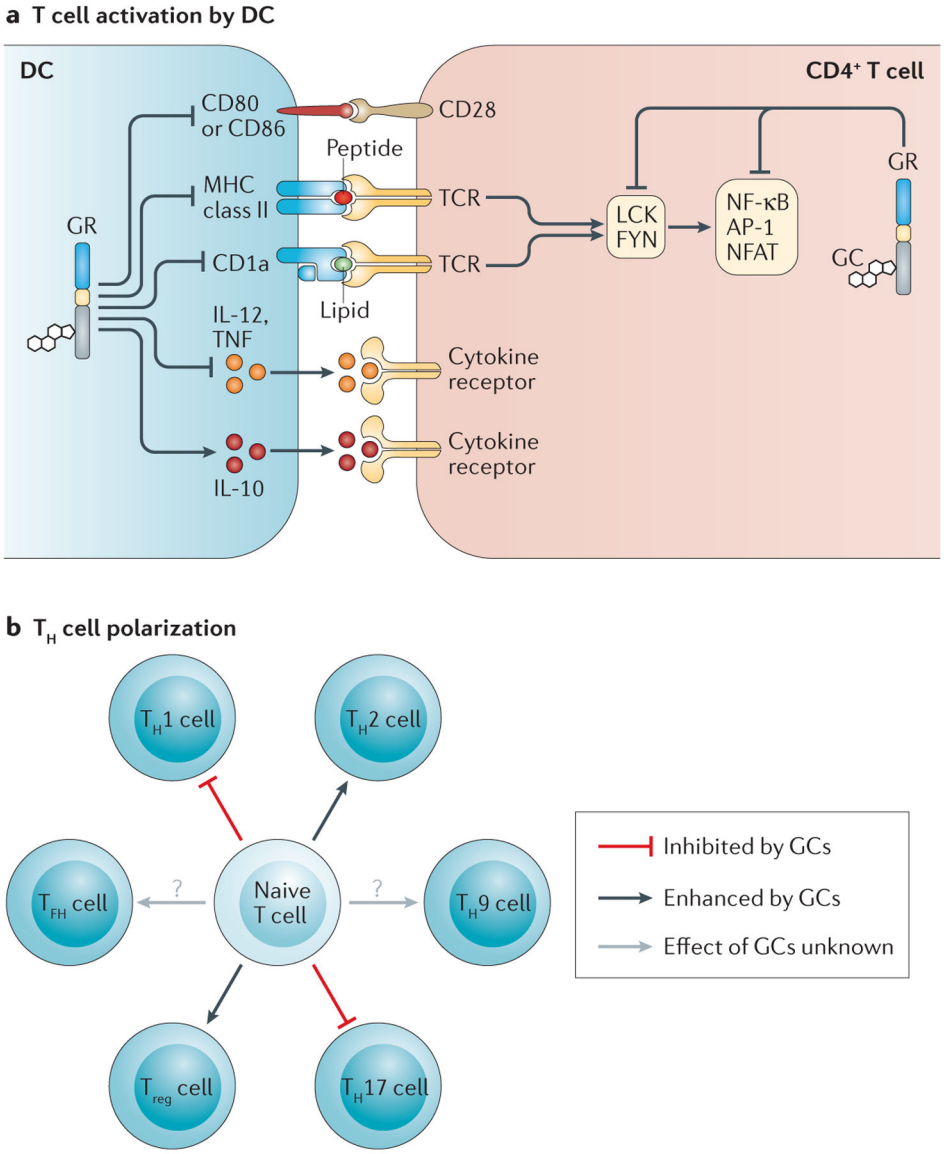

Figure 5 |. Glucocorticoids modulate T cell activity.

a | Glucocorticoids (GCs) suppress $CD4^+$ T cell activation indirectly by modulating dendritic cell (DC) function (antigen presentation, co-stimulation and cytokine production) and directly by regulating T cell receptor (TCR) signalling. **b** | GCs influence the polarization of T helper (T_H) cells, favouring the differentiation of T_H2 cells and regulatory T (T_{reg}) cells over that of T_H1 cells and T_H17 cells. The effects of GCs on the differentiation of T_H9 cells and T follicular helper (T_{FH}) cells require further investigation. AP-1, activator protein 1; GR, GC receptor; IL, interleukin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; TNF, tumour necrosis factor.

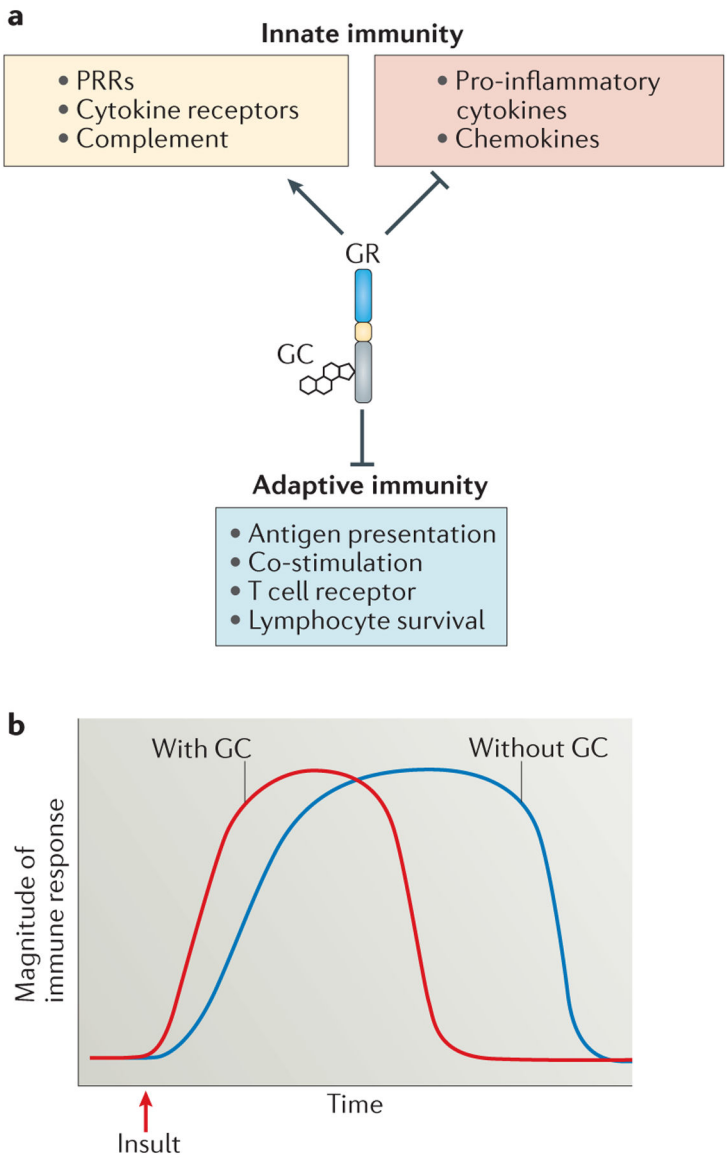

Figure 6 |. Glucocorticoid-induced sensitization of innate immunity.

a | Genome-wide expression studies indicate that glucocorticoids (GCs) upregulate the expression of genes that are involved in the detection of pathogens and tissue trauma, including pattern recognition receptors (PRRs), cytokine receptors and complement factors, while inhibiting the expression of pro-inflammatory cytokines and chemokines. These studies have also revealed that genes involved in adaptive immunity are inhibited by GC exposure. **b** | A hypothetical timeline for immune responses occurring in the presence (red line) or absence (blue line) of GCs is shown. We propose that GCs regulate the immune system in a biphasic manner, such that low doses promote the expression of innate immune genes and rapid responses to insults, but stress and/or pharmacological concentrations suppress signalling through immune receptors. According to this hypothesis, GC-sufficient animals (red line) mount rapid immune responses to pathogens and tissue injury, but these responses are of controlled duration. In GC-insufficient animals (blue line),

however, subnormal expression of PRRs and cytokine receptors results in a slower immune response. Furthermore, in the absence of GC-mediated suppression of immune receptor signalling, the duration of the immune response is prolonged. GR, GC receptor.