Corticosteroids are often used to treat a range of chronic autoimmune inflammatory diseases such as asthma, inflammatory bowel disease and rheumatoid arthritis (RA). RA is the most prevalent autoimmune chronic inflammatory rheumatic disorder with a prevalence of 1% in developed nations. It is more common in women than men, suggesting that perturbations of the hormonal systems may be involved in disease pathophysiology. The aetiology of the disease is unknown, but the physiological mechanisms of inflammation involved in this disease share common pathways with other inflammatory situations [1, 2]. However, the reasons why inflammation persists in RA remain unknown but might relate in part to a dysregulation of the interactions between neuroendocrine and immune systems at the onset of acute inflammation [2–6]. Acute inflammation can be initiated by a number of inflammatory triggers. This results in a programmed sequence of physiological mechanisms which begin with the release of tumour necrosis factor alpha (TNFα), interleukin-1β (IL-1β) and IL-6 [3]. These cytokines activate a cascade of reciprocal local and systemic responses which result in increased secretion of corticotrophin-releasing hormone (CRH) and arginine vaspressin by the hypothalamus and production of adrenocorticotropic hormone (ACTH), prolactin and macrophage migration inhibitory factor (MIF) by the pituitary gland and cortisol by the adrenal glands. Cortisol dampens inflammation by down-regulating the release of TNFα, IL-1β and IL-6 whilst MIF and prolactin counteract the effects of cortisol resulting in a balanced inflammatory/immune response [3–5]. If acute inflammation is not restrained, it enters a chronic phase, a central feature of many chronic autoimmune inflammatory diseases [6]. Neuroendocrine regulation of immune function is essential for survival during stress or infection and to modulate immune responses in inflammatory disease. Corticosteroids are the main effector endpoint of the neuroendocrine immune response to inflammation.

At the molecular level, IL-1β, IL-6 and TNFα initiate a number of pro-inflammatory intracellular signalling events which include the activation of the transcriptional activities of activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) by a phosphorylation-dependent dissociation and/or degradation of I-κB by specific kinases (I-κB kinase 1 and 2) in the case of NF-κB [7, 8]. These in turn enhance the production of a whole range of pro-inflammatory cytokines. These transcription factors are targets of action by cortisol and other corticosteroid type drugs [9]. NF-κB is involved in the pathogenesis of inflammation in RA [10]. In addition IL-1β and TNFα also activate the mitogen-activated protein kinase (MAPK) p38 pathway [11]. MAPK p38 activates the kinases MAPKAPK-2, which in turn targets adenosine/uridine-rich elements (AREs) of pro-inflammatory messenger ribonucleic acids (mRNAs) to bring about their stabilization [9, 12, 13]. IL-1β and TNFα activate the second wave of cytokine release mechanisms [IL-8, IL-12, IL-15, IL-17, IL-18, interferon-α and -β, granulocyte–macrophage colony-stimulating factor (GM-CSF), fibroblast growth factor etc.] that augment the homeostatic signals necessary for the subsequent complex cellular/cytokine cascades of reactions, endothelial activation and enhanced cell adhesion.

The body attempts to down-regulate inflammation by increasing corticosteroid production [3]. Synthetic corticosteroid analogues such as prednisolone have been made and are often used to treat chronic autoimmune inflammatory disease such as RA, asthma and inflammatory bowel disease. They can effectively reduce the parameters of inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and induce disease remission. However, in clinical practice, a proportion of patients fail to respond adequately to corticosteroid therapy [14–16]. On this basis, patients can be divided into corticosteroid sensitive (SS) and corticosteroid resistant (SR) subgroups. The underlying mechanisms involved in the SS and SR phenomenon in patients with RA remain unknown but are of considerable therapeutic interest.

The molecular basis of the biological activity of corticosteroids

The mechanisms of action of corticosteroid can be subdivided into genomic and non-genomic effects [17]. The non-genomic effects which occur very rapidly are either specific or non-specific. The exact mechanisms involved in the non-genomic effects are unknown at the moment but may be related to alterations in the functional status of the cell membrane which may include lipid rafts and/or are mediated via some unknown membrane-bound receptors. These effects include analgesia and inhibition of

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adhesion molecule expression. The genomic effects are mediated via the corticosteroid receptor (CR) whose principal functions of transactivation, DNA binding and ligand binding are localized to specific DNA domains [9]. The gene for CR (NR3C1) is located on chromosome 5 (5q31). Alternative splicing of mRNA results in a number of isoforms (Fig. 1). CRα, the only functional receptor, is encoded for by exons 2–9α [18]. The CRβ isoform is the alternative splice variant of exon 9β instead of 9α and does not bind corticosteroids. CRβ accounts for 0.2–1% of the total CR expression [19, 20]. CRβ is thought to have a dominant role as a negative inhibitor of CRα [21, 22]. However, there are conflicting data refuting this role [23, 24]. The insertion of arginine in the DNA-binding domain at exon 4 results in another receptor splice variant CRγ, which has decreased transactivation activity [25]. The CR-P isoform is encoded by exons 2–7 plus several base pairs from the subsequent intron region [26]. This isoform lacks the ligand-binding domain and therefore cannot bind corticosteroids. Its function is unknown. The CR-P transcripts account for 10–20% CR mRNA and are reported to be up-regulated in some haematological malignancies [27–29]. CR-A results from excision of exons 5–7, resulting in juxtaposition of exons 8 to 4; its function is unknown [26].

CRα is maintained in the cytoplasm as an inactive multicomplex protein consisting amongst other proteins of two Hsp90 molecules, Hsp70 and a number of other proteins such as immunophilin p59 and calreticulin which act as chaperones and co-chaperones. The binding of corticosteroid (CS) to the CRα to form the corticosteroid/receptor complex (CS/CR), induces a conformational change leading to dissociation of the receptor from the multi-protein complex. The CRα then dimerizes, transactivates and the CS/CR complex translocates to the nucleus to bind to the specific DNA motifs, the glucocorticosteroid response elements (GRE) (transactivation) [30]. GRE can mediate both positive and negative corticosteroid effects [30, 31] (Fig. 2).

The CS/CR complex also interferes with the transcriptional activity of AP-1 by inhibiting its binding to its DNA site by interfering with the protein to protein interactions (transrepression) [9]. Transrepression has also been demonstrated with other transcription factors such as NF-κB [32–34] and signal transducer and activator of transcription (STAT) proteins such as STAT3 [35], STAT5 [36] and STAT6 [37]. CRα has been shown to block the c-Jun N-terminal kinase (JNK) signalling cascade by abrogating the c-Jun phosphorylation on Ser-63/73 and thus inhibit AP-1 activation [38–40]. Corticosteroids up-regulate I-κBα production [7, 78]. I-κBα binds to NF-κB and masks the nuclear localizing sequence, thus sequestering it in the cytoplasm by inhibiting its nuclear translocation [7, 8]. In the cytoplasm, NF-κB exists as a heterodimer of mainly p50 and p65 subunits that are bound I-κBs which exists in a number of isoforms of which I-κBα is the most well characterized [41]. Cellular activation leads to the phosphorylation and degradation of I-κBs. NF-κB is then released as the active form, which then translocates to the nucleus to initiate the transcription of a number of target genes [42]. CS/CR complex also interferes with the binding of NF-κB to its site on DNA (Fig. 2).

The inhibition of the protein to protein interactions of AP-1 and NF-κB respectively by corticosteroids involves deacetylation of acetylated core histones [43, 44]. Acetylation of histones allows unwinding of the local DNA chromatin structure and enables RNA polymerase II to enhance gene transcription. Histone acetylation is regulated by a balance between the activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs) which reverses the process, leading to gene repression [44]. CRα acts as a direct inhibitor of the NF-κB-induced HAT activity and also recruits HDACs to the NF-κB/HAT complex [45]. The net effect will be in increased tightening of DNA around histone residues leading to reduced access to the DNA by transcription factors such as AP-1 and NF-κB and repression of pro-inflammatory genes [45]. One feature that is common to the repression of both AP-1- and NF-κB-dependent transcription mediated by CRα is that the effect is mutual. CRα is not only capable of repressing AP-1 and NF-κB, but that both transcription factors may repress CRα-dependent transcription. Co-activator molecules such as cAMP response element binding protein (CREB)-binding protein (CBP) [46] and the steroid receptor co-activator-1 (SRC-1) [47] both interact with CRα to modulate its activity. For instance CBP is associated with HAT activity and may account for the synergistic interactions between NF-κB and AP-1.

The CR/CS complex also interacts with phosphorylated STAT5 [36]. This association, which does not involve the binding to the GRE, enhances the transcriptional activity of STAT5 to increase IL-2 receptor alpha (IL-2Rα) expression and β-casein production in mammary glands amongst other effects. Corticosteroids also induce apoptosis of lymphocytes and thymocytes, but these effects may be secondary to the inhibition of cytokine growth and proliferation factors.

The activity of the pro-inflammatory kinase cascade systems, such as the extracellular regulated kinase (ERK) and JNK mitogen-activated kinases (MAPKs) [48–51] are modulated by corticosteroids. For instance, it has recently been shown that corticosteroids induce the sustained expression of MAPK phosphatase 1 (MKP-1) which inhibits the MAPK signalling.

**Fig. 1.** Human glucocorticosteroid receptor gene and alternatively spliced isoforms.
pathways by dephosphorylating proteins [52, 53]. The mRNAs encoding immune mediators contain AREs within their 3’ untranslated regions (UTRs) [54, 55]. AREs and MAPK p38 signalling pathways are involved in the regulation of mRNA stability [53]. The MAPK p38 pathway is activated by pro-inflammatory cytokines and in turn activated/phosphorylated MAPK p38 activates the kinase MAPKAPK-2, which in turn targets the AREs of pro-inflammatory mRNAs to bring about their stabilization [56]. Corticosteroids induce the production of MKP-1 which potently inactivates phosphorylated MAPK p38 leading to the destabilization of pro-inflammatory mRNAs by corticosteroids [52, 53, 56, 57].

Finally, corticosteroids also induce the production of lipocortin, an anti-inflammatory protein made by peripheral blood mononuclear cells which mediates a number of corticosteroid effects. The regulation of gene expression also requires an orchestrated and coordinated control of the cross-talk between transcription factors to regulated transcriptional, post-transcriptional, translational and post-translational events. These mechanisms are all modulated by corticosteroids.

The physiological regulation of corticosteroid effects

The body needs to regulate the biological effects of corticosteroids. The mechanisms involved in the regulation of corticosteroid effects include alterations in the bioavailability of corticosteroids within the respective microenvironment of the target tissues and counter-regulation by pro-inflammatory cytokines and hormones.

Modulation of corticosteroid bioavailability and bioactivity

Factors such as route of administration may be important in determining corticosteroid bioavailability and bioactivity. For instance, malabsorption of orally administered steroid may cause a failure to respond to therapy in some patients with small bowel disease given enteric-coated corticosteroid preparations. Nevertheless, corticosteroids pass through the cell membrane well. Once in the cell, prior to binding to the CRα, the multidrug resistant pump (MDR1) could potentially extrude the steroids from the cell [58]. Corticosteroid bioactivity may be regulated in target tissues and cells by the enzyme 11β-hydroxysteroid dehydrogenase (11-BHD). In humans, 11-BHD exists as two iso-enzymes type 1 and type 2 [59]. The type 2 11-BHD inactivates cortisol by converting it to cortisol which is not bioactive, whilst the type 1 isoenzyme converts cortisone to cortisol, and thus may amplify the biological activity of corticosteroids [59].

Cytokines as physiological regulators of corticosteroids

The pituitary gland secretes MIF in parallel to the secretory circadian pattern of ACTH [5]. MIF is also locally secreted by macrophages in response to pro-inflammatory stimuli and low levels of corticosteroids (10^{-12}–10^{-14} M) [5]. MIF down-regulates the immunosuppressive effects of corticosteroids [5]. The exact mechanisms have not been fully characterized. MIF activates the ERK1/ERK2-MAPK pathway signalling leading to enhanced phospholipase A2 (PLA2) production and cell proliferation [60].
PLA2 is a key target of the anti-inflammatory actions of corticosteroids. MIF regulates IL-2 secretion and T-cell proliferation [60], which may in part be mediated via increased cellular expression of prolactin [4].

**Hypothalamic–pituitary-mediated regulation of corticosteroid bioactivity**

Essentially, hormones may be divided into anti-inflammatory hormones, such as cortisol and melatonin, and pro-inflammatory hormones, such as CRH, prolactin, arginine vasopressin and substance P [3, 4, 61, 62–73]. The biological effects of prolactin have been studied more extensively. Prolactin, like MIF, is produced by the pituitary gland and peripheral blood mononuclear cells and antagonizes the effects of corticosteroids in vivo and in vitro [4, 62–65]. Prolactin is structurally related to the members of the cytokine and haematopoietin family which include erythropoietin, GM-CSF and IL-2 to IL-7 [66]. It is an essential co-mitogen for T and B cells and can activate natural killer (NK) cells and macrophages [57, 68]. Prolactin is essential for IL-2 and IL-2R expression, an important pre-requisite for T-cell proliferation and enhances gamma-interferon production [67, 69, 70].

At the molecular level, prolactin exerts its effects via prolactin receptors found on macrophages and T and B cells [71]. The coupling of the hormone to the prolactin receptor activates the JAK family of kinases which in turn phosphorylate and activate STAT5 [72–74]. Activated STAT5 then translocates to the nucleus to bind to the respective STAT5 response elements and activate STAT5 [72–74]. Activated STAT5 can complex with activated CRα can complex with activated STAT5 [36]. The CRα/STAT5 complex enhances STAT5-dependent transcription and potentially diminishes the levels of free intracellular CS/CRα complexes leading to reduced GRE-mediated effects [42]. The resultant effect would be increased levels of expression of activated NF-κB and STAT5 leading to diminished corticosteroid responsiveness. Prolactin also induces signalling via the MAPK pathways involving the p56Fyn/Sbc/SOS/Grb2/Ras/Raf/MAPK cascades [76–78]. This pathway leads to increased levels of AP-1 [79]. Prolactin stimulates phosphatidylinositol-3-kinase which in turn leads to the activation of Akt and subsequently IκB kinase complex, degradation of IκB and activation of NF-κB [7, 8, 31, 41, 80–84]. Thus, prolactin modulates corticosteroid responsiveness by enhancing cell proliferation and survival [83].

**What are the mechanisms of corticosteroid resistance?**

Corticosteroids are used to treat a variety of inflammatory conditions which include asthma, inflammatory bowel disease, chronic autoimmune inflammatory renal, skin and rheumatic diseases as well as being part of immunosuppressive therapy regimes for organ transplant rejection and chemotherapy treatment regimes. The failure of therapeutic corticosteroid doses to inhibit inflammatory disease in a number of conditions such as RA, asthma and inflammatory bowel disease has been intriguing. Up to 30% of patients fail to show an adequate response to corticosteroid therapy [14, 84–88]. In RA patients, this resistance to corticosteroids appears not to be related to disease severity as measured by clinical parameters. Interestingly, it can also be seen in normal individuals [14, 84–86, 88], suggesting that it may be an intrinsic property of the individual [14] which may, therefore, have a genetic basis. In lymphoproliferative disease, in particular acute lymphoblastic leukaemia (ALL), up to 30% of patients also fail to respond to adjunctive corticosteroid therapy [89]. Interestingly, the ALL cells appear to acquire resistance to corticosteroids during therapy, but this could reflect positive selection of steroid-resistant mutant leukaemic cells that fail to undergo apoptosis [89].

The molecular basis of corticosteroid resistance in RA patients remains largely unknown but may be related in part to perturbations and dysregulation of some of the known cellular and molecular mechanisms of corticosteroid action. It is not yet clear whether different mechanisms operate in different individuals or diseases or whether the SR phenomenon seen in RA patients is primary or secondary. The SR mechanisms have also been studied in asthma patients who are not responsive to corticosteroids. Some of the mechanisms observed in asthma patients are of relevance to the phenomenon of corticosteroid resistance seen in some patients with rheumatoid arthritis. These mechanisms relate in part to perturbations of the cytokines and pro-inflammatory hormonal balances, and at the molecular level, abnormalities in the intracellular signalling pathways, defects in the corticosteroid receptor/protein complex and alterations in the function of CRα as well as the balance of the CRα and CRβ cellular expression.

**Polymorphic and genetic variations of the corticosteroid receptor**

In 1976 Vingerhoeds et al. [90] conceived the concept of the corticosteroid resistance (SR) phenomenon and that it had a genetic basis. They reported a case of cortisol resistance in which high circulating cortisol blood levels were not associated with Cushing’s syndrome but appeared to be related to a ligand affinity defect of the corticosteroid receptor. This family has been re-studied and a defect in the affinity of corticosteroid receptor for cortisol was demonstrated [91, 92]. Polymorphic alterations in the CR gene were proposed as the underlying molecular basis of SR in this family. The term primary SR was coined. In a subsequent study, Huizenga et al. [93] studied five patients with clinical cortisol resistance and found alterations in the receptor number and ligand affinity. Polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) sequence analysis showed, however, no CR gene alterations [93]. This suggests that alterations somewhere in the cascade of events starting with ligand binding to the receptor, or alterations in the regulation of the expression of corticosteroid responsive genes, or post-receptor defects of interaction with other nuclear factors form the pathophysiological basis of the corticosteroid resistance. Such a systematic dissection of a genetically based study has not been performed in SR RA patients.

The expression of the corticosteroid receptor isoforms

The effects of corticosteroids are mediated by the CRα receptor, whilst CRβ has been shown by some investigators to have a dominant inhibitory role (see above). There is, however, some controversy over the inhibitory functional role of CRβ on CRα [23, 24]. Nevertheless, whilst in transfection experiments over-expression of CRβ reduces the effects of corticosteroids, the physiological relevance of this mechanism in vivo in humans, or indeed in other animal species, still remains to be proven. Its demonstration has, however, many pathophysiological and therapeutic implications.

The SS and SR phenotype appears to be stable when tested repeatedly over time in RA patients and normal subjects, suggesting that it may be an intrinsic property of the individual that is not necessarily acquired as a consequence of prolonged inflammation per se [14]. Lymphocytes from RA patients have decreased numbers of corticosteroid receptors but this does not result in a significant reduction of cell sensitivity to dexamethasone in vitro [94]. However, alterations in the expression of the CR isoforms may potentially contribute to a state of reduced
corticosteroid responsiveness in patients with RA. Studies in asthma patients show that CRβ is over-expressed by peripheral blood mononuclear cells (PBMC) and airway cells from SR asthmatics compared with SS asthma or healthy subjects [95-97], and that this can be enhanced further by treatment of cells with a combination of IL-2 and IL-4 [97]. We have recently shown that CRβ is over-expressed by PBMC from SR RA patients [98]. We have also previously shown that corticosteroids fail to inhibit IL-2 and IL-4 secretion by PBMC from SR RA patients [14]. Such a failure of therapeutic doses of corticosteroids in RA to inhibit IL-2 and IL-4 could therefore be responsible, in part, for the enhanced expression of CRβ in SR RA patients [98].

Perturbations of the relative levels of expression of the various chaperone and co-chaperone proteins could potentially contribute to the SR phenomenon. Over-expression of calreticulin, an important regulator of gene transcription induced by nuclear receptors, can inhibit the GRE transcriptional activity by blunting its interaction with the CS/CRα complex [99, 100]. A similar mechanism has been shown for Hsp90 [101]. Thus, polymorphic changes and/or over-expression of the Hsp90 gene could result in alterations in the activation of the CRα following its binding to the corticosteroid resulting in either defective dimerization or transactivation of the CRα/CS complex and therefore reduced corticosteroid responsiveness. A co-chaperone, receptor-associating protein 46 kDa (RAP46), which binds a complex of CRα with Hsp70, inhibits the DNA binding of the CS/CRα complex and interferes with transactivation [102]. The potential role played by defects in these chaperone proteins remains to be determined in RA, but nevertheless, investigation of these modifications in SR RA patients promises to be a particularly rich field for future scientific research.

The phosphorylation status of the corticosteroid receptor

The functional status of cellular receptors is generally regulated by phosphorylation and nitrosylation mechanisms. Corticosteroid receptors, like other steroid hormone receptors, are phosphoproteins and changes in their phosphorylation status modulate their activity. Several of the phosphorylation sites lie in the consensus sequences of proline-directed, cell-cycle-associated kinases and MAPK. Activation of the MAPK pathway members ERK, JNK and p38 has been shown to result in the inhibition of CRα activity [103-106]. JNK and p38 MAPK can phosphorylate CRα [105]. Modification of the CRα by nitrosylation or phosphorylation is therefore an important determinant of the cellular responsiveness to corticosteroids. Thus, perturbations of the receptor phosphorylation in RA may result in decreased receptor activity leading to reduced corticosteroid receptor responsiveness since dephosphorylation of CRα destabilizes the receptor, resulting in a shorter half-life. This supposition is supported by the observation that defects in the phosphorylation of the rat corticosteroid receptor inhibit corticosteroid-dependent gene transcription [107].

Cross-talk between transcription factors: alterations in intracellular signalling mechanisms

Pro-inflammatory cytokines initiate signalling via pathways which include NF-κB, STAT, MAPK and AP-1 activation, all of which can be modulated by corticosteroids. The inhibitory interactions involved in transrepression are mutual (see above). Thus, enhanced cellular expression and/or defective cross-talk between the transcription factors could contribute to a state of reduced corticosteroid sensitivity. Cells from SR asthma patients have been shown to have enhanced AP-1 activity [108] and phosphorylation of JNK not inhibited by corticosteroids [109].

We have recently shown that the intracellular levels of activated (p65) NF-κB are elevated in vivo in PBMCs from SR RA patients and that corticosteroids fail in vitro to inhibit activation of NF-κB in cells from the SR subjects [110]. Furthermore, corticosteroids fail to inhibit concanavalin A-induced degradation of I-κB in SR RA patients [110]. In asthma patients, p38 MAPK-induced glucocorticoid receptor phosphorylation reduces its activity and has a role in reduced corticosteroid sensitivity. This may also be of relevance to the SR phenomenon seen in RA. We are currently investigating the role played by the phosphorylation of JNK and p38 MAPK in SR RA patients.

STAT5 complexes with CR/CS complex, sequestering the latter and thus preventing its binding to respective DNA sites as well as diminishing the repressive effects of CR/CS complex on AP-1 and NF-κB transcriptional activities (see above). The STAT5/CR/CS complex enhances STAT5-mediated signalling, which leads to increased expression of IL-2 receptor and T-cell activation [42]. Thus, over-expression of activated STAT5, which could be secondary to prolactin over-expression, diminishes the induction of corticosteroid-responsive genes and contributes to a state of reduced corticosteroid responsiveness. It has recently been shown that STAT5 plays a role in IL-2-induced corticosteroid resistance in vitro [111]. CRα has been shown to interact with a number of other signalling pathways, including STAT3, Ets, Oct and CCAAT/enhancer binding protein [33, 112–114]. These mechanisms may be of relevance to the SR phenomenon in RA patients. We are at present investigating these possibilities.

Perturbations of the cytokine milieu in RA

MIF inhibits the effects of corticosteroids (see above). In vitro, the combination of IL-2 and IL-4, IL-8 alone, TNFα alone or IL-1β alone can induce increased CRβ expression in different cell types [115–120]. This might explain the previous observations that: TNFα decreases the sensitivity of human MNC to dexamethasone [117]; in vitro, a combination of IL-4 and IL-2 reduces the inhibition of cell proliferation induced by dexamethasone [118]; and IL-1β, IFN-γ and IL-6 together, synergistically abrogate corticosteroid-mediated inhibition of T-cell proliferation [119]. On the other hand, IL-10 increases the sensitivity of human MNC to dexamethasone [117] and inhibits the expression of MIF by T cells as well as MIF-activated effector functions of macrophages [120]. Thus, the prevailing cytokine milieu has profound effects on the sensitivity of cells to corticosteroids by influencing in part the cellular expression of activated NF-κB, p38 MAPK and differential expression of CRβ [121]. We have recently shown that the serum MIF levels as well as in vitro production by MNC from SR RA patients were up-regulated [122]. On the other hand, we have shown that whilst corticosteroids inhibit IL-2 and IL-4 expression [14] and secretion of IL-1β and IL-8 (unpublished data) by MNC from SS RA patients, they fail to do so in SR RA patients. Similar observations have been made in SR asthma patients [123]. A defect in corticosteroid-induced IL-10 secretion has been observed in SR asthma patients [124]. We are currently investigating this possibility in SR RA patients and also, in particular, the potential that such a defect in IL-10 production could contribute to the excessive MIF expression we have observed in SR RA patients. Since the half-life of expression of CRβ is relatively twice as long as that of CRα, perturbations of the cytokine milieu in SR RA subjects may lead to a disproportionate accumulation of CRβ protein over that of CRα, which would contribute to decreased sensitivity to the biological effects of corticosteroids.
Conclusions

The molecular pathways through which corticosteroids act are complex and involve multiple steps involving the cell membrane, steroid receptors, intracellular signalling pathways and interactions with the DNA and RNA machinery. Corticosteroid resistance may develop as a consequence of perturbation(s) at any point in the pathway. Unresponsiveness to corticosteroid therapy is a major therapeutic challenge in patients with RA. Alterations in the ratio of expression of receptors with decreased CRs and enhanced CRβ can diminish corticosteroid receptor function. SR RA patients have increased CRβ expression; corticosteroids fail to inhibit the secretion of some pro-inflammatory cytokines; in vivo and in vitro, MIF expression is increased. We have demonstrated a dysregulation of the NF-κB signalling pathway in SR RA patients. Finally, alterations in the bioavailability of corticosteroid may also play a part, and these remain to be determined. It is most likely that in any one given individual and/or disease state, different mechanisms may be operative. The full understanding of the molecular basis of SR in RA patients will lead to the development of more rational therapeutic strategies.

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