Published in final edited form as:

Cytokine Growth Factor Rev. 2016 October ; 31: 27–35. doi:10.1016/j.cytogfr.2016.05.002.

A gradient of glucocorticoid sensitivity among helper T cell cytokines

Jesus Banuelos^a and Nicholas Z. Lu^{a,*}

^aDivision of Allergy-Immunology, Feinberg School of Medicine, Northwestern University, Chicago, IL

Abstract

Helper T (Th) cells secrete specific cytokines that promote immune responses whereas glucocorticoids limit the extent of immune responses by inhibiting cytokine secretion and other functions of Th cells. However, glucocorticoid resistance develops in subgroups of patients with Th cell-driven diseases such as asthma and Crohn's disease. Recent evidence supports that Th1, Th2, and Th17 cells have distinct glucocorticoid sensitivity. Th1 cells are sensitive to glucocorticoid-induced apoptosis and cytokine suppression while Th2 cells are sensitive to the latter but not the former and Th17 cells are resistant to both. This gradient of glucocorticoid sensitivity of Th cells corresponds to the glucocorticoid sensitivity of the diseases they underlie. We identify the mechanisms contributing to distinct glucocorticoid sensitivity of Th cells and their cytokines in the literature, as this information is useful to improve treatment strategies for glucocorticoid resistant immunological disorders.

Keywords

glucocorticoid; Th1; Th2; Th17; IL-17

1. Introduction

CD4⁺ helper T (Th) cells play a crucial role in the immune system by secreting specific cytokines in response to diverse pathogenic insults. In addition to their protective role, Th cells are also key players in autoimmune disorders, allergies, and asthma. A mainstay for treating these immunological diseases is glucocorticoids. However, glucocorticoid resistance occurs in subsets of patients and the extent of glucocorticoid resistance differs among diseases. A comparison of these diseases reveals that different diseases have varying degrees of Th cell involvement. Recent reports support that in asthma, different Th cells underlie

*Corresponding author, Division of Allergy-Immunology, Department of Medicine, Feinberg School of Medicine, Northwestern University, McGaw, Room M301, 240 E. Huron, Chicago, IL 60611, Tel (312)503-1310; Fax (312)503-0078; <nickzlu@northwestern.edu>.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest
None.

distinct glucocorticoid responsiveness and disease severity. We summarize reports supporting that Th subsets have distinct glucocorticoid sensitivity. In addition, we identify molecular mechanisms underlying the distinct glucocorticoid sensitivity of Th subsets.

2. Th subsets

Th cell differentiation is initiated when a naïve T cell recognizes antigens presented by MHC II molecules on antigen presenting cells. The outcome of Th cell differentiation is determined by costimulation of specific cytokines (Figure 1) [1]. Differentiated Th cells are defined by their ability to express pivotal transcription factors, acquire distinct chemokine receptors, and produce specific cytokines.

2.1 Th1 cells

The key characteristics of Th1 cells include the expression of T-BET and the production of IFN γ [1]. Th1 cells are crucial for immune responses against intracellular pathogens and Th1 differentiation is stimulated by IL-12 and IFN γ . IL-12 produced by antigen presenting cells activates STAT4, which induces T-BET expression [1]. IFN γ produced by Th1 cells activates STAT1, which in turn further induces T-BET expression and IFN γ production in a positive feedback loop [1]. IFN γ plays a key role in activating macrophages and cytotoxic T cells for the clearance of pathogens such as *Listeria monocytogenes* and *Mycobacterium tuberculosis* [2]. In addition, IFN γ increases the levels of TLR and chemokines, enhances antigen processing and presentation, and promotes isotype switching to opsonizing IgG2a in B cells [3]. Although indispensable in immune responses against a variety of intracellular microbes, Th1 cells play a pathogenic role in autoimmune disorders such as inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis [3].

2.2 Th2 cells

Th2 cells orchestrate the immune response against helminths and allergens [1]. IL-4 induces Th2 differentiation by activating STAT6, which then induces expression of the master Th2 transcription factor, GATA-3 [1]. Th2 cells secrete IL-4, IL-5, and IL-13. IL-4 operates in a positive feedback loop to further support Th2 cell development. IL-5 promotes eosinophil recruitment, activation, and survival [4]. IL-13 increases mucus production and contributes to the induction of airway hyperresponsiveness [4]. Furthermore, IL-4 and IL-13 induce IgE class switching in B cells [4]. Thus, Th2 cells are pathogenic in allergy and asthma.

2.3 Th17 cells

Th17 cells express the transcription factor ROR γ t and produce IL-17A (or IL-17), IL-17F, IL-22, and GM-CSF [5]. Th17 differentiation occurs in the presence of IL-6, IL-1 β , IL-23, IL-21, and TGF- β [5]. Th17 cell cytokines are vital to the clearance of extracellular bacteria and fungi [5]. IL-17 and IL-17F promote neutrophil and macrophage recruitment and activation [5]. Although IL-17 and IL-17F have overlapping functions, IL-17 has some unique features [6, 7]. IL-17, but not IL-17F, induces airway hyperresponsiveness by directly acting on airway smooth muscle cells [7]. IL-17, but not IL-17F, is required for the induction of autoimmune disorders in mice but both are required for protection against *Staphylococcus aureus* [6]. The pathogenic role of IL-17 and IL-17F has been demonstrated in autoimmune

disorders [8]. In addition, IL-17 and IL-17F have been implicated in asthma and a variety of inflammatory conditions [9]. IL-22 acts on non-hematopoietic cells to induce cytokines, chemokines, anti-microbial peptides, and genes involved in tissue repair and wound healing to promote host defense and barrier function [10]. After exposure to radiation, IL-22 levels in the thymus are increased and IL-22 deficient mice have impaired thymic recovery [11]. IL-22 can also be pathogenic in certain instances. IL-22 is elevated in psoriasis and acts on keratinocytes to induce proliferation and hyperplasia [12]. In addition, IL-22 enhances the growth of *Salmonella enterica* by inducing anti-microbial peptides that suppress *E. coli*, a competitor of *Salmonella* [13]. GM-CSF is a pro-inflammatory cytokine produced by Th1, Th2, and Th17 cells [5]. Pathogenic Th17 cells produce more GM-CSF than non-pathogenic Th17 cells [14]. GM-CSF deficient Th17 cells are unable to induce experimental autoimmune encephalomyelitis, highlighting the importance of Th17-derived GM-CSF in driving disease pathology [14, 15].

2.4 Other CD4+ T cell subsets

Th9 cells express the transcription factor PU.1 and produce IL-9 [16]. IL-4 and TGF- β promote Th9 cell formation [16]. IL-9 has been suggested to be a key player in allergy and asthma via promoting mast cell growth and survival [17]. In addition, Th9 cells have been implicated in autoimmune diseases. Th22 cells develop in the presence of IL-6, TNF α , and the aryl hydrocarbon receptor (AHR) agonists because AHR is the master transcription regulator of Th22 differentiation [18]. Th22 cells are characterized by their production of IL-22, but not IL-17, which distinguishes them from Th17 cells [18]. Th22 cells are protective in the gut against enteropathogenic bacteria [19] but are pathogenic in psoriasis [20]. Follicular helper T cell (T_{fh}) cells are characterized by the transcription factor BCL-6 [21]. CXCR5, another marker for T_{fh} cells, and its ligand CXCL13 orchestrate the trafficking of T_{fh} cells into lymphoid follicles [21]. T_{fh}-derived IL-21 promotes B cell growth, survival, and antibody isotype switching [21]. CD4+ regulatory T cells (Tregs) are important in maintaining tolerance, preventing autoimmune diseases, and limiting chronic inflammation [1]. Tregs differentiate in the presence of IL-2 and TGF- β and express FOXP3 [1]. IL-10 is an important anti-inflammatory cytokine produced by Tregs [22]. The balance between Tregs and pro-inflammatory Th cells has been suggested to determine the outcome of an immune response [23].

3. Anti-inflammatory mechanisms of glucocorticoids

Endogenous glucocorticoids, such as cortisol, are hormones secreted by adrenal glands. The level of circulating glucocorticoids during homeostasis follows a circadian rhythm, reaching a peak early every morning. Stress induces additional production of glucocorticoids. Synthetic glucocorticoids are widely prescribed for their anti-inflammatory properties to treat a variety of inflammatory disorders including allergy, asthma, rheumatoid arthritis, multiple sclerosis, and Crohn's disease. The actions of glucocorticoids are mediated by the glucocorticoid receptor (GR), a member of the nuclear receptor superfamily [24].

3.1 The GR

The GR is composed of three domains: the N-terminal domain (NTD), the central DNA-binding domain (DBD), and the C-terminal ligand-binding domain (LBD) [24] (Figure 2). A hinge region links the DBD and the LBD. The NTD is responsible for the majority of the transcriptional activation function of the GR. The DBD is critical for dimerization, DNA-binding, and interaction with cofactors. The LBD has the ligand binding pocket, additional transcriptional activation function, and residues important for protein-protein interactions [24].

The GR gene, *NR3C1*, is composed of nine exons. Alternative splicing leads to the production of the GR- α , GR- β , GR- γ , GR-A, and GR-P isoforms with GR- α being the most abundant isoform [24]. GR- β binds to the GR antagonist RU-486, but not GR agonists, and has inhibitory effects on GR- α functions [25, 26]. GR- γ differs from GR- α by the insertion of an arginine between exons 3 and 4 in the DBD and has decreased activity [24]. GR-A lacks exons 5, 6, and 7 and GR-P is missing exons 8 and 9, both of which are associated with glucocorticoid resistance, although GR-P is also able to enhance GR- α activity [27, 28]. Each of the GR splice variants produces additional GR isoforms via alternative translation initiation [29]. For example, eight different start codons in exon 2 lead to the generation of 8 GR- α isoforms: GR- α -A, -B, -C1, -C2, -C3, -D1, -D2, and -D3 [29] (Figure 2). Because these GR translational isoforms have distinct NTDs, they have different transcriptional activities [30–34].

The level of the GR is one of the main determinants of glucocorticoid responsiveness [35]. Glucocorticoids limit their signaling autologously by downregulating the level of GR [36]. However, in some lymphoma cell lines, glucocorticoids increase GR expression [37]. Glucocorticoid downregulation of GR occurs mainly at the transcriptional level but posttranslational mechanisms also play a role [38]. The GR isoform composition within a cell also determines glucocorticoid responsiveness. GR- α -C3 is the most transcriptionally active isoform while GR- α -D isoforms are the least active [30–34]. Post-translational modifications such as phosphorylation, acetylation, ubiquitination, and sumoylation also alter GR activities (Figure 2). Human GR phosphorylation occurs in the NTD at positions S113, S134, S141, S143, S203, S211, S226, and S404 [39]. S211 phosphorylation increases whereas S226 phosphorylation decreases GR activity [39]. Although most phosphorylation occurs in response to glucocorticoid binding, S134 phosphorylation is regulated in a glucocorticoid-independent manner by p38 MAPK [39]. Acetylation of the GR at K494 and K495 inhibits GR activity [39]. Ubiquitination of the GR at K419 targets the GR for degradation [39]. Sumoylation is the process by which small ubiquitin-related (SUMO) peptides are attached at lysine residues. The GR is sumoylated K277, K293, and K703 [40]. Sumoylation at K277 and K293 negatively affect GR transcriptional activity while sumoylation at K703 increases GR activity [40].

3.2 GR signaling

The GR is expressed in virtually all cell types and tissues [41]. In an unbound state, the GR is held in the cytoplasm in a heterocomplex along with chaperone proteins Hsp90, Hsp70, Src, p23, FKBP51 and FKBP52 [41] (Figure 3). Upon glucocorticoid binding, the GR

undergoes a conformational change leading to its dissociation from chaperone proteins. The conformational change also exposes nuclear localization signals leading to nuclear translocation. Once in the nucleus the GR forms homodimers and mediates the majority of its effects through the regulation of gene expression [41] (Figure 3). Transactivation occurs by GR binding to glucocorticoid response elements (GRE) in the promoter of target genes. GREs are palindromes consisting of two inverted hexameric half-sites separated by 3 base pairs [41]. The interaction of the GR with DNA is dynamic and cycles between bound and unbound states in a matter of seconds [42, 43]. When bound to a GRE, the GR recruits coactivators, such as histone acetyltransferases CBP and p300, to increase gene transcription [41]. Examples of genes activated by the GR include the proapoptotic BIM (Bcl-2 interacting mediator of cell death) and antiinflammatory tristetraproline, dual specificity phosphatase 1, and I κ B α . Transrepression of genes by the GR can occur directly or indirectly. Direct transrepression occurs via binding to inverted repeat negative GREs (IR-nGRE), present in over 1000 genes [44]. IR-nGREs are also palindromic with up to 2 base pairs of spacers. Interestingly, the GR binds to each half-site of the IR-nGRE as a monomer rather than the usual dimer [44, 45]. Binding of the GR to IR-nGREs leads to the recruitment of corepressors such as SMRT/NCOR and HDACs [46]. Thymic stromal lymphopoietin (TSLP) is decreased by the GR through an IR-nGRE [44]. IL-17F promoter is predicted to contain IR-nGREs [44]. Indirect transrepression occurs through direct protein-protein interactions where the GR sequesters transcription factors away from the promoter. The GR suppresses cytokine expression via sequestering pro-inflammatory transcription factors such as NF- κ B, AP-1, and STATs [41].

Not all interactions between the GR and other transcription factors are antagonistic. Dexamethasone (DEX), a potent GR agonist, and 3-methylcholanthrene, an AHR agonist, synergistically activate methallothionein 2A in Hep2G hepatocytes [47]. STAT3 and the GR also interact with each other synergistically or antagonistically in a promoter-dependent manner. GR binding to DNA-bound STAT3 inhibits STAT3 gene expression whereas STAT3 binding to DNA-bound GR results in transcriptional synergy [48]. STAT3-GR interactions at a composite site containing a STAT3 response elements and a GRE can also lead to transcriptional synergy [48]. Composite GREs are promoter regions containing GRE overlapping with binding sites for other transcription factors [49, 50]. It has been found that AP-1 composite sites have chromatin structures that favor GR binding [51]. Thus, promoter contexts determine glucocorticoid responsiveness.

In addition to regulating gene expression at the transcriptional level, GR binds to mRNA of select chemokines and cytokines directly and expedites their decay [52, 53] (Figure 3). Furthermore, several rapid GR signaling pathways have been described. At high concentrations, glucocorticoids intercalate into the plasma and mitochondrial membrane where they interfere with ion transport and affect cellular functions [54]. Membrane GRs have been detected in human and mouse lymphoma cells and human peripheral blood mononuclear cells (PBMC) and induce apoptosis [54]. As described above, intracellular GR is held in the cytoplasm with a variety of chaperone proteins. Those chaperone proteins have independent functions after dissociating from the GR. For example, Src, as a kinase, activates lipocortin-1 and inhibits arachidonic acid release [55].

4. Glucocorticoid-induced apoptosis of T cells

Apoptosis of T cells is critical for T cell maturation and dissolution of an immune response. Earlier studies examined the sensitivity of T cells to glucocorticoid-induced apoptosis in mixed populations and found that T cells as a whole undergo glucocorticoid-induced apoptosis [56]. GR-null T cells are protected from apoptosis [57]. Although T cell receptor (TCR) and GR signaling both induce T cell apoptosis independently, they oppose each other when activated simultaneously. Signaling molecules activated by the TCR, such as AP-1 and NF- κ B, inhibit glucocorticoid-induced apoptosis and conversely glucocorticoids prevent TCR activation-induced cell death [58]. Cytokines such as, IL-2, IL-4, IL-10, and IL-12 also protect T cells from glucocorticoid-induced apoptosis [56, 59, 60].

Recent studies have begun to delineate the sensitivity of Th subsets to glucocorticoid-induced apoptosis (Table 1). Th1 cells are generally sensitive [61, 62] whereas Th2 and Th17 cells are resistant to glucocorticoid-induced apoptosis [62]. Glucocorticoid-induction of BIM in Th1 cells contributes to their sensitivity to glucocorticoid-induced apoptosis whereas high levels of antiapoptotic proteins such as BCL-2 underlie the resistance of Th17 cells to glucocorticoid-induced apoptosis [62]. The literature on the effect of glucocorticoids on Tregs is contradictory. Several reports indicate that glucocorticoids induce apoptosis in Tregs [63–65] while others suggest that glucocorticoids may increase the frequency of Tregs [66]. IL-2 protects Th1 cells and Tregs and IL-4 protects Th2 cells from glucocorticoid-induced apoptosis [61]. In addition, IL-15 and IL-7 protect both Tregs and effector T cells from glucocorticoid-induced apoptosis [63]. The mechanisms of cytokine inhibition of apoptosis are likely via inhibition of the glucocorticoid-induction of I κ B α , an inhibitor of NF- κ B [60].

5. Distinct sensitivity of Th cytokines to glucocorticoid suppression

5.1 Th1 and Th2 cytokines are sensitive to glucocorticoid suppression

Glucocorticoids decrease IFN γ production by human T cells *in vitro* [67] and by T cells from patients with rheumatoid arthritis [68]. In addition, Th1 cells from patients with immune thrombocytopenia are sensitive to glucocorticoid inhibition [69]. Similarly, glucocorticoids decrease Th2 cytokines IL-4, IL-5, and IL-13 *in vitro* [70, 71] as well as Th2 cytokines in T cells from asthma patients [72]. Mechanistically, glucocorticoids inhibit IL-12-induced STAT4 phosphorylation and T-BET in Th1 cells [73, 74] and GATA-3 phosphorylation, nuclear localization, and activity in Th2 cells [75, 76]. Glucocorticoids can also inhibit IL-4R α chain expression, which in turn, decreases the IL-4 responsiveness of Th2 cells [70].

Cytokines produced by Th9 and Th22 cells are generally sensitive to glucocorticoid suppression. IL-9 from human T cells is suppressed by glucocorticoids [77]. In patients with systemic lupus erythematosus, the level of IL-9 is also decreased by glucocorticoids [78]. In patients with immune thrombocytopenia, Th22 cells and IL-22 production are decreased by glucocorticoids [69]. IL-22 production in a Th17-adoptive transfer model of airway inflammation is resistant to suppression by glucocorticoids whereas in a mouse model of

bacterial infection, glucocorticoids suppress IL-22 [79, 80]. Interestingly, IL-10, an anti-inflammatory cytokine, can be increased by glucocorticoids [81].

5.2 Th17 cytokines have distinct glucocorticoid sensitivity

Th17-derived IL-17 and IL-17F are resistant whereas IL-22 is sensitive to glucocorticoid suppression [62] (Table 2). Direct and indirect transrepression or enhanced decay of mRNAs are likely mechanisms of suppression of IL-22 [52, 53]. Although IL-17A and -F are resistant to glucocorticoid suppression in primary Th17 cells, both cytokines have the capability to be decreased by glucocorticoids [82–84]. We have found that glucocorticoids decrease IL-17 in EL4 murine thymoma cells [85]. Although they have not been validated, IR-nGRE sequences have been identified in the promoter of IL-17F [44]. The resistance of IL-17 and IL-17F to glucocorticoid suppression likely depends on the Th17 cell microenvironment. In multiple sclerosis, elevated LPS and dopamine can induce resistance to glucocorticoid suppression of IL-17 [86, 87]. Both LPS and dopamine increase IL-6, which in turn acts on Th17 cells to induce their glucocorticoid resistance [86, 87]. IL-6R blocking antibodies enable glucocorticoid suppression of IL-17A [88]. Upon binding of its receptor, IL-6 activates STAT3, which in turn can interfere with GR activities [48]. Glucocorticoids reduce SOCS3, a negative regulator of STAT3 [89]. SOCS3 inhibition enhances IL-6-induced STAT3 phosphorylation [89]. However, glucocorticoids do not increase IL-6-induced STAT3 phosphorylation in Th17 cells [62], suggesting factors other than SOCS3 underlie the maintenance of STAT3 activity in Th17 cells. A multitude of transcription factors regulate the expression of Th17 cytokines and whether some of these factors interfere with GR activity at IL-17 and IL-17F promoters is unknown. I κ B ζ is an IL-17 inducer [90] and glucocorticoids elevate I κ B ζ levels in Th17 cells [91]. Interestingly, I κ B ζ mediates the synergism between glucocorticoids and LPS in inducing lipocalin 2 and pentraxin 3 in macrophages [92]. These observations suggest a potential role of I κ B ζ in the resistance of IL-17 to glucocorticoid suppression.

Since some, but not all, Th17 cytokines are resistant to glucocorticoid suppression, there is a promoter context-dependent glucocorticoid sensitivity within Th17 cells. It has been reported that MAP kinases inhibit glucocorticoid-induced MMTV-luciferase expression, but not TAT3-ADH-luciferase expression in the same cell [93]. It was found that complex binding sites in the MMTV promoter confer glucocorticoid resistance [93]. In addition, the spacing between GRE and NF- κ B-response elements in the target gene promoter changes the glucocorticoid responsiveness [94]. Furthermore, coactivator recruitment is required for glucocorticoid regulation of target genes, which could also contribute to cytokine-selective glucocorticoid sensitivity in Th17 cells [95].

In addition to cytokines secreted by Th17 cells, Th17 recruiting chemokines (e.g., CCL20) produced by other cells are also resistant to glucocorticoid suppression. Production of CCL20 from airway epithelial cells is increased by glucocorticoids in the sputum of asthmatics [96]. Increased CCL20 leads to an increase in Th17 cell recruitment in glucocorticoid-resistant inflammation. In addition, IL-17 promotes the recruitment of neutrophils via CXCL8 and G-CSF [97]. Neutrophils and Th17 cells co-localize in gut tissues isolated from patients with Crohn's disease [97], synovial fluid from patients with

rheumatoid arthritis [97], and sputum from asthmatics [98]. It has been suggested that neutrophils, in turn, promote Th17 cells [99]. Neutrophils stimulated with a combination of IFN γ and LPS produce Th17 and Th1 chemokines CCL20, CCL2 and CXCL10 [97]. Furthermore, glucocorticoids elevate blood neutrophil counts [100], expand all developmental stages of neutrophils [101], and inhibit neutrophil apoptosis [102]. Therefore, there is a positive feedback loop between Th17 cell activity and neutrophils, which is enhanced by glucocorticoids.

6. Distinct glucocorticoid sensitivity of Th subsets and diseases

Overall, there appears to be a gradient of glucocorticoid sensitivity among Th cells (Table 1). Th1 cells are sensitive to both glucocorticoid-induced apoptosis and cytokine suppression. Th2 cells are resistant to the former but sensitive to the latter whereas Th17 cells are resistant to both. The Th subset-specific glucocorticoid sensitivity helps to explain varying degrees of glucocorticoid resistance in autoimmune disorders, asthma, and several other inflammatory disorders. For example, approximately 20% of patients with Crohn's disease and up to 10% of asthma patients are resistant to glucocorticoids [103, 104]. We propose that varying Th subsets in these diseases underlie the glucocorticoid responsiveness of patients. Both Th1 and Th17 cells play a major role in Crohn's disease, rheumatoid arthritis, psoriasis, and multiple sclerosis [3] while Th2 and Th17 cells contribute to asthma [105]. It has been recently recognized that Th2 cells and eosinophils underlie only approximately 50% of asthma [105] and Th2-driven asthma is effectively controlled by glucocorticoids [72]. In contrast, glucocorticoid-resistant subgroups of asthma are attributed to Th17 cells [9]. Airway or blood IL-17 and IL-17F levels are positively correlated to asthma severity [106, 107]. Moreover, glucocorticoid-resistant Th17 cells have been detected in inflamed tissues in Crohn's disease [108]. Thus, one intriguing question is whether rheumatoid arthritis and Crohn's disease, like asthma, can be categorized into endotypes with distinct underlying Th subsets and glucocorticoid sensitivity. It will also be interesting to determine whether in the same individual, long-term glucocorticoid treatment shifts the etiology of a disease from a glucocorticoid-sensitive to a -resistant Th subset.

Th subsets have an extensive network of cross talk. Although IL-17A, IFN γ , and IL-4 are thought to be mutually antagonistic [109], cross talk between Th17 and other Th cells leads to synergistic responses in some instances. An endotype of glucocorticoid-resistant asthma with elevated levels of both IL-17 and IFN γ has been reported [110]. In addition, T cells double-positive for IL-4 and IL-17 have been found in another group of glucocorticoid-refractory asthma patients [111]. In an adoptive transfer model of airway inflammation, transfer of Th2 and Th17 cells induces eosinophil- and neutrophil-dominant inflammation, respectively, while co-transfer of Th2 and Th17 cells enhances the Th2 response, eosinophil infiltration, and airway hyperresponsiveness [112]. Similarly, IFN γ - and IL-17A-producing Th1/17 cells are increased in multiple sclerosis patients, cross the blood brain barrier, and accumulate in the central nervous system [113]. It will be interesting to determine whether these Th cells with dual identities have cell- and cytokine-specific glucocorticoid sensitivity. Continued investigation in this area will help to improve the quality of life for patients with glucocorticoid-resistant immunopathology.

Acknowledgments

Fundings: This study was funded by the National Institute of Allergy and Infectious Diseases, (R21AI113935), National Heart, Lung, and Blood Institute (R37HL068546), and the Ernest S. Bazley Foundation.

Abbreviations

ADH	alcohol dehydrogenase
AHR	aryl hydrocarbon receptor
AP-1	activator protein 1
BCL	B-cell lymphoma
BIM	Bcl-2 interacting mediator of cell death
CBP	CREB-binding protein
CCL	CC chemokine ligands
CXCL	CXC chemokine ligand
CXCR	CXC chemokine receptors
DBD	DNA-binding domain
DEX	dexamethasone
FKBP	FK506 binding protein
FOXP3	forkhead box P3
GATA-3	GATA binding protein 3
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GR	glucocorticoid receptor
GRE	glucocorticoid response element
HDAC	histone deacetylase
HSP	heat shock protein
IFNγ	interferon γ
Ig	immunoglobulin
IκBα	NF- κ B inhibitor α
IκBζ	NF- κ B inhibitor ζ
IL	interleukin

IR-nGRE	inverted repeat negative glucocorticoid response element
LBD	ligand binding domain
LPS	lipopolysaccharide
MAP	mitogen-activated protein
MHC	major histocompatibility complex
MIP	macrophage inflammatory protein
MMTV	mouse mammary tumor virus
NCoR	nuclear receptor co-repressor
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NTD	N-terminal domain
PBMC	peripheral blood mononuclear cells
Pol II	RNA polymerase II
RORγt	RAR-related orphan receptor γ
SMRT	silencing mediator for retinoid and thyroid hormone receptors
SOCS	suppressor of cytokine signaling
STAT	signal transducer and activator of transcription
TAT	tyrosine aminotransferase 3
T-BET	T-box expressed in T cells
Tfh	follicular helper T cell
TGF-β	transforming growth factor β
Th	helper T cell
TLR	toll-like receptor
TNF	tumor necrosis factor
Treg	regulatory T cells
TSLP	thymic stromal lymphopoietin

References

1. Zhou L, Chong MM, Littman DR. Plasticity of CD4⁺ T cell lineage differentiation. *Immunity*. 2009; 30:646–655. [PubMed: 19464987]
2. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-gamma: an overview of signals, mechanisms and functions. *Journal of leukocyte biology*. 2004; 75:163–189. [PubMed: 14525967]

3. Damsker JM, Hansen AM, Caspi RR. Th1 and Th17 cells: adversaries and collaborators. *Annals of the New York Academy of Sciences*. 2010; 1183:211–221. [PubMed: 20146717]
4. Barnes PJ. Th2 cytokines and asthma: an introduction. *Respir Res*. 2001; 2:64–65. [PubMed: 11686866]
5. Muranski P, Restifo NP. Essentials of Th17 cell commitment and plasticity. *Blood*. 2013; 121:2402–2414. [PubMed: 23325835]
6. Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, et al. Differential roles of interleukin-17A and-17F in host defense against mucocutaneous bacterial infection and allergic responses. *Immunity*. 2009; 30:108–119. [PubMed: 19144317]
7. Kudo M, Melton AC, Chen C, Engler MB, Huang KE, Ren X, et al. IL-17A produced by alphabeta T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction. *Nat Med*. 2012; 18:547–554. [PubMed: 22388091]
8. Patel DD, Kuchroo VK. Th17 Cell Pathway in Human Immunity: Lessons from Genetics and Therapeutic Interventions. *Immunity*. 2015; 43:1040–1051. [PubMed: 26682981]
9. Morishima Y, Ano S, Ishii Y, Ohtsuka S, Matsuyama M, Kawaguchi M, et al. Th17-Associated Cytokines as a Therapeutic Target for Steroid-Insensitive Asthma. *Clin Dev Immunol*. 2013
10. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. *Immunity*. 2004; 21:241–254. [PubMed: 15308104]
11. Dudakov JA, Hanash AM, Jenq RR, Young LF, Ghosh A, Singer NV, et al. Interleukin-22 Drives Endogenous Thymic Regeneration in Mice. *Science*. 2012; 336:91–95. [PubMed: 22383805]
12. Sa SM, Valdez PA, Wu J, Jung K, Zhong F, Hall L, et al. The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis. *J Immunol*. 2007; 178:2229–2240. [PubMed: 17277128]
13. Behnsen J, Jellbauer S, Wong CP, Edwards RA, George MD, Ouyang W, et al. The cytokine IL-22 promotes pathogen colonization by suppressing related commensal bacteria. *Immunity*. 2014; 40:262–273. [PubMed: 24508234]
14. El-Behi M, Ciric B, Dai H, Yan YP, Cullimore M, Safavi F, et al. The encephalitogenicity of T(H)17 cells is dependent on IL-1-and IL-23-induced production of the cytokine GM-CSF. *Nature immunology*. 2011; 12 568-U241.
15. Ponomarev ED, Shriver LP, Maresz K, Pedras-Vasconcelos J, Verthelyi D, Dittel BN. GM-CSF production by autoreactive T cells is required for the activation of microglial cells and the onset of experimental autoimmune encephalomyelitis. *J Immunol*. 2007; 178:39–48. [PubMed: 17182538]
16. Gerlach K, Hwang YY, Nikolaev A, Atreya R, Dornhoff H, Steiner S, et al. T(H)9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells. *Nature immunology*. 2014; 15:676–686. [PubMed: 24908389]
17. Goswami R, Kaplan MH. A Brief History of IL-9. *J Immunol*. 2011; 186:3283–3288. [PubMed: 21368237]
18. Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T-H-17, T(H)1 and T(H)2 cells. *Nature immunology*. 2009; 10 864-U73.
19. Basu R, O'Quinn DB, Silberberger DJ, Schoeb TR, Fouser L, Ouyang W, et al. Th22 cells are an important source of IL-22 for host protection against enteropathogenic bacteria. *Immunity*. 2012; 37:1061–1075. [PubMed: 23200827]
20. Luan L, Ding Y, Han S, Zhang Z, Liu X. An increased proportion of circulating Th22 and Tc22 cells in psoriasis. *Cell Immunol*. 2014; 290:196–200. [PubMed: 25046360]
21. Vinuesa CG, Tangye SG, Moser B, Mackay CR. Follicular B helper T cells in antibody responses and autoimmunity. *Nature reviews Immunology*. 2005; 5:853–865.
22. Chaudhry A, Samstein RM, Treuting P, Liang Y, Pils MC, Heinrich JM, et al. Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. *Immunity*. 2011; 34:566–578. [PubMed: 21511185]
23. Eisenstein EM, Williams CB. The T-reg/Th17 Cell Balance: A New Paradigm for Autoimmunity. *Pediatr Res*. 2009; 65:26r–31r.

24. Lu NZ, Cidlowski JA. The origin and functions of multiple human glucocorticoid receptor isoforms. *Annals of the New York Academy of Sciences*. 2004; 1024:102–123. [PubMed: 15265776]
25. Lewis-Tuffin LJ, Jewell CM, Bienstock RJ, Collins JB, Cidlowski JA. Human glucocorticoid receptor beta binds RU-486 and is transcriptionally active. *Mol Cell Biol*. 2007; 27:2266–2282. [PubMed: 17242213]
26. Hinds TD Jr, Ramakrishnan S, Cash HA, Stechschulte LA, Heinrich G, Najjar SM, et al. Discovery of glucocorticoid receptor-beta in mice with a role in metabolism. *Mol Endocrinol*. 2010; 24:1715–1727. [PubMed: 20660300]
27. Moalli PA, Pillay S, Krett NL, Rosen ST. Alternatively spliced glucocorticoid receptor messenger RNAs in glucocorticoid-resistant human multiple myeloma cells. *Cancer Res*. 1993; 53:3877–3879. [PubMed: 8358712]
28. de Lange P, Segeren CM, Koper JW, Wiemer E, Sonneveld P, Brinkmann AO, et al. Expression in hematological malignancies of a glucocorticoid receptor splice variant that augments glucocorticoid receptor-mediated effects in transfected cells. *Cancer Res*. 2001; 61:3937–3941. [PubMed: 11358809]
29. Lu NZ, Cidlowski JA. Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. *Mol Cell*. 2005; 18:331–342. [PubMed: 15866175]
30. Lu NZ, Cidlowski JA. Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. *Mol Cell*. 2005; 18:331–342. [PubMed: 15866175]
31. Lu NZ, Cidlowski JA. Glucocorticoid receptor isoforms generate transcription specificity. *Trends Cell Biol*. 2006; 16:301–307. [PubMed: 16697199]
32. Lu NZ, Collins JB, Grissom SF, Cidlowski JA. Selective regulation of bone cell apoptosis by translational isoforms of the glucocorticoid receptor. *Mol Cell Biol*. 2007; 27:7143–7160. [PubMed: 17682054]
33. Bender IK, Cao Y, Lu NZ. Determinants of the heightened activity of glucocorticoid receptor translational isoforms. *Mol Endocrinol*. 2013; 27:1577–1587. [PubMed: 23820903]
34. Cao Y, Bender IK, Konstantinidis AK, Shin SC, Jewell CM, Cidlowski JA, et al. Glucocorticoid receptor translational isoforms underlie maturational stage-specific glucocorticoid sensitivities of dendritic cells in mice and humans. *Blood*. 2013; 121:1553–1562. [PubMed: 23297131]
35. Vanderbilt JN, Miesfeld R, Maler BA, Yamamoto KR. Intracellular Receptor Concentration Limits Glucocorticoid-Dependent Enhancer Activity. *Mol Endocrinol*. 1987; 1:68–74. [PubMed: 2842660]
36. Burnstein KL, Bellingham DL, Jewell CM, Powell-Oliver FE, Cidlowski JA. Autoregulation of glucocorticoid receptor gene expression. *Steroids*. 1991; 56:52–58. [PubMed: 2020978]
37. Eisen LP, Elsasser MS, Harmon JM. Positive regulation of the glucocorticoid receptor in human T-cells sensitive to the cytolytic effects of glucocorticoids. *The Journal of biological chemistry*. 1988; 263:12044–12048. [PubMed: 3261297]
38. Dong Y, Poellinger L, Gustafsson JA, Okret S. Regulation of glucocorticoid receptor expression: evidence for transcriptional and posttranslational mechanisms. *Mol Endocrinol*. 1988; 2:1256–1264. [PubMed: 3216865]
39. Cruz-Topete D, Cidlowski JA. One hormone, two actions: anti- and pro-inflammatory effects of glucocorticoids. *Neuroimmunomodulation*. 2015; 22:20–32. [PubMed: 25227506]
40. Hua G, Ganti KP, Chambon P. Glucocorticoid-induced tethered transrepression requires SUMOylation of GR and formation of a SUMO-SMRT/NCoR1-HDAC3 repressing complex. *Proceedings of the National Academy of Sciences of the United States of America*. 2016; 113:E635–E643. [PubMed: 26712006]
41. Lu NZ, Wardell SE, Burnstein KL, Defranco D, Fuller PJ, Giguere V, et al. International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progesterone, and androgen receptors. *Pharmacol Rev*. 2006; 58:782–797. [PubMed: 17132855]

42. McNally JG, Muller WG, Walker D, Wolford R, Hager GL. The glucocorticoid receptor: rapid exchange with regulatory sites in living cells. *Science*. 2000; 287:1262–1265. [PubMed: 10678832]
43. John S, Sabo PJ, Thurman RE, Sung MH, Biddie SC, Johnson TA, et al. Chromatin accessibility pre-determines glucocorticoid receptor binding patterns. *Nat Genet*. 2011; 43:264–268. [PubMed: 21258342]
44. Surjit M, Ganti KP, Mukherji A, Ye T, Hua G, Metzger D, et al. Widespread Negative Response Elements Mediate Direct Repression by Agonist-Liganded Glucocorticoid Receptor. *Cell*. 2011; 145:224–241. [PubMed: 21496643]
45. Hudson WH, Youn C, Ortlund EA. The structural basis of direct glucocorticoid-mediated transrepression. *Nat Struct Mol Biol*. 2013; 20:U53–U69.
46. Hua G, Paulen L, Chambon P. GR SUMOylation and formation of an SUMO-SMRT/NCoR1-HDAC3 repressing complex is mandatory for GC-induced IR nGRE-mediated transrepression. *Proc Natl Acad Sci U S A*. 2016; 113:E626–E634. [PubMed: 26712002]
47. Sato S, Shirakawa H, Tomita S, Tohkin M, Gonzalez FJ, Komai M. The aryl hydrocarbon receptor and glucocorticoid receptor interact to activate human metallothionein 2A. *Toxicol Appl Pharmacol*. 2013; 273:90–99. [PubMed: 23994556]
48. Langlais D, Couture C, Balsalobre A, Drouin J. The Stat3/GR interaction code: predictive value of direct/indirect DNA recruitment for transcription outcome. *Mol Cell*. 2012; 47:38–49. [PubMed: 22633955]
49. Diamond MI, Miner JN, Yoshinaga SK, Yamamoto KR. Transcription factor interactions: selectors of positive or negative regulation from a single DNA element. *Science*. 1990; 249:1266–1272. [PubMed: 2119054]
50. Imai E, Stromstedt PE, Quinn PG, Carlstedt-Duke J, Gustafsson JA, Granner DK. Characterization of a complex glucocorticoid response unit in the phosphoenolpyruvate carboxykinase gene. *Mol Cell Biol*. 1990; 10:4712–4719. [PubMed: 2388623]
51. Biddie SC, John S, Sabo PJ, Thurman RE, Johnson TA, Schiltz RL, et al. Transcription Factor AP1 Potentiates Chromatin Accessibility and Glucocorticoid Receptor Binding. *Mol Cell*. 2011; 43:145–155. [PubMed: 21726817]
52. Ishmael FT, Fang X, Houser KR, Pearce K, Abdelmohsen K, Zhan M, et al. The human glucocorticoid receptor as an RNA-binding protein: global analysis of glucocorticoid receptor-associated transcripts and identification of a target RNA motif. *J Immunol*. 2011; 186:1189–1198. [PubMed: 21148795]
53. Cho H, Park OH, Park J, Ryu I, Kim J, Ko J, et al. Glucocorticoid receptor interacts with PNRC2 in a ligand-dependent manner to recruit UPF1 for rapid mRNA degradation. *Proc Natl Acad Sci U S A*. 2015
54. Alangari AA. Genomic and non-genomic actions of glucocorticoids in asthma. *Ann Thorac Med*. 2010; 5:133–139. [PubMed: 20835306]
55. Croxtall JD, Choudhary Q, Flower RJ. Glucocorticoids act within minutes to inhibit recruitment of signalling factors to activated EGF receptors through a receptor-dependent, transcription-independent mechanism. *Brit J Pharmacol*. 2000; 130:289–298. [PubMed: 10807665]
56. Brunetti M, Martelli N, Colasante A, Piantelli M, Musiani P, Aiello FB. Spontaneous and glucocorticoid-induced apoptosis in human mature T lymphocytes. *Blood*. 1995; 86:4199–4205. [PubMed: 7492778]
57. Purton JF, Zhan Y, Liddicoat DR, Hardy CL, Lew AM, Cole TJ, et al. Glucocorticoid receptor deficient thymic and peripheral T cells develop normally in adult mice. *Eur J Immunol*. 2002; 32:3546–3555. [PubMed: 12442337]
58. McKay LI, Cidlowski JA. Cross-talk between nuclear factor-kappa B and the steroid hormone receptors: Mechanisms of mutual antagonism. *Mol Endocrinol*. 1998; 12:45–56. [PubMed: 9440809]
59. Kawabe K, Lindsay D, Braitch M, Fahey AJ, Showe L, Constantinescu CS. IL-12 inhibits glucocorticoid-induced T cell apoptosis by inducing GMEB1 and activating PI3K/Akt pathway. *Immunobiology*. 2012; 217:118–123. [PubMed: 21840619]

60. Xie H, Seward RJ, Huber BT. Cytokine rescue from glucocorticoid induced apoptosis in T cells is mediated through inhibition of IkappaBalpha. *Molecular immunology*. 1997; 34:987–994. [PubMed: 9488049]
61. Zubiaga AM, Munoz E, Huber BT. IL-4 and IL-2 selectively rescue Th cell subsets from glucocorticoid-induced apoptosis. *J Immunol*. 1992; 149:107–112. [PubMed: 1535084]
62. Banuelos J, Shin S, Cao Y, Bochner BS, Morales-Nebreda L, Budinger GR, et al. BCL-2 protects human and mouse Th17 cells from glucocorticoid-induced apoptosis. *Allergy*. 2016; 71:640–650. [PubMed: 26752231]
63. Chen X, Murakami T, Oppenheim JJ, Howard OM. Differential response of murine CD4+CD25+ and CD4+CD25- T cells to dexamethasone-induced cell death. *Eur J Immunol*. 2004; 34:859–869. [PubMed: 14991616]
64. Pandolfi J, Baz P, Fernandez P, Discianni Lupi A, Payaslian F, Billordo LA, et al. Regulatory and effector T-cells are differentially modulated by Dexamethasone. *Clinical immunology (Orlando, Fla)*. 2013; 149:400–410.
65. Olsen PC, Kitoko JZ, Ferreira TP, de-Azevedo CT, Arantes AC, Martins Mu A. Glucocorticoids decrease Treg cell numbers in lungs of allergic mice. *Eur J Pharmacol*. 2015; 747:52–58. [PubMed: 25499819]
66. Singh AM, Dahlberg P, Burmeister K, Evans MD, Gangnon R, Roberg KA, et al. Inhaled corticosteroid use is associated with increased circulating T regulatory cells in children with asthma. *Clin Mol Allergy*. 2013; 11:1. [PubMed: 23347774]
67. Arya SK, Wong-Staal F, Gallo RC. Dexamethasone-mediated inhibition of human T cell growth factor and gamma-interferon messenger RNA. *J Immunol*. 1984; 133:273–276. [PubMed: 6427338]
68. Verhoef CM, van Roon JA, Vianen ME, Lafeber FP, Bijlsma JW. The immune suppressive effect of dexamethasone in rheumatoid arthritis is accompanied by upregulation of interleukin 10 and by differential changes in interferon gamma and interleukin 4 production. *Ann Rheum Dis*. 1999; 58:49–54. [PubMed: 10343540]
69. Cao J, Chen C, Li L, Ling-yu Z, Zhen-yu L, Zhi-ling Y, et al. Effects of high-dose dexamethasone on regulating interleukin-22 production and correcting Th1 and Th22 polarization in immune thrombocytopenia. *Journal of clinical immunology*. 2012; 32:523–529. [PubMed: 22289995]
70. Mozo L, Gayo A, Suarez A, Rivas D, Zamorano J, Gutierrez C. Glucocorticoids inhibit IL-4 and mitogen-induced IL-4R alpha chain expression by different posttranscriptional mechanisms. *J Allergy Clin Immun*. 1998; 102:968–976. [PubMed: 9847438]
71. Wu CY, Fargeas C, Nakajima T, Delespesse G. Glucocorticoids Suppress the Production of Interleukin-4 by Human-Lymphocytes. *Eur J Immunol*. 1991; 21:2645–2647. [PubMed: 1915563]
72. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nature reviews*. 2015; 15:57–65.
73. Franchimont D, Galon J, Gadina M, Visconti R, Zhou Y, Aringer M, et al. Inhibition of Th1 immune response by glucocorticoids: dexamethasone selectively inhibits IL-12-induced Stat4 phosphorylation in T lymphocytes. *J Immunol*. 2000; 164:1768–1774. [PubMed: 10657623]
74. Liberman AC, Refojo D, Druker J, Toscano M, Rein T, Holsboer F, et al. The activated glucocorticoid receptor inhibits the transcription factor T-bet by direct protein-protein interaction. *FASEB J*. 2007; 21:1177–1188. [PubMed: 17215482]
75. Liberman AC, Druker J, Refojo D, Holsboer F, Arzt E. Glucocorticoids inhibit GATA-3 phosphorylation and activity in T cells. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2009; 23:1558–1571. [PubMed: 19124555]
76. Maneechotesuwan K, Yao X, Ito K, Jazrawi E, Usmani OS, Adcock IM, et al. Suppression of GATA-3 Nuclear Import and Phosphorylation: A Novel Mechanism of Corticosteroid Action in Allergic Disease. *Plos Med*. 2009; 6
77. Holz LE, Jakobsen KP, Van Snick J, Cormont F, Sewell WA. Dexamethasone inhibits IL-9 production by human T cells. *J Inflamm (Lond)*. 2005; 2:3. [PubMed: 15840176]
78. Ouyang H, Shi YB, Liu ZC, Feng S, Li LY, Su N, et al. Increased interleukin-9 and CD4(+)IL-9(+) T cells in patients with systemic lupus erythematosus. *Mol Med Rep*. 2013; 7:1031–1037. [PubMed: 23291628]

79. McKinley L, Alcorn JF, Peterson A, Dupont RB, Kapadia S, Logar A, et al. TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice. *J Immunol.* 2008; 181:4089–4097. [PubMed: 18768865]
80. Ziesche E, Scheiermann P, Bachmann M, Sadik CD, Hofstetter C, Zwissler B, et al. Dexamethasone suppresses interleukin-22 associated with bacterial infection in vitro and in vivo. *Clinical and experimental immunology.* 2009; 157:370–376. [PubMed: 19664145]
81. Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *The Journal of clinical investigation.* 2006; 116:146–155. [PubMed: 16341266]
82. Lovato P, Norsgaard H, Tokura Y, Ropke MA. Calcipotriol and betamethasone dipropionate exert additive inhibitory effects on the cytokine expression of inflammatory dendritic cell-Th17 cell axis in psoriasis. *Journal of dermatological science.* 2016; 81:153–164. [PubMed: 26794805]
83. Liu M, Hu X, Wang Y, Peng F, Yang Y, Chen X, et al. Effect of high-dose methylprednisolone treatment on Th17 cells in patients with multiple sclerosis in relapse. *Acta Neurol Scand.* 2009; 120:235–241. [PubMed: 19769778]
84. Chakir J, Shannon J, Molet S, Fukakusa M, Elias J, Laviolette M, et al. Airway remodelling-associated mediators in moderate to severe asthma: effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression. *The Journal of allergy and clinical immunology.* 2003; 111:1293–1298. [PubMed: 12789232]
85. Banuelos J, Shin SC, Lu NZ. A hotspot in the glucocorticoid receptor DNA-binding domain susceptible to loss of function mutation. *Steroids.* 2015; 96:115–120. [PubMed: 25676786]
86. Teixeira B, Bittencourt VCB, Ferreira TB, Kasahara TM, Barros PO, Alvarenga R, et al. Low sensitivity to glucocorticoid inhibition of in vitro Th17-related cytokine production in multiple sclerosis patients is related to elevated plasma lipopolysaccharide levels. *Clinical Immunology.* 2013; 148:209–218. [PubMed: 23778260]
87. Ferreira TB, Barros PO, Teixeira B, Cassano T, Centuriao N, Kasahara TM, et al. Dopamine favors expansion of glucocorticoid-resistant IL-17-producing T cells in multiple sclerosis. *Brain Behav Immun.* 2014; 41:182–190. [PubMed: 24882215]
88. Ferreira TB, Hygino J, Barros PO, Teixeira B, Kasahara TM, Linhares UC, et al. Endogenous interleukin-6 amplifies interleukin-17 production and corticoid-resistance in peripheral T cells from patients with multiple sclerosis. *Immunology.* 2014; 143:560–568. [PubMed: 24919524]
89. Dittrich A, Khouri C, Sackett SD, Ehling C, Bohmer O, Albrecht U, et al. Glucocorticoids increase interleukin-6-dependent gene induction by interfering with the expression of the suppressor of cytokine signaling 3 feedback inhibitor. *Hepatology.* 2012; 55:256–266. [PubMed: 21898505]
90. Ciofani M, Madar A, Galan C, Sellars M, Mace K, Pauli F, et al. A validated regulatory network for Th17 cell specification. *Cell.* 2012; 151:289–303. [PubMed: 23021777]
91. Schewitz-Bowers LP, Lait PJ, Copland DA, Chen P, Wu W, Dhanda AD, et al. Glucocorticoid-resistant Th17 cells are selectively attenuated by cyclosporine A. *Proceedings of the National Academy of Sciences of the United States of America.* 2015; 112:4080–4085. [PubMed: 25775512]
92. Yamazaki S, Akira S, Sumimoto H. Glucocorticoid augments lipopolysaccharide-induced activation of the I kappa B zeta-dependent genes encoding the anti-microbial glycoproteins lipocalin 2 and pentraxin 3. *J Biochem.* 2015; 157:399–410. [PubMed: 25552549]
93. Szatmary Z, Kebis A. Promoter-context as a determinant of glucocorticoid receptor-responsiveness to activation of p38 and JNK mitogen-activated protein (MAP) kinases. *Gen Physiol Biophys.* 2012; 31:309–322. [PubMed: 23047944]
94. Hofmann TG, Schmitz ML. The promoter context determines mutual repression or synergism between NF-kappa B and the glucocorticoid receptor. *Biol Chem.* 2002; 383:1947–1951. [PubMed: 12553732]
95. Trousson A, Grenier J, Fonte C, Massaad-Massade L, Schumacher M, Massaad C. Recruitment of the p160 coactivators by the glucocorticoid receptor: Dependence on the promoter context and cell type but not hypoxic conditions. *J Steroid Biochem.* 2007; 104:305–311.

96. Zijlstra GJ, Fattahi F, Rozeveld D, Jonker MR, Kliphuis NM, van den Berge M, et al. Glucocorticoids induce the production of the chemoattractant CCL20 in airway epithelium. *Eur Respir J*. 2014; 44:361–370. [PubMed: 24627531]
97. Pelletier M, Maggi L, Micheletti A, Lazzeri E, Tamassia N, Costantini C, et al. Evidence for a cross-talk between human neutrophils and Th17 cells. *Blood*. 2010; 115:335–343. [PubMed: 19890092]
98. Bullens DM, Truyen E, Coteur L, Dilissen E, Hellings PW, Dupont LJ, et al. IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? *Respir Res*. 2006; 7:135. [PubMed: 17083726]
99. Kumar V, Sharma A. Neutrophils: Cinderella of innate immune system. *Int Immunopharmacol*. 2010; 10:1325–1234. [PubMed: 20828640]
100. Dale DC, Fauci AS, Guerry DI, Wolff SM. Comparison of agents producing a neutrophilic leukocytosis in man. Hydrocortisone, prednisone, endotoxin, and etiocholanolone. *J Clin Invest*. 1975; 56:808–813. [PubMed: 1159089]
101. Trottier MD, Newsted MM, King LE, Fraker PJ. Natural glucocorticoids induce expansion of all developmental stages of murine bone marrow granulocytes without inhibiting function. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105:2028–2033. [PubMed: 18250324]
102. Liles WC, Dale DC, Klebanoff SJ. Glucocorticoids inhibit apoptosis of human neutrophils. *Blood*. 1995; 86:3181–3188. [PubMed: 7579413]
103. Creed TJ, Probert CS. Review article: steroid resistance in inflammatory bowel disease - mechanisms and therapeutic strategies. *Aliment Pharmacol Ther*. 2007; 25:111–122. [PubMed: 17229236]
104. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *American journal of respiratory and critical care medicine*. 2000; 162:2341–2351. [PubMed: 11112161]
105. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *American journal of respiratory and critical care medicine*. 2012; 185:612–619. [PubMed: 22268133]
106. Agache I, Ciobanu C, Agache C, Anghel M. Increased serum IL-17 is an independent risk factor for severe asthma. *Resp Med*. 2010; 104:1131–1137.
107. Chien JW, Lin CY, Yang KD, Lin CH, Kao JK, Tsai YG. Increased IL-17A secreting CD4(+) T cells, serum IL-17 levels and exhaled nitric oxide are correlated with childhood asthma severity. *Clin Exp Allergy*. 2013; 43:1018–1026. [PubMed: 23957337]
108. Ramesh R, Kozhaya L, McKevitt K, Djuretic IM, Carlson TJ, Quintero MA, et al. Pro-inflammatory human Th17 cells selectively express P-glycoprotein and are refractory to glucocorticoids. *The Journal of experimental medicine*. 2014; 211:89–104. [PubMed: 24395888]
109. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol*. 2005; 6:1123–1132. [PubMed: 16200070]
110. Chambers ES, Nanzer AM, Pfeffer PE, Richards DF, Timms PM, Martineau AR, et al. Distinct endotypes of steroid-resistant asthma characterized by IL-17A(high) and IFN-gamma(high) immunophenotypes: Potential benefits of calcitriol. *J Allergy Clin Immunol*. 2015; 136:628–637. e4. [PubMed: 25772594]
111. Irvin C, Zafar I, Good J, Rollins D, Christianson C, Gorska MM, et al. Increased frequency of dual-positive TH2/TH17 cells in bronchoalveolar lavage fluid characterizes a population of patients with severe asthma. *J Allergy Clin Immunol*. 2014; 134:1175–1186. e7. [PubMed: 25042748]
112. Wakashin H, Hirose K, Maezawa Y, Kagami S, Suto A, Watanabe N, et al. IL-23 and Th17 cells enhance Th2-cell-mediated eosinophilic airway inflammation in mice. *American journal of respiratory and critical care medicine*. 2008; 178:1023–1032. [PubMed: 18787221]
113. Kebir H, Ifergan I, Alvarez JI, Bernard M, Poirier J, Arbour N, et al. Preferential recruitment of interferon-gamma-expressing TH17 cells in multiple sclerosis. *Ann Neurol*. 2009; 66:390–402. [PubMed: 19810097]

Biographies

Jesus Banuelos recently obtained his PhD in the Division of Allergy-Immunology at Northwestern University Feinberg School of Medicine in Chicago, Illinois. His dissertation project is on the mechanisms of glucocorticoid resistance of Th17 cells. He is a member of the American Association of Immunologists (AAI). He is the recipient of the AAI travel award, FASEB MARC Travel Award, John Wallace Diversity Scholarship, and the Immunology and Molecular Pathogenesis T32 Training Program Award.

Nick Z. Lu completed his PhD in Physiology and Pharmacology in 2002 at Oregon Health and Sciences University in Portland, Oregon. He then undertook post-doctoral work at National Institute of Environmental Health Science at Research Triangle Park, NC. In 2006, he established his independent group at Northwestern University. His research interests focus on glucocorticoid mechanisms of action and glucocorticoid resistance. His lab investigates the function and activity of glucocorticoid receptor isoforms in cancer and asthma. He is a member and an Endocrine Scholar of the Endocrine Society.

Highlights

- Th1, Th2, and Th17 cells have distinct glucocorticoid sensitivity.
- Th1 cells are sensitive to glucocorticoid-induced apoptosis and cytokine suppression.
- Th2 cells are sensitive to glucocorticoid suppression of cytokines but resistant to glucocorticoid-induced apoptosis.
- Th17 cells are resistant to glucocorticoid-induced apoptosis and cytokine suppression.
- Underlying Th cells mediate distinct glucocorticoid responsiveness and severity of diseases.
- Distinct glucocorticoid sensitivity of Th cells and their cytokines is mediated by cell and promoter-specific glucocorticoid receptor signaling.

Figure 1. Th cell subsets

CD4⁺ T cells can differentiate into different Th subsets depending on the cytokine milieu when the cell is activated. AHR, aryl hydrocarbon receptor; BCL-6, B-cell lymphoma 6; FOXP3, forkhead box P3; GATA-3, GATA binding protein 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; RA, retinoic acid; ROR γ t, RAR-related orphan receptor gamma; T-BET, T-box expressed in T cells; Tfh, follicular Th cell; TGF- β , transforming growth factor β ; Th, helper T cells; TNF, tumor necrosis factor; Treg, regulatory T cells.

Figure 2. GR- α isoforms and post-translational modifications

Alternative translation initiation leads to the production of different GR- α isoforms. Alternative translation initiation sites, domain boundaries, and residues subject to post-translational modifications are indicated. A, acetylation; DBD, DNA-binding domain; LBD, ligand binding domain; NTD, N-terminal domain; P, phosphorylation; S, sumoylation; U, ubiquitination.

Figure 3. GR signaling

In the absence of glucocorticoids, the GR is held in the cytoplasm by chaperone proteins such as HSP70, HSP90, and SRC. Glucocorticoids passively diffuse into the cell where they bind the GR, leading to disassociation of GR from chaperone proteins and translocation into the nucleus. The GR mediates the majority of its effects through regulation of gene expression. The mechanisms of gene regulation include transactivation, direct repression, or indirect repression. Coactivators such as CBP is recruited for transactivation whereas corepressors such as SMRT/NCOR are necessary for gene repression. The activated GR is also able to regulate gene expression by enhancing the decay of specific mRNAs such as TNF and CCL2. Additional mechanisms of action include rapid signaling by membrane-bound GR.

BIM, Bcl-2 interacting mediator of cell death; CBP, CREB binding protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; GR, glucocorticoid receptor; GRE, glucocorticoid response element; HSP, heat shock protein; I κ B α , NF- κ B inhibitor α ; IL, interleukin; IR-nGRE, inverted repeat negative GRE; NCoR, nuclear receptor co-repressor; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PNRC2, proline-rich nuclear receptor coactivator 2; SMRT, silencing mediator for retinoid and thyroid hormone

receptors; Pol II, RNA polymerase II; SRC, v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog; UPF1, regulator of nonsense transcripts 1.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Distinct glucocorticoid sensitivity of Th1, Th2, and Th17 cells.

	Th1	Th2	Th17
Glucocorticoid-induced apoptosis	Sensitive	Resistant	Resistant
Glucocorticoid suppression of cytokines	Sensitive	Sensitive	Resistant/Sensitive

Table 2

Distinct glucocorticoid sensitivity of Th cell cytokines and chemokines.

Glucocorticoid regulation		Proposed mechanisms
IFNγ	Suppressed	Indirect repression
IL-4	Suppressed	Indirect repression
IL-22	Suppressed	Direct/indirect repression; enhanced mRNA decay
IL-17A/F	Not changed/increased	GR interaction with STAT3 and other transcription factors
CCL-20	Increased	Transactivation; ADAM17 activation