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Immunopathology alters Th17 cell glucocorticoid sensitivity

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Abstract

Th17 cells contribute to several inflammatory conditions and increasing evidence supports that Th17 cells are glucocorticoid resistant. However, Th17 cells in psoriasis and related diseases are glucocorticoid sensitive. We compare glucocorticoid sensitive and resistant immunological diseases and suggest that several aspects in Th-17 related diseases alter glucocorticoid sensitivity of Th17 cells. We identify molecular pathways that are implicated in glucocorticoid sensitivity of Th17 cells in the literature, as this information is useful for developing approaches to overcome glucocorticoid-resistant immunopathology.

Keywords

Th17 cells; glucocorticoids; glucocorticoid resistance; asthma; autoimmunity

Introduction

CD4+ helper T (Th) cells play a crucial role in immunity against diverse pathogenic insults. In addition to their protective role, Th cells are also key players in autoimmune disorders, allergies, and asthma. Th17 cells are a subset of Th cells capable of producing IL-17A, IL-17F, IL-22, GM-CSF, and other proinflammatory cytokines (1). IL-17A, the signature cytokine of Th17 cells, is pivotal in immunity against fungi and extracellular bacteria. In addition, Th17 cells have been proposed to contribute to multiple chronic inflammatory diseases. Psoriasis, for instance, has been successfully treated with anti-IL-17A therapy (2, 3).

Glucocorticoids are extensively used for inflammatory conditions. However, glucocorticoid resistance occurs in a subset of patients. Multiple mechanisms have been proposed to underlie glucocorticoid resistance (4) and recently the distinct glucocorticoid sensitivity of Th subsets has been suggested to underlie the distinct glucocorticoid sensitivity of different patient subsets (5). Th1 and Th2 cells are sensitive to glucocorticoid inhibition whereas

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Conflict of interest

All authors declare that they have no relevant conflict of interests.

Author contributions

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Th17 cells are resistant to glucocorticoid suppression (6). However, Th17 cells in certain diseases such as psoriasis appear to be sensitive to glucocorticoid inhibition while Th17 cells in some other diseases such as Crohn's disease are resistant to glucocorticoids (7, 8). Therefore, certain aspects of diseases appear to influence glucocorticoid sensitivity of Th17 cells. We propose that mechanisms altering glucocorticoid sensitivity of Th17 cells originate from molecules necessary for Th17 differentiation, proliferation, recruitment, survival, and signaling. We begin by considering some key features of Th17 cells and Th17 cytokines.

Th17 cytokine redundancy, synergism and antagonism

While the focus of this article is to review the role and glucocorticoid sensitivity of Th17 cells in diseases, it is important to appreciate that accumulating evidence indicates the ability of other immune cells to produce IL-17A, IL-17F, and IL-22 (Figure 1). Patients with multiple sclerosis have elevated CD8+ IL-17A-producing (Tc17) cells in the cerebrospinal fluid (9). γδT cells, a T cell subset that acts as a bridge between innate and adaptive responses, can also produce IL-17A and promote multiple sclerosis-like symptoms in animal models (10). Interestingly, IL-17A produced by γδT cells helps to clear inflammation in the airways (11). Invariant natural killer T cells (iNKT) are another subset of T cells that can produce IL-17A and recruit neutrophils to the airways in response to alpha-galactosylceramide or ozone challenges (12, 13). RAG-deficient mice lacking T cells still produce IL-17A, suggesting myeloid cells are also able to secrete IL-17A (14). In an ischemia-reperfusion kidney injury model, IL-17A from neutrophils promotes tissue damage (15). In a mouse model of arthritis, neutrophils from wild type animals, but not from IL-17A knockout littermates, exacerbate the disease (16). Type 3 innate lymphoid cells (ILC3) in the oral mucosa respond to *Candida albicans* and act as the main and rapid source of IL-17A and IL-17F (17). Depletion of these cells leads to uncontrolled *C. albicans* infection (17). In addition, ILC3 and associated cytokines are increased in inflammatory bowel disease (18) and asthma (19). Lymphoid tissue inducer (LTi) cells and LTi-like cells are subsets of ILC3 that contribute to lymphoid tissue development (20). LTi-like cells can respond to zymosan, a yeast wall product, and produce IL-17A (21). In an airway inflammation model, macrophages secrete IL-17A that promotes allergen-induced airway inflammation (22). Mast cells stimulated with TNFα, IgG complexes, C5a, or LPS produce IL-17A (23). Mast cells producing IL-17A are elevated in rheumatoid arthritis synovium (23). Mast cells also increase IL-17A production in macrophages via releasing IL-6 and other cytokines (22). In addition, B cells have also been identified as IL-17A producers (24). This redundancy in cellular sources of IL-17A supports that IL-17A is indispensable in immune responses. Multiple sources of IL-17A and their wide anatomical distributions allow for a rapid rise of IL-17A and related cytokines before Th17 cells arrive. Although pivotal in disease development, these non-Th17 IL-17A producing cells are relatively scarcely studied for their glucocorticoid sensitivity.

Cytokines produced by Th17 cells synergistically strengthen innate immunity. For example, epithelial cells respond to both IL-17A and IL-22. IL-17A increases production of IL-6, CXCL1, and CCL20 (25) and IL-22 promotes epithelial proliferation (26). In diseases, Th17 cytokines other than IL-17A have been identified as culprits. Thus, IL-22 is overexpressed in psoriasis and can induce epidermal thickening, a characteristic of plaque psoriasis (26). GM-

CSF is a pro-inflammatory cytokine produced by Th1 and Th2 as well as Th17 cells (27, 28). Pathogenic Th17 cells produce more GM-CSF than non-pathogenic Th17 cells (29). GM-CSF deficient Th17 cells are unable to induce experimental autoimmune encephalitis, highlighting the importance of Th17-derived GM-CSF in driving disease pathology (29, 30).

Whilst pathogenic Th17 cells are proinflammatory and produce proinflammatory cytokines indicated above, non-pathogenic Th17 cells produce more IL-10, which limits Th17-driven inflammation (31) (Figure 2). Pathogenicity of Th17 cells can be enhanced by certain stimuli such as NaCl and IL-23 (32–34) while inhibited by other signals such as IL-4 and IL-13 (35–37). Thus, multiple pathways determine the function of a Th17 cell.

Th17 differentiation

IL-6, TGF-β, IL-21, and IL-1β are key cytokines while RORγt and STAT3 are the pivotal transcription factors for Th17 differentiation (Figure 3). IL-6 directly activates STAT3 whereas TGF-β1 inhibits SOCS3, a negative regulator of STAT3 signaling, and activates SMAD2, which promotes RORγt and IL-17A expression (38–40). TGF-β1 can also have a negative effect on Th17 differentiation by activating SMAD3, an inhibitor of Th17 differentiation (40). ERK signaling, downstream of the IL-6R, promotes phosphorylation of SMAD2 and Th17 differentiation. Together, IL-6 and TGF-β1 induce the expression of RORγt, the master regulator of transcription for Th17 cells (41). IL-6, in a STAT3-dependent manner, induces the expression of IL-21, which acts in an autocrine feed forward loop to further promote STAT3 activation and RORγt expression (42, 43). IL-1β can promote Th17 differentiation by inducing the expression of IRF4, which stimulates the expression of RORγt and IL-17A (44, 45). In addition, IL-1β, via NF-κB activation, also inhibits SOCS3, leading to STAT3 activation (46). While promoting RORγt, STAT3 activation also induces IL-23R and IL-23 is important in the maintenance and stability of Th17 cells (47, 48).

In addition to the key cytokines and transcription factors mentioned above, a myriad of factors have been identified to enhance or suppress Th17 differentiation (Figure 3). Among the Th17-enhancing molecules are transcription factors BATF (49), IKAROS (50, 51), FICZ-mediated activation of aryl hydrocarbon receptor (AHR) (52), RUNX1 (53), C-MAF (54), and NFAT5 (33), signaling molecules and enzymes FAS (55), MINA, a histone lysine demethylase (55), SIRT1 (56), IκBζ (57), p300 (58), and SGK1 (33, 34), and micro RNAs (miRNA) miR-21 (59) and miR-155 (60). Several of these Th17 enhancing molecules work by increasing the activity of the master transcription factors STAT3 and RORγt. In contrast, negative regulators of Th17 differentiation generally inhibit STAT3 and RORγt. They include Jagged-1 (61), HES-1 (61), ER-α (62), iNOS (63), FOXP3 (64), FOXO1 (65), STAT1 (66), STAT5 (67), STAT6 (36), T-BET (53), NR2F6 (68), and GILZ (glucocorticoid-induced leucine zipper) (55, 69). AHR bound to TCDD, in contrast to that bound to FICZ, inhibits Th17 differentiation (52). These multiple regulatory factors orchestrate Th17 cell differentiation in three phases: the early (up to 4 h), the intermediate (4–20 h), and the late (20–72 h) phase (24). The early phase is characterized by an IL-6 and TGF-β1 signature and transcription factors such as STAT3, IRF4, and BATF, and expression of the IL-23R (55). The intermediate phase involves the expression of RORγt and AHR among others (55). By

the late phase, key Th17 cytokines are expressed (55). As indicated below, some of these Th17-regulatory molecules have been implicated in altering Th17 glucocorticoid sensitivity in diseases.

Th17 cells in diseases

Mutations of genes necessary for Th17 function and blockade of Th17 pathways in clinical trials definitively indicate the role of Th17 cells in several autoimmune diseases. An arginine381 to glutamine (R381Q) in the cytoplasmic domain of IL-23R is highly associated with low incidence of Crohn's disease (70). R381Q impairs IL-17A production and has also been inversely correlated to psoriasis (71) and rheumatoid arthritis (72). In addition, Th17 cells have been found at inflamed tissues in rheumatoid arthritis (73, 74), multiple sclerosis (75, 76), psoriasis (77), inflammatory bowel diseases (78), and severe asthma (79–82) among others. These diseases with Th17 involvement have varied glucocorticoid sensitivity, from psoriasis being glucocorticoid sensitive to subsets of Crohn's disease on the other end of the spectrum. As discussed below, Th17-driven diseases have varied glucocorticoid sensitivity likely because each disease has varying amounts of glucocorticoid-sensitive components that intersect with Th17 cell functions. Because the term glucocorticoid sensitivity is context-dependent, examining glucocorticoid sensitivity begins with defining the entity to be questioned as well as the context. We focus on the glucocorticoid sensitivity of Th17 cell counts and their ability to produce signature cytokines such as IL-17A in immunopathology. One caveat of this focus is that changes in Th17 cell numbers in blood could be interpreted in several ways. Increased Th17 cell numbers in circulation might reflect increased inflammation. However, reduced numbers could indicate greater recruitment to disease tissues, rather than reduced inflammation. Therefore, we also reference studies that examine whether glucocorticoids alleviate symptoms of Th17-related diseases.

Th17 cells are intrinsically glucocorticoid resistant

Th17 cells isolated from various tissues express memory T cell markers and are highly proliferative (83). Memory Th17 cells are relatively resistant to activation- or chemotherapy drug (i.e., cisplatin and paclitaxel)-induced apoptosis due to elevated Notch, hypoxia-inducible factor 1-α, and BCL-2 (83, 84). Th17 cells isolated from peripheral blood of healthy subjects or from donors with mild allergies are resistant to glucocorticoid killing, the mechanism of which has also been linked to high levels of BCL-2 in Th17 cells (6). ROR-γt, the master transcription factor of Th17 cells, counteracts glucocorticoid-induced apoptosis (85) and STAT3, another key transcription factor in Th17 cells, can antagonize glucocorticoid receptor (GR) functions (86). Glucocorticoids promote Th17 differentiation *in vitro* (87). When glucocorticoid sensitivity is compared among Th1, Th2, and Th17 cells, Th2 and Th17 cells are resistant to glucocorticoid-induced apoptosis (6). A prerequisite for tissue Th17 activity is their recruitment to site of inflammations. CCL20, the Th17 chemokine, is increased by glucocorticoids in the sputum of asthmatics (88).

IL-17A, but not IL-22 or GM-CSF, from the same Th17 cells is resistant to glucocorticoid suppression, suggesting that gene promoter-specific mechanisms mediate glucocorticoid

sensitivity in Th17 cells (6). Glucocorticoids can even elevate IL-17A in certain diseases (81, 89). Once secreted, IL-17A promotes recruitment of neutrophils via CXCL8 (90). Neutrophils and Th17 cell co-localize in gut tissues isolated from patients with Crohn's disease, synovial fluid from rheumatoid arthritis patients (90), and sputum from asthmatics (91). Glucocorticoids elevate blood neutrophil counts (92) and inhibit neutrophil apoptosis (93). It has been suggested that neutrophils, in turn, promote Th17 cells (94). Neutrophils stimulated with a combination of IFN-γ and LPS produce Th17 and Th1 chemokines CCL20, CCL2 and CXCL10 (90). Therefore, there is a feedforward loop between Th17 cell activity and neutrophils, which is enhanced by glucocorticoids. In epithelial cells and other IL-17A targets cells, IL-17A receptors signal through p38 MAPK, extracellular signal-related kinase, and phosphoinositide-3-kinase pathways that antagonize glucocorticoid signaling (95). Thus, IL-17A reduces the sensitivity of TNF-α-induced IL-8 production to budesonide in airway epithelium (95). In addition, IL-17A reduces HDAC activity and overexpression of HDAC2 can reverse IL-17A-induced glucocorticoid insensitivity (95). Even though these findings support that Th17 cells are intrinsically resistant to glucocorticoid suppression, recent evidence indicates that Th17 cells in certain diseases are sensitive to glucocorticoids (Table 1).

Wide-ranging glucocorticoid sensitivity of diseases and Th17 cells

Psoriasis

Topical glucocorticoids are the most frequently prescribed medication for controlling outbreaks of psoriasis (96). Glucocorticoids, independently or together with vitamin D3, through their anti-inflammatory actions reduce plaques and relieve associated symptoms (96, 97). Recent clinical trials targeting Th17 pathways have been remarkably successful. Anti-IL-17A mAbs secukinumab (2) and ixekizumab (3) are highly effective for psoriasis. Other Th17 targeting therapeutics, brodalumumab (anti-IL-17RA) (98) and guselkumab, tildrakizumab, BI-655066, AMG139, and LY3074828 (anti-IL-23p19 mAbs) (99–102) are also excellent for psoriasis. Since Th17 cells play a major role in psoriasis and glucocorticoids are effective in controlling the symptoms of psoriasis, it is not surprising that glucocorticoids decrease the frequency of Th17 cells in the circulation in psoriatic patients (7). In an *ex vivo* psoriatic skin cell culture system, betamethasone suppresses IL-17A and IL-22 (97). Therefore, the majority of symptoms of psoriasis are glucocorticoid sensitive and both Th17 cell number and function are sensitive to glucocorticoid inhibition in psoriasis (Table 1).

Activated keratinocytes and multiple immune cells including Th1 and dendritic cells are involved in pathogenesis psoriasis (103). Reducing overall inflammation via inhibition of these other immune cells by glucocorticoids provides a means to reduce signals that promote Th17 cells. In addition, recent reports suggest that GILZ is a direct mediator of glucocorticoid sensitivity of Th17 cells in psoriasis. Low levels of GILZ have been found in lesional skin of psoriasis patients and GILZ is inversely correlated with levels of IL-23, IL-17A, IL-22, and STAT3, suggesting GILZ could be inhibitory to Th17 activity (69). GILZ null mice subjected to the imiquimod model of psoriasis have worse inflammation than wild type animals (69). Correspondingly, dendritic cells lacking GILZ produce more

IL-1, IL-23 and IL-6 in response to imiquimod stimulation than those with intact GILZ (69). GILZ has also been suggested to limit Th17 cell differentiation by acting as a negative regulator of the Th17 transcriptional program via directly binding to promoter regions of key Th17 genes BATF, STAT3, IRF4 and ROR-γt (55). Glucocorticoids highly elevate GILZ in Th17 cells (6), suggesting a role of GILZ in the ability of glucocorticoids to decrease Th17 cell number and activity in psoriasis (Table 1).

Multiple sclerosis

Glucocorticoids are the mainstay in managing relapse of multiple sclerosis (104) and the role of Th17 cells in pathogenesis of multiple sclerosis is accumulating. IL-17A and IL-6 are among the most highly expressed genes in brain lesions (75) and IL-17A is elevated in serum and cerebrospinal fluid of multiple sclerosis patients (76, 105). Glucocorticoids not only improve functional recovery in patients with multiple sclerosis during relapse, but also decrease IL-17A production and Th17 cell counts in circulation (106). Since IL-6 is upstream of Th17 cell activity and glucocorticoids effectively inhibit IL-6 in multiple sclerosis, this cytokine may mediate the glucocorticoid sensitivity of Th17 cells in multiple sclerosis. When high levels of IL-6 persists, Th17 cells become glucocorticoid resistant in multiple sclerosis (107). Additional factors including dopamine (108) and endotoxin levels (109) have also been suggested to promote glucocorticoid resistance of Th17 cells in multiple sclerosis (Table 1). T cells from patients with progressive multiple sclerosis are resistant to glucocorticoid-induced apoptosis, whereas T cells from relapse-remitting multiple sclerosis patients are sensitive (110), the mechanism of which has not been examined.

Rheumatoid arthritis

Glucocorticoids are indispensable in managing inflammation in rheumatoid arthritis (111, 112). Morning stiffness and flares both are suppressed by glucocorticoids. However, clinical studies indicate that despite the antiinflammatory benefits of glucocorticoids in rheumatoid arthritis, they are not effective in managing several aspects of arthritis including loss of cartilage and bone (Table 1). Early treatment of undifferentiated arthritis with glucocorticoids provides only limited benefits with regard to remission rates (113). The SAVE trial (114) indicates that a single 120 mg dose of methylprednisolone in patients with arthritis of less than 16 weeks helps only 17% of patients to achieve remission, comparable to placebo. The STIVEA trial (115) indicates that three injections of 80 mg methylprednisolone over 3 weeks also have a low (20%) remission rate. In contrast, anti-IL-17A secukinumab (116), AIN457 (117), and ixekizumab (118) are effective in patients who are inadequate responders to anti-TNFα therapy. Glucocorticoids reduce blood Th17 cells in active rheumatoid arthritis (119). Therefore, the inflammation aspect of rheumatoid arthritis and Th17 cell counts are sensitive to glucocorticoids whereas other key aspects of the disease are glucocorticoid resistant (Table 1).

Th17-driven diseases such as rheumatoid arthritis have significant underpinnings from additional T helper cell types. Thus, Th1 cells play a major role in rheumatoid arthritis, psoriasis, multiple sclerosis, and Crohn’s disease and may collaborate with Th17 cells in exacerbating inflammation (120). Glucocorticoids induce apoptosis of Th1 cells (6) and

decrease IFN-γ production by T cells from patients with rheumatoid arthritis (121). Inhibition of Th1 activity by glucocorticoids may help to reduce overall inflammation. On the other hand, the glucocorticoid resistant aspects of rheumatoid arthritis may be driven by neutrophils. Neutrophils are the culprit of cartilage and bone damage (122) and as mentioned above, neutrophils are expanded by glucocorticoids (93).

Crohn's disease

While glucocorticoids are effective to control exacerbations and induce remission of Crohn's disease in the majority of patients, approximately 20% of patients with Crohn's disease are resistant to glucocorticoids (123) (Table 2). Elevated Th17 cells (78, 124, 125) and increased IL-17A levels have been found in lesions of Crohn's disease (126, 127). Th17 cells isolated from the gut of active Crohn's diseases are resistant to glucocorticoid suppression (8). It is not known whether Th17 cells underlie the subgroup of glucocorticoid-resistant Crohn's disease.

Th17-high asthma

It has been recently recognized that the etiology of asthma varies and Th2 cells and eosinophils underlie only approximately 50% of asthma (128). Th2 activity, eosinophils, and related asthma are effectively controlled by glucocorticoids (129). In contrast, Th17 cells have been suggested to contribute to subsets of glucocorticoid-resistant asthma (130) (Table 2). His161Arg mutation in IL-17F has been inversely correlated with asthma (131) and a significant association of asthma with polymorphisms in IL-1R1 and RORA has been reported (132). Increased Th17 cells are found in asthmatic tissues (77). Airway or blood IL-17A and IL-17F levels are positively correlated to asthma severity (133–137). Elevated IL-17A is correlated with increased neutrophils (91, 135) and methacholine induced airway hyperresponsiveness in asthmatics (80). Although several studies suggest that Th17 cell number and IL-17A levels in asthmatics are resistant to glucocorticoid inhibition (80–82, 91, 138), airway IL-17A detected by immunocytochemistry has been found to be decreased by 2 weeks of oral glucocorticoids in a cohort of moderate-to-severe asthmatics (133). The source of the glucocorticoid-sensitive IL-17A in those patients was not identified. Glucocorticoid inhibition of IL-6 could underlie glucocorticoid inhibition of IL-17A in some asthma patients as methylprednisolone downregulates IL-6, IL-17A, and IFN-γ in stimulated PBMCs from asthmatic children (139). A recent trial using brodalumab (anti-IL-17RA) suggests possible benefits in a select group of patients with highly reversible asthma (140). It will be interesting to determine whether blocking Th17 activity is effective in the Th17-high asthmatics. A recent preclinical study indicates that neutralizing IL-17A and IL-13 together, but not each cytokine alone, abolishes airway hyperreactivity in house dust mite sensitized and challenged mice (37).

Mechanisms underlying Th17 cell glucocorticoid sensitivity in diseases

From available data on glucocorticoid sensitivity of Th17 cells in several diseases detailed above, some key factors can be identified that sensitize Th17 cells to glucocorticoids. Suppression of cytokines such as IL-6 may sensitize Th17 cells to glucocorticoid suppression. Glucocorticoids are highly effective in suppressing IL-6 and anti-IL-6R mAbs potentiate the ability of glucocorticoids to suppress Th17 cytokines (141). Tocilizumab, a

humanized anti-IL-6 receptor monoclonal antibody, has outstanding efficacy against rheumatoid arthritis (142). Since dendritic cells are a major producer of IL-6 and other Th17 promoting cytokines (143), inhibition of dendritic cells will allow glucocorticoids to suppress Th17 differentiation. Dendritic cells have maturational stage-specific glucocorticoid sensitivity (144). Immature dendritic cells are resistant and mature dendritic cells are sensitive to glucocorticoid killing due to a switch of GR isoforms (144). Furthermore, dendritic cells are biased by glucocorticoids to expand Tregs (145). Thus, glucocorticoid sensitivity of Th17-promoting dendritic cells could underlie the glucocorticoid sensitivity of Th17 cells. In addition, recent reports indicate that GITR (glucocorticoid-induced TNFR family-related protein) and its ligand play a critical role in the pathogenesis of rheumatoid arthritis by enhancing the Th17 cell response via p38 MAPK and STAT3 (146). High levels of p38 phosphorylation have been detected in rheumatoid arthritis patients, which correlate with the serum level of anti-cyclic citrullinated peptide antibody (146). GITR is significantly increased by glucocorticoids (147) and could underlie the glucocorticoid-resistant aspect of Th17 cells in diseases.

Th17 cells and the other Th subsets have an extensive network of cross talk. IL-17A, IFN-γ, and IL-4 are thought to be mutually antagonistic (35, 37). IL-4 inhibits STAT3 binding at the IL-17A promoter (36) and neutralizing IL-13 in a mouse asthma model elevates IL-17A and vice versa (37). However, it has been demonstrated that in severe/chronic diseases Th17 and other Th cells can synergize with each other. Th17 cells from collagen immunized animals or those differentiated *in vitro* for 3 weeks are resistant to suppression by IL-4 due to impaired IL-4R signaling in mature Th17 cells (36). Double-positive IL-4/IL-17A T cells have been found in asthmatics (148, 149). In addition, an endotype of glucocorticoid-resistant asthma with elevated levels of both IL-17A and IFN-γ has been reported (138). 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 [95]. 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 (150). Reducing overall inflammation via blocking Th1/Th2 cell activity could provide another means for glucocorticoids to inhibit Th17 recruitment and function.

It is possible that there are distinct subsets of Th17 cells with distinct glucocorticoid sensitivity. It has been reported that glucocorticoid-resistant and pathogenic Th17 cells are restricted to a subset expressing MDR1 (multi-drug resistant type 1, ABCB1) (8). Glucocorticoids increase the level of MDR1 in brain endothelial cells (151) and in lymphocytes from rheumatoid arthritis patients (152). Polymorphisms that increase the level and activity of MDR1 have been suggested to contribute to glucocorticoid resistance in inflammatory bowl diseases (153). However, blocking MDR1 in Th17 cells does not increase glucocorticoid sensitivity (8). Nonetheless, glucocorticoids specifically expand MDR1+ Th17 subsets within mixed T cell cultures (8), suggesting that the underlying Th subsets in diseases can be altered by glucocorticoids. Long-term glucocorticoids that eliminate glucocorticoid-sensitive T cells will select and favor Th17 subsets that are glucocorticoid resistant, which in turn exacerbate disease.

Perspective

It will be interesting to determine whether in the same individual, long-term glucocorticoid treatment shifts the etiology of a disease from glucocorticoid-sensitive to a resistant Th subset. Another intriguing question is whether rheumatoid arthritis and Crohn's disease, like asthma, can be categorized into endotypes with distinct underlying T helper cell subsets and glucocorticoid sensitivity. Further research is also needed to identify the role of Th17 regulatory factors, for example those presented in Figure 3, in glucocorticoid sensitivity in order to overcome glucocorticoid resistance of Th17 cells in diseases. Vitamin D3 has been suggested to be effective in inhibiting Th17 cytokines in patients with glucocorticoid refractory asthma (81). In addition, vitamin D3 has been frequently given together with glucocorticoids to effectively manage psoriasis (97). Continued investigation in novel approaches to overcome glucocorticoid resistance of Th17 cells will help to improve the quality of life for patients with glucocorticoid resistant immunopathology.

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LIST OF ABBREVIATIONS

AHR	aryl hydrocarbon receptor
BATF	basic leucine zipper transcription Factor, ATF-like
BCL-2	B-cell lymphoma 2
CCL	CC chemokine ligands
CCR	CC chemokine receptor
CXCL	CXC chemokine ligand
CXCR	CXC chemokine receptors
ER	estrogen receptor
ERK	extracellular-signal-regulated kinase
FICZ	6-formylindolo (3, 2-b) carbazole
FOXO1	forkhead box protein O1
FOXP3	forkhead box P3
G-CSF	granulocyte-colony stimulating factor
GILZ	glucocorticoid-induced leucine zipper
GM-CSF	granulocyte-macrophage colony-stimulating factor
GR	glucocorticoid receptor

HDAC	histone deacetylase
HES1	HES family BHLH transcription factor 1
IFNγ	interferon γ
IκBζ	NFκB inhibitor ζ
IL	interleukin
ILC	innate lymphoid cell
INKT	invariant NKT
INOS	inducible nitric oxide synthase
IRF4	interferon regulatory factor 4
LPS	lipopolysaccharide
LTI	lymphoid tissue inducer
MAPK	mitogen-activated protein kinase
MDR1	multi-drug resistance 1
MEK1	mitogen-activated protein kinase kinase 1
miRNA	micro RNA
MS	multiple sclerosis
NFAT	nuclear factor of activated T cells
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
PI3K	phosphoinositide 3-kinase
RA	rheumatoid arthritis
RAG	recombination activating gene
RORγt	RAR-related orphan receptor γ
RUNX	Runt-related transcription factor
SGK1	serum and glucocorticoid-regulated kinase 1
SIRT1	sirtuin 1
SOCS	suppressor of cytokine signaling
STAT	signal transducer and activator of transcription
TGFβ	transforming growth factor β
Th	helper T cell

TNF	tumor necrosis factor
Treg	regulatory T cells

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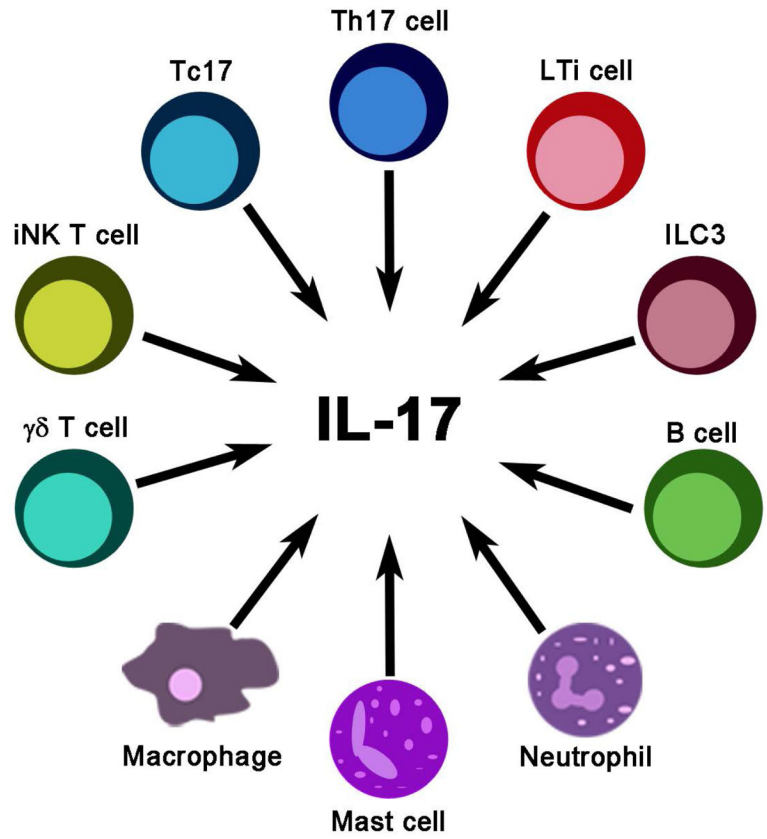

Figure 1.

A multitude of immune cells are capable of producing IL-17A. IL, interleukin; ILC, innate lymphoid cell; iNK, invariant natural killer; LTi, lymphoid tissue inducer; Th, helper T cell.

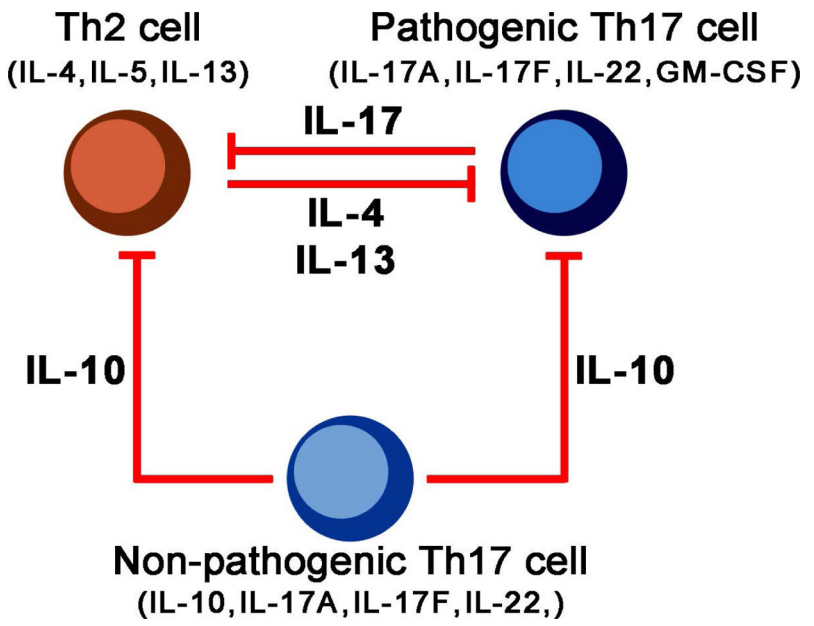

Figure 2.

Th-2 and non-pathogenic Th17 cells exert antagonistic effects towards pathogenic Th17 cells. Th2 cell-derived IL-4 or IL-13 can inhibit Th17 cell functions. Conversely, IL-17A can inhibit Th2 cell responses. Th17 cells have pathogenic or non-pathogenic subsets. Non-pathogenic Th17 cell-derived IL-10 can act on Th2 or Th17 cells and inhibit their pro-inflammatory activities. GM-CSF, Granulocyte macrophage colony-stimulating factor; IL, interleukin; Th, helper T cell.

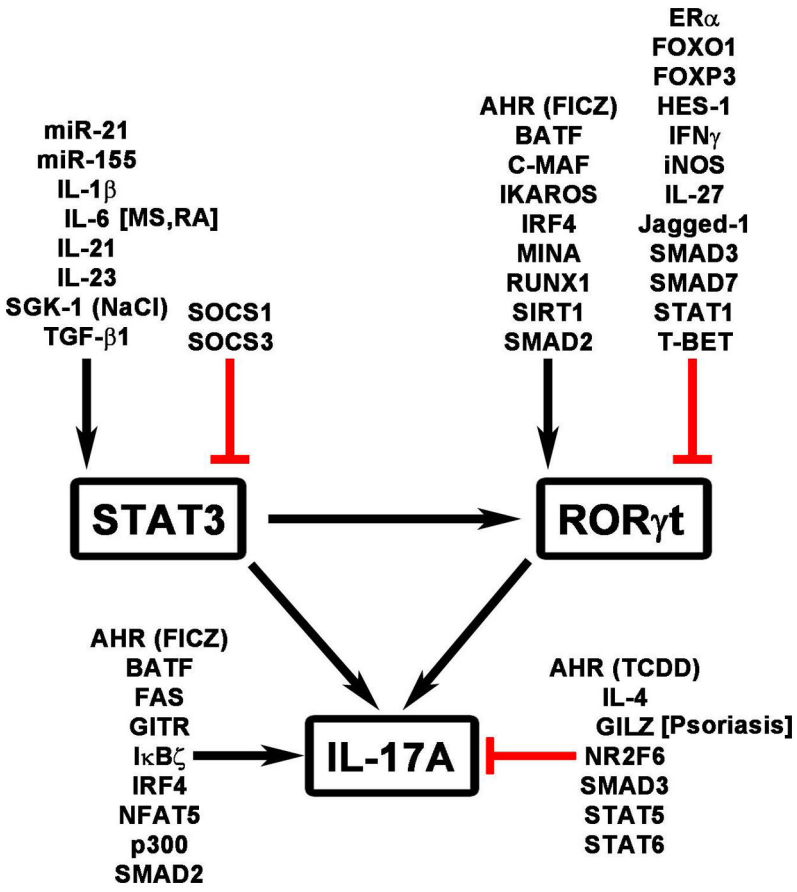

Figure 3.

Th17 regulators. Some of the regulators, e.g., GILZ, GITR, and IL-6, have been identified as candidates that alter glucocorticoid sensitivity of IL-17A in select diseases. Related diseases are shown in brackets. Black arrowhead, positive regulators. Red flat line, inhibitory factors. AHR, aryl hydrocarbon receptor; BATF, basic leucine zipper transcription Factor, ATF-like; C-MAF, v-MAF avian musculoaponeurotic fibrosarcoma oncogene homolog; ER, estrogen receptor; FICZ, 6-formylindolo (3, 2-b) carbazole; FOX, forkhead box protein; GILZ, glucocorticoid-induced leucine zipper; GITR, glucocorticoid-induced TNFR-related protein; HES, HES family BHLH transcription factor; IFN, interferon; IκBζ, NFκB inhibitor ζ; IL, interleukin; iNOS, inducible nitric oxide synthase; IRF, interferon regulatory factor; miR, micro RNA; MS, multiple sclerosis; NaCl, sodium chloride; NFAT, nuclear factor of activated T cells; NR2F6, nuclear receptor subfamily 2, group F, member 6; RA, rheumatoid arthritis; RORγt, RAR-related orphan receptor γ; RUNX, Runt-related transcription factor; SGK, serum and glucocorticoid-regulated kinase; SIRT1, sirtuin 1; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; T-BET, T-box expressed in T cells; TGF, transforming growth factor.

Table 1

Th17 cells are sensitive to glucocorticoid suppression in certain diseases.

	Glucocorticoid effects	References
Psoriasis		
Th17 cell number	Decrease	(7)
IL-17A level	Decrease	(97)
Symptoms	Reduce plaques and relieve associated symptoms	(96, 97)
Proposed mechanisms	Inhibit overall inflammation	
	Inhibit Th17 via inducing GILZ	(55, 69)
Multiple Sclerosis		
Th17 cell number	Decrease	(106)
IL-17A level	Decrease	(106)
Symptoms	Improve functional recovery during relapse	(104, 106)
Proposed mechanisms	Inhibit overall inflammation	
	Inhibit Th17 via suppressing IL-6	(107)
	Do not inhibit Th17 when IL-6, dopamine, LPS are high	(107–109)
Rheumatoid arthritis		
Th17 cell number	Decrease	(119)
IL-17A level	Decrease	(119)
Symptoms	Suppress morning stiffness and flares	(111, 112)
	Do not prevent loss of cartilage and bone	(113–115)
Proposed mechanisms	Inhibit Th1 inflammation	(121)
	Do not inhibit neutrophils, which cause damage to joints	(93)

Table 2

Th17 cells are resistant to glucocorticoid suppression in certain diseases.

	Glucocorticoid effects	References
Crohn's disease		
Th17 cell number	Do not decrease	(8)
IL-17A level	Do not decrease	(8)
Symptoms	Control exacerbations and induce remission in ~80% patients	(123)
Proposed mechanisms	Inhibit overall inflammation	
	Do not inhibit pathogenic Th17 cells in gut	(8)
Th17 high asthma		
Th17 cell number	Do not decrease	(80–82, 91, 138)
IL-17A level	Do not decrease	(80–82, 91, 138)
	Decrease	(133, 139)
Symptoms	Do not improve lung function	(81, 138)
Proposed mechanisms	Glucocorticoid resistant Th17 cells/neutrophils	(80–82, 91, 138)