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Glucocorticoid Resistant Asthma: The Potential Contribution of IL-17

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Abstract

Background: Asthma is a complex disease in which environmental and genetic factors can contribute to its development. The glucocorticoid is the main drug used to treat it. However, glucocorticoid resistant asthma is an important cause of patient morbidity, and some studies have identified a subpopulation of TCD4$^+$ effector cells (Th17 lymphocytes) producers of cytokines such as IL-17A and IL17-F, associated with this condition. Our aim was to investigate in literature the potential role of Th17 in the development of asthma glucocorticoid resistant.

Methods and findings: The literature search was conducted in PubMed, Web of science, Scielo, Medline and Cochrane databases to identify relevant studies published in English, from 1993 to 2015. The keywords used in this search were "glucocorticoids", "IL-17", "asthma" and "polymorphism". Those studies have shown that IL-17A and IL-17F are important regulators of neutrophilic inflammation in airways, suggesting a potential role for TH17 cells in asthma severity through upregulation of β glucocorticoid receptor. There are few studies evaluating the association of polymorphisms in IL-17 genes with different asthma phenotypes, especially with glucocorticoid resistant asthma.

Conclusion: IL-17 is an important mediator of response to glucocorticoid treatment. Further studies are necessary to elucidate the mechanism in which Th17 components interfere in glucocorticoid resistance. We believe that in the future IL-17 can be used as a biomarker to predict the glucocorticoid response in asthmatics.

Keywords: Th17; Glucocorticoid resistance; Asthma

Abbreviations: AP-1: Activating Protein-1 Complex Transcription Factors; CRS: Corticosteroids Resistance; GC: Glucocorticoids; GR: Glucocorticoid Receptors; IL: Interleukin; MEK1: Mitogen-Activated Protein Kinase Phosphatase; NFKB: Nuclear Factor Kappa-B; NLRP3: Nucleotide-Binding Oligomerization Domain-Like Receptor Family, Pyrin Domain Containing 3 Activation; PBMC: Peripheral Blood Mononuclear Cell

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Introduction

Glucocorticoids (GCs) have been widely used in the treatment of numerous inflammatory conditions such as arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, cancer and applied in post-transplant treatment. Also, the asthma treatment was revolutionized through inhaled corticosteroids and have now become the main therapy for patients with persistent asthma [1].

It was reported that almost 1% of the UK adult population uses oral glucocorticoids and 2.5% of them were people between 70 and 79 years old. This prevalence was similar between in men and women [2].

Glucocorticoid controls several physiological processes due to pleiotropic capacity to act in multiple signaling pathways. This effect is a consequence of the same glucocorticoid hormones

by acting on the glucocorticoid receptors (GR) present in the hypothalamus and the pituitary gland and also in the cytoplasm of most cells in the body [3].

The protein structure encoded by the GR gene belongs to the nuclear receptors family. Two GR isoforms exists, GR-α and GR-β, which are derived from alternative splicing of GR primary mRNA. GR-α mediates glucocorticoid action, whereas GR-β is unable to bind steroids. When GR-β is more expressed then GR-α, it acts as a dominant-negative inhibitor of GR-α transactivation activity [4]. When not stimulated, the GR is inactivated by integration in a complex of multiple proteins associated with the molecular chaperone-like proteins. When the GCs bind to its receptor, there is a dissociation of the complex and migration to the nucleus, where develops its function [5].

The glucocorticoid-receptor complex modulates, positively or negatively, the target genes transcription, depending on the co-activator or co-repressive proteins. These would be the direct genomic mechanisms [6]. Besides, the complex GCs-receptor interacts with transcription factors, such as AP-1 (activating protein-1 complex transcription factors) NFKB (nuclear factor kappa-B), Stat4, Stat5 and NF-1 and inhibits the transcriptional activation of genes normally regulated by these factors. They account for the major anti-inflammatory and immunosuppressive effects of glucocorticoids [7-10].

Because of the extensive range of clinical applications and number of patients treated with GC, these drugs still widely used in clinical medicine [11]. Nevertheless, it may present some limitations such as insulin-resistance/diabetes [12], loss/osteoporosis [13] and sarcopenia [14]. GCs may suppress osteoblast function, reduce bone mineral density as much as cause negative effects on muscle function and bone quality [15]. Although clinical treatment with GCs appears to be highly efficient, unfortunately up to 30% of patients fail to show an adequate response to corticosteroid therapy [16, 17].

Molecular Mechanisms of Corticosteroids Resistance

Several mechanisms associated with corticosteroid resistance (CRS) are mainly related to abnormalities in the intracellular signaling pathway, such as defects in the corticosteroid receptor/protein complex and reduction in the ability of the CR to bind to DNA. The list continues with alterations in the affinity of the ligand for CR and in the function of CR-α, as well as the balance of the CR-α and CR-β cellular expression or the increase expression of inflammatory transcription factors, such as NFκB and AP1 [16].

The expression of the corticosteroid receptor isoforms

The effects of corticosteroids are mediated by the CR-α receptor, while CR-β has been shown by some investigators to have a dominant inhibitory role. CR-β inhibits CR-α mediated transactivation of target genes, the increased expression of CR-β in inflammatory cells might be a critical mechanism for conferring CSR [18]. Alterations in the expression of the CR isoforms may potentially contribute to a state of reduced corticosteroid responsiveness in patients with rheumatoid arthritis (RA). Failure of therapeutic doses of corticosteroids in RA related to IL-2 and IL-4 inhibition could therefore be consequence, at least in part, of the enhanced expression of CR-β in CSR RA patients [19].

Alterations in the activation of the CR-α following its binding to the corticosteroid resulting in either defective dimerization or transactivation of the CR-α/GC complex and therefore reduced corticosteroid responsiveness could be caused by polymorphic changes and/or over-expression of the Hsp90 gene [20].

Alterations in intracellular signaling mechanisms

Pro-inflammatory cytokines initiate signaling via pathways by NFκB, STAT, MAPK and AP-1 activation, modulated by corticosteroids. Corticosteroids suppress the expression of inflammatory genes regulated by these pro-inflammatory cytokines [21]. Enhanced cellular expression and/or defective cross-talk between the transcription factors could contribute to a state of increased corticosteroid resistance. Cells from glucocorticoid-resistant asthma patients have been shown to have enhanced AP-1 activity, this suggest that the ability of the GR to bind to glucocorticoid response elements and AP1 is altered in steroid-resistant patients or that increased levels of AP-1 prevent GR/DNA binding. This reduction on DNA binding was due to a decrease in the number of receptors available rather than an alteration in affinity for DNA [22, 23].

Perturbations of the cytokine milieu

Pro-inflammatory interleukin (IL)-2, IL-4, and IL-13, which have increased expression in bronchial biopsies of patients with glucocorticoid resistant asthma, induce a reduction in affinity of CR in inflammatory cells, such as T-lymphocytes and monocytes [24, 25].

The combination of IL-2 and IL-4 induces steroid resistance *in vitro* through activation of p38 mitogen activated protein (MAP) kinase, which phosphorylates GR and reduces corticosteroid binding affinity and steroid-induced nuclear translocation of CR. p38 MAPK inhibitors may have potential in reversing glucocorticoid insensitivity and reestablishing the beneficial effects of glucocorticoids in patients with severe asthma [21, 26].

Corticosteroids increase macrophage secretion of IL-10, and this may contribute to their anti-inflammatory actions. There is a reduction in T-lymphocyte secretion of IL-10 in patients with glucocorticoid resistant asthma, and this may contribute to the reduced responsiveness to the anti-inflammatory actions of corticosteroids [2].

IL17 in the Corticosteroids Resistance

High levels of IL-17 has been reported in chronic inflammatory disorders, during bacterial infections [27, 28], in synovial fluid from arthritis patients [29], and bronchoalveolar lavage fluid from asthmatic patients [30, 31]. The IL-17 plasma levels to >20 pg/mL has been considered an independent risk factor for severe asthma [32]. The severe clinical form of the asthma is often characterized by difficult to manage due the frequent steroid resistance [33].

Th17 is a subpopulations of T CD4+ cell lineage distinct from Th1 and Th2 cells, which differentiation is controlling by transcription factor ROR γt [34]. Th17 lymphocytes act by producing various pro- inflammatory cytokines, including IL-17A, IL-17F, IL-21 and IL-22 [35] promoting tissue inflammation and mobilizing innate immunity [35]. These cytokines have pro-inflammatory effects mediated by stimulation of a receptor complex consisting of IL-17 receptor A (IL-17RA) and IL-17 receptor C (IL-17RC) subunits, coupled to a signaling network leading to NFkB activation. Furthermore IL-17 induce granulopoiesis, neutrophil chemotaxis, and the antiapoptotic properties of G-CSF [36, 37], correlates with CXCL8 levels and the number of neutrophils in the sputum [38].

The role of the Th17 cell in the pathophysiology of severe asthma can be explained through the participation of NLRP3 (nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 activation) inflammasome and intracellular multiprotein complex that facilitates the autoactivation of the proinflammatory cysteine protease caspase-1 [39-43]. NRLP3 is activated by serum amyloid A (SAA) protein, which is produced upon exposure of airway epithelial cells to microbes and is detectable at high concentrations in both serum and induced sputum of asthmatic patients [44].

In this regard, allergens and other environmental stimulus can trigger Th17-mediated airway inflammation in asthmatics [45] that has been associated with overexpression of IL-17A and IL-17F in the lung tissue section [38]. The RORγt mRNA level in PBMCs from severe asthmatics is increased when compared with PBMCs from healthy controls [34]. Nanzer et al. showed that the blood T-cell IL-17A expression is increased 7-fold in patients with glucocorticoid resistance asthma compared glucocorticoid sensitive asthma, and the synthetic glucocorticoid dexamethasone did not inhibit IL-17A production [46]. Also, IL-17 is associated with neutrophilia in the lung tissues and blood of some asthmatic patients [47] (**Figure 1**).

Many studies have shown that the neutrophilic inflammation is correlated with decreased responsiveness following GC treatment [48, 49]. Studies that assessed the neutrophilic airway inflammation, AHR, and mucus metaplasia in mice demonstrated that when transfer Ova-specific Th17 cells to donor mice these components of allergic airway disease were not abrogated by GC treatment, in contrast whereas GCs were effective in inhibiting TH2-driven disease. In fact, GCs enhanced airway neutrophilia in Th17-transferred mice [30, 50]. The degree of neutrophilic inflammation correlates with decreased improvement in FEV1 (Forced expiratory volume in first second) following GC treatment.

Reduced active glucocorticoid receptor expression in airway neutrophils may be a mechanism that contributes to glucocorticoid resistance. Some studies showed that IL-17A and IL-17F are associated with overexpression of the inhibitory β-isoform of the GR (GR-β) in neutrophils and other airway and blood cells [51]. Such as previously showed, the stimulation of primary airway epithelial cells with Th17- associated cytokines increased GR-β expression correlated with a decreased response to steroid [52]. Another study showed that when PBMC is stimulated with IL-17A e IL-17F, GR-β mRNA expression was significantly upregulated [33]. These data suggest that Th17 cells are sufficient to promote many of the hallmark characteristics of asthma *in vivo* and this response is steroid insensitive (Figure 1). Taken together, these data suggest a role of IL-17 to recruit neutrophils to airways and, consequently, to mediate the steroid-resistant and severe asthma.

Th17 cells could antagonize the steroid response through GR-β independent mechanisms [53]. Study with bronchoalveolar lavage cells from severe asthmatic patients demonstrated that Th17 cells express higher levels of MEK1 (Mitogen-activated protein kinase phosphatase 1), responsible to active the pathways that antagonize the inhibitory action of glucocorticoids. The $CD4^+$ T cells from patients with moderate-to-severe asthma have increased expression of MEK1 and ERK and do not respond to dexamethasone treatment. Moreover, Glucocorticoid-Induced PBMC apoptosis is decreased by IL-17 stimulation and IL-17A stimulation can induces effector T cells to proliferate [34].

Nanzer et al. showed that calcitriol, the active form of vitamin D, significantly inhibited IL-17A production in a glucocorticoid-independent manner [54]. Epidemiologic data have suggested that vitamin D insufficiency is strongly associated with impaired respiratory health, risk of asthma, asthma severity, and refractoriness to current therapy [54]. Futhermore, treatment with calcitriol resulted in significant improvement in steroid responsiveness in these patients [54]. Conversely, calcitriol therapy also restores the impaired, corticosteroid-induced anti-inflammatory IL-10 response that characterizes patients with glucocorticoid resistant asthma. In addition to effects on IL-10 synthesis, calcitriol might reduce the induction of IL-17A through enhancement of a number of regulatory mechanisms, including the inhibitory CD39/adenosine pathway and regulatory T cells [54]. Thus, calcitriol is an attractive short-term adjunct to oral glucocorticoid therapy for severe exacerbations of disease in patients with glucocorticoid resistance asthma, particularly those already taking maintenance oral glucocorticoids [55].

An important aspect that can influence the severity of asthma as well the absence of response to treatment with corticosteroids is the interindividual genetic variability. Genetic polymorphisms of the GR gene (NR3C1) give rise to well-described rare glucocorticoid resistance syndromes [56]. Also, polymorphisms in the *IL17* gene may be also involved in resistance to glucocorticoids observed in asthmatic patients. However, to date, there is no study evaluating this correlation.

Single nucleotide polymorphisms (SNPs) are the most common variations in the genome and are responsible for phenotypic differences among individuals [57]. Polymorphisms can affect the structure or function of certain proteins if they are located in coding regions. Furthermore, polymorphism in introns and promoter regions may affect the gene transcription, splicing, stability and levels of mRNA translation [58]. Many SNPs in the *IL17* were identified and the most studied are located in the *IL17A* and *IL17F* genes. IL17A and IL17F are closely located in the 6p12.2 and have similar structures and can form a heterodimer IL17A/IL17F.

IL17F gene contains 7857 bp, consisting of three exons and

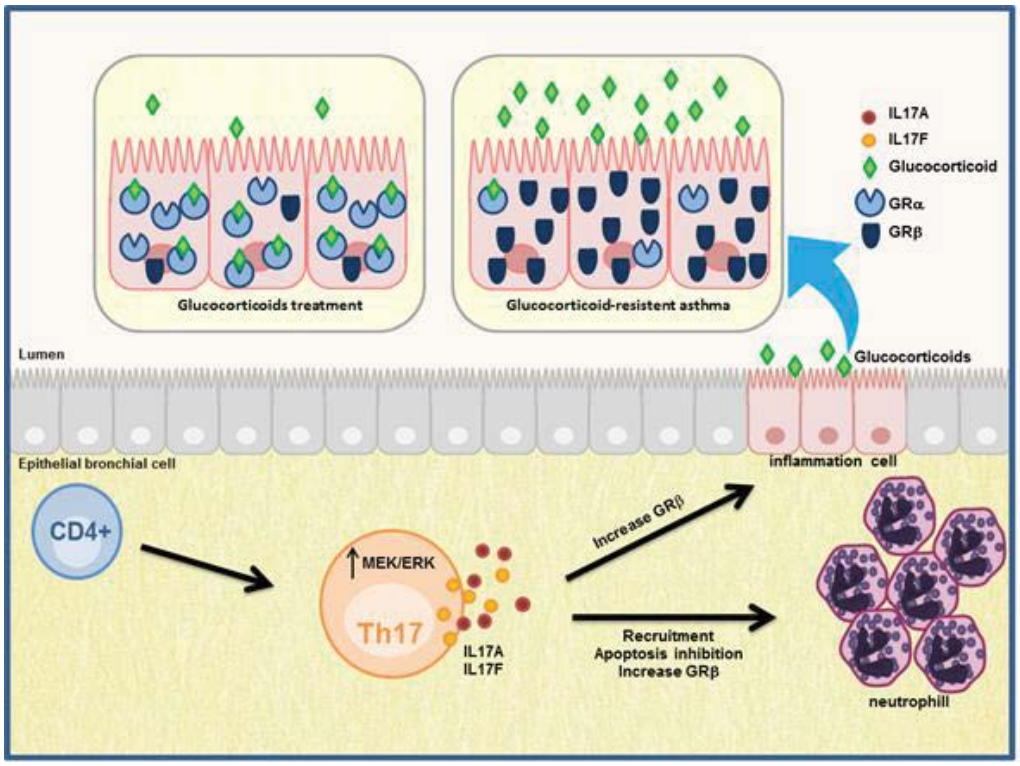

Figure 1 **Th17 regulation of neutrophilic inflammation and glucocorticoids response.**
TH17-cytokines, IL-17A and IL-17F, induce numerous pro-inflammatory chemokines and growth factors to promote neutrophil accumulation at the site of injury. In addition, TH17 cytokines up regulate GR-β (innate isoform of GR) and the down regulate GR-α (active isoform), resulting in no response of glucocorticoids treatment.

encodes a protein with 163 amino acids [59-61]. The most studied SNPs on *IL17F* are rs9382084, rs763780 and rs2397084 , which were previously described to be related to cancer [59-61], ulcerative colitis [60] and rheumatoid arthritis [62]. In addition, the SNP rs763780 is linked to reduced IL-17F levels in asthmatics patients [63]. Although it has not been evaluated yet, this SNP can be associated with sensitivity to glucocorticoid.

IL17A gene contains 4252 bp, three exons and encodes a 155 amino acid protein [64]. Several SNPs were described and the most studied SNPs are rs3819024, rs2275913, rs8193037 and rs3819025. Many association studies were conducted for different diseases, such as atherosclerosis [65], Graves' disease [66] , cervical cancer [59] and oral squamous cell cancer [60]. Studies that evaluated the association these polymorphisms with asthma show that the rs2275913 and rs2397084 was positively associated with asthma development in children [67, 68]. The rs3819024 was also associated with asthma in children [69]. The rs763780 was associated with the protection to asthma in a Japanese population [70]. However, the real impact of such SNPs the glucocorticoid response still unclear.

Conclusion

In conclusion, IL-17A and IL-17F have an important role to regulate neutrophilic inflammation in airway, which could interfere in glucocorticoids response. Polymorphisms in these genes can lead to protection or susceptibility to develop asthma. Additional studies involving gene expression are needed and may clarify the function of the *IL17* SNPs and its impact at a protein level as well as its correlation with glucocorticoid resistance.

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