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Perspective

Emerging roles and therapeutic implications of HDAC2 and IL-17A in steroid-resistant asthma

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ABSTRACT

Steroid resistance represents a major clinical problem in the treatment of severe asthma, and therefore a better understanding of its pathogenesis is warranted. Recent studies indicated that histone deacetylase 2 (HDAC2) and interleukin 17A (IL-17A) play important roles in severe asthma. HDAC2 activity is reduced in patients with severe asthma and smoking-induced asthma, perhaps accounting for the amplified expression of inflammatory genes, which is associated with increased acetylation of glucocorticoid receptors. Neutrophilic inflammation contributes to severe asthma and may be related to T helper (Th) 17 rather than Th2 cytokines. IL-17A levels are elevated in severe asthma and correlate with the presence of neutrophils. Restoring the activity of HDAC2 or targeting the Th17 signaling pathway is a potential therapeutic approach to reverse steroid insensitivity.

Introduction

Asthma is one of the most common chronic inflammatory diseases of the airways, affecting an estimated 300 million individuals worldwide. It is a serious global health problem affecting all age groups, with increasing prevalence in many developing countries and representing a rising burden for patients and the community.[1] Although steroids are the most effective anti-inflammatory therapy available for asthma, a subset of asthmatic patients who proceed to develop severe asthma with steroid resistance, frequent exacerbation, or decreased lung function still exists.[2] These patients suffer greater morbidity, face a higher risk of death from asthma, and impose a larger burden on health resources than other asthma patients.[1] Steroid resistance represents a major barrier to treating severe asthma, the mechanisms of which are still poorly understood. Several molecular mechanisms have now been identified to account for steroid insensitivity in severe asthma, including genetic susceptibility, defective glucocorticosteroid receptor (GR) binding and nuclear translocation, increased GRβ expression, transcription factor activation, abnormal histone acetylation, and decreased regulatory T cells.[3] Recent studies have shown that histone deacetylase-2 (HDAC2) and T helper 17 (Th17) cells play important roles in steroid-resistant asthma. Although eosinophils are the most characteristic inflammatory cell type present in mild to moderate asthma, evidence suggests that neutrophils play an important role in patients with severe asthma.[4] Neutrophilic airway inflammation appears to be resistant to steroids and may be related to Th17 rather than Th2 cytokines.[5] IL-17A is a proinflammatory cytokine mainly secreted from Th17 cells and is important for the induction of neutrophil recruitment and migration at sites of inflammation.[6] The increased expression of inflammatory genes in inflammatory lung diseases is regulated by the acetylation of core histones, whereas HDAC2 suppresses inflammatory gene expression.[7] An understanding of the roles of HDAC2 and Th17 cells is now providing important insights into the mechanisms of resistance to steroids in asthma and other inflammatory diseases such as chronic obstructive pulmonary disease (COPD). These concepts are also pointing the way towards the development of novel therapeutic approaches.

This review highlights the roles of HDAC2 and IL-17A in steroid-resistant asthma. We further discuss the novel therapeutic options targeting this resistance. The literature search was carried out only in English with the following index words: “asthma”, “neutrophilic inflammation”, “steroid resistance”, “histone deacetylase 2”, and “Th17 cells”. We also reviewed reference lists of the identified articles for relevant citations.

General characters of histone deacetylases

Histone deacetylases (HDACs) are divided into two major classes: class I (HDAC1–3 and 8) and class II (HDAC4–7, 9, and 10). Class I HDACs are predominantly localized in the nucleus, whereas class II HDACs shuttle into and out of the nucleus in response to intracellular signaling. HDACs interact with corepressor molecules, which aid HDACs in gene repression and might provide specificity by selecting genes which are regulated by individual HDACs.[8] In contrast, histone acetylation is a major modification that increases gene transcription and

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is regulated by histone acetyltransferases (HATs) and HDACs. HATs and HDACs are key enzymes involved in modifying the expression of inflammatory genes in airway diseases.[9] The role of other HDACs in inflammatory diseases is far less clear, but the regulation of inflammatory genes by HDAC2 appears to be of critical importance.

HDAC2 in steroid-resistant asthma

HDAC2 expression and activity are decreased in alveolar macrophages and PBMC in patients with severe asthma who are known to be resistant to the anti-inflammatory effects of steroids.[10,11] Further studies have demonstrated that HDAC2 activity was decreased in peripheral blood mononuclear cells (PBMC) from severe asthmatic patients compared with the level in normal subjects, and the decrease was correlated with impaired sensitivity to corticosteroid therapy *in vitro*.[10,12] Even more importantly, HDAC2 activity was negatively associated with the expression of inflammatory genes in alveolar macrophages.[13] A recent study showed that passive smoking impairs HDAC2 function via phosphoinositide-3 kinase (PI3K) signaling activation, which could contribute to corticosteroid-insensitive inflammation in children with severe asthma.[14]

The reasons for the reduction in HDAC2 activity are not yet clearly known. The recruitment of HDAC2 to activated inflammatory genes is a major mechanism of inflammatory gene repression by corticosteroids.[3] Activated glucocorticoid receptor (GR) interacts with coactivator complexes to induce HDACs, particularly HDAC2, to perform transrepression. Growing evidence shows that a reduction of HDAC2 activity amplifies the expression of inflammatory genes and is associated with increased acetylation of GR in severe asthma, as well as in COPD, which may be a major mechanism accounting for steroid resistance in these diseases.[15] S-nitrosylation of HDAC2 on Cys262 and Cys274 has been reported to affect its chromatin binding capacity and this may contribute to reduced GR function.[16]

Glucocorticoid receptor β (GRβ) may also contribute to steroid insensitivity by competing for the transcriptional coactivator molecules or by competing with GRα for binding to the glucocorticoid response element (GRE) site. Increased GRβ with resultant reduction in HDAC2 expression has been implicated in the pathogenesis of steroid resistance in severe asthma. However, a recent study by Butler et al.[17] has shown that GRβ messenger RNA (mRNA) is expressed at low levels in a minority of severe asthmatics and that HDAC2 expression is not downregulated in severe asthma. These findings do not support upregulated GRβ and resultant reduced HDAC expression as the principal mechanism underlying steroid insensitivity in severe asthma. The conflicting reports on GRβ may be explained in part by clathrin cross-reactivity with commercial antibodies.[17] Cigarette smoke downregulates HDAC2 activity by promoting its phosphorylation and and inducing proteasomal degradation in human macrophages and lung epithelial cells *in vitro* and in mouse lung *in vivo*, which may be a critical factor in the development of steroid insensitivity in some severe asthma patients who smoke cigarettes.[18] Oxidative stress also activates the PI3K pathway, which results in phosphorylation and inactivation of HDAC2.[19]

Collectively, these studies indicated that HDAC2 is necessary for corticosteroid-associated anti-inflammation, implying that steroid-resistant asthma is associated with HDAC2. However, the detailed molecular mechanisms involved need to be further investigated. Medicines that restore HDAC2 activity and expression might alleviate GC insensitivity.

General characters of Th17 cells

For a long time, CD4$^+$ T cells were classified as type 1 T helper (Th1) and type 2 Th (Th2) based on their cytokine expression profile. Classically, Th1 cells produce interferon (IFN)-γ, whereas Th2 cells produce IL-4, IL-5, IL-9, and IL-13 accompanied by eosinophil recruitment to the airways, which have been shown to be critical for the pathogenesis of allergic inflammation.[20] However, the T helper cell population was clearly not limited to these two subsets. In recent years, a novel subset of CD4$^+$ effector T cells, Th17 cells, has been demonstrated in humans and mice. Th17 cells differentiate when naïve T cells are triggered by transforming growth factor (TGF)-β, IL-6, IL-1β, IL-21, and IL-23 during stimulation by a cognate antigen. Other T-cell lineages and their associated cytokines such as IFN-γ and IL-4 also promote the development of Th17 cells.[21,22] Differentiated Th17 cells selectively secrete IL-17A, IL-17F, IL-21, and IL-22.[23] IL-17A and IL-17F are members of the IL-17 cytokine family that share common receptor subunits, IL-17 receptor A (IL-17RA), and IL-17 receptor C (IL-17RC).[21] IL-17A has critical roles in the development of inflammation, tumors, and autoimmunity, and is also involved in the host defenses against bacterial and fungal infections, whereas IL-17F has a role mainly in mucosal host defense mechanisms.[6] IL-17A and IL-17F are predominantly expressed by CD4$^+$ T helper 17 (Th17) cells, but they can be produced by other lymphocytes as well.[24] Notably, IL-25 (IL-17E) is unique in that, unlike other family members, it augments Th2 cell immune response.[25]

Th17 cells in steroid-resistant asthma

The Th1/Th2 paradigm has provided important insights into the pathogenesis of asthma. However, the pathological characteristics of patients with severe asthma failed to be completely explained by either classic Th1 or Th2 cells. In addition to eosinophilic inflammation, increased neutrophil levels have been found in patients with steroid-resistant asthma compared with the levels in controls. Neutrophilic inflammation may contribute to severe asthma and may be related to Th17 rather than Th2 cytokines.[4,26] Elevated levels of IL-17 mRNA and protein were found in the serum,[27] peripheral mononuclear cells, bronchoalveolar lavage fluid (BALF), sputum,[28,29] and bronchial tissues[30] from asthmatic patients. Increased IL-17A and IL-17F levels have also been reported to be positively correlated with airway hyperresponsiveness (AHR) and disease severity.[31] Furthermore, increased IL-17A has been correlated with increased neutrophilic inflammation.[32] Similarly, *in vitro* studies demonstrated that IL-17A reduced HDAC activity in a bronchial epithelial cell line, and appeared to be involved in IL-17A-induced GC insensitivity[14] (Fig. 1). Overexpression of HDAC2 reversed IL-17A-induced GC insensitivity, suggesting a possible molecular mechanism behind this insensitivity.[14]

Notably, our previous study revealed that the expression of retinoid-related orphan nuclear receptor γt (RORγt) was significantly increased in human bronchial epithelium (HBE) cells exposed to house dust mite (HDM) when HDAC2 was knocked down.[33] Manel et al[34] demonstrated that the overexpression of RORγt significantly induced IL-17A expression, and vice versa. RORγt is a key transcription factor that orchestrates IL-17A expression.[35] More specifically, RORγt plays an important role in the differentiation from naïve CD4$^+$ T cells to Th17 cells, in which HDAC2 is involved. Singh et al[36] showed that HDAC2 interacts with IL-17A promoter and inhibits IL-17A transcription through SUMOylation of RORγt. Taken together, these findings support a protective role of HDAC2 in HDM-induced airway inflammation by suppressing IL-17A production via inhibiting RORγt transcriptional activity. They might also suggest that the activation of HDAC2 and/or inhibition of IL-17A production could prevent the development of allergic airway inflammation (Fig. 2). However, further studies are needed to determine the interaction between HDAC2 and IL-17A signaling pathways, and the identification of the RORγt/HDAC2 axis that controls IL-17A expression may provide new ideas for developing novel therapeutic approaches.

Therapeutic implications

Steroid resistance in severe asthma is a major clinical barrier that cannot be overcome by high-dose inhaled cortisteroid (ICS) or oral corticosteroids. Restoring the activity of HDAC2 or targeting the Th17 sig-

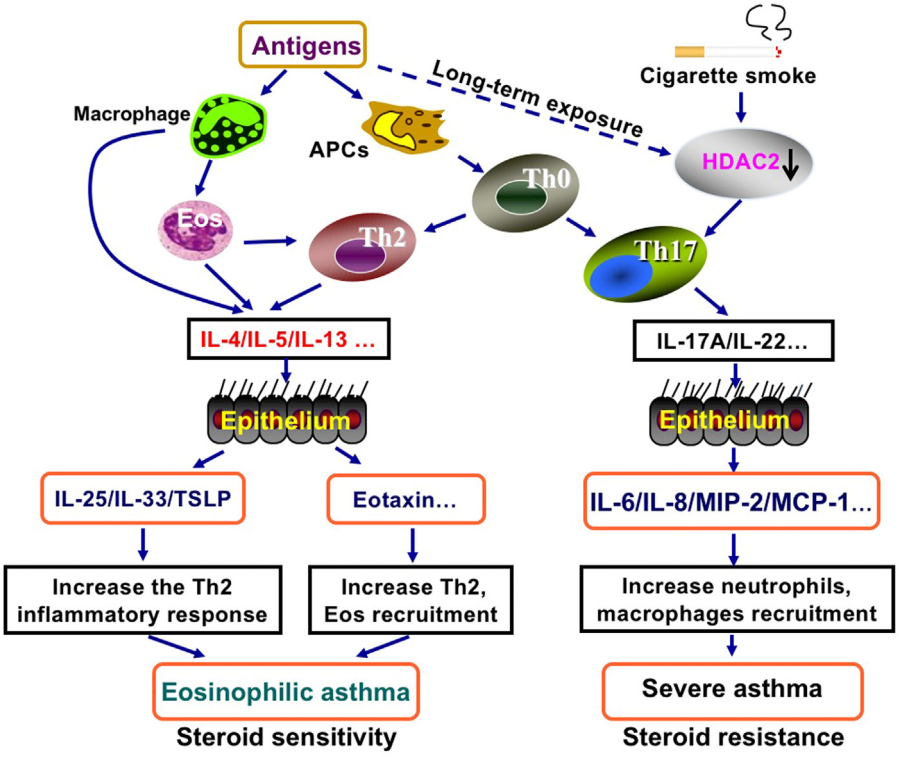

Fig. 1. Proposed mechanism of steroid resistance in severe asthma. Th17 cells differentiate when naïve T cells are triggered by cigarette smoke or repeated antigen exposure. Th17-related cytokines (e.g., IL-17A, IL-22) and oxidative stress impair the activity of HDAC2 and increase neutrophil recruitment. This amplifies the inflammatory response to NF-κB activation, but also reduces the anti-inflammatory effect of corticosteroids. APC: antigen-presenting cell; Eos: eosinophil; HDAC2: histone deacetylase 2; IL: Interleukin; MCP-1: monocyte chemoattractant protein-1; MIP-2: macrophage inflammatory protein 2; NF-κB: Nuclear factor-κB; Th2: T helper 2; Th17: T helper 17; TSLP: thymic stromal lymphopoietin.

naling pathway, which facilitates the suppression of proinflammatory cytokines by corticosteroid, is a potential therapeutic approach to reverse steroid insensitivity. Antioxidants, which inhibit steroid-resistant airway inflammation, are another potential treatment for overcoming steroid resistance.

Theophylline is an old drug that has been used in the treatment of airway disease for many years. Low concentrations (10^{-6} mol/L) of theophylline have been shown to activate HDAC and reverse corticosteroid sensitivity.[37] Such low concentrations were also shown to have inhibitory effects on phosphoinositide metabolism and the oxidant-activated PI3K pathway.[38] Bin et al[39] showed that thephylline inhibits cigarette smoke (CS)-induced IL-8 and tumor necrosis factor-α (TNF-α) levels elevation by enhancing HDAC2 expression and decreasing nuclear factor-κBp65 (NF-κBp65) activation.

Low-dose macrolides such as azithromycin and erythromycin have also been shown to restore HDAC2 activity. Maintenance treatment with low-dose azithromycin (500 mg three times a week) in randomized placebo-controlled trials (RCTs) has been reported to achieve a significant reduction in the rate of exacerbation in patients with neutrophilic severe asthma.[40,41]

Statins are lipid-lowering agents that also have anti-inflammatory and immunomodulatory properties, which could benefit asthma patients. Previous studies have reported the use of statins in the treatment of asthma, but inconsistent results have been described. Some recent systematic reviews include a meta-analysis showing that statins may reduce airway inflammation in asthmatics, without having a significant effect on lung function, asthma control, or steroid-sparing.[42,43] However, a retrospective, cross-sectional study on patients with severe asthma showed that statin users had better asthma symptom control than non-users.[44]

Curcumin, a dietary polyphenol, also reverses steroid resistance induced by either cigarette smoke extract (CSE) or oxidative stress in human monocytes. Thus, curcumin may have the potential to reverse steroid insensitivity in asthma and COPD.[45] Several nonselective HDAC inhibitors, such as trichostatin A and valproate acid, have potent anti-asthmatic activity, but their molecular mechanisms remain largely unresolved. Additionally, many novel drugs that are currently being investigated for the treatment of asthma may find a therapeutic role in reversing the steroid insensitivity in patients with severe asthma and smokers with asthma.

Several monoclonal antibodies against IL-17A or IL-17RA are currently in clinical trials for asthma. A clinical trial (NCT01478360) is underway to investigate the efficacy and safety of AIN457 (secukinumab) in patients with uncontrolled asthma, in which favorable results are expected.[46,47] In addition, a phase II clinical trial was recently completed for the anti-IL-17RA monoclonal antibody AMG-827 (brodalumab).[48,49] It showed the benefits of brodalumab in improving bronchodilator reversibility, despite failing to achieve clinical improvements in Asthma Quality Control (AQC) score. Because IL-1β, IL-23, and IL-6 are crucial to the development of Th17 cells, blocking these cytokines may also be a therapeutic target for steroid-insensitive asthma.[50] Clinical trials of agents that block IL-1β, IL-23, or IL-6 have been conducted in patients with Th17-related diseases such as rheumatoid arthritis and multiple sclerosis. However, more studies are needed to determine the potential efficacy of targeting IL-17RA signaling in the treatment of steroid-resistance asthma.

Future directions for research

Steroid-resistant asthma is resistant to current therapies and consumes 50–60% of healthcare costs attributed to asthma.[51] However, the mechanisms underlying the steroid resistance in severe asthma are not completely understood. Epigenetic mechanisms such as histone acetylation/methylation and DNA methylation have been reported as key

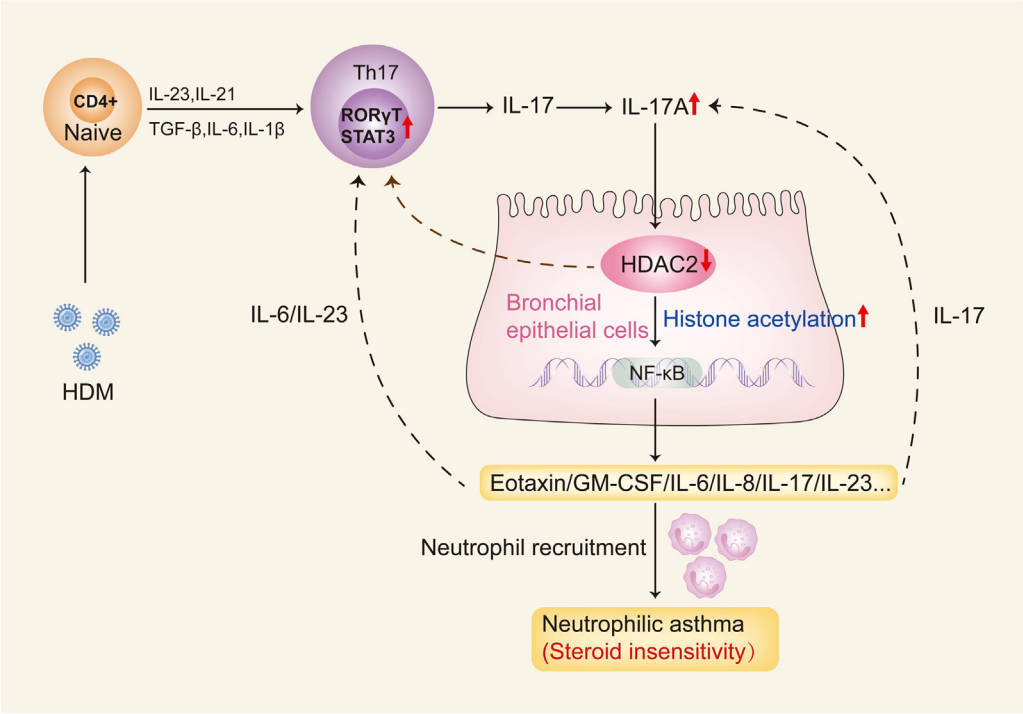

Fig. 2. Schematic diagram on the role of the interplay between HDAC2 and IL-17A in HDM-induced allergic inflammation. When naïve T cells are triggered by TGF-β, IL-6, IL-1β, IL-21, and IL-23 under HDM stimulation, Th17 cells differentiate and IL-17A expression is subsequently initiated. Among these, the differentiation of Th17 cells secreting IL-17A requires expression of the transcription factors RORγt and STAT3. HDM exposure significantly reduces HDAC2 expression in HBE cells and co-stimulation with IL-17A further reduces HDAC2 activity in the bronchial epithelial cell line. When HDAC2 is reduced, the expression of RORγT increases, and the binding of RORγT to the IL-17A promoter is facilitated, which further reduces HDAC2 expression, thus creating a vicious cycle that ultimately leads to a diminished protective function of HDAC2 in airway inflammation as well as increased neutrophil recruitment, amplifying the inflammatory response to NF-κB activation and causing neutrophilic asthma. GM-CSF: granulocyte-macrophage colony-stimulating factor; HDAC2: histone deacetylase 2; HDM: house dust mite; HBE cell: human bronchial epithelium cell; IL: Interleukin; NF-κB: nuclear factor κB; TGF-β: transforming growth factor-β; RORγT: retinoid-related orphan nuclear receptor γt; STAT3: signal transducer and activator of transcription 3; Th17: T helper 17.

players in severe asthma.[52] Previous studies found that HDAC2 expression was downregulated in steroid-resistant asthma.[12] The significant interaction between HDAC2 and IL-17A creates a vicious cycle that leads to the exacerbation of asthma. However, the roles of HDAC2 and Th17 cells in steroid-resistant asthma remain largely unknown and some research questions on this issue need to be addressed. First, although airway neutrophilia and activity of the Th17/IL-17 axis are readily observed in a subset of steroid-insensitive asthmatics, whether they play causative roles in the disease pathogenesis remains to be determined. Second, HDAC2 and Th17 cells play important roles in alveolar macrophages of steroid-resistant asthma. However, their roles in human bronchial epithelial cells are still largely unknown. The specific molecular mechanisms of the interaction between HDAC2 and IL-17A also require further investigation.Third, low-dose theophylline and macrolide have been shown to restore HDAC2 activity, but the molecular mechanisms behind this remain to be determined. Lastly, the deleterious effects of smoking on airway inflammation, lung function, and corticosteroid responsiveness in asthma are well known, but whether the effect of smoking cessation on corticosteroid responsiveness is mediated by HDAC2 and IL-17A in severe asthma remains largely unknown.

In conclusion, corticosteroids are widely used in the treatment of asthma, despite the lack of a clinical benefit in patients with severe asthma. Several mechanisms behind the emergence of corticosteroid resistance have been postulated. In patients with steroid-resistant asthma, there is a reduction in HDAC2 expression, which may be due to oxidative stress. Th17 cells are important for the development of neutrophilic airway inflammation and appear to be steroid-resistant. Currently, only a few selective drugs are available for corticosteroid unresponsiveness in severe asthma. Understanding the mechanisms of steroid insensitivity may lead to novel therapeutic approaches for the treatment of severe asthma.

Conflicts of interest

The authors declare that they have no competing interests.

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