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MINI REVIEW

Targeted inhibition of histone deacetylase 6 in inflammatory diseases

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Abstract

Targeting epigenetic modification of gene expression represents a promising new approach under investigation for the treatment of inflammatory diseases. Accumulating evidence suggests that epigenetic mechanisms, such as histone modification, play a crucial role in a number of inflammatory diseases, including rheumatoid arthritis, asthma, and contact hypersensitivity. Consistent with this role, histone deacetylase (HDAC) inhibitors have shown efficacy in the treatment of inflammatory diseases. In particular, selective inhibitors of HDAC6, a cytoplasmic member of the HDAC family that contains two deacetylase domains, are under investigation as a potential treatment strategy for inflammatory diseases due to their ability to regulate inflammatory cells and cytokines. Here, we review recent findings highlighting the critical roles of HDAC6 in a variety of inflammatory diseases, and discuss the therapeutic potential of HDAC6 inhibitors in these settings.

Introduction

Inflammation is a common and important physiological process that is activated in response to infections, such as bacteria and virus, of the body surface and organs of body surfaces, and organs in mammals.[1–3] Many common lesions and frequently occurring diseases, such as boils, carbuncles, pneumonia, hepatitis, and nephritis, are associated with inflammation.[4–8] Thus, the molecular pathways associated with inflammation are under active investigation to identify new therapeutic targets for treatment of a variety of illnesses.

Histone deacetylase 6 (HDAC6) is a unique member of the HDAC family that has been shown to be involved in multiple cellular processes, including cell migration and intracellular transport.[9–11] Recent studies also showed the vital role of HDAC6 in the innate immune response to intracellular bacterial infections through Toll-like receptor-mediated signaling.[12] Improper activation of HDAC6 has been observed in a variety of diseases, including cancer and neurodegenerative disorders, and small molecule drugs targeting HDAC6 are under active investigation as therapeutic agents.[13–18] Recent studies have implicated HDAC6 in the pathogenesis of a variety of inflammatory diseases, and HDAC6 inhibition has been suggested as a potential therapeutic strategy.[19–23] In this review, we analyze the molecular mechanisms and pathological functions of HDAC6 in inflammation, and discuss the potential value of HDAC6 as a therapeutic target in the setting of inflammatory diseases.

Inflammation and inflammatory disorders

The immune system is composed of immune organs and immune cells. When the body is exposed to damage from an external source, such as bacteria and virus, immune responses are activated to protect the body from further damage.[24–31] Among these responses, inflammatory reactions are very common, and manifest physically as redness, swelling, and accompanying fever and pain. These manifestations primarily arise from chemotactic infiltration of inflammatory cells into the site of damage.[32] For example, activated inflammatory cells stimulate relaxation of vascular endothelial cells, thereby increasing the permeability of the vascular endothelium, and finally resulting in tissue

swelling through the release of inflammatory cytokines, such as interleukin (IL-6, serotonin, and tumor necrosis factor (TNF)-α.[33]

At the initiation of the inflammatory response, stimulation of dendritic cells and macrophages by foreign antigens leads to secretion of a series of pro-inflammatory cytokines.[34] At the same time, the pathogen itself may also produce metabolites that accumulate and spread to the surrounding tissues, forming a concentration gradient centered around the site of infection.[35] Inflammatory cells, such as monocytes and neutrophil cells, recognize and respond to these chemotactic signals, attaching to the endothelial cells from rolling to firm adhesion, and finally moving towards the site of inflammation with the help and guidance of chemokines (Fig 1).[36]

Inflammation is a defensive response to a lesion present in living tissue with a vascular system.[37] Generally, inflammation serves a beneficial role as the body's automatic defense system; however, dysregulated or excessive inflammation can be harmful, such as in the case of autoimmune diseases. Inflammatory diseases include a wide range of disorders that underlie the majority of human diseases. Examples of pathological immune system activation include allergic reactions, inflammatory bowel disease (IBD), synovitis, contact hypersensitivity, otitis, pelvic inflammatory disease, rheumatoid arthritis (RA), asthma, and chronic obstructive pulmonary disease (COPD).[38,39]

Structure and function of HDAC6

HDAC6 is a cytoplasmic member of the HDAC family that is composed of 1215 amino acid residues encoded by the X-linked gene, *hdac6*.[40] In terms of its domain organization, the N-terminus is characterized by an arginine and lysine-enriched nuclear localization signal, which is followed by a leucine-enriched nuclear export signal that facilitates export of newly synthesized HDAC6 into the cytoplasm. Two deacetylase domains (DD1 and DD2) serve as the center of catalytic activity and are followed by a tetradecapeptide serine glutamic acid repeat sequence (SE14) that acts as a cytoplasmic retention signal.[41] A ubiquitin-binding domain (BUZ) present at the C-terminus interacts with misfolded ubiquitinated proteins and is involved in protein degradation (Fig 2a).[42]

Among the 18 members of the HDAC family, HDAC6 belongs to the HDAC IIb family, whose members predominantly localize to the cytoplasm.[43] Unlike most other HDACs, HDAC6 primarily deacetylates non-histone proteins, including α-tubulin, cortactin, HSP90, and Prx1, thereby playing important roles in a variety of cellular processes, such as cell adhesion and migration, protein transport, immune synapse formation, and degradation of misfolded proteins.[9,10,44,45] Accumulating evidence also implicates HDAC6 in the regulation of inflammation and the immune response.[46]

HDAC6 regulates the duplication of HIV through modulating the deacetylation of Tat and thus inhibiting viral transactivation.[10,47] HDAC6 is also involved in Sendai virus infection through the deacetylation of β-catenin, which acts as a co-activator of IRF3-mediated transcription.[48] The role of HDAC6 in the adaptive $CD4^+$ T-cell response has been studied in several autoimmune and inflammatory situations, such as colitis and cardiac allograft rejection.[19,49] In the process of an innate immune response to fight against intracellular bacterial infections, HDAC6 participates in the indication of the pro-inflammatory transcriptional program through the Toll-like receptor pathway, which is triggered by sensing of cell-surface and endo-phagosomal bacteria.[12,34,50–53]

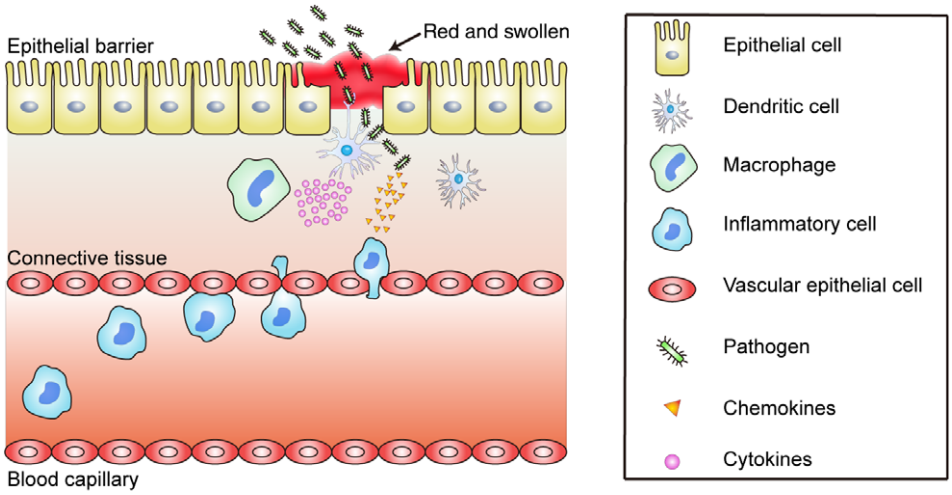

Figure 1 Schematic representation of inflammatory response. In the process of inflammatory response, foreign pathogens itself produce the chemokines, resulting in the infiltration of inflammatory cells and the activation of dendritic cells, thereby increasing the relaxation of vascular endothelial cells and the production of inflammatory cytokines, finally leading to tissue swelling, redness, and accompanying fever and pain.

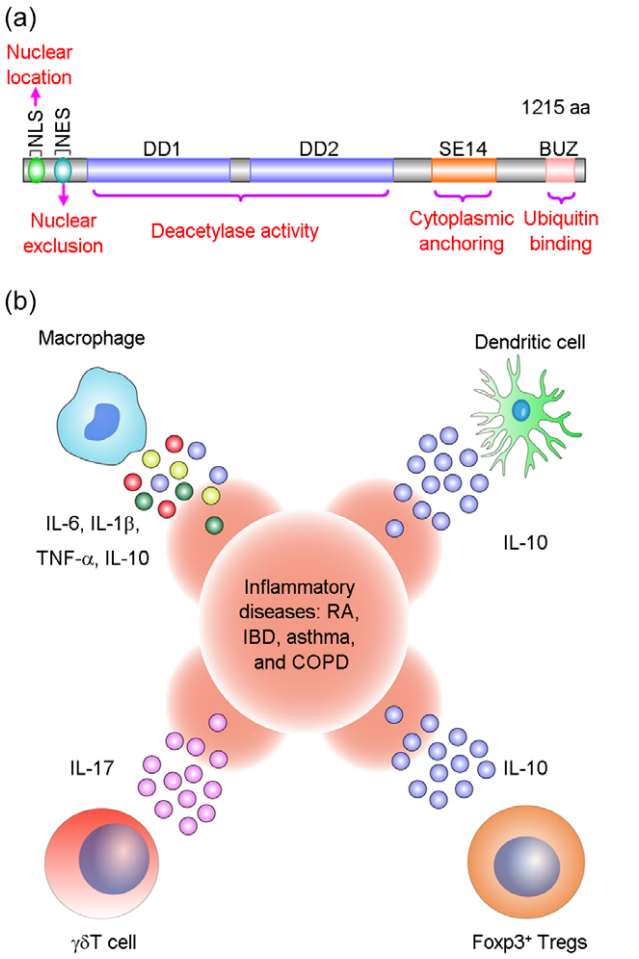

Figure 2 The structure of histone deacetylase (HDAC)6 and its pathological function in inflammation. (**a**) The schematic structure of HDAC6. (**b**) The role of HDAC6 in the regulation of inflammatory cells (macrophage, dendritic cell, γδT cell, Foxp3$^+$ regulatory t cells [Tregs]) and cytokines (interleukin [IL]-6, IL-1β, tumor necrosis factor [TNF]-α, IL-17, IL-10), and the targeted inhibition of HDAC6 in inflammatory disorders, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, and chronic obstructive pulmonary disease (COPD).

Regulation of inflammatory cytokines by HDAC6

HDAC6 significantly impacts the production of inflammatory cytokines, including both pro-inflammatory cytokines (IL-6, IL-1β, TNF-α, IL-17) and anti-inflammatory cytokines (IL-10; Fig 2b). Inhibition of HDAC6 has been shown to downregulate the production of IL-6, IL-1β, and TNF-α in several mouse models of inflammatory disease, such as a breast silicone implant-induced mouse model of the immune response, a Freund's complete adjuvant-induced mouse model of inflammation, and a collagen antibody-induced arthritis mouse model of synovial inflammation and joint destruction. In contrast, HDAC6 deficiency has been shown to increase expression of IL-17.[54] However, the effects of HDAC6 on the production of the anti-inflammatory cytokine, IL-10, remain controversial. Two reports show that HDAC6 inhibition promotes IL-10 production, one of the studies shows that HDAC6 deficiency leads to hyper-induction of IL-10 through modulation of microtubule acetylation, and another also found the HDAC6 inhibitor in the silicone-triggered immune response. However, two other reports demonstrate that disruption of HDAC6 results in diminished production of IL-10 in macrophages and dendritic cells. The investigators attributed this effect to the role of HDAC6 in a complex that also contained the transcription factor, STAT3, or another member of the HDAC family, HDAC11. Thus, the precise roles of HDAC6 in the regulation of IL-10 remain unclear and may vary by cell type and setting.

Regulation of inflammatory cells by HDAC6

Inflammatory cells play a vital role in the inflammatory response by infiltrating into the inflammatory site and releasing inflammatory cytokines, and HDAC6 has been implicated in the regulation of these cells (Fig 2b). For example, disruption of HDAC6 results in induction of inflammatory antigen-presenting cells, which are critical for the induction of T-cell activation and T-cell tolerance.[55,56] Furthermore, in models of autoimmunity and inflammation, depletion of HDAC6 promotes the suppressive activity of Foxp3$^+$ regulatory T cells.[19] Foxp3$^+$ regulatory T cells play a vital role in immune homeostasis, and defects in either their numbers or function can result in autoimmunity. Suppression of HDAC6 deacetylase activity through targeted inhibition has been shown to upregulate the population of γδ T cells, which are responsible for the production of the pro-inflammatory cytokine, IL-17, in the innate immune response. Suppression of HDAC6 activity also reduces lipopolysaccharide-induced macrophage activation and production of pro-inflammatory cytokines.[57] Together, these studies suggest that HDAC6 activity regulates a wide array of inflammatory cell types.

Potential of HDAC6 inhibitors as treatments for inflammatory diseases

Given the fact that inflammation impacts a wide range of organs, it is not surprising that inflammatory disorders include a variety of diseases that affect multiple organs.[58–61] As a result of its roles in the regulation of inflammation, HDAC6 inhibition might be an effective treatment in a variety of inflammatory diseases, including RA, IBD,

asthma, and COPD (Fig 2b). Importantly, unlike other HDAC inhibitors, selective HDAC6 inhibitors have no serious side-effects, as evidenced by data from trials of these compounds in various disease settings, including neurodegenerative disorders and cancer. Below, we detail the pre-clinical and clinical data supporting the use of HDAC6 inhibitors in the treatment of inflammatory diseases in mammals.

Rheumatoid arthritis

RA is a chronic inflammatory disease that is characterized by inflammatory synovitis, and proliferation and invasion of synovial tissues, leading to the destruction of bone and cartilage.[62] Treatment with small molecular inhibitors of HDAC6 has been shown to reduce the production of the pro-inflammatory cytokines, IL-6, TNF-α, and IL-1β, and successfully ameliorate synovial inflammation, suggesting a potential role for these drugs in the treatment of RA. For example, in the collagen-induced arthritis mouse models and in RA patients, the HDAC6-selective inhibitor, CKD-L, inhibits IL-6, TNF-α, and IL-1β expression, and increases IL-10 production, resulting in a decrease in the arthritis score and inhibition of the proliferation of effector T cells.[63] Similarly, tubastatin A, another HDAC6 inhibitor, has been shown to successfully ameliorate synovial inflammation and protect against joint destruction in collagen antibody-induced arthritis mice. These results suggest that HDAC6-selective inhibitors may have anti-inflammatory effects in RA (Table 1).

Inflammatory bowel disease

IBD is an increasingly common chronic inflammatory disorder of the intestinal tract. Chronic active disease is associated with a high burden of morbidity and a marked impact on quality of life.[28,64] Clinical strategies for treatment of IBD include anti-inflammatory drugs, antibiotics, and biologics that are often not effective and can produce adverse effects.[65,66] Studies in knockout mice and using small molecule inhibitors show that HDAC6 plays an important role in the progression of IBD. For example, HDAC6-selective inhibitors, such as BML-281 and LTB2, effectively alleviate dextran sulfate sodium-induced colitis in mice. In mouse models of acute dextran sulfate sodium-induced colitis, treatment with BML-281 protects against colonic inflammation, and prevents activation and colon infiltration of inflammatory neutrophils, a driver of disease pathology.[67] LTB2 also exerts a significant protective effect in dextran sulfate sodium-induced colitis, and LTB2 treatment was associated with diminished rectal bleeding and diarrhea, and longer colon lengths in mice.[68] Furthermore, potassium acetate, which serves as a decoy substrate for HDAC6, reduces cytotoxicity and inflammation in a toxin A-induced mouse enteritis model.[69] These results highlight the potential clinical role of HDAC6 inhibition in prevention and treatment of colonic inflammation and IBD in humans.

Table 1 HDAC6-selective inhibitors potential to inflammatory diseases

HDAC6-selective inhibitor	Animal model or patient	Inflammatory diseases
CKD-L, Tubastatin A	Collagen-induced arthritis mouse models, rheumatoid arthritis patients	Rheumatoid arthritis
BML-281, LTB2	Dextran sulfate sodium-induced colitis mouse model	Inflammatory bowel disease
Tubastatin A HCl, Tubastatin A	Chronic allergic airway disease mouse model	Airway inflammation

Airway inflammation

Airway inflammation underlies many chronic respiratory diseases, such as asthma and COPD. Asthma is a chronic respiratory disorder that involves aberrant airway inflammation, airway remodeling, and airway hyperresponsiveness. Long-term asthma damage leads to bronchial smooth muscle thickness and subepithelial fibrosis. Current treatment strategies for asthma primarily consist of corticosteroids and long-acting β2-agonists. However, these agents have no substantive effects on airway remodeling.[70] Tubastatin A HCl, a selective HDAC6 inhibitor, has been shown to effectively alleviate airway inflammation, airway remodeling, and airway hyperresponsiveness in a mouse model of chronic allergic airway disease, suggesting a potential role for HDAC6 inhibition in asthma treatment.[71]

COPD is the fourth leading cause of morbidity and mortality worldwide. In the case of COPD, the aberrant airway inflammation is mainly caused by chronic exposure to cigarette smoke. COPD is also characterized by epithelial cell dysfunction, ciliary shortening, and disruption of mucociliary clearance. Current therapies for COPD are insufficient and seem to have no effect on exacerbations. In contrast, pharmacological inhibition of HDAC6 with tubastatin A significantly inhibits cigarette smoke-induced airway dysfunction, and thereby has the potential to be an effective therapeutic strategy for COPD.[72]

Perspectives

A compelling body of evidence has established HDAC6 as a critical regulator of inflammation and a potential clinical

target for treatment of a number of inflammatory diseases. With roles in mediating the production of inflammatory cytokines and regulating the action of inflammatory cells, HDAC6 exerts complicated effects during inflammation. As a result, numerous questions remain regarding the precise functions of HDAC6 in inflammation. For example, HDAC6 harbors two functional deacetylase catalytic domains, as well as a ubiquitin-binding zinc finger domain, suggesting that it functions at the crossroads of at least two cellular signaling systems: protein acetylation and ubiquitination.[42,73] It will be particularly interesting to define whether cross-talk occurs between the deacetylase and ubiquitin-binding roles of HDAC6 in the context of inflammation and inflammatory disease.

We must also note that unlike most other members of the HDAC family, HDAC6 is unique in that it mainly deacetylates non-histone substrates. A large number of proteins have been identified as HDAC6 substrates, including α-tubulin, cortactin, peroxiredoxin, Hsp90, and Tat. These substrates implicate HDAC6 in diverse cellular processes, such as cell motility and signaling, among others. HDAC6 substrates have also been identified as key players in the progression of inflammation and the development of inflammatory disease. For example, HDAC6 inhibition prevents the progression of murine colitis and allograft injection through regulation of HSP90. In a different model, HDAC6 inhibition enhances anti-inflammatory activity and reduces lipopolysaccharide toxicity by elevating microtubule acetylation and stabilizing microtubules. In the viral infection, which is more intractable than bacterial infection, HDAC6 functions through deacetylation of Tat or β-catenin.[74–76] Therefore, it will be interesting in the future studies to determine whether other substrates also contribute to the roles of HDAC6 in inflammation and inflammatory disease.

Over the past decades, HDAC6 has become a particularly attractive target for the development of drugs to treat a wide range of diseases.[14,15] More importantly, small-molecule compounds targeting HDAC6 have not been associated with serious toxicities. For example, the HDAC6-selective inhibitor, tubastatin A, has been investigated in the treatment of neurodegenerative disorders, cancer, and COPD, and has demonstrated no obvious adverse reactions. Another HDAC6-selective inhibitor, CAY10603, has showed a crucial role in the regulation of sperm flagellar length, and a potential treatment for fertility.[57,77–79] However, some HDAC6 inhibitors do not display high selectivity and may inhibit related HDACs. Thus, further research is required to identify novel effective HDAC6 inhibitors with higher selectivity. Overall, the positive safety profile of HDAC6 inhibitors and evidence implicating HDAC6 in a number of inflammatory diseases provide strong support for the development of selective HDAC inhibitors in the treatment of inflammatory disease.

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Disclosure

No authors report any conflict of interest.

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