Joint Bone Spine 77 (2010) 395–398

Available online at ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Review

Histone deacetylase inhibitors: New treatment options for inflammatory joint disease?☆

Éric Toussirot[a,*,b,c], Kashif Aziz Khan[b,d], Ewa Bertolini[a], Daniel Wendling[a,b], Georges Herbein[b,d]

[a] *Service de rhumatologie, CHU hôpital Minjoz, pôle pathologies aiguës et chroniques, transplantation, éducation (Pacte), boulevard A.- Fleming, 25000 Besançon, France*
[b] *Équipe d'accueil 4266 « agents pathogènes et inflammation », IFR133, université de Franche-Comté, 25000 Besançon, France*
[c] *CIC-biothérapie 506, CHU hôpital St-Jacques, 25000 Besançon, France*
[d] *Laboratoire de virologie, CHU hôpital St-Jacques, pôle gestion des risques infectieux et sanitaires (Geris), 25000 Besançon, France*

ARTICLE INFO

Article history:
Accepted 16 January 2010
Available online 21 August 2010

Keywords:
Histone acetylase
Histone deacetylase inhibitors
Gene regulation

ABSTRACT

Histone deacetylase inhibitors (HDIs) are a new class of compounds that are being developed for the treatment of malignancies such as cutaneous T-cell lymphoma. HDIs inhibit the removal of acetyl groups from histones. The histone acetylation process is dependent on two enzymes, histone acetyl transferase (HAT) and histone deacetylase (HDAC), and regulates the expression of genes, including those encoding cell survival or apoptosis. In addition to regulating cell growth, HDIs exert anti-inflammatory effects by controlling the production of anti-inflammatory cytokines; modulating the function of cells such as T cells, monocytes-macrophages, chondrocytes, and osteoclasts; and modulating angiogenesis. In several animal models of arthritis, HDIs improve the clinical manifestations and prevent damage to the bone and cartilage. In humans, the only relevant data available so far come from studies of HAT and HDAC expression in the synovial membrane of patients with rheumatoid arthritis. HDIs may hold promise for the treatment of inflammatory joint disease.

1. Introduction

The inflammatory response that characterizes chronic inflammatory joint diseases such as rheumatoid arthritis (RA) results from complex interactions between environmental insults, incompletely identified genetic factors, and various cells involved in innate and specific adaptive immunity. These cells are activated and recruited to the sites of active inflammation (the synovial membrane in RA), where they persist. Cell activation is due to the orchestrated effects of various cytokines, chemokines, growth factors, activation and costimulation pathways, and cell–cell interactions. New insights into the pathophysiology of RA and other chronic inflammatory joint diseases (ankylosing spondylitis and psoriatic arthritis) has led to the development of targeted therapies, which have been proved highly effective [1,2]. The intracellular signaling pathways that mediate inflammation are being characterized in increasing detail, and their contribution to the inflammatory response has been firmly established. These pathways, most notably the nuclear factor kappa B (NFκB) and JAK/STAT pathways, may hold promise as new treatment targets for controlling the inflammatory response [3].

Another approach to inflammation control involves regulating the transcription of genes that encode proinflammatory cytokines or affect transcription factors. Treatment strategies targeting one or more genes involved in regulating the inflammation pathways are being developed. These strategies rely on pharmacological inhibitors, small interfering RNAs, or gene therapy [4].

Histone deacetylase inhibitors (HDIs) are a new class of compounds that are being actively developed for the treatment of malignancies [5]. HDIs exert anti-inflammatory effects and may therefore hold promise for the treatment of chronic inflammatory joint diseases such as RA [6].

2. Histone acetyl transferases and histones deacetylases: background

Histones are nuclear proteins that constitute the nucleosome core, around which the double strand of DNA is wound. Histones are associated with nonhistone proteins involved in DNA repair or gene expression. Chromatin is composed of histones, DNA, and nonhistone proteins. Gene transcription is regulated by various mechanisms including DNA methylation and histone modification by methylation, phosphorylation, poly-ADP ribosylation, ubiquitinylation, SUMOylation, carboxylation, glycosylation, and acetylation [7,8]. These epigenetic regulation mechanisms affect

☆ This work was supported by a grant from the nonprofit organization Association franc-comtoise pour la recherche et l'enseignement en rhumatologie.
* Corresponding author.
E-mail address: etoussirot@chu-besancon.fr (É. Toussirot).

1297-319X/$ – see front matter © 2010 Société française de rhumatologie. Published by Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.jbspin.2010.03.009

the level of gene expression without changing the sequence of base pairs in the DNA chain. The histone tails contain abundant lysine residues, which are the substrate for the acetylation reaction. Histone acetylation is dependent on the enzymes histone acetyl transferases (HATs) and histone deacetylation on the histone deacetylases (HDACs). Histone acetylation loosens the chromatin coils, thereby exposing transcription-factor binding sites and promoting gene transcription. On the opposite, HDACs condense the chromatin and prevent transcription factors from accessing the genome. Thus, HATs are believed to promote the transcription of genes, including those for proinflammatory cytokines, whereas HDACs are thought to prevent gene transcription [7,8].

HDACs are classified in four groups. Class I HDACs (HDAC1, 2, 3, and 8) are expressed chiefly in the cell nucleus, whereas class II HDACs (HDAC4, 5, 6, 7, 9, and 10) are expressed in the cytoplasm but can translocate to the nucleus. Class III HDACs are also known as silent information regulator proteins or sirtuins (SIRT 1–7) and are dependent on NADP. Only SIRT1 is known to exert HDAC activity, and the function of the other sirtuins has not yet been determined. Class IV contains only HDAC11. The HDAC expression profile varies across tissues and cells, with some HDACs, most notably those in class I and class II, being expressed only in some tissues. HDAC1, 2, and 3 (in class I) are found in various immune-system tissues [7–9].

HDIs are being developed as therapeutic tools, most notably in oncology [5,6]. HDIs are synthetic or naturally occurring compounds that are classified in four groups based on their structure: hydroxamic acid derivates such as trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA or vorinostat), and pyroxamide; short-chain fatty acids such as valproic acid, butyrates, and phenylacetate; cyclic tetrapeptides or epoxides such as FK228; and synthetic benzamide derivates such as MS-275 and CI-994. In addition, sirtuin inhibitors such as sirtinol are HDIs. Some HDIs (e.g., hydroxamic acid) inhibit all HDACs, whereas others selectively inhibit class I HDACs in low concentrations or class II HDACs in high concentrations (valproic acid and MS-275).

3. Biological properties of histone deacetylase inhibitors

HDIs were first evaluated in oncology [5]. In malignant cells, some genes are overexpressed and others are suppressed, such as the tumor suppressor genes. Modulation of HDAC expression occurs in malignant cells, either in isolation or in combination with modulation of the tumor suppressor p53 or the transcriptional repressor protein $p21^{Waf1}$ [10]. In patients with promyelocytic leukemia, disease progression was associated with HDAC activity [6]. Increased histone acetylation via the administration of HDIs may either restore the expression of abnormally suppressed genes or enable the expression of genes involved in cell control and apoptosis. Compounds that are being developed in oncology include vorinostat for the treatment of cutaneous T-cell lymphoma [11].

However, chromatin undergoes epigenetic changes during various cellular processes such as embryonic development, cell growth, cell differentiation, apoptosis, and DNA repair. Thus, HDIs may be helpful in a variety of diseases. Furthermore, butyrate and TSA regulate the production of proinflammatory cytokines by the colonic epithelial cells and may therefore hold promise for the treatment of inflammatory bowel disease [12,13]. HDIs may either promote transcription (e.g., of suppressed genes) or inhibit transcription, thereby exerting anti-inflammatory or proinflammatory effects depending on the HDI, targeted HDAC class, and cellular specificity of the drug [9].

The biological effects of HDIs that may result in anti-inflammatory effects are extremely varied. They are not confined to effects on histone acetylation/deacetylation. The acetylation process targets not only histones, but also nonhistone proteins such as transcription factors. Thus, HDIs can modulate cytokine production without modifying histone acetylation [9]. Transcription factors regulate genes for proinflammatory cytokines involved in joint disease, including TNFα. Among signaling pathways that activate proinflammatory cytokines, two of the most important activate the transcription factor NF-κB and the MAP kinases (MAPK), respectively. Thus, protein p65 (also known as RelA) contained in NF-κB interacts directly with HDAC1, whereas HDAC2 does not interact directly with protein p65 but modulates its activity by associating with HDAC1 [14]. HDACs promote the deacetylation of p65 and stabilize the interaction of p65 with the κB inhibitor (iκB) [15]. In addition, NF-κB can be activated via sequestration of IκB in the cytoplasm by HDAC1 and HDAC3 [16]. In addition to the NF-kB activation pathway, the MAPK pathway can be controlled by HDAC3, which thus blocks TNFα activation induced by the transcription factor ATF-2 [17]. Due to the pleiotropic effects of HDACs and the location of these enzymes in the cytoplasm and/or nucleus, HDIs may have contradictory or unexpected effects. However, the overall net effect is usually anti-inflammatory, suggesting a role for HDIs in the treatment of various inflammatory diseases.

The O forkhead box (FOXO) transcription factors are also affected by acetylation/deacetylation. FOXO proteins are involved in cell growth, cell survival, and apoptosis, and they can affect some of the inflammation pathways. Mice lacking FoxO3a develop an immune system disease characterized by T-cell proliferation and activation. The JAK/STAT pathway is also involved in various cell processes, and HDAC is required to regulate STAT [9]. These data indicate that acetylation/deacetylation reactions play a key role in the cell signaling events that regulate cell activation, cytokine production, cell growth, and apoptosis, all of which are related to the inflammatory process [18].

In parallel, HDIs can act on various cell types involved in the inflammatory response. HDIs limit the activation of effector and memory T cells and stimulate the function of regulatory T cells [19]. Incubating mononuclear cells from healthy individuals with TSA during stimulation with phytohemagglutinin decreases the production of Th1 cytokines [20]. Systemic administration of TSA to mice increases the number of naturally occurring regulatory T cells. When monocytes are stimulated by lipopolysaccharide, the addition of SAHA inhibits the release of TNFα, IL-1β, IL-12, and IFNγ [18]. Other HDIs can decrease cytokine production by monocytes. When used to treat macrophages and dendritic cells, HDIs inhibit the production of chemokines, cytokines, or costimulation pathway molecules [21]. In tumor models, HDIs used on endothelial cells inhibit angiogenesis by affecting the acetylation of hypoxia inducible factor 1α (HIF1α), which regulates pro-and antiangiogenic factors [22].

HATs and HDACs are also involved in resistance to glucocorticoids. Data on the interaction between HDAC and the clinical glucocorticoid response have been obtained in patients with asthma or chronic obstructive pulmonary disease (COPD). Compared to asthma, COPD responds less well to glucocorticoids as a result of decreases in HDAC2 expression and activity, which may affect glucocorticoid receptor deacetylation. The decrease in HDAC2 expression does not affect the nuclear translocation of the glucocorticoid receptor, its binding to DNA, or its effects on the expression or suppression of gene transcription, but inhibits glucocorticoid receptor binding to NF-κB [23]. A similar mechanism may exist in RA and may contribute to explain why some RA patients are resistant to glucocorticoid therapy [9].

4. Histone deacetylase inhibitors: relevance to rheumatoid arthritis

The anti-inflammatory effects of HDIs might prove useful for the treatment of inflammatory joint disease. Data from animal studies support the development of HDIs for the treatment of RA. The