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EDITORIAL

Histone deacetylase inhibitors: a new and promising drug class for the treatment of arthritis?

Éric Toussirot · Kashif Aziz Khan · Georges Herbein

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Rheumatoid arthritis (RA) is the prototype of a group of disorders characterized by chronic inflammatory reaction of the joints. The persistent inflammation results from the coordinated infiltration of the synovial tissue by distinct cellular populations which are activated and release a complex network of cytokines, chemokines, and growth factors. Progress in the understanding of the pathophysiology of RA and other forms of inflammatory arthritis has led to the concept of targeting cellular activation or cytokines in an attempt to better control the inflammatory process. In this sense, biological therapies blocking TNFα, IL-1 or IL-6, or controlling costimulatory pathways or alternatively B cells have emerged. These new therapies are currently available in the treatment of patients with RA, contributing to a better management of the disease.

The various mediators driving inflammation in RA and different forms of arthritis do so through the activation of conserved intracellular signaling proteins and pathways such as NF-κB, JAK/STAT or PI3 kinases which can be additional targets for a therapeutic intervention (Morel and Berenbaum 2004). Indeed, extracellular stimuli mediate their message to the nucleus through these signaling pathways and by means of transcriptional factors which interact with the promoter region of responder genes. Gene transcription may be modulated by epigenetic modifications which involved different reactions such as methylation of DNA and phosphorylation, sumoylation, ubiquitination, or acetylation of histone proteins (Huber et al. 2007a). All these histone reactions induce changes in the chromatin conformation and regulate transcriptional factor access to gene encoding regions of DNA (Karouzakis et al. 2009; Rosato and Grant 2004; Blanchard and Chipoy 2005; Glaser 2007; Halili et al. 2009; Grabiec et al. 2008).

Acetylation of histone proteins is regulated by the opposite action of histone acetyl transferase (HAT) and histone deacetylase (HDAC) enzymes. It is accepted that HAT activity promotes chromatin relaxation, favors the fixation of transcriptional factors and consequently transcriptional activation (including the transcription of inflammatory genes) while HDAC reverses this process, inducing chromatin condensation and preventing transcriptional factor access to gene promoters (Blanchard and Chipoy 2005; Glaser 2007; Halili et al. 2009; Grabiec et al. 2008). However, it has also been demonstrated that HDAC enzymes (and HAT enzymes as well) also interact with non-histone proteins including proteins for signaling pathways or transcriptional factors. Therefore, HDAC may have histone-independent effects in gene regulation (Grabiec et al. 2008).

Since HDAC activity may prevent the recruitment of transcriptional factors and silent gene transcription, including tumor repressor genes, HDAC inhibitors (HDACi) have been developed in the treatment of cancer (Lane and Chabner 2009). In fact, epigenetic modifications are

É. Toussirot (✉)
Department of Rheumatology, University Hospital Jean Minjoz,
25000 Besançon, France
e-mail: etoussirot@chu-besancon.fr

K. A. Khan · G. Herbein
Department of Virology, University Hospital St Jacques,
25000 Besançon, France

É. Toussirot · K. A. Khan · G. Herbein
UPRES EA 4266 Pathogens and Inflammation,
University of Franche-Comté,
25000 Besançon, France

É. Toussirot
CIC-Biotherapy 506, University Hospital St Jacques,
25000 Besançon, France

involved in the onset and progression of cancer and it has been demonstrated that HDACi partially control some epigenetic alterations associated with tumorigenesis. Hyperacetylation of histones by HDACi leads to the expression of repressed genes that inhibits cell proliferation and induces cell differentiation or apoptosis in tumor cells. Various HDACi are currently being tested in different forms of cancer, and vorinostat (SAHA, a pan-HDACi), for instance, has recently been approved for the treatment of cutaneous T cell lymphoma (Duvic et al. 2007). Four classes of HDAC (HDACI, II, III, and IV) have been described and they are grouped based on their structural homology with HDAC found in yeast (Rosato and Grant 2004; Blanchard and Chipoy 2005; Glaser 2007; Halili et al. 2009). Histone deacetylase inhibitors are synthetic or naturally derived and a wide range of products is currently being tested in cancer or various inflammatory or degenerative disorders (MA et al. 2009). These inhibitors can be structurally grouped into four classes, including hydroxamate, cyclic peptide, aliphatic acids, and benzamide. They are pan or selective inhibitors of HDAC activities. Many HDACi used up to now are active against Class I and Class II enzyme activities (trichostatin A and vorinostat for instance) while certain compounds are selective for HDAC Class (FK 228 inhibits HDAC1 and 2).

Besides their anti-neoplastic properties, it has been reported that HDACi may be used to treat inflammatory diseases via inhibition of cell proliferation and reduction of inflammatory cytokine production. This was observed with trichostatin A (TSA) and butyrate in ulcerative colitis, which inhibited IL-8 production (Yin et al. 2001). Thus, HDACi were investigated as potent anti-inflammatory drugs in different inflammatory conditions including arthritis (Segain et al. 2000).

Studies in animal models of arthritis have given the rationale for testing HDACi in human conditions and particularly in RA:

- The first report of HDACi in the treatment of arthritis was reported by Chung et al. (2003). Topical application of phenylbutyrate or TSA on rat paws prior to the induction of adjuvant-induced arthritis reduced joint swelling. Histological examination of the treated joints showed that synovial infiltration, synovial hyperplasia, and bone erosion were reduced. In addition, TNFα expression in the synovium was reduced while there was an accumulation of acetylated histones and an increased expression of the cell cycle inhibitors $p16^{lnk4}$ and $p21^{Waf1}$.
- Another HDACi, FK228, was tested in the same model of arthritis. When it was given systemically prior to the induction of arthritis, FK228 may prevent joint inflammation and the development of joint erosions. When it was given after the onset of arthritis, it also reduced paw swelling and bone erosions. In addition, FK228 suppressed osteoclast function by the expression of IFNβ, an osteoclast inhibitory protein (Nakamura et al. 2005).
- FK228 was also tested in the autoantibody-mediated arthritis in mice. A single systemic injection of this compound inhibited joint swelling, synovial inflammation and cartilage and bone destruction. Histone proteins were hyperacetylated in the synovial cells and TNFα and IL-1β expression was reduced. Again, the expression of $p16^{lnk4}$ was induced and $p21^{waf1}$ was up-regulated (Nishida et al. 2004).
- Collagen-induced arthritis is another animal model of RA. The effects of 2 HDACi, vorinostat (SAHA), and MS-275 were evaluated in murine and rat collagen-induced arthritis. A subcutaneous injection of SAHA attenuated joint inflammation and reduced bone erosions. By contrast, the administration of MS-275 was associated with complete resolution of arthritis. MS-275 was effective both in a prophylactic and in a therapeutic intervention. In addition, serum IL-6 and IL-1β levels were reduced with MS-275. A histological examination confirmed the anti-rheumatic activity of MS-275, showing no synovial hyperplasia, pannus formation, or cartilage or bone destruction (Lin et al. 2007).
- Trichostatin A given subcutaneously in the mouse model of collagen-induced arthritis also displayed anti-inflammatory activity. It improved arthritis and synovial inflammation, and limited bone destruction. In addition, positive chondrocytes for metalloproteinase MMP-3 and MMP-13 were reduced under TSA (Nasu et al. 2008).
- In the mouse model of collagen-induced arthritis, the intra-peritoneal administration of valproic acid decreased arthritis incidence and severity. This treatment was associated with an increase in the number and function of CD25+ Foxp3+ regulatory T cells (Saouaf et al. 2009).

All these data demonstrated the anti-inflammatory properties of different HDACi in the prevention and treatment of various forms of animal models of arthritis. These compounds were able to reduce inflammation in the joints, down-regulate the production of pro-inflammatory cytokines and control cartilage and bone erosions.

Conversely, only a limited number of studies have examined the role and influence of HAT and HDAC activities in patients with RA:

- Huber et al. examined the synovial expression of HAT and HDAC in a small number of patients with RA,

osteoarthritis (OA) and healthy subjects. HDAC activity was reduced in synovial tissue samples from patients with RA compared to the other groups, while there was no difference in the HAT activity between the three groups. This result was interpreted by the authors as a situation favoring transcription of pro-inflammatory genes (Huber et al. 2007b).

– By contrast, Horiuchi et al. found that synovial fibroblasts from patients with RA expressed more HDAC1 mRNA than the same cells from patients with OA. The blockade of HDAC1 and HDAC2 activities using small interfering RNA resulted in a decreased cell proliferation and an increased apoptosis in RA synovial fibroblasts (Horiuchi et al. 2009).
– It has also been demonstrated that Trichostatin A induced the cell death of RA synovial fibroblasts in a synergistic and dose-dependent manner when given with a TNF related apoptosis-inducing ligand (TRAIL; Jüngel et al. 2006).

Together with the data from animal models of arthritis, all these results strongly support the potential involvement of HDAC and HAT activities in the regulation of cellular activation and the production of pro-inflammatory cytokines in animal models of arthritis and also in patients with RA. The anti-inflammatory properties of HDACi may be explained in part by the regulation in the HAT/HDAC balance but also by interfering with non-histone proteins, including transcriptional factors such as p65 NF-κB, IκB, FoxO and JAK/STAT (Ashburner et al. 2001; Imre et al. 2006; Viatour et al. 2003; Mahlknecht et al. 2004). The final result is that HDACi may have an impact on several cellular populations: they can limit T lymphocyte activation and stimulate T regulatory cells (Brogdon et al. 2007; Wang et al. 2009); they can inhibit TNFα, IL-1β, IL-12, and IFNγ production by monocytes and the release of chemokines and cytokines by macrophages and dendritic cells (Leoni et al. 2002; Su et al. 2008); they can inhibit the angiogenesis process (Wang et al. 2009); they inhibit osteoclast function as well as metalloprotease and aggrecan-degrading enzyme production by chondrocytes (Young et al. 2005; Chabane et al. 2008). Because of all these mechanisms, the new HDACi class drug seems very attractive for the treatment of RA and other forms of arthritis (Choo et al. 2008).

However, for a better understanding of the role of the HAT/HDAC enzyme activities in RA, the following questions must be considered:

– Although the consequences of acetylation and deacetylation on histone proteins are relatively well understood (with some paradoxical findings), the interactions between HDAC and HAT with non-histone proteins remain only partially characterized. In particular, the exact influence of HDAC enzymes on the different transcriptional factors that play a role in the inflammatory response of RA must be evaluated. We have some responses, but more studies on these interactions are needed.
– We have limited and partially contradictory data on the expression of HAT and HDAC in patients with RA (Huber et al. 2007b; Horiuchi et al. 2009). In particular, we do not know about the distribution and expression of the distinct HDAC activities in the different cellular populations that infiltrate the RA synovium. Determining which HDAC is important for the activation and survival of these cell populations will indicate whether a selective HDACi or a pan-HDACi would be useful in the therapeutic management of patients. This question is relevant in order to identify the right therapeutic target and to define the adequate therapeutic tool.
– We do not know if the current treatments that we are using in RA (both traditional disease modifying anti-rheumatic drugs and biologics) have an influence on HAT and HDAC activities.

Thus, all these studies have provided the rationale for the use of this new and promising therapeutic drug class for arthritis, but further analyses are required to better understand the contribution of HAT and HDAC to the synovial inflammation. It seems particularly crucial to clarify the anti-inflammatory mechanisms of these drugs, which are certainly more complex than the single acetylation/deacetylation of histone proteins. In particular, an imbalance in the ratio acetylation/deacetylation of both histone and non-histone proteins could lead to a sustained inflammatory state leading to arthritis. Thus, a better understanding of the molecular mechanisms involved in the RA pathogenesis could lead to the development of new therapeutic approaches, allowing for further developments in clinical trials in the very near future (Kwon et al. 2002).

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Conflict of Interest None.

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