Commentary

Histone deacetylases – a new target for suppression of cartilage degradation?

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Abstract

Increased expression of metalloproteinases is a fundamental aspect of arthritis pathology and its control is a major therapeutic objective. In cartilage cultured in the presence of the cytokines interleukin-1 and oncostatin M, chondrocytes produce enhanced levels of metalloproteinases of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) and MMP (matrix metalloproteinase) families, resulting in the degradation of aggrecan and collagen. The histone deacetylase inhibitors trichostatin A and butyrate were shown to drastically reduce expression of these enzymes relatively selectively, with concomitant inhibition of breakdown of matrix components. This family of enzymes is therefore a promising target for therapeutic intervention.

Proteolytic activity in articular cartilage is central to joint destruction in arthritis. Proteinase expression is well known to be modulated by cytokines, intracellular signaling, and transcription factor action, but recent work by Young and colleagues [1] indicates that there is significantly more to this process than has been generally believed.

The human genome is packed in a matrix of histones that shield it from transcription by RNA polymerase II. The basic unit of chromatin is the nucleosome core particle, which consists of 147 bp of DNA wound 1.7 times around a histone octamer composed of two copies each of four histone partners (H2A, H2B, H3, and H4). The core particles are separated by a 10- to 60-bp linker region and the resulting 'beads-on-a-string' are further condensed into thicker fibers, which make up chromatin [2].

While structural studies suggested the nucleosome to be a stable particle, it is now clear that *in vivo* it is much more dynamic [3]; histone units can be exchanged and the whole complex is able to slide along the DNA in an ATP-dependent mechanism through the action of members of the Swi2/Snf2 family of ATPases. In addition to a conserved globular core protein region, each histone molecule contains an N-terminal tail rich in basic residues, which project beyond the surrounding DNA. In the case of H3 and H4, specific lysine sidechains undergo acetylation, through the action of histone acetyltransferases, by way of acetyl coenzyme A, a step which is associated with transcriptional activation. These modifications can be reversed by histone deacetylases (HDACs), of which there are four families [4].

Three of the families (I, II, and IV) are zinc-dependent enzymes, catalytically resembling the metalloproteinases, but family III (the recently discover SIR2 enzymes) uses a completely different mechanism depending on NAD^+ (oxidized nicotinamide-adenine dinucleotide) as a cofactor [5]. The members of family II are of particular importance because they are modular proteins with binding domains for protein–protein interaction with, among others, transcription factors.

The specific roles of various HDACs have been investigated by gene deletion in mice. Of special interest with regard to cartilage and bone development is the recently determined phenotype of the HDAC4-null animals [6]. HDAC4 is expressed in prehypertrophic chondrocytes and interacts with the key transcription factor Runx2 (also termed Cbfa1). The null animals develop ectopic calcification and early-onset chondrocyte hypertrophy, as is also seen in mice constitutively expressing Runx2. Conversely, mice over-expressing HDAC4 in cartilage show greatly reduced chondrocyte hypertrophy, similar to that in the Runx2-null phenotype.

ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs; bp = base pairs; HDAC = histone deacetylase; MMP = matrix metalloproteinase; TIMP = tissue inhibitor of metalloproteinases.

In a more general way, the role of the HDACs can be investigated using inhibitors. HDACs of families I, II, and IV are inhibited by hydroxamate derivatives such as the natural product trichostatin A [7]. Although at the moment such HDAC inhibitors show little specificity for individual HDAC family members [8], efforts have been made to develop specific small-molecule inhibitors, and various compounds are currently in clinical trials for various forms of cancer [9]. Butyrate has long been known to be an effective HDAC inhibitor and is currently in phase II clinical trials [9]. Initial evidence also points to the use of HDAC inhibitors in inflammatory arthritis [10,11].

HDACs show a varied tissue distribution, and mapping of cartilage transcripts shows evidence for expression of many HDACs in this tissue [12]. The recent work from Young and colleagues [1] shows the effective use of HDAC inhibitors for decreasing metalloproteinase expression in cartilage and demonstrates that the paradigm of inhibition of histone deacetylation leading to gene silencing is not absolute. Cawston and colleagues showed many years ago that cartilage cultured in the presence of a mixture of the cytokines interleukin-1 and oncostatin M undergoes rapid aggrecan loss followed later by collagen degradation and the release of degraded collagen fragments into the medium [13]. These degradative processes have been attributed to the action of specific ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family members and matrix metalloproteinase 13 (MMP13 or collagenase 3), respectively. Addition of either trichostatin A or butyrate resulted in a dramatic reduction of glycosaminoglycan loss (aggrecan degradation) and collagen release. These processes are associated with decreased levels of ADAMTS-4 and -5 and of MMP13, respectively, and message levels of these gene products were correspondingly reduced as determined by real-time polymerase chain reaction. In contrast, expression of the major cartilage structural molecules aggrecan and type II collagen and a number of other metalloproteinases was unaffected by the presence of the inhibitors. The findings using bovine nasal cartilage were reinforced by cell culture studies using a human chondrosarcoma cell line and primary human chondrocytes.

In a second paper [14], Young and colleagues address the other side of metalloproteinase action, the expression of the inhibitor TIMP (tissue inhibitor of metalloproteinases). Here they show that HDAC inhibitors have opposing effects on TIMP-1 expression, depending on whether phorbol ester or transforming growth factor β is used for induction, with the latter showing an impressive repression with HDAC inhibitors whereas the phorbol ester increases TIMP-1 expression.

Conclusion

Both of these studies by Young and colleagues [1,14] suggest the potential for HDAC inhibitors in the control of cartilage catabolism and demonstrate that more work is required to understand the molecular mechanisms underlying their action and in the regulation of these enzymes.

Competing interests

The author(s) declare that they have no competing interests.

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