IBMS BoneKEy. 2011 November;8(11):467-469
http://www.bonekey-ibms.org/cgi/content/full/ibmske;8/11/467
doi: 10.1138/20110539

COMMENTARIES

When Parathyroid Hormone-Related Protein Protects Mice Against Osteoarthritis

Martine Cohen-Solal

INSERM U606, Hôpital Lariboisière and Université Paris Diderot - Paris 7, Paris, France

Commentary on: Macica C, Liang G, Nasiri A, Broadus AE. Genetic evidence of the regulatory role of parathyroid hormone-related protein in articular chondrocyte maintenance in an experimental mouse model. *Arthritis Rheum*. 2011 Nov;63(11):3333-43.

Recent work by Macica and colleagues (1) focuses on the role of parathyroid hormone-related protein (PTHrP) in the maintenance of chondrocyte function in mice. In particular, this new research addresses several interesting issues with regard to the validity of animal models and also provides new insight into the role of PTHrP in the development of osteoarthritis (OA).

The paper's basis is that articular chondrocytes have the capacity to proliferate while they are at early stages of differentiation, which protects these cells from hypertrophy and apoptosis (2). In the articular cartilage, chondrocyte proliferation is reduced and the cells are arrested before the progression to hypertrophic stages that ultimately leads to hypertrophy and apoptosis. This phenomenon is called maintenance and is a feature of OA. Several molecules are involved in the balance of chondrocyte proliferation/differentiation (3); these molecules have been studied primarily at the growth plate. Among them, PTHrP and Indian hedgehog (Ihh) are major players, since Ihh positively modulates PTHrP expression, thus inhibiting hypertrophic differentiation of chondrocytes. To better understand the differentiation process in OA, the authors used mice in which the *PTHrP* gene was conditionally deleted by a transgenic mouse in which recombinase expression is driven by the growth and differentiation factor 5 (*GDF5*) promoter. This resulted in the absence of expression of PTHrP in chondrocytes of the articular region.

The first new finding from the current study concerns the impact of the absence of PTHrP in the development of OA. This is an important issue since PTHrP can be involved in regulation not only during growth but during aging as well. The lack of expression of PTHrP at the articular zone did not produce any structural abnormalities at any age, which suggests either that PTHrP might not play a crucial role in the maintenance of articular cartilage or that the lack of expression might induce compensatory molecular changes that control the program of proliferation-differentiation-hypertrophy of chondrocytes.

The authors then addressed the question of the impact of PTHrP in the remodeling of articular cartilage in mature mice. To do so, they challenged adult mice for OA using the well-described model of destabilization of the medial meniscus and quantified the OA score by Safranin-O staining that reflects the loss of proteoglycan. They found that PTHrP-knockout mice were highly susceptible to OA as the osteoarthritis score was doubled by meniscectomy in these animals. Consistent with previous reports, only male mice displayed OA lesions while female mice were resistant to OA, indicating some gender specificity for OA development in mice, unlike in humans, and also showing that such experiments should be conducted mainly in male mice. Thus, challenging mice

with meniscectomy reveals the protective role of PTHrP in the maintenance of chondrocytes under mechanical stress. Challenging mice with meniscectomy, using the method of Macica *et al*. or by using other activators of cartilage degradation such as collagenase, is therefore necessary to assess the role of molecular factors in OA, similar to how challenging mice with ovariectomy is used in the bone field, for instance, to understand the pathogenesis of osteoporosis. In the OA field, clearly the meniscectomy model is a useful tool to understand the pathogenesis of cartilage loss and to assess the role of local factors such as hormones or transcription factors. Indeed, this method is relevant for human OA as histological features in mice are close to those observed in humans. Here, Macica *et al*. show in particular that mechanical stress governs the regulation of expression of molecules produced by chondrocytes and likely regulates the interaction between PTHrP and Ihh expression. Nevertheless, the mechanism involved in this regulation induced by mechanical stress remains to be elucidated.

An explanation for the protective effect of PTHrP on cartilage is based on the concomitant expression of Ihh. As the PTHrP-Ihh loop is now well-established during growth (4), the authors tried to show that lack of PTHrP increases the expression of Ihh and showed that this reduces articular chondrocyte differentiation. Therefore, they provide evidence that lack of PTHrP promotes OA by increasing the number of pre- and hypertrophic chondrocytes.

The most remarkable finding of the work by Macica *et al*. is the enhanced cartilage damage in mice lacking PTHrP. Whatever the mechanisms involved, these results are consistent with several previous observations in animal models. The expression of PTH receptors is reduced in OA rabbit chondrocytes (5). *In vivo*, PTH administration prevents chemical-induced OA in rats (6) and promotes cartilage repair by preventing the differentiation of chondrocytes (7). However, PTHrP is more abundant in human OA cartilage than in controls (8) and the effect of PTH or PTHrP in articular cartilage remodeling has not yet been addressed in humans.

In conclusion, the article by Macica *et al*. provides evidence of the role of PTHrP in the pathophysiology of articular cartilage damage; the authors show that this might be mediated through PTHrP control of chondrocyte differentiation and hypertrophy. Future studies should address the mechanisms by which cartilage protection is achieved in mice. Moreover, the role of PTHrP in cartilage remodeling should be demonstrated in adult humans as well as the potential use in human OA.

Conflict of Interest: None reported.

Peer Review: This article has been peer-reviewed.

References

1. Macica C, Liang G, Nasiri A, Broadus AE. Genetic evidence of the regulatory role of parathyroid hormone-related protein in articular chondrocyte maintenance in an experimental mouse model. *Arthritis Rheum*. 2011 Nov;63(11):3333-43.

2. Goldring MB. Update on the biology of the chondrocyte and new approaches to treating cartilage diseases. *Best Pract Res Clin Rheumatol*. 2006 Oct;20(5):1003-25.

3. Dreier R. Hypertrophic differentiation of chondrocytes in osteoarthritis: the developmental aspect of degenerative joint disorders. *Arthritis Res Ther*. 2010;12(5):216.

4. Chen X, Macica CM, Nasiri A, Broadus AE. Regulation of articular chondrocyte proliferation and differentiation by Indian hedgehog and parathyroid hormone-related protein in mice. *Arthritis Rheum*. 2008 Dec;58(12):3788-97.

5. Becher C, Szuwart T, Ronstedt P, Ostermeier S, Skwara A, Fuchs-Winkelmann S, Tibesku CO. Decrease

in the expression of the type 1 PTH/PTHrP receptor (PTH1R) on chondrocytes in animals with osteoarthritis. *J Orthop Surg Res*. 2010 Apr 26;5:28.

6. Chang JK, Chang LH, Hung SH, Wu SC, Lee HY, Lin YS, Chen CH, Fu YC, Wang GJ, Ho ML. Parathyroid hormone 1-34 inhibits terminal differentiation of human articular chondrocytes and osteoarthritis progression in rats. *Arthritis Rheum*. 2009 Oct;60(10):3049-60.

7. Mizuta H, Kudo S, Nakamura E, Takagi K, Hiraki Y. Expression of the PTH/PTHrP receptor in chondrogenic cells during the repair of full-thickness defects of articular cartilage. *Osteoarthritis Cartilage*. 2006 Sep;14(9):944-52.

8. Terkeltaub R, Lotz M, Johnson K, Deng D, Hashimoto S, Goldring MB, Burton D, Deftos LJ. Parathyroid hormone-related protein is abundant in osteoarthritic cartilage, and the parathyroid hormone-related protein 1-173 isoform is selectively induced by transforming growth factor beta in articular chondrocytes and suppresses generation of extracellular inorganic pyrophosphate. *Arthritis Rheum*. 1998 Dec;41(12):2152-64.