Commentary

Aging, osteoarthritis and transforming growth factor-β signaling in cartilage

A Hari Reddi

Lawrence J Ellison Center for Tissue Regeneration, University of California, Davis, School of Medicine, Sacramento, CA 95817, USA

Corresponding author: A Hari Reddi, ahreddi@ucdavis.edu

Published: 28 November 2005
This article is online at http://arthritis-research.com/content/8/1/101

Arthritis Research & Therapy 2006, **8:**101 (doi:10.1186/ar1858)

See related research by Davidson *et al.* in issue 7.6 [http://arthritis-research.com/content/7/6/R1338]

Abstract

Osteoarthritis is a common malady of the musculoskeletal system affecting the articular cartilage. The increased frequency of osteoarthritis with aging indicates the complex etiology of this disease, which includes pathophysiology and joint stability including biomechanics. The balance between anabolic morphogens and growth factors and catabolic cytokines is at the crux of the problem of osteoarthritis. One such signal is transforming growth factor-β (TGF-β). The impaired TGF-β signaling has been identified as a culprit in old mice in a recent article in this journal. This commentary places this discovery in the context of anabolic and catabolic signals and articular cartilage homeostasis in the joint.

It is common knowledge that with aging one confronts the generally inevitable pain in the joints that limits mobility as a result of osteoarthritis. Osteoarthritis is characterized by articular cartilage damage and the resultant repair response including osteophyte formation and joint capsule thickening. The etiology of osteoarthritis remains unknown. At steady state the homeostasis and response of articular cartilage is determined by the exquisite control of the cells and extracellular matrix by anabolic morphogens and catabolic cytokines [1]. The aim of this commentary is to place in context a recent article in this journal of anabolic growth factor, transforming growth factor-β (TGF-β) signaling in articular cartilage in aging mice [2]. This commentary will discuss TGF-β signaling and osteoarthritis in an experimental investigation in the mouse. It is important to bear in mind that results obtained in mice may not be directly extrapolated to humans.

TGF-β is a secreted homodimeric pleiotropic protein regulating proliferation, migration, differentiation, and death in a variety of cell types including articular chondrocytes in the joint. There are three isoforms of TGF-β, designated TGF-β_1, TGF-β_2, and TGF-β_3, in mice and humans. TGF-β isoforms have wide-ranging roles in the development, maintenance and homeostasis of articular cartilage along with related bone morphogenetic proteins (BMPs). In several human diseases such as autoimmunity, cancer, and fibrosis, there is a perturbation of TGF-β signaling [3,4]. The related BMPs have fundamental roles in the lineage, morphogenesis, maintenance, and homeostasis of articular cartilage [5,6].

The members of the TGF-β family bind to a heteromeric receptor complex on the cell surface and activate an intracellular signal transducing the Smad complex (a composite term derived from *Sma* genes from *Caenorhabditis elegans* and *Mad* gene (*Drosophila melanogaster*) involved as intracellular substrate for TGF-β and BMP signaling). The receptor complex initiating the TGF-β response consists of two type II and two type I TGF-β receptors. These receptors are transmembrane serine/threonine protein kinases. The receptor protein kinases phosphorylate the cytosolic Smads 2 and 3, which are also referred to as R-Smads and receptor-activated Smads. Phosphorylation of Smads 2 and 3 results in a conformational change and permits interaction with a common Smad (C-Smad) and initiates the translocation into the nucleus. In the nucleus they act in collaboration with sequence-specific transcription coactive factors to initiate and regulate gene expression.

The Smads are intracellular signaling complexes and consist of TGF-β receptor-activated R-Smads (such as Smads 2 and 3), a common partner Smad (C-Smad; also known as Smad 4) and inhibitory Smads (Smads 6 and 7). The

BMP = bone morphogenetic protein; C-Smad = common Smad (Smad 4); IL = interleukin; LAP = latency-associated protein; MH = Mad homology domain in the Smads; R-Smad = receptor-activated Smad (Smads 2 and 3 for TGF-β signaling; Smads 1, 5 and 8 for BMP signaling); Smad = a composite term derived from *Sma* genes from *Caenorhabditis elegans* and *Mad* gene (*Drosophila melanogaster*) involved as intracellular substrate for TGF-β and BMP signaling; TGF-β = transforming growth factor-β.

R-Smads and the C-Smad have a highly conserved Mad homology domains (MH 1 in the amino terminus and MH 2 in the carboxy terminus).

Binding of the TGF-β isoforms to the TGF-β receptors (TGF-βRs) results in the recruitment and phosphorylation of R-Smads by type I TGF-βR (also known as activin receptor-like kinase-5, or ALK-5). A trimeric complex of two R-Smads and one common Smad, Smad 4, is translocated from the cytoplasm into the nucleus to act as transcription factors [3,4].

In the article published recently in *Arthritis Research and Therapy* [2], the authors examined TGF-β in the knee joints of mice aged 5 months or 2 years. The mice were challenged with IL-1 to initiate cartilage catabolism. The authors examined the response of the articular cartilage to TGF-β_1 as an anabolic factor that can counteract the actions of catabolic cytokine IL-1. To gain insights into the cell types and cellular compartments, immunocytochemical methods were employed. TGF-β isoforms 1, 2, and 3, TGF-β receptors I and II, Smads 2, 3, 4, 6, and 7, and phosphorylated Smad 2 (Smad-2P) were localized in the joints of young and old mice. In 2-year-old mice there was a decline in the expression of TGF-β_2, TGF-β_3 and TGF-β receptor. It is noteworthy that the number of cells expressing phosphorylated Smad 2 decreased in old mice. In addition, blockade of TGF-β signaling by the latency-associated protein (LAP) delivered by an adenoviral vector was employed. The LAP attenuated the loss of proteoglycan in response to treatment with IL-1. This indicates that the TGF-β signaling induced as a repair response to IL-1 is curtailed by TGF-β depleting LAP. The LAP binds to TGF-β and prevents its bioavailability to the receptors.

Although it is clear that TGF-β-mediated anabolic signaling is an important aspect of joint homeostasis, future studies need to focus on members of the BMP family such as BMP-2, BMP-7, and growth differentiation factor 5 (GDF-5). GDF-5 is also known as cartilage-derived morphogenetic protein 1 (CDMP 1) and has been implicated in articular cartilage development and maintenance [6,7].

Conclusion

Continued investigations of the articular cartilage homeostasis and regeneration are likely to suggest novel therapeutic approaches to the amelioration of the horrendous, painful consequences of osteoarthritis in aging humans.

Competing interests

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

Acknowledgements

I thank Ms Danielle Neff for dedicated and enthusiastic help in the preparation of this commentary. Our research on articular cartilage is supported by the Lawrence J Ellison Chair and grants from the NIH (1-RO1-AR-47345).

References

1. Reddi AH: **Cartilage morphogenetic proteins: role in joint development, homoeostasis, and regeneration.** *Ann Rheum Dis* 2003, **62 Suppl 2:**ii73-ii88.
2. Davidson ENB, Schartstuhl A, Vitters EL, van der Kraan PM, van der Berg WB: **Reduced transforming growth factor-beta signaling in cartilage of old mice: role in impaired repair capacity.** *Arthritis Res Ther* 2005, **7:**R1338-R1347.
3. ten Dijike P, Hill CS: **New insights into TGF-β–Smad signaling.** *Trends Biochem Sci* 2004, **29:**265-273.
4. Feng XH, Derynck R: **Specificity and versatility in TGF-β signaling through Smads.** *Annu Rev Cell Dev Biol* 2005, **21:**659-693.
5. Reddi AH: **BMPs: from bone morphogenetic proteins to body morphogenetic proteins.** *Cytokine Growth Factor Rev* 2005, **16:** 249-250.
6. Lories RJU, Luyten FP: **Bone morphogenetic protein signaling in joint homeostasis and disease.** *Cytokine Growth Factor Rev* 2005, **16:**287-298.
7. Rountree RB, Schoor M, Chen H, Marks NE, Harley V, Mishina Y, Kingsley DN: **BMP receptor signaling is required for potential maintenance of articular cartilage.** *PLoS Biol* 2004, **2:**355-365.