OSTEOARTHRITIS

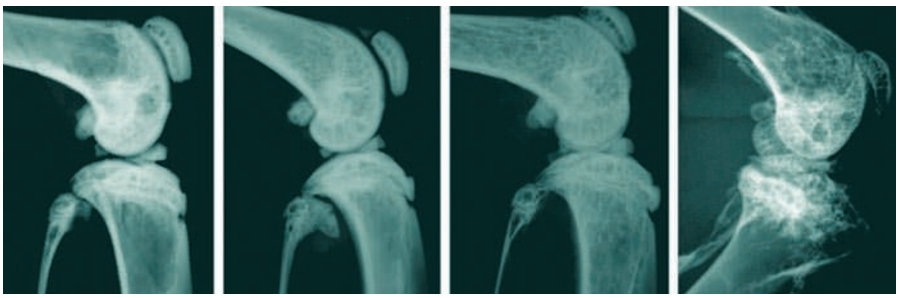
Blocking hedgehog signaling might have therapeutic potential in OA

The hedgehog (Hh) signaling pathway regulates the differentiation and growth of numerous cell types, including chondrocytes, and thus is essential for normal skeletal development. Pharmacological agents that block Hh signaling are soon to enter clinical trials for certain cancers. Given the central role for chondrocytes in the development of osteoarthritis (OA), could the therapeutic potential of these agents also extend to this disease? To answer this question, we first need to further understand what role Hh signaling has in the pathogenesis of OA; a paper on this topic has just been published in *Nature Medicine*.

"We were investigating the role of hedgehog signaling in the development of sarcomas in mice when we stumbled upon an unexpected observation," explains Benjamin Alman, the lead researcher on this paper. "We found that when hedgehog signaling is activated in mice, the animals developed OA. Based on this finding we decided to study the role of hedgehog signaling in OA in mice and humans."

First, the researchers from the Hospital for Sick Children at the University of Toronto investigated whether Hh signaling was activated in samples from osteoarthritic knee joints of patients undergoing total knee replacement and also in mice in which OA was surgically induced by performing medial meniscectomy. In humans and mice, the knees that were categorized as having the most severe OA (determined using the International Cartilage and Repair Society [ICRS] grading scale) expressed the highest levels of Hh downstream target genes (*GLI1*, *PTCH1* and *HHIP*) in articular cartilage, confirming that Hh signaling is activated in mice and humans with OA.

Next, Alman and colleagues used three different lines of transgenic mice in which Hh signaling is activated to see whether this increased signaling would predispose the mice to develop OA in comparison with control mice. Not only did the transgenic mice develop OA, whereas the control mice did not, but also the severity of disease (according to ICRS grading) directly correlated with the level of Hh signaling activation.



Radiographic images of mouse knees showing progressively worsening radiographic features of OA. © Nature Publishing Group

What effect would inhibiting Hh signaling have on OA development? Alman says, "We used both transgenic mice and mice treated with an hedgehog-blocking drug to determine that inhibiting hedgehog signaling substantially attenuates the severity of OA that develops following interarticular trauma." Similar results were also found in human cartilage explant cultures: pharmacological blockade of Hh signaling resulted in reduced expression of OA markers (e.g. a disintegrin and metalloproteinase with thrombospondin type 1 motif 5 [ADAMTS5] and runt-related transcription factor 2 [RUNX2]), whereas treatment with an Hh ligand to upregulate Hh signaling led to increased expression of these markers.

Further experiments to dissect which downstream pathways might be involved showed that Hh signaling, through direct effects on RUNX2, indirectly increased the expression of ADAMTS5, which is known to be a key mediator of damage in OA development.

When asked about this work, Tom Aigner, from the Institute of Pathology, University Hospital Leipzig, Germany, agreed that "The approach is technically sound and provides some interesting insight into mouse cartilage biology." He did, however, raise concerns about the relevance of these data to human disease. "The mouse, although a versatile system, is not a good model for human OA: mouse articular cartilage is much thinner than human articular cartilage, differently structured, the mouse growth plate never closes, and mechanisms of mouse cartilage homeostasis and degeneration are, as far as we know, different than those seen in humans."

So, this study has provided an insight into the role of Hh signaling in OA and suggests that blockade of Hh signaling, performed genetically or pharmacologically, might inhibit articular degeneration and thereby reduce the severity of OA. As Alman explained in a press release from the University of Toronto, "We may have found a very promising approach to blocking the amount of joint damage and slowing down the progression of the disease."

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Original article Lin, A. C. *et al.* Modulating hedgehog signaling can attenuate the severity of osteoarthritis. *Nat. Med.* **15**, 1421–1425 (2009)