optimizing the balance between potency and safety.

However, using the structural understanding gained from previous experiments, the authors used *in silico* screening followed by *in vitro* testing to identify a number of improved CPEs. They selected the best CPEs from the 10 different chemical classes and 'mutated' them to generate variants. A significant number of the 'mutants' were better fluidizers. The lead candidate, stearyl methacrylate, was tested *in vitro*, and yielded a predicted ER/IP value of about 12, which is substantially higher than the commonly used oleic acid with a value of 3.8.

With further safety testing, these second-generation molecules could broaden the repertoire of CPEs available for transdermal applications in the future.

Melanie Brazil

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PROTEASES

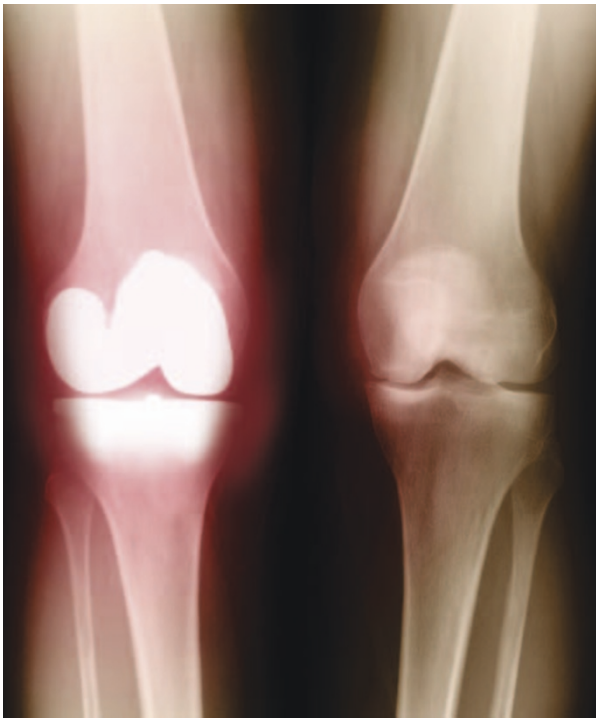
Joint advantage

Two studies simultaneously published in *Nature* suggest that the metalloprotease ADAMTS5 is the main culprit of cartilage degradation in arthritis. The results, which were obtained with ADAMTS5-null mice, need corroborating in human tissue but provide the first evidence of a single gene deletion directing the progression of cartilage degradation in models of arthritis. Developing targeted protease inhibitors against ADAMTS5 to halt the progression of joint destruction would be a significant step forward in treating this debilitating, progressive disease.

Arthritis is characterized by the breakdown of cartilage, which is thought to be caused by dysregulated proteolytic activity within the extracellular matrix. A major target for proteolytic breakdown is the proteoglycan aggrecan, which is cleaved at a specific site by several members of the ADAMTS protease family. Two members of this family seem to be particularly active aggrecanases in cartilage — ADAMTS4 and ADAMTS5 — but the extent to which either plays a role in aggrecan degradation in arthritis has not been determined. By using mice in which the gene for either ADAMTS4 or ADAMTS5 has been knocked out, two groups have now convincingly shown that ADAMTS5 is the primary aggrecanase responsible for degrading cartilage in mouse models of osteoarthritis (OA) and rheumatoid arthritis (RA).

Amanda Fosang and colleagues examined the presence of ADAMTS-specific aggrecan degradation products in cartilage extracted from unmanipulated mice and found a reduction of these products in both ADAMTS4- and ADAMTS5-null mice, indicating that both enzymes might have a role in normal cartilage turnover. The reduction of the degradation products was more substantial in the ADAMTS5-null mice cartilage extracts.

In the study by Elisabeth Morris and colleagues, cartilage degradation was initiated in wild-type mice and ADAMTS5-null mice, by surgical induction of joint instability (an established model of OA). Mice lacking functional ADAMTS5 had significantly reduced cartilage degradation compared with wild-type mice. Analysis of joints using an antibody against the cleavage product generated by ADAMTS4 and ADAMTS5 showed that aggrecan degradation was markedly reduced in the ADAMTS5-null mice.



Inflammatory modulators have been reported to induce degradative enzyme activity and the release of aggrecan *in vitro*, and are known to be implicated in the pathogenesis of both OA and RA. Both studies looked at the effects of inflammatory modulators on aggrecan release in a culture of articular cartilage, and found that interleukin-1α (IL-1α) caused a significant increase in the release of aggrecan in cultures of cartilage from the wild-type and the ADAMTS4-null mice. Characterization of this released aggrecan confirmed it had been cleaved at the ADAMTS-specific cleavage site. By contrast, there was little aggrecan release from cartilage of mice lacking ADAMTS5. Finally, Fosang and colleagues showed that when ADAMTS5 activity was ablated in a mouse model of inflammatory arthritis (an established model of acute RA), only 7% of joints showed cartilage erosion, compared with 36% of joints in the control mice.

Both reports clearly demonstrate that ADAMTS5 is the major aggrecanase in mouse cartilage and suggest that inhibiting its activity could be a new therapeutic strategy for human arthritis.

Joanna Owens

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