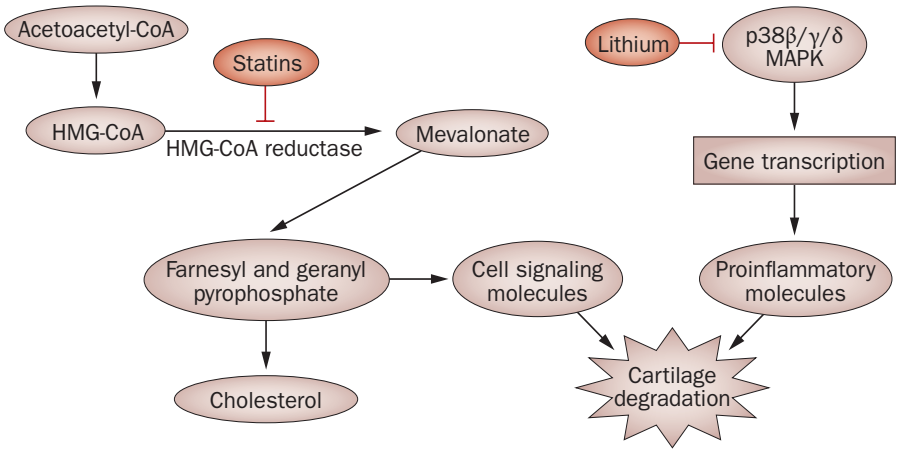
CARTILAGE

Commonly used drugs prevent cartilage degradation

The development of new strategies for the treatment of osteoarthritis (OA) might be advanced by research into drugs widely used for other indications: statins, commonly prescribed as lipid-lowering agents, and the mood-stabilizer lithium. In bovine cartilage tissue and in human chondrocytes, both of these drugs prevented cartilage degradation and reduced the expression of matrix metalloproteinases (MMPs) including the collagenases MMP-1 and MMP-13.

The studies of lithium and statins were both undertaken by a group led by David Young at Newcastle University, UK. "There was already evidence in the literature that statins and lithium could regulate the expression of certain MMPs in other systems," says Young. The current work was undertaken to determine whether these agents could specifically protect against the cartilage degradation induced by proinflammatory cytokines, in particular IL-1. To study the drugs' effects, the investigators cultured cartilage with cytokines for 2 weeks in the absence or presence of lithium or statins, after which they assessed collagen degradation by use of a hydroxyproline assay.

"We originally examined lithium because of its known ability to regulate GSK3 [glycogen synthase kinase-3]," explains Young. "However, in this study we found the effects of lithium to be independent of GSK3 inhibition." In fact, mechanistic studies showed that lithium targets the p38 pathway, a finding consistent with other recent observations that point to lithium as a regulator of mitogen-activated protein kinase (MAPK) pathways. Pathway analysis determined that the drug selectively inhibits the phosphorylation of the p38 β, γ and δ isoforms.



To work out the mechanism of action of the statins, the researchers used various intermediates in the cholesterol biosynthesis pathway to attempt to override their effects. This approach led them to conclude that the lipophilic statins simvastatin and mevastatin block cartilage degradation not through the depletion of cholesterol but by blocking geranylgeranylation, a post-translational modification to proteins such as Rho and Rac.

The relatively low cost and proven safety record of lithium and statins could prompt further studies into the use of these drugs as potential new strategies for the treatment of OA.

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Original articles Hui, W. *et al.* Lithium protects cartilage from cytokine-mediated degradation by reducing collagen-degrading MMP production via inhibition of the P38 mitogen-activated protein kinase pathway. *Rheumatology (Oxford)* doi:10.1093/rheumatology/keq217 | Barter, M. J. *et al.* Lipophilic statins prevent matrix metalloproteinase-mediated cartilage collagen breakdown by inhibiting protein geranylgeranylation. *Ann. Rheum. Dis.* doi:10.1136/ard.2010.129197