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Editorial

A new prescription for growth? Statins, cholesterol and cartilage homeostasis

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Activating mutations in the *FGFR3* gene cause Achondroplasia (ACH)[1,2] and Thanatophoric Dysplasia (TD)[3,4]. Both syndromes present with severely shortened limbs and other skeletal abnormalities, but TD is usually fatal in the perinatal period[3,4]. While activating mutations in ACH and TD lead to mutant forms of FGFR3 that impair chondrocyte proliferation and cartilage development[5], loss of *Fgfr3* in mice enhances endochondral bone growth[6], revealing that FGFR3 acts as a negative regulator of this process. Unfortunately, most individuals with TD die shortly after birth due to skeletal malformations that occur before the disease is diagnosed, preventing pharmacological intervention, and treatment for ACH is currently limited to symptom management. However, C-type natriuretic peptide (CNP) has recently been identified as potential therapeutic agent for ACH. CNP rescued growth defects in a mouse model of ACH[7] and a Phase 2 clinical trial is currently evaluating the effect of CNP on ACH (BioMarin; BMN-111). Nevertheless, further studies into the underlying mechanisms and novel therapeutic possibilities are highly warranted.

In a ground-breaking study, Yamashita and colleagues[8] created induced pluripotent stem (iPS) cells derived from the skin of ACH and TD patients, as well as controls, and screened candidate drugs for restorative effects during chondrogenic induction. The result: Statins, drugs that are commonly prescribed to lower cholesterol, significantly improved chondrogenesis of mutant iPS cells. Moreover, statins also corrected skeletal development in a mouse model of ACH. The authors conclude that these results are due to reduced cholesterol levels. These findings are intriguing from a therapeutic perspective, in particular for the treatment of ACH, and increase our understanding of skeletal development. However, they are somewhat at odds with prior studies on cholesterol signaling and FGFR3 function in chondrocytes, as well as statin use in patients with osteoarthritis (OA).

Cholesterol signaling plays an important role during embryonic development, including the development of the skeletal system. Pharmacological inhibition of local cholesterol synthesis in the developing growth plate reduces expression of Indian hedgehog (*Ihh*), a critical regulator of cartilage development, decreases expression of the hypertrophic transcript *Col10a1*, and results in dwarfism in rats[9]. Evidence from our group suggests that cytoskeletal modulation stimulates the retinoid-related receptor alpha (RORα), a known receptor for cholesterol, to promote chondrocyte hypertrophy[10]. Furthermore, statin administration retarded bone growth in control mouse embryonic tibial explants[10], similar to the effects seen in[9]. Somewhat contradictory to these observations, Yamashita and colleagues report that statin treatment, and therefore inhibition of cholesterol synthesis, increases bone growth by reducing constitutively active FGFR3 protein levels via proteasomal destruction[8]. Although statin treatment rescued dwarfism in mice bearing *FGFR3* ACH mutations, drug administration did not affect bone development in controls. These findings highlight a complex interplay between cholesterol signaling and cartilage development, and suggest that statins play a role in regulating aberrant protein abundance, at least in the case of mutant FGFR3. Further studies that examine Ihh, RORα activation, and other effectors of cholesterol signaling in ACH and TD iPS cells may help to elucidate the molecular cross talk occurring upon mutant FGFR3 activation in chondrogenesis. Potential explanations for the apparent discrepancy in results include dose-dependent effects of cholesterol or statins, and/or additional effects of statins discussed below.

Given that OA pathogenesis recapitulates aspects of cartilage development, studies of chondrogenesis can inform approaches for OA prevention and treatment[11]. In fact, the reciprocal may also be true. The relationship between statin use and OA has been an active area of investigation for the past decade. Statins act by inhibiting HMG-CoA reductase, a primary, rate-limiting enzyme involved in cholesterol synthesis. However, statins also influence other pathways downstream of HMG-CoA reductase (Fig. 1). Amongst these pathways, protein farnesylation and geranylgeranylation (forms of prenylation) may be the most important since they regulate the activity of many crucial signaling molecules, including Ras and Rho GTPases. Interestingly, statins and inhibitors of farnesyl and geranylgeranyl transferases have protective effects in models of OA. Expression of the collagenases *MMP1*, *MMP3*, and *MMP13* is reduced in OA chondrocytes upon statin treatment *in vitro*[12–14], an effect that is mimicked by geranylgeranyl transferase inhibition[14] and that can be reversed by mevalonate, farnesol, or geranylgeranyl pyrophosphate supplementation[12–14]. Statin treatment has also been shown to positively regulate components of the extracellular matrix in a rabbit model of OA[15], as well as in chondrocytes cultured from OA patients[13,14]. Thus, statins have been shown to be cartilage-protective in several studies, but at least some of these effects are likely mediated by pathways other than those involving cholesterol synthesis. Studies by us and others have also demonstrated multiple roles of Rho GTPases during cartilage development (reviewed in[16]), raising the possibility that the

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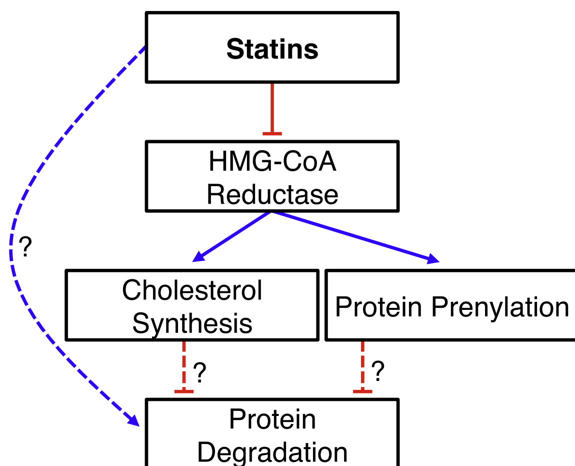

Fig. 1. Statins influence multiple cellular pathways. Statins inhibit HMG-CoA Reductase and, consequently, cholesterol synthesis and protein prenylation. How statins influence protein degradation via the proteasome is not completely understood. Blue lines indicate activation, Red lines indicate inhibition, and dashed lines indicate possible but unconfirmed interactions.

effects observed by Yamashita *et al.* might be partially due to cholesterol-independent activities. Furthermore, the effects of statins on articular chondrocytes may provide novel insight regarding the role of cholesterol homeostasis and signaling during cartilage development.

From a clinical perspective, numerous large-cohort longitudinal OA studies have generated intriguing yet contradictory observations. Statin use has been found to increase the risk of OA[17] or to have no effect on OA symptoms[18], whereas other studies reported that statin use decreased the prevalence of certain forms of OA[19–21]. These discrepancies have been attributed to differences in population demographics and study methodology, suggesting that further investigations are needed to fully evaluate the potential benefits of statin use in preventing or treating OA.

Earlier interest in pursuing statin treatment for OA was mostly based on the hypothesis that the anti-inflammatory effects of statins may be effective in this situation. However, could there be a connection between OA pathogenesis and FGFR3 signaling? Based on *in vitro* data obtained from control- and OA patient-derived articular chondrocytes[22], one would actually expect decreased FGFR3 signaling to exacerbate cartilage destruction and OA pathogenesis. In fact, deletion of *Fgfr3* in articular chondrocytes leads to early cartilage degradation and OA-like changes[23]. Furthermore, genetic deletion of *Fgfr1* in mice confers resistance to OA with concomitant up-regulation of *Fgfr3*[24], suggesting that FGFR3 is protective against OA. However, it is likely that statins have pleiotropic effects, perhaps also acting to modulate the protein abundance of other signaling factors, such as FGFR1. Additional transcriptional and proteomic studies in iPS cells from ACH and TD patients, as well as in chondrocytes from OA patients, will be required to address the complete effects of statins on developing and mature chondrocytes.

One particularly interesting aspect of Yamashita and colleague's work is the creation of patient-derived iPS cells and their screening of drugs during *in vitro* iPS cell chondrogenesis[8]. While this approach has proven valuable for elucidating the cellular pathology of a number of monogenic diseases (in Marfan syndrome, for example[25]), it has not been widely employed to study polygenic or genetically heterogeneous conditions. Generating iPS cells from OA patients (and controls) and subsequent differentiation into articular chondrocytes could help to determine whether chondrocytes from OA patients share similar, identifiable and modifiable phenotypes. However, serious limitations to this approach must be considered (see below), including the fact that many non-genetic causes contribute to OA risk ad pathology. Provided that chondrogenesis of iPS cells derived from OA patients recapitulates some aspects of the disease, as did those from patients with genetic diseases (ACH, TD, and Marfan[8,25]), OA iPS cells would provide a resource for screening drugs and testing therapies *in vitro*. Combined with whole-genome sequencing, genotype–phenotype correlations could also be made, potentially paving the way for OA therapeutics based on genetic predispositions. Preliminary studies using iPS cells derived from synovial cells have been encouraging[26,27], and it will be interesting to see whether those derived from skin fibroblasts will behave similarly. Given the difficulties associated with surgically obtaining chondrocytes from patients (and in particular from controls), generating iPS cells from skin fibroblasts and coaxing them to become chondrocytes may offer a novel alternative to study the cellular defects in OA.

Still, several important caveats must be considered when proposing to study iPS cells from OA patients. First, increasing evidence demonstrates that OA is a disease of the whole joint, not only cartilage[28]. It might be helpful to differentiate additional populations of patient-derived iPS cells towards alternative lineages, such as osteoblasts or synovial cells, to further characterize the various cellular behaviors in relevant tissue types. A second caveat is the limited applicability of *in vitro* models for OA research. It is unclear how much iPS cell-induced chondrocytes would mimic articular cartilage, whose phenotype is fundamentally different from the growth plate chondrocytes recapitulated by Yamashita and colleagues. Furthermore, while osteoarthritic chondrocytes have endured decades of mechanical strain and environmental influence, chondrocytes derived from iPS cells will be naïve in this sense, and may not accurately reflect the disease phenotype at the cellular level. Finally, unlike ACH and TD, OA is not a purely genetic disease, as physical or physiological insults are thought to initiate and drive the progression of the disease in many cases[28]. Moreover, GWAS studies of OA patients have yielded many genetic variants, but these common polymorphisms seem to have mild to modest individual effects[29]. It is therefore apparent that multiple genetic polymorphisms underlie the hereditary components in OA and that studies of genetically heterogeneous iPS cells differentiated to chondrocytes may not facilitate testable hypotheses or widely applicable results.

In conclusion, the discovery that statins can improve chondrogenesis in ACH and TD iPS cells, as well as in an *in vivo* mouse model of ACH, holds great promise for treating ACH. Additionally, the successful use of patient-derived iPS cells differentiated to chondrocytes to screen therapeutic compounds highlights the potential of this approach to develop treatments for monogenic disorders. Similar approaches may be useful in identifying disease-relevant pathways in OA but will be hampered by the heterogeneous and multigenic nature of this complex disease that affects multiple tissues in the joint. While the findings by Yamashita and colleagues point to a potentially life-changing therapy for individuals coping with ACH, they further obfuscate the relationship between statins, FGFR3, and cartilage homeostasis. Additional studies are required to elucidate the full suite of mechanisms by which statins correct chondrogenesis in ACH and TD iPS cells, and to understand how statin use and cholesterol homeostasis may differentially influence chondrocytes in developmental stage-, context-, or genotype-specific manners.

Author contributions

J.R.B., N.G.B., and F.B. contributed to the conception and writing of this article.

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