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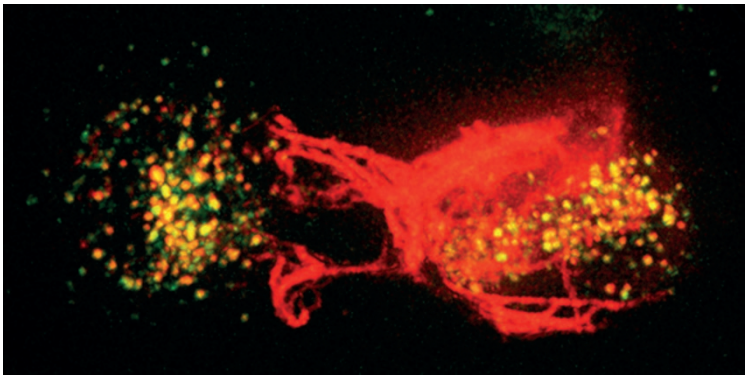
BONE

Autophagy regulates bone growth in mice

The secretion of type II collagen in growth plate chondrocytes is regulated by autophagy, according to newly published results. Furthermore, the study demonstrated that autophagy is regulated by a growth factor signalling pathway.

"It is well known that skeletal growth relies on biosynthetic processes; however, clinical observations have also suggested an essential, but unexplored, role for the lysosomal-autophagy pathway during bone growth," explains corresponding author Carmine Settembre.

The researchers started by analysing the femoral growth plates of transgenic mice that expressed an autophagosome marker tagged with green fluorescent protein. They observed that the number of autophagic vesicles was increased during postnatal development. In addition, mice that lacked the autophagy-related gene 7 (*Atg7*) in chondrocytes had reduced femoral and tibial lengths compared with wild-type mice. In the mutated mice, type II procollagen was stored in the endoplasmic reticulum (rather than being secreted and converted into type II collagen, as in wild-type mice) and formation of the type II collagen fibrillary network in the extracellular matrix was defective.



Z-stack and 3D reconstruction image of rat chondrocytes coexpressing Col2a1-mCherry and Lamp1-EGFP showing collagen fibrils secreted in the extracellular space and intracellular colocalization of Col2a1 molecules with lysosomes. Image courtesy of C. Settembre.

Interestingly, fibroblast growth factor 18 (FGF18) seems to mediate the postnatal induction of autophagy in chondrocytes. At embryonic day 18.5, the growth plates of *Fgf18*$^{+/-}$ mice had undetectable levels of LC3II (an autophagosome marker), whereas the autophagy receptor SQSTM1 had accumulated. After birth, the induction of autophagy was defective and autophagic vesicle biogenesis was reduced in *Fgf18*$^{+/-}$ mice compared with wild-type mice. Settembre and colleagues were able to rescue the collagen defects in the *Fgf18*$^{+/-}$ mice with pharmacological activation of autophagy. The authors conclude that autophagy is a developmentally regulated process that is necessary for bone growth, and that FGF signalling is a crucial regulator of autophagy in chondrocytes.

"More than 15 genetic disorders are caused by mutations in members of the FGF signalling pathways," says Settembre. "We want to define the physiological role of autophagy regulation by FGF molecules in bone and cartilage *in vivo* to understand if autophagy could become a new therapeutic target for the treatment of these disorders."

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ORIGINAL ARTICLE Cinque, L. *et al.* FGF signalling regulates bone growth through autophagy. *Nature* http://dx.doi.org/10.1038/nature16063