

# Genetic disorder sheds light on enzyme's role in bone metabolism

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Pycnodysostosis, a condition from which the painter Henri de Toulouse-Lautrec suffered, is a genetic disease characterized by short stature. This rare disease, surprisingly, provides a window into how joints are destroyed by arthritis. It is caused by deficiency of an enzyme known as cathepsin K which hampers osteoclasts (the cells that break down bone in bone modeling and repair), leading to poor bone resorption and dense, brittle bones.

Cathepsin K's role in bone metabolism has largely been studied using mouse models, but a new study examines the enzyme's role in bone resorption in a human patient and shows that it is not required to break down bone. The study was published in the November issue of *Arthritis & Rheumatism* (<http://www3.interscience.wiley.com/journal/76509746/home>).

Led by Professor Yrjö T. Konttinen of Helsinki University Central Hospital in Helsinki, Finland, the study involved a 55-year-old female patient with pycnodysostosis who also developed psoriatic arthritis. Since the patient lacked cathepsin K due to her condition, researchers hypothesized that this would protect her from the bone erosions in the hands and feet normally seen in psoriatic arthritis. However, she did in fact develop extensive erosions and destructive bone changes in her hands. Blood analysis was conducted to examine the proteinases (enzymes that break down proteins) responsible for bone degradation as well as the cellular mechanisms of bone resorption.

The analyses showed that the osteoclasts formed by the patient lacked cathepsin K, which was expected. Surprisingly, however, this deficiency did not prevent cells from resorbing bone, although the resorption was abnormal. In bone resorption, osteoclasts attach to the bone and dissolve bone mineral in the matrix, a process that appears to proceed normally even in pycnodysostosis. In a second step, known as collagenolysis, peptide bonds in the collagen of the demineralized bone matrix are broken down. The authors expected that this step would be defective in the cells of a patient who lacked cathepsin K, but instead found that it was not, since the patient's osteoclasts showed evidence of bone resorption.

"The results of our study indicate that, against the dogma, cathepsin K is not necessary for osteoclast-mediated bone resorption," the authors state. "The present results and some very recent findings suggest that even total inhibition of cathepsin K does not protect against pathologic bone destruction in arthritis." This indicates that other proteinases may play a role in bone collagen destruction when cathepsin K is not present. The authors conclude: "These findings may be pertinent to our understanding of the functions of cathepsin K inhibitors, which are currently being developed as drugs to treat metabolic bone diseases.

Source: Wiley

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