OSTEOPOROSIS

Linking osteoporosis with Alzheimer disease

Alzheimer disease is frequently associated with fractures and reductions in bone mineral density, even at early stages of disease when patients are still active. However, the mechanisms underlying this link are unclear. Using mouse models, Wen-Cheng Xiong and colleagues have now provided some insight into this connection, by identifying a cell-autonomous defect in osteoblast differentiation, as published in the *Journal of Bone and Mineral Research*.

In preliminary experiments, the investigators confirmed the expression of amyloid precursor protein (APP) in bone marrow stromal cells (BMSCs) from wild-type mice, and showed that the levels of this protein increased with age. Next, they used transgenic mice expressing an Alzheimer disease-associated mutant form of APP, known as APP_{swe}, to explore the effects of mutant APP on bone. From a young age, these mice displayed defects in bone formation compared with wild-type controls. Moreover, a concomitant

increase in adipocytes was observed in their bone marrow, resembling a skeletal ageing phenotype.

“...Alzheimer disease and osteoporosis may share conserved pathogenic mechanisms...”

In accordance with these findings, the differentiation of APP_{swe}-transgenic BMSCs into osteoblasts was reduced in *ex vivo* culture experiments, whereas adipocyte generation was enhanced, suggesting that the presence of APP_{swe} skews BMSC differentiation towards the adipocyte lineage. But how does APP_{swe} exert this effect?

Given the key part oxidative stress is thought to play in the pathogenesis of Alzheimer disease, the researchers examined whether an antioxidant could reduce the bone phenotypes of the transgenic mice. Indeed, treatment with *N*-acetylcysteine ameliorated the impact of APP_{swe} on BMSC differentiation, and

increased bone volume in the transgenic mice. Thus, “reactive oxygen species may be a conserved mechanism underlying APP_{swe}-induced neurodegenerative and osteoporotic deficits,” suggests Xiong.

Finally, similar bone loss and diminished osteoblast formation were observed in mice selectively expressing APP_{swe} in mature osteoblasts, demonstrating that the skeletal effects of mutant APP are likely to be, at least in part, osteoblast autonomous.

“These results support the view that Alzheimer disease risk genes may also be a risk factor for osteoporosis, and that Alzheimer disease and osteoporosis may share conserved pathogenic mechanisms,” concludes Xiong, who plans to further test such ideas in future work.

Isabel Woodman

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