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Hematopoietic autophagy deterioration links to osteoporosis

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Statement of the Problem: Disorders of hematopoiesis affect skeletal system. Osteoporosis is a major risk of complications in hematopoietic disease such as hematopoietic malignancy, anemia, b-thalassemia and hematopoietic stem cell transplantation. We examine the correlation between hematopoietic system and bone homeostasis.

Findings: In clinical, we found positive correlation between red blood cell count and femur neck Bone Mineral Density (BMD) in 4964 healthy samples. Then femur-derived bone marrow of 30 patients was obtained from young normal BMD (BMD>-1.0, age<40y) or aged osteoporosis (BMD<-2.5, age>60y) during total hip replacement surgery. Human hematopoietic stem progenitor cells (CD34+CD45+) LC3 protein was inhibited in aged osteoporosis patients associated with descending autophagy gene expression, with Atg7, Atg5, Atg12, LC3b, Lam2a, P62 involved. To verify the clinical observation, deletion of Atg7 gene in hematopoietic system mice (Atg7f/f; Vav-iCre) were established, which led to autophagy dysfunction specifically in hematopoietic system. Atg7 null in hematopoietic system caused decreased BMD, low bone formation rate and weak bone biomechanical strength properties. Scanning electron microscope as well as H&E and Masson staining depicted trabecular microstructure destruction. However, there was no size difference in skeleton Alcian blue and Alizarin red S staining. Immunofluorescence of cortical bone revealed abnormal osteocyte size and number in Atg7f/f; Vav-iCre mice, accompanied by osteocyte DNA damaged and increased ROS level. Bone homeostasis related gene expression, including SP7, RUNX2, BMP2, BMP6, CTSK, TRAP5, was inhibited in Atg7f/f; Vav-iCre mice. Integrative proteomics functional enrichment showed Atg7f/f; Vav-iCre mice bone tissue skeletal systme morphogenesis and development were down-regulated, with Extra Celluar Matrix (ECM) pathway by KEGG analysis, which confirmed by collagen1 immunohistochemistry staining.

Conclusion & Significance: These findings suggest that deterioration of autophagy in hematopoietic system undermines osteogenesis, which are apparently caused by aberrant alteration in the ECM pathway, extending new potential cause and potential therapy of osteoporosis.

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