Nuclear factor I A (NFIA) regulates osteoblast differentiation of skeletal progenitor cells in bone growth and fracture healing in mice

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Objectives : NFIA is a transcription factor belonging to the nuclear factor I family and has key roles in the development of multiple organs. However, the function of NFIA in skeletal development remains unknown. We evaluated the skeletal phenotype of mice in which NFIA was conditionally deleted in a cell type-specific manner.

Experimental Methods and Results: Nfia-floxed mice were crossed with Col2a1-cre (chondrocytes), Osx-creER (osteoblasts) or Prrx1-cre (skeletal progenitor cells) drivers. Deletion of NFIA in chondrocytes or osteoblasts did not cause any apparent bone phenotype. In contrast, NFIA deletion in skeletal progenitor cells using Prrx1-cre (Prrx1-NFIA cKO) resulted in a significant decrease in trabecular bone mass at P21 and 8 weeks of age. Bone histomorphometry revealed a reduction in osteoblast numbers and an unchanged osteoclast number per bone perimeter in Prrx1-NFIA cKO mice, associated with decreased trabecular as determined by calcein double labeling, accompanied by the significant reduction of the serum bone formation marker PINP level. In addition, upon the complete fracture of the mid-shaft, Prrx1-NFIA cKO femurs showed normal callus formation but delayed calcification of the healing site. In primary cell culture, bone marrow stromal cells (BMSCs) isolated from Prrx1-NFIA cKO mice showed reduced alkaline phosphatase and alizarin red staining, indicating impaired osteogenic potential of skeletal progenitor cells. Bulk RNA-seq analyses of NFIA-deficient BMSCs identified 53 differentially expressed genes including downregulation of Ibsp, Igfbp2, and Spon1, which are known to play important roles in osteoblast differentiation. Interestingly, inspection of the genome-wide association study revealed 6 SNPs statistically significantly associated with heel bone mineral density, implicating a role of NFIA in human bone metabolism. including data and statistics where appropriate

Conclusion: Our study demonstrates for the first time that NFIA plays an important role in osteoblast differentiation of skeletal progenitor cells in bone growth and fracture healing.

This study was supported by grants from National Institutes of Health, R01DE026666