Identification of Gene Signature Associated with Elevated Bone Formation Rate in Aging Mice

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Identification of a gene signature associated with elevated bone formation rate in aging mice

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Osteoporosis, a disease of low bone mass that results from bone resorption exceeding bone formation, places individuals at enhanced risk for fracture, disability, and death. There is an urgent and unmet need for novel targets in treating osteoporosis, requiring a better understanding of the endogenous mechanisms regulating bone formation. We reported that deletion of the Bmp2 gene in skeletal progenitor cells of mice causes substantially elevated bone mass in young adulthood due to increased bone formation rate (Lowery et al., 2015). As yet unpublished work indicates the age-related decline in bone mass of Bmp2 mutant mice is reduced approximately three-fold compared to control mice; quantification of serum bone turnover markers indicates this is caused by a sustained increase in bone formation rate at least 35 weeks of age with no alteration in bone resorption. Here, we determine the gene signature associated with elevated bone formation rate using genome-wide transcriptome profiling in bones of 35-week-old control and Bmp2 mutant mice. Applying stringent criteria comparing the expression data to eight well-accepted housekeeping genes (Ppia, Gusb, Gapdh, Hprt, Tbp, Ppip, Gusl, Pkg1, and Ywhaz), we found that, out of 24,980 exon-containing transcripts detected in both genotypes, 334 genes were up-regulated and 330 were down-regulated at least two-fold compared to controls. An additional 704 genes were detected in only one genotype. We refined this putative signature by performing transcriptome profiling in these animals at 55 weeks of age when bone formation rate is no longer elevated. This revealed that, of those genes altered at 35 weeks of age, 461 (71.5%) were either no longer up-regulated or down-regulated in Bmp2 mutant mice by 55 weeks of age. Bioinformatic analyses on this refined gene set indicates that elevated bone formation rate in Bmp2 mutant mice correlates with enrichment for genes containing binding sites for transcription factors associated with skeletal homeostasis, including Foxp1, Sox2, Egr1, E2f1, Klf4, Cnot3, Stat4, and Foxa1. Further, several genes corresponding with osteoblast differentiation and activity, such as Pak4 and Pla2g6a, the latter of which encodes cytosolic phospholipase A2 and whose deletion causes osteopenia, are up-regulated in Bmp2 mutant mice. Collectively, our findings provide insight into the mechanisms regulating age-related bone loss and highlight potential targets for therapeutic modulation of bone mass.

**Figure 3:** A: Results of RNA-Seq analyses at 35 and 55 weeks of age; expressed relative to control. B-C: Comparison of Bmp2 mutant results relative to control at 35 and 55 weeks of age represented in Venn diagram (B) and tabular (C) forms.

**Conclusions, Significance & Future Directions:**

- Bmp2 mutant mice display high bone mass in young adulthood and reduced age-related bone loss.
- Genome-wide transcriptome profiling of Bmp2 mutant mice identified 461 differentially expressed genes associated with increased osteoblast activity.
- The differential gene signature is enriched for genes containing binding sites for transcription factors associated with skeletal homeostasis. Several genes corresponding with osteoblast differentiation and activity are up-regulated in Bmp2 mutant mice.
- Collectively, our findings provide insight into the mechanisms regulating age-related bone loss and highlight potential targets for therapeutic modulation of bone mass.
- Future studies will involve functional studies to narrow the gene signature to those that regulate osteoblast function.

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