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BONE

PPARγ controls marrow adiposity

Marrow adipose tissue (MAT) accumulation is a hallmark of many skeletal diseases, such as osteoporosis and disuse osteopenia. Previous work has shown that the mitogen-activated protein kinase (MAPK) pathway promotes osteogenesis and inhibits marrow adipogenesis *in vitro* through phosphorylation of runt-related transcription factor 2 (RUNX2) and peroxisome proliferator-activated receptor γ (PPARγ), respectively. Now, a new study evaluating the *in vivo* significance of these findings shows that the phosphorylation state of PPARγ controls bone formation and marrow adiposity in mouse models.

Micro-CT imaging revealed that mice with the PPARγ-S112A mutation (which prevents MAPK-dependent PPARγ phosphorylation) had markedly lower trabecular bone volume than wild-type mice; this was accompanied by reduced bone formation and osteoblast activity, independent of osteoclastic resorption. By contrast, PPARγ-S112A mice had greater than threefold increases in MAT volume, upregulation of adipocyte differentiation markers and elevated serum levels of adiponectin.

Bone marrow stromal cells isolated from PPARγ-S112A mice preferentially differentiated into adipocytes; consistently, these cells had elevated levels of total PPARγ and decreased levels of total and phosphorylated RUNX2. Furthermore, bone marrow-derived mesenchymal stem cells (MSCs) from PPARγ-S112A mice had a reduced ability to form osteoblast colonies and an increased capacity to form adipocyte colonies *in vitro*, indicating that PPARγ-S112 phosphorylation influences MSC lineage allocation.

"These findings provide *in vivo* support for our hypothesis concerning the role of MAPK signalling in lineage switching between osteoblasts and adipocytes and bone and/or MAT formation," concludes lead investigator Renny Franceschi. "Blocking RUNX2 phosphorylation is also of equal importance, a goal that is being actively pursued by us".

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ORIGINAL ARTICLE Ge, C. *et al.* Genetic inhibition of PPARγ S112 phosphorylation reduces bone formation and stimulates marrow adipogenesis. *Bone* http://dx.doi.org/10.1016/j.bone.2017.10.023 (2017)