USF3 modulates osteoporosis risk by targeting *WNT16*, *RANKL* and *RUNX2*

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Abstract

Osteoporotic fractures cause major morbidity and mortality in the aging population. Genome-wide association studies (GWAS) have identified *USF3* as the novel susceptibility gene of osteoporosis. However, the functional role in bone metabolism and the target gene of the bHLH transcription factor USF3 are unclear. Here we show that *USF3* enhances osteoblast differentiation and suppresses osteoclastogenesis in cultured human osteoblast-like U-2OS cells. Mechanistic studies revealed that transcription factor USF3 antagonistically interacts with anti-osteogenic TWIST1/TCF12 heterodimer in the *WNT16* and *RUNX2* promoter, and counteracts CREB1 and JUN/FOS in the *RANKL* promoter. Importantly, the osteoporosis GWAS lead SNP rs2908007 risk A allele abolishes USF3 binding in the *WNT16* promoter, conferring allele-specific downregulation of the osteoclastogenesis suppressor *WNT16*. While the risk G allele of osteoporosis GWAS lead SNP rs4531631 facilitates binding of CREB1 and JUN/FOS in the *RANKL* promoter, resulting in enhanced transactivation of *RANKL*, the principal contributor to osteoclastogenesis. Our findings uncovered functional mechanisms of osteoporosis novel GWAS associated gene *USF3* and lead SNPs rs2908007 and rs4531631 in the regulation of bone formation and resorption.

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