Abstract (english):

Sphingosine-1-phosphate is involved in bone metabolism but its precise role and potential use for therapeutic applications are unknown. In male human subjects, we observed that plasma S1P levels were positively associated with activity markers of enhanced bone turnover and negatively with bone mineral density, respectively. In search of potential therapeutic applications in adult mice, we raised S1P levels by conditionally deleting or pharmacologically inhibiting the S1P lyase and observed an impressive increase in bone mass that, surprisingly, was accompanied by striking reduction of adipose tissue. This was due to S1P receptor 2 signaling affecting fundamental osteoblast and osteoclast functions: S1P potently stimulated osteoblastogenesis at the expense of adipogenesis through osterix and PPARγ, while simultaneously inhibiting osteoclast differentiation through increased osteoprotegerin production involving both the p38/GSK3β/β-catenin and non-canonical Wnt5a/Lrp5 pathways. Accordingly, S1P2-deficient mice were osteopenic and obese, whereas lyase inhibition prevented both the osteoporosis and obesity developing under high-fat diet in apolipoprotein E-deficient mice or in the absence of the leptin receptor. In humans, body mass index and leptin levels correlated with plasma S1P. Thus tonic and amplified S1P/S1P2 signaling reciprocally connects bone and adipose tissue homeostasis and represents an endogenous autoregulatory mechanism that could be exploited for novel therapeutic approaches to osteoporosis and obesity.