

Invited Speaker Abstract

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A non-canonical Wnt signal induces osteoblastogenesis through attenuating PPAR γ -mediated adipogenesis

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Pluripotent mesenchymal stem cells in bone marrow differentiate into osteoblasts, adipocytes and the other cells. Balanced cytodifferentiation of stem cells is essential for the formation and maintenance of bone marrow, however the mechanism of these differentiation switch is largely unknown. PPAR γ is known as a major inducer of adipogenesis, serving as a ligand-dependent transcription factor. Fatty acid derivatives as well as some anti-DM compounds such as the TZDs activate this receptor function. In addition, several cytokine signals are considered to modulate the PPAR γ function in gene regulation and cell differentiation.

Here, we show that non-canonical Wnt pathway through CaMKII-TAK1/TAB2-NLK transrepresses PPAR γ transactivation with Runx2 induction, promoting osteoblastogenesis over adipogenesis from bone marrow mesenchymal progenitors. A non-canonical Wnt ligand (5a) activated NLK (Nemo-like kinase) that in turn phosphorylates a histone methyltransferase, SETDB1, leading to formation of a co-repressor complex that inactivates PPAR- γ function through histone H3-K9 methylation. Wnt-5 α ^{+/-} mice showed a clear bone loss with decreased trabecular bone mass, but rather significantly elevated number of adipocytes in bone marrow, while increased bone mass together with enhanced osteoblastogenesis was seen in PPAR- γ ^{+/-} mice. These findings suggest that the non-canonical Wnt signaling pathway suppresses PPAR- γ function through chromatin inactivation, leading to an osteoblastic cell lineage decision from mesenchymal stem cells in bone marrow.

Reference; Takada *et al.*, Nat. Cell Biol., 9, 1273-85, 2007