

Runx2 Deficiency Promotes Adipogenesis by Regulating Insulin Signaling

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- A. Insulin-signaling is critical for the regulation of glucose homeostasis and energy metabolism. Alterations in insulin-signaling are associated with aging, obesity, and diabetes, all of which are associated with a concomitant increase in fat formation and a decrease in bone synthesis. Fat-producing adipocytes and bone-forming osteoblasts are derived from a common progenitor. Runx2 is essential for bone formation and osteoblast differentiation but its role in commitment of mesenchymal cells (MC) to other lineages and insulin-signaling is unknown.
- B. MC from Runx2 null mice were isolated to establish monoclonal lines. For a molecular understanding of the regulatory network, we performed gene microarray analysis of control and insulin treated Runx2 null and 3T3L-1 pre-adipocytes. For a mechanistic understanding, we performed in-situ and biochemical analyses.
- C. Runx2-deficiency resulted in a preferential commitment of MC to the adipocyte lineage. Rosiglitazone, a PPAR γ agonist, resulted in a robust adipogenesis. Addition of insulin to the Runx2 null cells results in strong inhibition of adipocyte formation. This data suggests that Runx2-deficient MC bypass the critical requirement of insulin. Reconstitution of these cells with Runx2 restores insulin response. Surprisingly, in the control condition, more than 95% of the genes (122/128) associated with insulin-signaling were expressed at higher levels in Runx2 null MC compared to preadipocytes. Addition of insulin evoked a differential response, with 85% genes induced in 3T3L-1 and only 3% in Runx2 null MC. Shockingly, a strong suppression of insulin-signaling pathway at both the pre- and post- receptor level was evident in Runx2-null MC. Although the insulin receptor was expressed in both cell types, a differential isoform is utilized during adipocyte formation. The paradoxical insulin response is due to an impaired internalization of the activated insulin receptor in Runx2 null MC.
- D. Taken together, Runx2 is essential for regulation MC lineage commitment as well as energy metabolism.