P1-1

An Adiponectin Receptor Agonist Promote Osteogenesis via Regulating Bone-Fat Balance

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Background Adiponectin signaling has been considered to be a promising target to treat diabetes related osteoporosis resulting from excessive osteoclastogenesis and bone-fat imbalance. However, contradictory results regarding bone formation were observed due to the complex paracrine feedback regulation and various isoforms of adiponectin. Therefore, it is urgently needed to investigate the role of adiponectin receptor signals on bone-fat balance in order to having a comprehensive understanding of the biological effect of adiponectin.

Methods We primarily applied a newly discovered specific adiponectin receptor agonist AdipoRon to treat pre-osteoblast, pre-osteoclast and two kinds of mesenchymal stromal cells to investigate the role of Adiponectin receptor signals on bone-fat balance including osteoblast-osteoclast and osteoblast-adipocyte differentiation balance. We then established femur defect mouse model and treated them with AdipoRon to see whether adiponectin receptor activation could promote bone regeneration and further confirm its effect in adipogenesis of inguinal adipocytes.

Results In our study, we found that AdipoRon could slightly inhibit the proliferation of pre-osteoblast and pre-osteoclast, but AdipoRon showed no effect on the viability of mesenchymal stromal cells. AdipoRon could remarkably promote cell migration of mesenchymal stromal cells. Additionally, AdipoRon promoted osteogenesis in both pre-osteoblasts and mesenchymal cells including bone marrow mesenchymal stromal stem cells and adipose derived stem cells. Besides, AdipoRon significantly inhibited osteoclastogenesis via its direct impact on pre-osteoclast and its indirect inhibition of RANKL in osteoblast. Moreover, both bone marrow mesenchymal stromal stems cells and adipose derived stem cells showed obviously decreased adipogenesis when treated with AdipoRon. Consistently, AdipoRon treated mice showed faster bone regeneration and repressed adipogenesis in inguinal adipocytes.

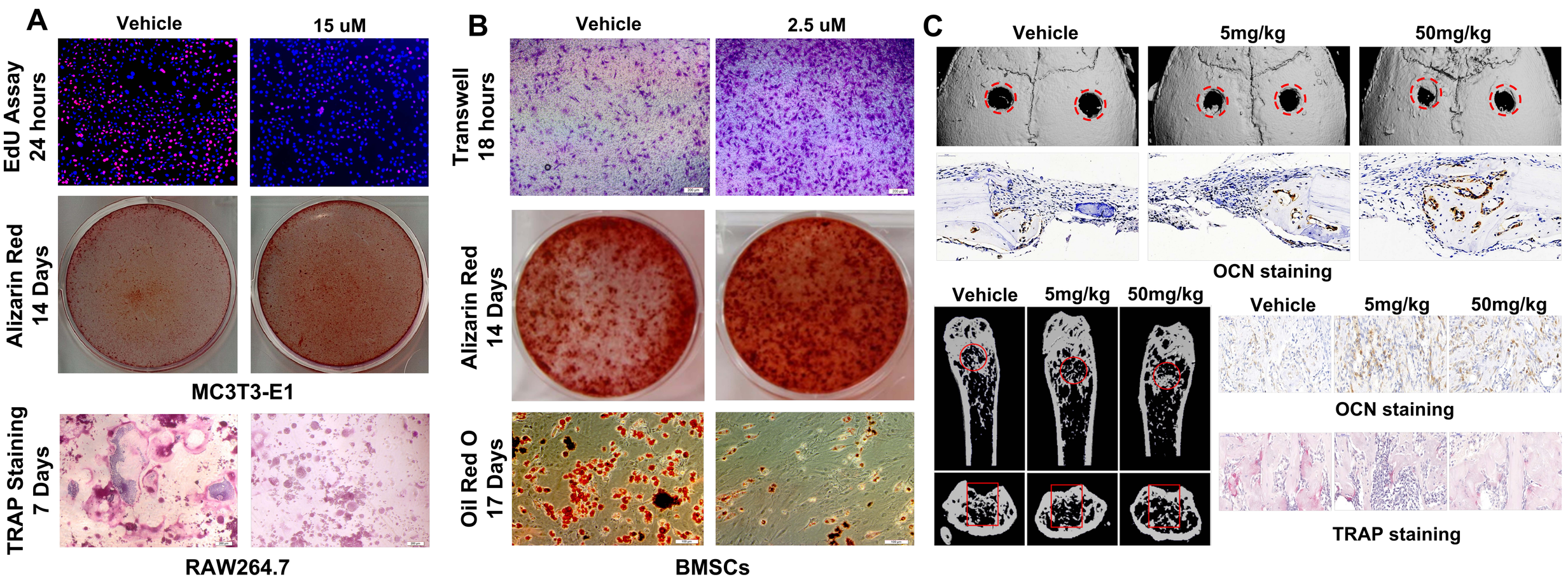

Figure (A) Adiponectin receptor activation increased osteogenesis of MC3T3-E1 and inhibited osteoclastogenesis of RAW264.7; (B) Adiponectin receptor activation promoted cell migration and osteogenic differentiation, and decreased adipogenic differentiation of BMSCs; (C) Adiponetin receptor activation up-regulated the expression level of OCN and accelerated skull and femur defect repairing.

Conclusion Our study demonstrated a pro-osteogenic, anti-adipogenic and anti-osteoclastogenic effect of adiponectin receptor activation in young mice, which suggested adiponectin receptor signaling was involved in bone regeneration and bone-fat balance regulation. Thus, AdipoRon could be a promising target for the treatment or prevention of osteoporosis.