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Differential regulation of homeostatic and pathological bone resorption by Notch-RBP-J signaling

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The maintenance of bone homeostasis is tightly regulated by the balance between bone formation and resorption. Pathological bone destruction is a severe consequence of inflammatory arthritis such as Rheumatoid arthritis (RA) and a major cause of morbidity and disability in RA patients. Abnormal osteoclast formation and activation in joints are responsible for pathological osteolysis. TNF-α plays a key role in the pathogenesis of inflammatory osteoclastogenesis and bone resorption in diseases such as RA. Recently, allelic variantsof RBPJ, the master transcription factor in Notch signaling have been found to be linked with RA. Although previous literature suggested different or opposing roles of Notch in *in vitro* osteoclastogenesis, in this study we elucidate that Notch-RBP-J signaling plays a minor role in homeostatic bone resorption based on genetic evidence that mice with a myeloid-specific deletion of RBP-J (RBP-$J^{f/f}$LysM-Cre) or mice with constitutively active NICD1 expression in myeloid compartment ($NICD1^{M}$) did not exhibit significant bone defects under physiological conditions. However, the role of Notch-RBP-J signaling in pathological osteoclastogenesis and bone resorption was not known. In this study, the role of RBP-J in osteoclastogenesis and bone resorption under inflammatory conditions was investigated. TNF-α did not detectably induce osteoclastogenesis in wild type (WT) bone marrow macrophages (BMMs). Deletion of RBP-J resulted in dramatic induction of osteoclastogenesis by TNF-α in the absence of exogenous RANKL, comparable to that induced by RANKL in WT cells. TNF-α-induced mouse osteoclasts derived from RBP-J deficient cells formed actin rings and resorbed dentin slices *in vitro*. Similar results were obtained using TNF-α-treated human osteoclast precursors in which RBP-J expression was knocked down using RNA interference. RBP-J deficiency had a much more modest augmenting effect on RANKL-induced osteoclastogenesis. Furthermore, RBP-$J^{f/f}$LysM-Cre mice showed dramatically increased osteoclast formation, severe bone destruction and increased serum TRAP levels relative to littermate controls in a TNF-α-induced model of pathological inflammatory bone resorption. Importantly, gain of function of RBP-J by using $NICD1^{M}$ mice significantly prevented inflammatory bone resorption in both a TNF-induced local osteolysis mouse model and an antibody-induced arthritis model. Mechanistically, TNF-α induced dramatically increased levels of the osteoclast master regulator NFATc1 and osteoclast marker genes including TRAP, cathepsin K, and integrin α3 in RBP-J deficient relative to WT cells. RBP-J deficiency resulted in increased TNF-α-induced NFATc1 transcription and RNA Pol II occupancy at the NFATc1 gene locus. These results show that RBP-J negatively regulates TNF-α-induced osteoclastogenesis by suppressing induction of NFATc1. RBP-J suppressed NFATc1 induction by attenuating c-Fos activation and suppressing induction of Blimp1, thereby preventing downregulation of transcriptional repressor IRF-8 that blocks osteoclast differentiation. These findings identify a key role for RBP-J in restraining TNF-α-induced inflammatory osteoclastogenesis and provide mechanisms by which RBP-J suppresses NFATc1 induction. Notch-RBP-J signaling plays a prominent role in inhibiting osteoclastogenesis in inflammatory settings, thereby identifying Notch-RBP-J as an attractive potential therapeutic target for excessive pathological bone resorption.

Biography

Baohong Zhao obtained a PhD degree in Biochemistry in Showa University in Japan in 2008 and finished her postdoctoral training in the Research Division of the Hospital for Special Surgery affiliated to Weill Cornell Medical College. She is an Assistant Scientist (equivalent to Assistant Professor) in the Hospital for Special Surgery and the Department of Medicine of Weill Cornell Medical College. Her lab currently focuses on inflammatory regulation of bone metabolism especially in osteoclastogenesis and bone resorption. She has identified several key negative regulators and underlying mechanisms for osteoclastogenesis, including IRF-8 and RBP-J. She has published over 25 papers in peer-reviewed journals and is well recognized in the field of bone biology. She serves as a reviewer for *Arthritis & Rheumatism, Arthritis Research & Therapy,Journal of Experimental Medicine* and many other reputed journals.

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