DOCTORAL THESIS

Osteoblastic PLEKHO1 contributes to joint inflammation in rheumatoid arthritis

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Abstract

Background: Osteoblasts participating in the inflammation regulation gradually obtain concerns. However, its role in joint inflammation of rheumatoid arthritis (RA) is largely unknown. Here, we investigated the role of osteoblastic pleckstrin homology domain-containing family O member 1 (PLEKHO1), a negative regulator of osteogenic lineage activity, in regulating joint inflammation in RA.

Methods: The level of osteoblastic PLEKHO1 in RA patients and collagen-induced arthritis (CIA) mice was examined. The role of osteoblastic PLEKHO1 in joint inflammation was evaluated by a CIA mice model which was induced in osteoblast-specific *Plekho1* conditional knockout mice and mice expressing high *Plekho1* exclusively in osteoblasts, respectively. The effect of osteoblastic PLEKHO1 inhibition was explored in a CIA mice model. The mechanism of osteoblastic PLEKHO1 in regulating joint inflammation was performed by a series of *in vitro* studies.

Results: PLEKHO1 was highly expressed in osteoblasts from RA patients and CIA mice. Osteoblastic *Plekho1* deletion ameliorated joint inflammation, whereas overexpressing *Plekho1* only within osteoblasts exacerbated local inflammation in CIA mice. PLEKHO1 was required for TNF receptor-associated factor 2 (TRAF2)-mediated the ubiquitination of receptor-interacting serine/threonine-protein kinase 1 (RIP1) to activate nuclear factor kappa-light-chain-enhancer of activated B (NF-kB) pathway for inducing inflammatory cytokines production in osteoblasts. Moreover, osteoblastic PLEKHO1 inhibition improved joint inflammation and attenuated bone formation reduction in CIA mice.

Conclusions: These data strongly suggest that highly expressed PLEKHO1 in osteoblasts mediates joint inflammation in RA. Targeting osteoblastic PLEKHO1 may exert dual therapeutic action of alleviating joint inflammation and promoting bone repair in RA.

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