

DOCTORAL THESIS

Role of CKIP-1 in suppression of osteoblast mediated bone repair in a collagen induced non-human primate arthritis model

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Abstract

Rheumatoid arthritis (RA) is a systemic, inflammatory disease, which predominantly affects multiple joints. RA is characterized by swollen joints and peri-articular bone erosion. Conventional RA treatments have shown to reduce inflammation and slow down bone erosion, but repair of bone erosion is limited. Additionally, failure to repair for bone erosion in rheumatoid arthritis (RA) is caused by inadequate osteoblast-mediated bone formation resulting from focal inflammatory environment. Hence, there is immediate need to facilitate greater insight and develop a new therapeutic strategy to aid osteoblast -mediated repair of bone loss in RA. CKIP-1 is an intracellular inhibitor, that can negatively regulate osteoblast lineage cells differentiation and activity. CKIP-1 levels were found to be aberrantly over expressed in bone specimens from RA patients and arthritis mice, which was associated with reduced bone formation and increased disease severity. By genetic approach, overexpressed CKIP-1 in osteoblast exacerbated bone erosion and articular inflammation in CIA mice, whereas deficiency of CKIP-1 in osteoblast alleviates bone erosion in CIA mice. By pharmacological approach, RNA interference-based silencing of osteoblastic CKIP-1 led to bone formation-mediated reparative process at erosive site and reduced articular inflammation in arthritis induced mice. To extend above findings to a more relevant species that more closely

resemble humans, we aimed to investigate the role of osteoblastic Casein kinase-2 interacting protein-1 (CKIP-1) in failure to repair bone erosion in non-human primate (NHP) arthritis model in this study. We found that CKIP-1 mRNA expression in osteoblasts of arthritic NHP was significantly suppressed by CKIP-1 siRNA treatment. Moreover, silencing of CKIP-1 in osteoblast of arthritis monkey improved clinical signs such as reduction in arthritis score, joint swelling and increase in body weight. Similarly, suppression of osteoblastic CKIP-1 resulted in better organized bony and articular structure with, fewer bone erosion sites as observed in x ray and micro CT images. Moreover, we found increase in bone mass, bone formation parameters such as BFR/BS and MAR and histological examination revealed attenuation of peri articular bone erosion and intraarticular inflammation in CKIP-1 siRNA treated arthritis monkeys.

Taken together, these data strongly suggest that highly expressed osteoblastic CKIP-1 plays an important role in failure to repair articular bone erosion by inhibiting bone formation in RA. Targeting osteoblastic CKIP-1 could serve as a new therapeutic strategy by bone repair augmentation in RA.

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