S100A8 Enhances Osteoclast-Mediated Bone Resorption in Experimental Antigen-Induced Arthritis Through Activation of Toll-Like Receptor 4


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Abstract

Background: Bone destruction is an important hallmark of rheumatoid arthritis (RA) and results from enhanced formation and activity of osteoclasts in affected joints. The inflamed synovium is an active site of interplay between immune and bone cells, and plays an important role in inflammatory bone pathology. Little is known about the involvement of alarmins, even though large amounts of S100A8 and S100A9 are produced within the inflamed synovium and their levels are significantly correlated with the development of joint destruction in RA. The aim of the present study was to investigate the role of S100A8 and S100A9 in osteoclast-mediated bone destruction in murine antigen-induced arthritis (AIA).

Methods: Bone destruction was analyzed on days 7 and 21 after AIA induction in knee joints of S100A9-/- mice, which also lack S100A8 protein expression, and wild type controls. Bone marrow-derived osteoclast precursors of S100A9-/- and wild type mice were differentiated into osteoclasts in vitro. Additionally, osteoclast precursors were stimulated with 1.0 μg/ml recombinant S100A8 or S100A9 during osteoclastogenesis. Receptor involvement was investigated by blocking receptor for advanced glycation end products (RAGE) signaling or using Toll-like receptor (TLR)4-/- osteoclast precursors. In vitro experiments were analyzed for the formation of osteoclasts and actin rings, expression levels of osteoclast markers, and resorption pit formation on bone.

Results: Bone erosions and osteoclast numbers were significantly reduced in arthritic knee joints of S100A9-/- mice. In vitro, bone marrow-derived precursors of S100A9-/- mice developed normally into functional osteoclasts, excluding an intrinsic role for S100A8/S100A9. In contrast to S100A9, addition of S100A8 during osteoclastogenesis resulted in significantly increased osteoclast numbers in conjunction with enhanced actin ring formation and increased bone resorption levels (83%, 94%, and 85% increase, respectively; P < 0.01). The stimulatory effects of S100A8 on osteoclast differentiation and activation could not be inhibited by RAGE blockade, whereas the increase in osteoclast numbers, actin rings, and bone resorption levels was completely abrogated using TLR4-/- osteoclasts.

Conclusion: This study demonstrates that S100A8 stimulates osteoclast formation and activity, and indicates that both S100A8 and TLR4 are important factors in mediating osteoclastic bone destruction in experimental arthritis.