## A85 S100A8 ENHANCES OSTEOCLAST-MEDIATED BONE RESORPTION IN EXPERIMENTAL ANTIGEN-INDUCED ARTHRITIS THROUGH ACTIVATION OF TOLL-LIKE RECEPTOR 4

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**Objective** Rheumatoid arthritis (RA) is characterised by severe bone erosions caused by enhanced osteoclast formation and activity. Significantly elevated S100A8 and S100A9 levels in serum and synovial fluid of RA patients are strongly correlated to joint destruction. The aim of the present study was to investigate the role of S100A8 on osteoclastic bone resorption in murine antigen-induced arthritis (AIA).

**Methods** Bone destruction was analysed 7 and 21 days after AIA induction in knee joints of S100A9$^{-/-}$ mice, also lacking S100A8 protein expression, and wild type controls. Bone marrow precursors from S100A9$^{-/-}$ and wild type mice were

differentiated into osteoclasts in vitro. Additionally, precursors were stimulated with recombinant S100A8 during osteoclastogenesis. Receptor involvement was investigated using an anti-receptor for advanced end products (anti-RAGE) blocking antibody or toll-like receptor 4 negative ($TLR4^{-/-}$) osteoclast precursors. Experiments were analysed for the formation of tartrate-resistant acid phosphatase-positive multinucleated cells ($TRACP^{+}$ MNCs), actin rings, mRNA expression levels of osteoclast markers and resorption pit formation on bone.

**Results** Bone erosions and cathepsin K staining were significantly suppressed in $S100A9^{-/-}$ mice after AIA induction. In vitro however, bone marrow-derived precursors from $S100A9^{-/-}$ mice developed normally into functional osteoclasts, excluding a role for intrinsic S100A8/A9. Addition of S100A8 during osteoclastogenesis resulted in increased osteoclast formation The mRNA expression levels of osteoclast markers were not affected by S100A8 stimulation, but the formation of actin rings, essential for the bone resorptive capacity of osteoclasts, was significantly enhanced in conjunction increased bone resorption levels. The stimulatory effects of S100A8 on osteoclast maturation and function could not be inhibited by RAGE blockade, whereas the increased osteoclast numbers, actin ring formation and resorption pit formation were completely abrogated using $TLR4^{-/-}$ osteoclasts.

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

**Topic** Myeloid cells and innate immune receptors.