Ly6C^{-} resident monocytes with osteoclastogenic potential arise before clinical onset of arthritis

A.Puchner, B., V. Saferding, Eliana Goncalves Alves, H. Leiss, J.S. Smolen, K. Redlich, S. Blüml
Dept. of Rheumatology, Medical University of Vienna, Austria.

Introduction. Bone erosions and systemic bone loss in rheumatoid arthritis patients results from an increased activity of osteoclast, which are derived from precursor cells of the myeloid lineage. Although there is much known about the mechanisms regulating the formation and activation of mature osteoclasts, the identity of an osteoclast precursor population in and its regulation by inflammatory cytokines during arthritis is poorly understood.

Methods. HTNFtg mice were clinically scored once per week for grip strength and swelling. In addition, blood was collected every week starting on week 4. Mice were sacrificed at week 10 - blood, spleen and bone marrow were collected for flow cytometry analysis. CCR2$^{-/-}$ mice were crossed into hTNFtg mice and histological analysis was performed. Different monocyte subsets were Facs-sorted and cultured in the presence of RANKL and MCSF to induce osteoclasts.

Results. We show that during TNF-driven arthritis CD11b^{+} CD115^{+} cells are elevated in blood before the onset of clinical symptoms and remain elevated throughout. These cells are also elevated in spleen and bone marrow during arthritis. In blood, these cells can be separated by their expression of Ly6C into inflammatory monocytes (CD115^{+}Ly6C^{high}) and resident monocytes (CD115^{+L}y6C^{low}). Interestingly, especially resident monocytes are elevated preclinical. Upon sorting resident and inflammatory monocyes from blood, we demonstrate that only resident monocytes are able to form multinucleated TRAP+ osteoclasts, but inflammatory monocytes do not. In order to further investigate the role of these monocyte subsets in the development of arthritic bone destruction and osteoclast formation we used CCR2 deficient mice, which lack circulating inflammatory monocytes and crossed them into hTNFtg animals. In line with our in vitro data, hTNFtg

mice lacking CCR2 (i.e. inflammatory monocytes) showed no reduction in the amount of joint destruction but even enhanced local bone erosion and osteoclast generation.

Conclusion. $CD115^{+}$ $CD11b^{+}$ cells, especially Ly6C- resident monocytes with osteoclastogenic potential, increase during inflammatory arthritis. Elevated numbers of these cells can be detected before clinical onset of disease and therefore may provide a biomarker for erosive inflammatory arthritis and even a possible target for therapeutically intervention.