Resident non-classical monocytes are critically important for tissue destruction in 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.

Bone destruction in rheumatoid arthritis is mediated by osteoclasts, which are derived from precursor cells of the myeloid lineage. Although there is much known about mature osteoclasts, the identity of an osteoclast precursor population and its regulation by inflammatory cytokines during arthritis is poorly understood.

Here we show that during TNF-driven arthritis monocytes, both inflammatory monocytes ($CD115^{+}Ly6C^{high}CCR2^{+}$), but in particular resident non-classical monocytes ($CD115^{+}Ly6C^{low}CCR2^{-}$), are elevated in blood before the onset of clinical symptoms and remain elevated throughout. Of note, when we correlated the number of the two monocyte subpopulations in blood with histological signs of joint destruction, we found the number of resident monocytes to significantly correlate with the area of erosion and number of osteoclasts in arthritic hind paws, whereas the number of inflammatory monocytes did not correlate at all with those parameters. These correlations were not confined to the hTNFtg model of arthritis, but could be observed also in K/BxN serum transfer arthritis. Upon sorting resident and inflammatory monocytes from blood, we further demonstrate that resident monocytes are more potent to form osteoclasts *ex vivo* after stimulation with MCSF and RANKL. Submitting sorted inflammatory and resident monocytes to RNA-sequencing after stimulation with MCSF and RANKL, we found increased expression of osteoclast related genes, including some which are required for pre-osteoclast fusion in RANKL-stimulated resident MC. Finally, we crossed CCR2 deficient mice, which lack circulating inflammatory monocytes, into hTNFtg animals. In line with our in vitro data, hTNFtg mice lacking CCR2 showed even enhanced local bone erosion and osteoclast generation.

Conclusion: Resident non classical monocytes are elevated during chronic inflammatory arthritis

and the numbers in blood correlate with histological markers of joint destruction in models of inflammatory arthritis. In addition, resident monocytes display an increased osteoclastogenic potential and might therefore be primarily responsible for arthritis-mediated bone destruction. Therefore these cells may provide a biomarker for erosive inflammatory arthritis and even a possible target for therapeutically intervention.