The role of microRNA-146a in inflammatory Arthritis

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Background:

MicroRNA (MiR)146a is a key regulator of the innate immune response and has also been shown to suppress cancer development in myeloid cells. Elevated expression of miR-146a has been detected in synovial tissue of rheumatoid arthritis patients, but its function is not clear yet. Thus the role of miR-146a in inflammatory arthritis needs to be clarified.

Materials and Methods:

We induced K/BxN serum transfer arthritis in wild type and miR-146a$^{-/-}$ mice. As a second inflammatory arthritis model we crossed miR-146a deficient into hTNFtg mice. Disease severity was assessed clinically and histologically in both arthritis models. Serum cytokine levels were measured by Elisa.

Results:

Absence of miR-146a leads to increased clinical signs of the induced serum transfer arthritis. In line, higher serum levels of the proinflammatory cytokines IL12 and TNF were measured in miR146a deficient mice compared to wt mice. When we crossed miR-146a$^{-/-}$ mice into hTNFtg mice, while detecting no clinical difference between hTNFtg and miR146a/hTNFtg mice, we found a significant increase in synovial inflammation. Even more striking, miR146a/hTNFtg mice displayed a more than twofold increase in local bone destruction and number of osteoclasts in the tarsal joints of the mice. Of note, in vitro osteoclast generation was reduced in miR146a$^{-/-}$ mice.

Conclusion:

Data from these two arthritis models reveal a negative regulatory role of the miR-146a in inflammatory arthritis. Mice lacking miR-146a are clinically worse than their wild type counterparts with concomitant higher proinflammatory cytokine production in serum transfer arthritis. In addition, microRNA 146a has important anti-erosive properties in TNF-driven local bone destruction and osteoclastogenesis, as mice lacking this microRNA display highly

increased joint destruction compared to WT. These results identify an important anti-inflammatory role of miR-146a, which might possibly be exploited for therapeutic purposes.