# Important Role of microRNA-146a in Inflammatory Arthritis by Controlling Local Bone Destruction

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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., Although in late stages of arthritis elevated expression of miR-146a in synovial tissue of rheumatoid arthritis patients was detected, the level of this miRNA was found to be down regulated in early disease, but its role in the development of inflammatory arthritis is yet unknown.

Materials and Methods:

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

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 IL-12 and IL-6 were measured in miR146a deficient compared to wt mice. When we crossed miR-146a$^{-/-}$ into hTNFtg mice, histological examination revealed a significant increase in synovial inflammation and even more striking a more than twofold increase in local bone destruction due to increased generation of osteoclasts in the tarsal joints in miR-146a$^{-/-}$/hTNFtg mice compared to hTNFtg mice. Interestingly, systemic bone loss was comparable in hTNFtg compared to miR-146a$^{-/-}$

/hTNFtg mice, suggesting an important local role of miR-146a. Indeed, we detected increased levels of IL-1β and RANKL and decreased expression of OPG locally in the paws of miR-146a$^{-/-}$/hTNFtg compared to hTNFtg mice. Analysing the content of myeloid cells in the blood of arthritis diseased mice, revealed significantly increased numbers of circulating CD11b$^{+}$ as well as CD11c$^{+}$ cells in mice lacking miR-146a. Bone marrow transplants demonstrated a pivotal role for miR-146a in mesenchymal cells in controlling local osteoclast generation and bone destruction.

Conclusion:

These data demonstrate an important mitigating role of miR-146a in inflammatory arthritis, most importantly in local bone destruction, by controlling mesenchymal expression of osteoclastogenic factors. This shows a crucial anti-inflammatory role of miR-146a, which might possibly be exploited for therapeutic purposes.