

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

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. Blood of arthritis animals was analyzed by flow cytometry. Serum cytokine levels were measured by Elisa. MiR-146a and cytokine expression levels in bone marrow, spleen and paws were analysed by real time PCR.

Results: Both arthritis disease models led to a significantly reduced expression of miR-146a in spleen and bone marrow cells of arthritic wild type mice compared to healthy mice. 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 miR-146a^{-/-}/hTNFtg mice, we found a significant increase in circulating CD11b⁺ myeloid cells as well as CD11c⁺ dendritic cells in blood of miR-146a^{-/-}/hTNFtg mice compared to hTNFtg mice. Histological examination revealed a significant increase in synovial inflammation in miR-146a^{-/-}/hTNFtg mice compared to hTNFtg mice. Even more striking, miR-146a^{-/-}/hTNFtg mice displayed a more than twofold increase in local bone destruction which was due to increased generation of osteoclasts in the tarsal joints of the mice. Measuring cytokine levels in serum, we show that IL-1β levels are increased in mice lacking miR-146a. Moreover mRNA expression levels of IL6 and IL-1β in arthritic paws of these mice were significantly elevated in miR-146a^{-/-}/hTNFtg mice compared to hTNFtg mice.

Conclusions: These data clearly demonstrate a negative regulatory role of miR-146a in inflammatory arthritis. During arthritis, miR-146a is centrally involved in the regulation of proinflammatory cytokines as well as local bone destruction. These results identify an important anti-inflammatory role of miR-146a, which might possibly be exploited for therapeutic purposes.