AUTOIMMUNITY

MicroRNA-23b keeps TABs on tissue inflammation

Most studies of microRNAs (miRNAs) in autoimmunity have focused on their functions in leukocytes or in a single disease. Youcun Qian and colleagues now show that miR-23b limits pathology in multiple autoimmune diseases by suppressing proinflammatory signalling pathways in tissue-resident cells.

To determine whether any miRNAs are commonly upregulated or downregulated in autoimmunity, the authors screened tissue samples from patients with rheumatoid arthritis or systemic lupus erythematosus (SLE). Samples from mice with collagen-induced arthritis (CIA) or experimental autoimmune encephalomyelitis (EAE), and from lupus-prone MRL-*lpr* mice, were also assessed. Compared with control tissues, the samples from patients or mice with autoimmune disease all showed upregulation of miR-146a and miR-214 expression, and downregulation of miR-30a and, most prominently, miR-23b.

As few studies have examined downregulation of miRNAs in autoimmunity, the authors concentrated on miR-23b. They generated miR-23b-transgenic mice and found that these animals had a delayed disease onset and lower overall clinical scores in the CIA and EAE models. Similarly, adenovirus-mediated ectopic expression of miR-23b reduced disease severity in mice with

CIA and in MRL-*lpr* mice. Lethally irradiated miR-23b-transgenic mice that were reconstituted with wild-type bone marrow also showed reduced CIA and EAE disease, suggesting that miR-23b expression by tissue-resident cells is key for suppressing autoimmunity.

Further investigation showed that miR-23b targets multiple genes that are involved in proinflammatory signalling pathways. The overexpression of miR-23b in a human cell line suppressed the activation of nuclear factor κ B (NF κ B) following treatment with IL-1 β , IL-17 or TNF. Overexpression of miR-23b also suppressed proinflammatory cytokine signalling in human fibroblast-like synoviocytes, as well as in primary kidney cells and astrocytes from mice. Interestingly, treatment of the same cell types with IL-17 led to downregulation of miR-23b expression, suggesting that miR-23b and IL-17 are mutually antagonistic.

The authors showed that miR-23b suppresses IL-1 β -, IL-17- and TNF-mediated signalling by targeting the 3' untranslated regions of the genes encoding TAK1-binding protein 2 (TAB2), TAB3 and I κ B kinase- α (IKK α). This finding was interesting, as although TAB2 and TAB3 are known to promote NF κ B activation in response to IL-1 β and TNF, their involvement in IL-17-mediated

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signalling had not been appreciated. Finally, in fibroblast-like synoviocytes transfected with constructs containing TAB2 and TAB3 genes with mutated miR-23b target sites, miR-23b could no longer inhibit TNF- or IL-17-mediated signalling.

These data indicate that miR-23b can suppress autoimmune pathology by limiting the actions of key proinflammatory cytokines. Importantly, miR-23b may have therapeutic relevance in a variety of inflammatory diseases.

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