

## MIRNA BIOMARKERS MODULATE T-CELL DIFFERENTIATION IN MULTIPLE SCLEROSIS

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**Background:** In multiple sclerosis (MS) patients, myelinspecific T cells acquire pathogenic Th1/Th17 phenotypes. However, the factors that drive this pathogenic differentiation are unclear. miRNAs have been recently described as posttranscriptional regulators of gene expression that regulate cellular processes.

**Objectives:** We investigated whether miRNAs are differentially expressed in MS patients as potential disease biomarkers. In addition, we explored whether and how miRNAs contribute to pathogenic T-cell differentiation in MS.

### Methods

: We profiled miRNA expression in naive CD4<sup>+</sup>CD45RA<sup>+</sup>T cells of healthy (n = 8) and untreated MS (n = 22) donors. Specific miRNAs were transfected into T cells to evaluate their effects on proinflammatory Th1 versus more benign Th2 cell differentiation and effector cytokine production, as well as their encephalitogenic potential in experimental autoimmune encephalomyelitis (EAE).

### Results

: miR-128, miR-27a/b, and miR-340 were significantly increased in naive CD4<sup>+</sup>T cells from MS patients. miR-128, -27a/b, and -340 directly and specifically suppressed the pro-Th2 factor Bmi1, resulting in decreased GATA-3 expression in T cells. In addition, miR-340 directly and specifically suppressed the Th2 cytokine IL-4. Moreover, when transfected into myelin-specific T cells, these miRNAs worsened EAE. Overall, these miRNAs suppressed Th2 and enhanced pathogenic proinflammatory Th1 responses. In contrast, treatment of MS patient cells with miRNA inhibitors led to the restoration of more benign Th2 responses.

### Conclusion

: These findings link miR-128, -27ab, and -340 overexpression in MS patients' naive CD4<sup>+</sup> T cells to the proinflammatory T-cell differentiation observed in MS and illustrate the potential of these miRNAs as biologically relevant biomarkers and therapeutic targets.

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