18 REGULATION OF PATHOGENIC EFFECTOR/MEMORY T HELPER 1 LYMPHOCYTE SURVIVAL BY MICRORNA

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Background and objectives Auto-antigen specific effector memory T helper type 1 lymphocytes (Th1) are critically involved in the development and maintenance of chronic inflammation in autoimmune diseases. These cells reside at inflamed tissues, function independently of antigenic stimulation and proliferation, and therefore are resistant against physiological regulation and conventional immunosuppressive therapies. The acquirement of these properties is probably mediated by reduced expression of the pro-apoptotic proteins BIM and Pten. Recent results suggest that microRNA (miRNA) mediated regulation of *BIM* and *Pten* may play an important role for the development, function and persistence of chronically activated effector memory Th1 cells in autoimmune disease. Therefore, the authors aimed to identify miRNAs with the ability to suppress the expression of *BIM* and *Pten* in such cells.

Material and methods Assuming that Th1 cells involved in autoimmune inflammation have a history of repeated restimulation by persistent (auto) antigens, the authors have in vitro generated acutely (once) activated and chronically (four times) activated murine memory/effector Th1 cells. By using high-throughput sequencing of miRNA expression libraries, the authors have identified miRNAs differentially expressed between once and repeatedly reactivated Th1 cells. The functional role of specific candidate miRNAs in mediating the persistence of chronically activated effector memory Th1 cells was examined by loss- and gain of function experiments.

Results The authors have identified a candidate miRNA, specifically induced in chronically activated effector/memory Th1 cells. This miRNA post-transcriptionally inhibits the pro-apoptotic genes *Bim* and *Pten*. Expression of both genes is reduced in chronically activated memory effector Th1 cells. Overexpression of this miRNA in activated Th1 cells results in 50% downregulation of endogenous *Bim* and *Pten* expression. Conversely, inhibition of the candidate miRNA in chronically activated memory Th1 cells by antagomirs results in induced levels of BIM protein and significantly enhanced cell death. Under Th1 polarising conditions, the expression of the candidate miRNA is regulated by the master transcription factor Tbet.

Conclusions With its targets BIM and Pten having important roles for survival and proliferation of pathogenic effector memory Th1 cells, this candidate miRNA represents a promising molecular target for the treatment of immune mediated disease by antagomirs.