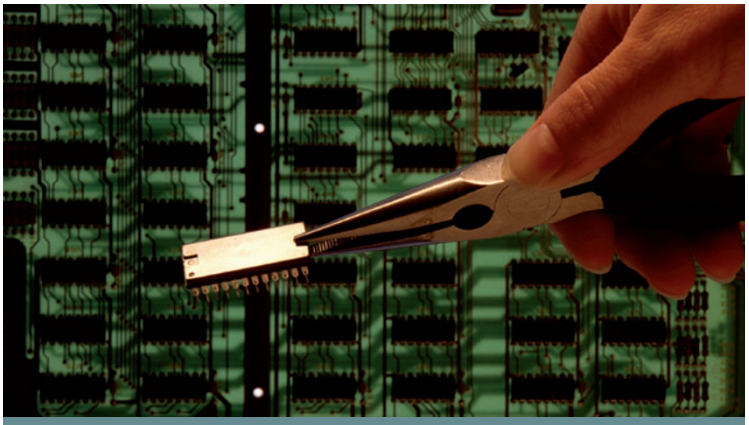

IMMUNE REGULATION

(micro)Control of IFNγ

Although microRNAs are known to have roles in regulating immune responses, our understanding of the exact functions of individual microRNAs in the immune system is still in its infancy. Two papers, published in *Immunity* and *Nature Immunology*, now show that the microRNA miR-29 suppresses interferon-γ (IFNγ) production, although different mechanisms of action were reported.

It has previously been shown that T cells from mice deficient in microRNAs produce high levels of IFNγ. The double-stranded RNA-binding factor DGCR8, along with Drosha, is required for the processing of microRNAs from their primary transcripts, and Steiner *et al.* showed that the dysregulation of IFNγ production in DGCR8-deficient T cells (which lack microRNAs) was due to a cell-intrinsic mechanism. By screening for the function of individual microRNAs in $CD4^+$ T cells, they went on to show that the cell-intrinsic factor that repressed IFNγ production was miR-29.

To investigate how miR-29 controls IFNγ expression, Steiner *et al.* performed gene expression analysis under gain- and loss-of-function conditions, which were induced by transfecting DGCR8-deficient cells with synthetic miR-29 or by transfecting wild-type cells with antisense inhibitors of miR-29, respectively. They found that the expression of *Tbx21* (which encodes T-bet) and *Eomes* (which encodes eomesodermin) was reduced under gain-of-function conditions and elevated under loss-of-function conditions. T-bet and eomesodermin are known to regulate IFNγ production, and further investigation showed that the 3′ UTRs (untranslated regions) of *Tbx21* and *Eomes* (but not that of *Ifng*) are directly responsive to miR-29 in $CD4^+$ T cells. Furthermore, miR-29 was shown to contribute to the regulation of T-bet expression in both $CD4^+$ and $CD8^+$ T cells in an *in vivo* virus infection model. Finally, the authors found that the regulation of IFNγ production by miR-29 involves the simultaneous targeting of both T-bet and eomesodermin.

Ma *et al.* found an inverse correlation between IFNγ production and levels of miR-29 in natural killer (NK) cells and T cells from mice infected with *Listeria monocytogenes* or *Mycobacterium bovis* bacillus Calmette–Guérin (BCG). miR-29 expression was lower in activated IFNγ-producing NK cells and T cells than in non-activated cells from both humans and mice, and this downregulation of miR-29 was mediated by nuclear factor-κB (NF-κB). However, in contrast to the study described above, Ma *et al.* found that miR-29 directly targets the 3′ UTR of *Ifng* mRNA in HEK293T cells and promotes its association with AGO2 (an essential component of an RNA-induced silencing complex), suggesting that miR-29 functions to suppress the expression of IFNγ post-transcriptionally.

Next, the authors generated mice with transgenic expression of a miR-29 'sponge' sequence that competes with endogenous miR-29 (termed GS29 mice). NK cells, $CD4^+$ T cells, polarized T helper 1 (T_H1) cells and $CD8^+$ T cells from these mice produced more IFNγ than cells from control mice following activation. However, the expression levels of T-bet and eomesodermin were unaffected in $CD4^+$ or $CD8^+$ T cells from GS29 mice. GS29 mice cleared *L. monocytogenes* infection more effectively than control mice. Furthermore, GS29 mice infected with *M. bovis* BCG showed less inflammation, lower bacterial burden and increased numbers of IFNγ-producing $CD4^+$ T cells in their lungs compared with control mice.

Together, these papers describe a role for miR-29 in the regulation of IFNγ production, suggesting that targeting of this microRNA may have therapeutic benefits. However, further studies are required to fully understand how exactly miR-29 mediates its suppressive function.

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ORIGINAL RESEARCH PAPERS Steiner, D. F. *et al.* MicroRNA-29 regulates T-box transcription factors and interferon-γ production in helper T cells. *Immunity* 4 Aug 2011 (doi:10.1016/j.immuni.2011.07.009) | Ma, F. *et al.* The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-γ. *Nature Immunol.* 24 Jul 2011 (doi:10.1038/ni.2073)
FURTHER READING O'Connell, R. M. *et al.* Physiological and pathological roles for microRNAs in the immune system. *Nature Rev. Immunol.* **10**, 111–122 (2010)