IMMUNE REGULATION

MicroRNAs and the immune response

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MicroRNAs are small RNAs that regulate gene expression in many biological processes and there is increasing evidence that they are also important in immune regulation. Two papers in *Science* now report a role for microRNA-155 (miR-155) in regulating T-cell-dependent antibody responses and in immune-cell function.

miR-155 is generated from the non-coding transcript of the *BIC* gene. It is known to be expressed in human B-cell lymphomas, in activated mature B and T cells, and in activated macrophages and DCs.

Thai and colleagues generated a loss-of-function mutant mouse (*Bic/miR-155^{-/-}*) by replacing a portion of the *Bic* gene, including the miR-155 region, with a β -galactosidase reporter gene. They also generated a gain-of-function mutant mouse (*B-cell^{miR-155}*) using a knock-in strategy to express miR-155 in mature B cells. The authors detected reduced fractions

of germinal centre (GC) B cells in the gut-associated lymphoid tissue of *Bic/miR-155^{-/-}* mice compared with wild-type mice, and increased fractions in *B-cell^{miR-155}* mice. The authors next induced GC responses in the spleen by immunizing mice with alum-precipitated (3-hydroxy-4-nitrophenyl)acetyl (NP) coupled to chicken γ -globulin. They found that *Bic/miR-155^{-/-}* mice produced much lower titres of NP-specific antibodies and the numbers of GC B cells were reduced compared with littermate control mice. These results suggest that miR-155 might have a role in the GC reaction. The authors found no evidence that miR-155 had a role in controlling B-cell proliferation, but when cytokine production by activated B cells from the knockout mice was examined, they observed decreased production of tumour-necrosis factor and compromised expression of lymphotoxin- α compared with control mice. *In vitro* analysis of T-cell responses showed that T helper 1 (T_H1)- and T_H2 -cell differentiation proceeds normally in the knockout mice, but under conditions in which neither differentiation pathway is promoted, *Bic/miR-155^{-/-}* cells produced more interleukin-4 (IL-4) and less interferon- γ (IFN γ) than control cells, which are characteristics of T_H2 cells.

Rodriguez and colleagues generated BIC-deficient mice (*Bic^{m1/m1}* and *Bic^{m2/m2}*) by inserting mutant alleles into embryonic stem cells. At approximately 350 days of age, just over half of the mice displayed significant airway remodelling. No gross defects in myeloid or lymphoid

development were detected but *Bic^{m2/m2}* mice were less well protected by vaccination with a live attenuated form of *Salmonella typhimurium* against infection with a virulent form of *S. typhimurium* compared with wild-type mice. The authors then examined B- and T-cell responses in *Bic^{m1/m1}* mice immunized with the T-cell-dependent antigen tetanus toxin fragment C protein. B cells produced less IgM and antigen-specific switched antibodies compared with wild-type controls and, when T cells were re-stimulated *in vitro*, they failed to produce the increased levels of IL-2 and IFN γ observed in wild-type mice. Consistent with the results from the study by Thai and colleagues, further experiments revealed that CD4⁺ T cells from BIC-deficient mice were intrinsically biased towards differentiation into T_H2 cells. Furthermore, BIC-deficient T_H2 cells produced enhanced levels of IL-4, IL-5 and IL-10. Gene-expression analysis of miR-155 in BIC-deficient cells showed that miR-155 targets a wide variety of genes, including the transcription factor *Maf*, with diverse functions and this provides insight into T_H2 -cell-cytokine regulation by miR-155.

Taken together, these studies reveal a key role for miR-155 in regulating immune-system homeostasis and function.

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ORIGINAL RESEARCH PAPERS Thai, T. et al. Regulation of the germinal centre response by microRNA-155. *Science* **316**, 604–608 (2007) | Rodriguez, A. et al. Requirement of *bic/microRNA-155* for normal immune function. *Science* **316**, 608–611 (2007)