Nature Reviews Immunology | AOP, published online 13 June 2008; doi:10.1038/nri2364

B CELLS

(micro)Restraint of AID

MicroRNAs (miRNAs) are small non-coding RNAs of ~21 nucleotides in length that regulate gene expression at the post-transcriptional level. Recent studies using loss- or gain-of-function approaches have indicated a role for the miRNA miR-155 in regulating the expression of hundreds of mRNAs and in germinal-centre reactions. However, the direct target(s) of miR-155 in B cells is still unclear. Now, two papers published in *Immunity* identify activation-induced cytidine deaminase (AID), a potent DNA mutator that is required for antibody diversification in B cells, as a direct target for miR-155-mediated suppression.

AID initiates the induction of somatic hypermutation and class-switch recombination (CSR), which together lead to the selection of high-affinity B cells in germinal centres, but because it is a DNA mutator, AID expression must be tightly regulated in the cell. Using several miRNA target-prediction algorithms, Teng *et al.* confirmed that *Aicda*, the gene encoding AID, contains a target sequence for miR-155 in its 3′-untranslated region. In addition, miR-155 expression was shown to be upregulated in B cells undergoing CSR induced by lipopolysaccharide (LPS) and interleukin-4 (IL-4).

To determine whether there is a functional interaction between miR-155 and AID, the authors generated transgenic mice expressing an *Aicda* transgene that contained a mutated miR-155 target site and that was tagged with green fluorescent protein (mutant *Aicda* mice). Following *in vitro* stimulation with LPS and IL-4, AID was more rapidly induced and its level of expression was higher in splenic B cells from mutant *Aicda* mice than in cells from control mice. In addition, increased CSR was observed in B cells from *Aicda* mutant mice crossed with $Aicda^{-/-}$ mice (to exclude the contribution of endogenous AID) following stimulation. So, the data show that miR-155 directly regulates the quantitative and temporal expression of AID in B cells. These observations were confirmed *in vivo* and further analysis revealed that the disruption of the interaction between miR-155 and *Aicda* in mutant mice resulted in impaired affinity maturation of B cells.

Dorsett *et al.* also generated mice in which the miR-155 target site in *Aicda* was mutated ($Aicda^{155/+}$ mice) and these mice were then crossed with $Aicda^{-/-}$ mice to produce $Aicda^{155/-}$ mice. Similar to the results of Teng *et al.*, the amount of AID expressed and the level of CSR was higher in B cells from $Aicda^{155/-}$ mice compared with those from $Aicda^{+/-}$ mice following stimulation with LPS and IL-4.

It is known that AID induces oncogenic chromosomal translocations between *Myc* and *Igh*, which are associated with Burkitt's lymphoma. The authors found that the frequency of *Myc–Igh* translocations was higher in $Aicda^{155/-}$ mice than $Aicda^{+/-}$ mice. In addition, the frequency of translocations was even higher in miR-155-deficient mice, indicating that miR-155 expression suppresses *Myc–Igh* translocations, at least in part, through the regulation of AID expression.

Taken together, these studies show that miR-155 suppresses the expression of AID in activated B cells and that removal of this suppression results in defective affinity maturation and increased *Myc–Igh* translocations.

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ORIGINAL RESEARCH PAPERS Teng, G. *et al.* MicroRNA-155 is a negative regulator of activation-induced cytidine deaminase. *Immunity* **28**, 621–629 (2008) | Dorsett, Y. *et al.* MicroRNA-155 suppresses activation-induced cytidine deaminase-mediated *Myc-Igh* translocation. *Immunity* **28**, 630–638 (2008)
FURTHER READING Lodish, H. F. *et al.* Micromanagement of the immune system by microRNAs. *Nature Rev. Immunol.* **8**, 120–130 (2008)

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