B-CELL DEVELOPMENT

(micro)Control of B-cell development

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MicroRNAs (miRNAs) are ~22-nucleotide, evolutionarily conserved, small RNAs that can control gene expression by targeting mRNA for degradation or translational repression. Now, Xiao *et al.* show that the miRNA miR-150 (which is specifically expressed in mature, resting lymphocytes but not in their progenitors) controls B-cell development by regulating the expression of the transcription factor c-Myb.

c-Myb is a key factor in the regulation of lymphocyte development, especially in the development of the B-1 subset of B cells. It is highly expressed by lymphocyte progenitors, but its expression is downregulated on their maturation and upregulated again after activation of the mature cells. Following bioinformatic analyses, and because the expression patterns of c-Myb and miR-150 are complementary to each other, the authors suspected that c-Myb might be a target for regulation by miR-150.

To determine if this was the case, the authors generated mice that ectopically expressed miR-150 in their germline at moderate levels relative to the levels in mature lymphocytes under physiological conditions. B-cell development in these *mir150*-transgenic mice was significantly blocked at the pro- to pre-B-cell transition. This is similar to what was previously described for mice deficient for c-Myb, indicating that the moderate expression of miR-150 in B-cell progenitors (which usually do not express miR-150) might suppress c-Myb *in vivo* with functional consequences.

Further analysis showed that the block on pro- to pre-B-cell transition in heterozygous *Myb*-knockout mice, in which c-Myb expression is reduced by only approximately 26%, was similar to that observed in *mir150*-transgenic mice, indicating that small changes in c-Myb protein levels have functional consequences, which can be replicated by the moderate expression of miR-150. Therefore, the data suggest that the block on B-cell development in *mir150*-transgenic mice is due to the downregulation of c-Myb by miR-150 in B-cell progenitors. The inverse was observed in *mir150*$^{-/-}$ mice, which had increased numbers of B-1 cells in the spleen and peritoneal cavity compared with control mice.

In vitro analysis using a reporter assay showed that miR-150 directly inhibits c-Myb, and deletion of two of the three putative miR-150 binding sites in the 3′ untranslated region of c-Myb completely abolished this inhibition. These two sites are evolutionarily conserved and perfectly align with positions 1–8 of miR-150.

So, that data show that stage-specifically expressed miR-150 controls the expression of c-Myb *in vivo*, thereby regulating B-cell development, which suggests that miRNAs might have evolved to regulate the concentration of key target proteins in particular cellular contexts.

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ORIGINAL RESEARCH PAPER Xiao, C., *et al.* MiR-150 controls B cell differentiation by targeting the transcription factor c-Myb. *Cell* **131**, 146–159 (2007)