Nature Reviews Neuroscience | AOP, published online 13 May 2009; doi:10.1038/nrn2655

MICRORNA

Keeping an eye on cell death

Cell proliferation and programmed cell death (apoptosis) regulate the shape and size of developing organs. Apoptosis is particularly prominent in the development of the retina, where up to 90% of newborn ganglion cells die. Pro-apoptotic caspases have been shown to be largely responsible for preventing retinal overgrowth, but the factors that regulate these molecules were unknown. Reporting in *Genes and Development*, Walker and Harland show that the microRNA miR-24a negatively regulates caspase 9 and apoptosis protease-activating factor 1 (apaf1) and is required for normal eye morphogenesis in *Xenopus*.

MicroRNAs are short, evolutionarily conserved, single-stranded non-coding transcripts that become incorporated into the RNA-induced silencing complex (RISC) to block the translation or induce the degradation of target mRNAs. Recent studies have highlighted their roles in both the development and demise of the nervous system — where they are implicated in the regulation of neurogenesis and the maintenance of synaptic plasticity — and in cancer, where both pro- and anti-apoptotic roles have been described.

Here the authors show that miR-24a is specifically expressed in the retina throughout the development of the eye. Knocking down this microRNA in embryos with an antisense morpholino resulted in a significant reduction in eye size but had no effect on the expression of patterning and differentiation markers or on the number of proliferating cells in the eye. Rather, miR-24a depletion led to an increase in apoptosis, as measured by the number of TUNEL-positive nuclei. Furthermore, the levels of caspase 9 protein were significantly increased in the miR-24a-depleted embryos, whereas caspase 9 mRNA levels were unaffected, suggesting that miR-24a represses caspase 9 translation. Indeed, the authors found that both the caspase 9 and the apaf1 mRNAs contain miR-24a binding sites. Moreover, addition of this microRNA to reporter constructs containing the 3′ untranslated regions of these genes fused to green fluorescent protein confirmed that miR-24a can directly repress their translation.

Together these findings indicate that, by downregulating caspase 9 and apaf1 levels, miR-24a is able to prevent apoptosis in the developing retina, thus helping to ensure normal eye morphogenesis. It is likely that microRNAs exert similar effects in other neural structures that require the levels of proliferating and dying cells to be kept in check.

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ORIGINAL RESEARCH PAPER Walker, J. C. & Harland, R. M. *microRNA-24a* is required to repress apoptosis in the developing neural retina. *Genes Dev.* 16 Apr 2009 (doi:10.1101/gad.1777709)