STEM CELLS

MicroRNAs promote differentiation

Correct regulation of the process by which stem cells start differentiating is crucial to normal development and to the avoidance of cancer. Two new studies show the importance of specific microRNAs (miRNAs) in the transition to differentiation.

MiRNAs are known to have a role in the differentiation of skin cells, so Fuchs and colleagues constructed miRNA libraries from mouse skin at different stages of development. One of the most striking observations was that the miRNA *miR-203* went from almost no expression at E13.5 to being one of the most abundant miRNAs at E15.5. Moreover, it was expressed ~25-fold more in the differentiated suprabasal cells than in the undifferentiated basal cells. The authors therefore selected *miR-203* for further investigation.

Transgenic mice that precociously activated *miR-203* expression in epidermal stem cells had a range of phenotypes, including reduced epidermal thickness. Furthermore, their epidermal stem cells showed a reduced proliferative potential. Interestingly, these phenotypes resembled the depletion of epidermal stem cells that is observed in p63-null epidermis (p63 is an essential regulator of stem-cell maintenance), and p63 levels were found to be reduced in keratinocytes that overexpress *miR-203*. Conversely, the authors used antagomirs to knock down *miR-203* expression and found increased proliferative ability and higher p63 levels in differentiating epidermal cells. Bioinformatic studies showed that the *TP63* mRNA contains two target sites for *miR-203* in its 3′ UTR, and the authors showed that mutating these sites abolished the *miR-203*-mediated p63 repression. *TP63* is not the only target of *miR-203*, and the authors suggest that *miR-203* acts as a negative regulator of stemness by suppressing the expression of this and other basal genes in the suprabasal cells.

In the second study, Gregory and colleagues looked at the expression of the *let-7g* miRNA, which is known to be downregulated in embryonic stem (ES) cells and in some cancers. Although the mature miRNA is undetectable in ES cells, the unprocessed primary *let-7g* (pri-*let-7g*) is present at levels similar to those that are observed later in development. The authors therefore used biochemical methods to identify the factor that is responsible for this post-transcriptional blocking of *let-7g* expression. Sequencing the proteins that co-purified with pre-*let-7g* in ES cells and embryonal carcinoma (EC) cells but not in differentiated cells identified the RNA-binding protein LIN-28 as a good candidate, and further *in vitro* assays confirmed that it can inhibit *let-7g* processing.

The authors then confirmed that this blocking also occurs *in vivo*, by introducing pri-miRNAs and *Lin-28* cDNA into cell lines lacking endogenous LIN-28. Conversely, they used RNAi to knock down endogenous LIN-28 in EC cells and ES cells. This caused the upregulation of all members of the *let-7* family but not of any other miRNAs, confirming that LIN-28 is a specific inhibitor of this particular miRNA. Interestingly, a LIN-28 homologue, LIN-28B, is overexpressed in several cancers, and the authors showed that it also inhibits *let-7* processing.

These two papers show how two different miRNAs function in the differentiation of stem cells. The ability of miRNAs to rapidly downregulate the expression of many genes probably makes them particularly suited to a role in a process that requires coordinated changes in gene expression.

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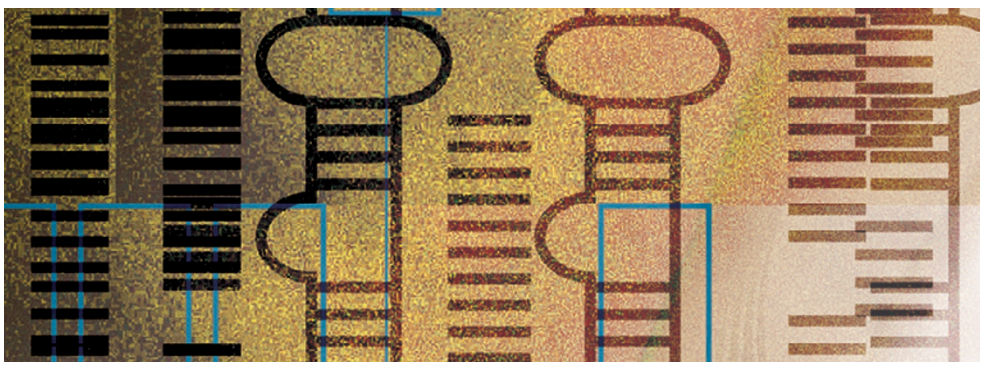

ORIGINAL RESEARCH PAPERS Yi, R., Poy, M. N., Stoffel, M. & Fuchs, E. A skin microRNA promotes differentiation by repressing 'stemness'. *Nature* 4 Mar 2008 (doi:10.1038/nature06642) | Viswanathan, S. R., Daley, G. Q. & Gregory, R. I. Selective blockade of microRNA processing by LIN-28. *Science* 21 Feb 2008 (doi:10.1126/science.1154040)

FURTHER READING Esquela-Kerscher, A. & Slack, F. J. Oncomirs — microRNAs with a role in cancer. *Nature Rev. Cancer* **6**, 254–269 (2006).