MYELOID DEVELOPMENT

How microRNAs manage myeloid cells

The differentiation of haematopoietic stem cells (HSCs) is traditionally viewed in terms of regulation by cytokines and transcription factors. However, studies in the past few years have shed light on the role of post-transcriptional regulation of gene expression by microRNAs — which target messenger RNAs for degradation or translational repression — in cell-fate specification in the immune system. Much of this work has focused on the function of microRNAs (such as miR-181a) in lymphocytes, but two new studies now describe the effects of miR-223 and miR-155 on the granulocyte–monocyte cells of the myeloid lineage.

Johnnidis *et al.* showed that miR-223 negatively regulates the differentiation and activation of granulocytes. miR-223-deficient mice have a significant increase in the number of circulating neutrophils and have granulocyte hyperplasia in the bone marrow as a result of the increased proliferation of granulocyte–monocyte progenitors. Neutrophils deficient in miR-223 had an increased oxidative burst in response to stimulation and showed increased killing when cultured with *Candida albicans*. By contrast, O'Connell *et al.* showed that miR-155 is a positive regulator of the granulocyte–monocyte population. Forced expression of miR-155 in HSCs followed by engraftment in lethally irradiated mice led to a marked increase in the proportion of granulocyte–monocyte cells in the bone marrow compared with mice that received control HSCs. Mice that overexpressed miR-155 also had an increase in the number of granulocyte-monocyte cells in peripheral blood.

Granulocytes and monocytes are a crucial part of the innate immune response to bacteria and fungi. Infection is known to have a marked impact on haematopoiesis by increasing the production of granulocyte–monocyte populations to replace those that have been depleted. In line with this, O'Connell *et al.* showed that administering lipopolysaccharide to mice induces the expression of miR-155 in the bone marrow followed by the expansion of myeloid populations.

As miR-155 and miR-223 are proposed to have opposite effects on granulocyte–monocyte cells, they illustrate the importance of maintaining a balance in the immune system between responding adequately to potential threats (positive regulation through miR-155) and avoiding bystander damage to the host (negative regulation through miR-223), as well as the pathology that can result when this balance is disrupted. Indeed, miR-223-deficient mice had inflammatory lung pathology dominated by neutrophils and delayed recovery from endotoxaemia as a result of inflammation-induced tissue damage. In addition, a subset of patients with acute myelomonocytic and acute monocytic leukaemia were shown to have significant overexpression of miR-155 compared with normal controls.

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ORIGINAL RESEARCH PAPERS Johnnidis, J. B. *et al.* Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. *Nature* 17 February 2008 (doi:101.1038/nature06607) | O'Connell, R. M. *et al.* Sustained expression of microRNA-155 in hematopoietic stem cells causes a myeloproliferative disorder. *J. Exp. Med.* 25 February 2008 (doi:10.1084/jem.20072108)

FURTHER READING Lodish, H. F., Zhou, B., Liu, G. & Chen, C.-Z. Micromanagement of the immune system by microRNAs. *Nature Rev. Immunol.* **8**, 120–130 (2008)