

HAEMATOPOIESIS

Death-defying factor identified



Cytokines such as stem-cell factor (SCF) and erythropoietin (EPO) have a crucial role in haematopoiesis, inducing mitogenic and anti-apoptotic factors. Although the molecular pathways by which these cytokines mediate their effects remain ill defined, a report in *The Journal of Experimental Medicine* has now shed light on the signalling cascades involved, identifying anamorsin as a novel anti-apoptotic factor induced by cytokines during definitive haematopoiesis.

Shibayama *et al.* used an interleukin-3 (IL-3)-independent variant of a mouse IL-3-dependent cell line to isolate molecules that conferred resistance to apoptosis induced by IL-3 starvation. cDNA encoding anamorsin — a novel protein with no homology to any known anti-apoptotic molecule — was isolated from cells that survived IL-3 deprivation. The anti-apoptotic effect of this protein was confirmed by the observation that stable expression of anamorsin by the parental cell line and by a second IL-3-dependent cell line conferred resistance to apoptosis after IL-3 withdrawal.

In addition to IL-3, anamorsin expression was induced by other cytokines, including SCF and EPO, indicating that it probably has a general role in mediating the anti-apoptotic effects of cytokine exposure *in vitro*.

The *in vivo* significance of this molecule was highlighted by the observation that anamorsin-deficient mice die in late gestation. Anamorsin-deficient embryos were anaemic, having half the number of peripheral red blood cells as littermate

controls, and a marked proportion of cells in the fetal liver, which was less than a third of the size of that in anamorsin-sufficient embryos, were apoptotic. Interestingly, the absolute number of haematopoietic stem cells and immature pro-erythrocytes was normal in the fetal liver of anamorsin-deficient embryos, indicating that anamorsin probably has a role in the late stages of haematopoiesis and terminal differentiation. This was confirmed by the observation that anamorsin-deficient fetal liver cells were severely impaired in their ability to generate myeloid and erythroid colonies when cultured in the presence of the appropriate cytokines.

This study identifies anamorsin as a fundamental anti-apoptotic factor induced by cytokines during haematopoiesis. Future studies will focus on the mechanisms by which the anti-apoptotic effects of anamorsin are mediated, and initial studies by the authors indicating that expression of Bcl-X_L and Jak2 is downregulated in the absence of anamorsin should provide a good basis to initiate these investigations.

Karen Honey

References and links

ORIGINAL RESEARCH PAPER Shibayama, H. *et al.* Identification of a cytokine-induced antiapoptotic molecule anamorsin essential for definitive haematopoiesis. *J. Exp. Med.* **199**, 581–592 (2004)

REPRODUCTIVE IMMUNOLOGY

Pregnancy regulators

How does the maternal immune system tolerate the persistence of paternal alloantigens during pregnancy? A report in *Nature Immunology* addresses this question and describes the systemic expansion of maternal regulatory T-cell populations, which can suppress aggressive allogeneic immune responses against the fetus.

Several localized mechanisms have previously been described that contribute to fetal evasion from immune attack, including expression of HLA-G and FAS ligand (CD95L) by fetal tissues, which inhibits the activation of natural killer (NK) cells and induces apoptosis of activated maternal lymphocytes, respectively. Nevertheless, maternal alloreactive lymphocytes can still be detected.

In this study, Betz and colleagues showed that the number of naturally occurring regulatory T cells (CD4⁺CD25⁺) in the lymph nodes and spleen of pregnant mice was markedly increased compared with non-pregnant control mice. This expansion of the CD4⁺CD25⁺ T-cell population even occurred

when mice were mated with syngeneic males, indicating that the presence of fetal alloantigen is not required to drive expansion of the CD4⁺CD25⁺ T-cell pool. *In vitro*, these cells could suppress the proliferation of alloreactive cells in a mixed lymphocyte reaction. Furthermore, when whole lymphocyte preparations or CD25⁺ cell-depleted preparations from pregnant mice were adoptively transferred to nude female mice that were subsequently mated, those that received samples depleted of CD25⁺ cells did not sustain normal pregnancy. However, if the mice that received CD25⁺ cell-depleted preparations were mated with a syngeneic male, pregnancy was normal, indicating that the regulatory function of these T cells is only required when the fetus expresses alloantigen, which is inevitable under non-experimental circumstances.

The presence of these regulatory populations might explain the observed remission of some autoimmune diseases and enhanced maternal tolerance to some paternal grafts during pregnancy. Future



experiments hope to determine whether these cells are important in preventing pregnancy failures in humans.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Aluvihare, V. R., Kallikourdis, M. & Betz, A. G. Regulatory T cells mediate maternal tolerance to the fetus. *Nature Immunol.* **3**, 266–271 (2004)