SIGNAL TRANSDUCTION

Escape from death

The cytokine erythropoietin is best known for its use in the treatment of anaemia, but work over recent years has shown that it can also protect neurons from apoptosis induced by reactive oxygen and nitrogen species. The mechanism of this protection has remained elusive, but, reporting in *Nature*, Digicaylioglu and Lipton now provide compelling evidence that preconditioning neurons with erythropoietin protects them by activating NF-κB through Janus kinase 2 (Jak2).

NF-κB transcription factors are critical regulators of apoptosis, and are themselves controlled by the inhibitor of NF-κB (IκB) proteins. Extracellular signals — including those emanating from cytokines — induce the phosphorylation (and hence degradation) of IκBs, allowing NF-κB dimers to enter the nucleus and activate gene transcription.

Studies have shown that NF-κB promotes cell survival through the transcriptional activation of anti-apoptotic genes. Expression of *NF-κB* in the brain is strongly induced after stress, leading Digicaylioglu and Lipton to investigate whether the anti-apoptotic function of erythropoietin is mediated through NF-κB. Biochemical assays revealed that treatment of neurons with erythropoietin resulted in sustained activation of NF-κB, leading to its translocation into the nucleus followed by DNA binding. As expected, inhibition of NF-κB blocked the protection.

In non-neuronal cells, binding of erythropoietin to its receptor triggers activation of several intracellular signalling cascades — including phosphorylation of Jak2. The authors extended these observations to neurons and found that interactions between erythropoietin and its receptor also trigger Jak2 phosphorylation. So is Jak2 signalling necessary for NF-κB activation? Expression of a kinase-dead version of Jak2 completely abrogated the anti-apoptotic effect of erythropoietin by preventing the activation of NF-κB. This was specific, as co-transfection with wild-type Jak2 reversed the NF-κB inhibition. An *in vitro* kinase assay directly showed that Jak2 could phosphorylate IκB inhibitors, leading to the activation of NF-κB.

Numerous studies indicate that NF-κB protects cells from death by transcriptionally activating genes, the products of which block apoptosis. Extrapolating from this, Digicaylioglu and Lipton show that pre-incubation of neurons with erythropoietin increases the expression of inhibitor-of-apoptosis gene products, *XIAP* and *cIAP2*. These results indicate that erythropoietin can regulate NF-κB activity through Jak2 signalling, leading to neuroprotection.

This study neatly ties two signalling pathways — Jak2 and NF-κB — together in erythropoietin-stimulated neurons. So why doesn't erythropoietin activate NF-κB in non-neuronal cells? As NF-κB transcription factors are expressed ubiquitously, it is important to find out whether additional neural-specific components are required for this pathway *in vivo*, and we now need to discover whether recombinant erythropoietin or its mimics can be used for the treatment of neurodegenerative disorders.

Deepa Nath, Associate Editor, Nature

References and links

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FURTHER READING Siebenlist, U. Barriers come down. *Nature* **412**, 601–602 (2001)

SIGNAL TRANSDUCTION

The chemistry of attraction

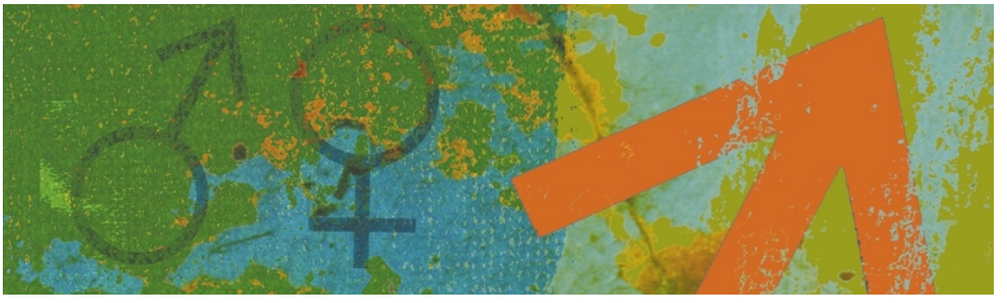
Chemokines, or chemoattractant cytokines, regulate lymphocyte activation and migration, and are vital for the efficient function of the immune system. Processes from the influx of lymphocytes into sites of inflammation to the retention of haematopoietic precursors in the bone marrow, rely on directional cues provided by these proteins. Chemokines act by binding to serpentine G-protein-coupled receptors, but the details of the signalling pathways by which these receptors regulate lymphocyte migration are incompletely characterized.

Work by Ottoson and colleagues in the *Journal of Immunology*, studying T-cell migration in response to CXCR4 chemokine receptor signalling, now shows a new role for the tyrosine kinase ZAP-70 in these pathways. The importance of ZAP-70 in T-cell receptor (TCR) signalling is well known, but this is the first time a role for this kinase in chemokine receptor signalling has been shown.

The authors studied the movement of human Jurkat T cells through fibronectin or bovine serum albumin-coated filters in response to the CXCR4-ligand CXCL12. Whereas wild-type Jurkat T cells migrated rapidly in response to a CXCL12 gradient, P116 cells (which lack expression of ZAP-70) showed a two to threefold reduced migratory response to the same dose of CXCL12. Reconstitution of P116 cells with wild-type ZAP-70 markedly enhanced the migration of these cells, but expression of a kinase-inactive form of ZAP-70 (K369R) had minimal effect, showing that this is a ZAP-70-dependent migratory process.

Activation of ZAP-70 on TCR stimulation leads to tyrosine phosphorylation of the adaptor protein SH2 domain-containing leukocyte protein of 76 kDa (SLP-76), which is vital for T-cell development and activation. The authors showed that CXCL12-mediated stimulation of Jurkat T cells also results in ZAP-70-dependent tyrosine phosphorylation of SLP-76. Although CXCL12-dependent migration of SLP-76-deficient Jurkat T cells was impaired, re-expression of SLP-76 in these cells did not enhance migration.

These results show for the first time a role for ZAP-70, but not SLP-76, in CXCR4 chemokine receptor signalling in human T cells. The authors conclude that ZAP-70 might represent a point of convergence between chemokine receptor and TCR signalling pathways.



Jenny Buckland
Associate Editor, Nature Reviews Immunology

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