APOPTOSIS

Deadly cuts

Many classic hallmarks of apoptosis — namely, activation of caspases, chromatin condensation, and DNA fragmentation — are triggered by molecules that lead a mysterious double life. One example is cytochrome *c*; this 'Clark Kent' factor acts as an electron carrier in the mitochondrial inner membrane but, once apoptosis is triggered, it takes on an alter ego, being released from the mitochondria to ensure apoptosis. Two groups now report in *Nature* that endonuclease G (endoG) — thought to have a day job aiding replication of mitochondrial DNA — also moonlights, mediating DNA fragmentation during apoptosis.

In the first paper, Parrish and colleagues identify *cps-6*, and show that it is crucial for the normal progression of programmed cell death (PCD) in worms. In the absence of *cps-6*, there is an overall delay in cell-corpse appearance, indicating that the progression of apoptosis is delayed. BLAST analysis shows that CPS-6 is 48% identical to mouse endoG. So, to test whether they are functional homologues, the authors expressed mouse *endoG* in a *cps-6* mutant, and showed that it could fully rescue the mutant phenotype.

Li and colleagues identify endoG as an apoptotic nuclease that, unlike other nucleases implicated in apoptosis, is activated by its release from mitochondria. They go on to show that purified endoG has nuclease activity on both isolated nuclei and plasmid DNA. Finally, the authors find that, unlike other apoptotic nucleases, endoG is activated independently of caspases, which may explain why it is beneficial for cells to have this additional nuclease.

Curiously, endoG appears to localize to the intermembrane space of mitochondria. This is based on the observation, by Li and colleagues, that endoG colocalizes with cytochrome *c* and that the triggers for their release are different to those for the inner mitochondrial membrane protein Hsp70. So how can we reconcile this localization with endoG's job in the inner membrane?

Together, these findings indicate that the function of endoG as a mediator of DNA fragmentation as well as the role of mitochondria as an important regulator of apoptosis are evolutionarily conserved between invertebrates and vertebrates. Importantly, this work shows that, at least in worms, DNA fragmentation is not just part of the 'cell dismantling' process, but is also crucial for the progression of apoptosis.

Alison Schuldt

References and links

ORIGINAL RESEARCH PAPERS Parrish, J. *et al.* Mitochondrial endonuclease G is important for apoptosis in *C. elegans*. *Nature* **412**, 90–94 (2001) | Li, L. Y. *et al.* Endonuclease G is an apoptotic DNase when released from mitochondria. *Nature* **412**, 95–99 (2001)

CHEMOKINES

Pulmonary paramedics

For paramedics to provide life-saving treatment for people involved in car accidents, the ambulance driver needs to ensure their safe arrival at the site of the crash by following road signs and signals. In the same way, for a protective cellular immune response to infection by *Mycobacterium tuberculosis*, macrophages and T cells need to be rapidly recruited to the lung. The signals that guide these cells to the site of infection have, until now, been unknown. Recent work, published in *Proceedings of the National Academy of Sciences* by Peters and colleagues, shows that the C-C chemokine receptor 2 (CCR2) is essential in these processes.

Chemokines are low-molecular-mass chemotactic cytokines that control leukocyte migration and activation. Mice that are deficient for certain chemokine receptors, including CCR2 (the receptor for monocyte chemoattractant proteins), show defects in leukocyte migration to sites of inflammation. Here, the authors used *CCR2*-deficient mice to investigate the role of this receptor in resistance to *M. tuberculosis*.

When infected with *M. tuberculosis*, the $CCR2^{-/-}$ mice had a rapid and fatal course of infection, and had 100-fold more bacteria in their lungs than wild-type mice. Early after infection, the $CCR2^{-/-}$ mice showed a defect in the recruitment of macrophages and a later defect in the recruitment of dendritic cells and T cells into the lung.

Macrophages have been implicated in the transport of phagocytosed particles from the lung to the lymph nodes, an essential process for the generation of a cellular immune response. So, Peters and co-workers next asked whether this defect in macrophage recruitment to the lungs might result in fewer macrophages (which bear *M. tuberculosis* antigens) reaching the draining lymph nodes, resulting in defective priming of T cells in the $CCR2^{-/-}$ mice. The $CCR2^{-/-}$ mice had fewer macrophages and dendritic cells recruited to these lymph nodes after infection and, although T-cell migration through the lymph nodes was normal in these mice, T-cell priming was delayed. Following on from this, the authors also showed that fewer T cells expressing the CD4 and CD8 cells were primed to produce interferon-γ — and, therefore, a protective response — were present in the lungs of the $CCR2^{-/-}$ mice.

Although previous work has demonstrated a role for CCR2 in leukocyte recruitment to sites of inflammation, this is the first demonstration of the importance of CCR2-dependent cell recruitment in the protective response to *M. tuberculosis*. The authors conclude that these findings have important implications for human disease. CCR2 antagonists are being developed for use as treatment for anti-inflammatory diseases. These results indicate that increased susceptibility to intracellular pathogens, such as *M. tuberculosis*, might be a possible side effect of the long-term use of such antagonists.

Jenny Buckland
Associate Editor, Nature Reviews Immunology

References and links

ORIGINAL RESEARCH PAPER Peters, W. *et al*. Chemokine receptor 2 serves an early and essential role in resistance to *Mycobacterium tuberculosis*. *Proc. Natl Acad. Sci. USA* **98**, 7958–7963 (2001)