CARDIOVASCULAR DISEASE

Another string to LXR's bow

Macrophages have a key role in atherosclerosis through two processes: first, the production of inflammatory mediators; and second, the accumulation of oxidized lipids, as a result of which they become 'foam cells' — macrophages that have taken up massive amounts of lipids, which are the main component of early atherosclerotic lesions. The activation of a class of nuclear-hormone transcription factors known as liver X receptors (LXRs) by oxidized lipids induces the expression of genes involved in lipid efflux in macrophages, thereby acting to protect them from lipid overload. Indeed, recent studies have shown that activating LXR with synthetic agonists can reduce atherosclerosis in mice. Now, Peter Tontonoz, David Mangelsdorf and colleagues have shown that the atheroprotective effect of LXR agonists could be due to a reduction in the the production of inflammatory mediators by macrophages as well as to their established effects on lipid metabolism.

First, the authors assessed the effects of LXR activation on the expression of genes involved in the innate immune response. Macrophages from wild-type mice and from mice lacking LXRs were treated with an LXR agonist, before inducing an immune response by adding bacterial lipopolysaccharide. A comparison of gene expression between cells with and without LXRs using DNA microarrays showed that in cells with LXR present the genes most highly induced by the LXR agonist were those involved in lipid metabolism, as expected from previous understanding. But in addition, the expression of several genes involved in the macrophage innate immune response — such as those encoding inducible nitric oxide synthase (iNOS), interleukin-6 (IL-6) and matrix metalloproteinase 9 (MMP9) — were inhibited by the LXR agonist. Therefore, in activated macrophages, the cholesterol-efflux pathway and the innate immune response are reciprocally regulated by LXRs.

What influence could such effects have in atherosclerosis, in which inflammatory mediators such as IL-6 and MMP9 are important? To investigate this, the authors analysed gene expression in the aortas of atherosclerotic mice, and found that treatment with an LXR agonist substantially reduced the expression of MMP9 (although iNOS expression levels did not differ significantly, indicating that some genes are more sensitive than others to loss of LXR signalling). So, it seems that LXR agonists might reduce atherosclerosis not only by promoting cholesterol efflux, but also by acting to limit the production of inflammatory mediators in the artery wall. Furthermore, LXR agonists might also have potential for other chronic inflammatory diseases in which activated macrophages have a key role, such as rheumatoid arthritis.

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References and links

ORIGINAL RESEARCH PAPER Joseph, S. B. *et al*. Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. *Nature Med.* Jan 13 (2003) (doi: 10.1038/nm820)

FURTHER READING Repa, J. J. & Mangelsdorf, D. J. The liver X receptor gene team: potential new players in atherosclerosis. *Nature Med.* **8**, 1243–1248 (2002)

APOPTOSIS

If I had a hammer…

Dissecting biological systems often depends crucially on having the right tools for the job. The process of discovering small-molecule tools that disrupt cell-signalling pathways, and then using them to probe the identity of individual components of that pathway, has come to be known as forward chemical genetics. An elegant demonstration of the power of this technique was published in the 10 January issue of *Science*, in which Wang and colleagues reported the use of an apoptosis-promoting compound identified by high-throughput screening to reveal the distinct roles of two proteins, both with links to cancer, in the progression of cell death.

Most cell death is initiated by a mitochondrial pathway that follows a series of recognized steps: release of cytochrome c from the mitochondria and induction of apoptosome formation, followed by successive activation of the proteolytic enzymes caspase-9 and caspase-3. In this study, Jiang *et al.* screened an Abbott library of 184,000 compounds for activators of caspase-3 in extracts of HeLa cells, and came up with α-(trichloromethyl)-4-pyridine-ethanol (PETCM), which was also shown to promote apoptosome formation. Fractionating HeLa cell extracts then allowed them to isolate the stimulatory activity and to identify the proteins mediating the PETCM effect as tumour-suppressor putative HLA-DR-associated proteins (PHAPs) and the oncoprotein prothymosin-α (ProT).

PHAP and ProT were found to act in opposite ways, promoting and inhibiting caspase activation, respectively. ProT blocks formation of the apoptosome, a finding that was confirmed by using RNA interference to knock down ProT in HeLa cells, which subsequently showed higher rates of apoptosis than controls when challenged with UV irradiation. PHAP, on the other hand, acts after apoptosome formation, accelerating its ability to activate caspase-9. PETCM promotes caspase activation by antagonizing ProT, and so only in the presence of PETCM, and with the consequent removal of the inhibitory effect of ProT on apoptosome formation, could the pro-apoptotic activity of PHAP be observed.

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References and links

ORIGINAL RESEARCH PAPER Jiang, X. *et al*. Distinctive roles of PHAP proteins and prothymosin-α in a death regulatory pathway. *Science* **299**, 223–226 (2003)