Online links

Lipocalin 2
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=16819
TLR4
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=16819

INNATE IMMUNITY

The fight for iron

Bacterial survival and growth depends on iron, much of which is acquired from the host by siderophores that scavenge iron and transport it into the pathogen. However, as described in this recent *Nature* paper, the innate immune system of the host can prevent bacteria from obtaining iron by producing lipocalin 2, which sequesters bacterial siderophores, in response to Toll-like receptor (TLR) triggering.

In this report, Flo *et al.* demonstrate that stimulation of macrophages through TLRs induces marked upregulation of transcription of lipocalin 2, and confirm these results *in vivo*, showing that injection of mice with the TLR4 ligand lipopolysaccharide induces increased expression of lipocalin 2 in a TLR4-dependent manner. The authors generated lipocalin-2-deficient mice to assess the role of lipocalin 2 in bacterial infection. Although these mice remain healthy in specific pathogen-free conditions, when challenged with *Escherichia coli* (strain H9049), they develop marked bacteraemia, have high bacterial loads in the blood, liver and spleen, and show accelerated lethality at high doses, indicating that lipocalin 2 has an important role in innate defence against bacterial infection.

In the serum, the concentration of free iron is tightly regulated by iron-binding proteins such as transferrin, so invading pathogens must acquire iron by secreting siderophores, which effectively compete for iron. The authors have previously shown that lipocalin 2 can bind catecholate-type siderophores (such as enterochelin) but not other types of siderophore (such as ferrichrome). As *E. coli* strain H9049 depends on enterochelin for importing iron, its growth was inhibited when cultured in acute-phase serum from wild-type mice but not from lipocalin-2-deficient mice. By contrast, the *in vitro* growth of *Staphylococcus aureus*, which does not depend on enterochelin, was not affected by the presence of lipocalin 2.

The specificity of the protective effect of lipocalin 2 against enterochelin-dependent bacterial infection was then examined *in vivo*. Mice were challenged with *E. coli*, with or without co-injection of ferrichrome, which allows bacteria to acquire iron in an enterochelin-independent manner. Similar to lipocalin-2-deficient mice, wild-type mice that received bacteria and ferrichrome showed markedly increased lethality, indicating that lipocalin 2 confers resistance to bacterial infection by abrogating enterochelin-dependent iron uptake by bacteria.

Lucy Bird, Associate Editor,
Nature Reviews Immunology

References and links

ORIGINAL RESEARCH PAPER Flo, T. H. *et al.* Lipocalin 2 mediates an innate immune response to bacterial infection by sequestering iron. *Nature* 7 Nov 2004 (doi:10.1038/nature03104)

WEB SITE
Alan Aderem's laboratory:
http://www.systemsbiology.org/Default.aspx?pagename=alanaderem