BACTERIAL PATHOGENESIS

Envelopes and the inflammatory response

Although *Mycobacterium tuberculosis* envelope (cell wall) lipids have been linked to pathogenesis, how these lipids function isn't clear. Do lipids affect cell-wall integrity, thereby affecting pathogenesis, or do they have specific roles in pathogenesis and in the modulation of the host response to infection? Now, Rao *et al.* report in the *Journal of Experimental Medicine* that cyclopropane modification of a cell envelope glycolipid functions to control the host innate immune response in the earliest part of infection.

In addition to peptidoglycan, which is the most common constituent of bacterial cell walls, more than 60% of the cell wall of *M. tuberculosis* comprises complex lipids, making this cell wall unique among prokaryotes. Mutations in genes that encode cell-wall components, or affect their secretion, result in reduced virulence, but as different mutations have different effects on bacterial growth and pathogenesis, it seems that specific cell-wall components might have distinct roles in pathogenesis.

Mycolic acids, which are long, branched fatty acids, are the major lipid component of these unusual cell walls, and are only synthesized by *Mycobacterium* and *Corynebacterium* spp. In addition to their structural roles, mycolates are presented to T cells as part of the adaptive immune response. In pathogenic mycobacteria, mycolic acids are modified with cyclopropane residues by a family of methyltransferases, one of which is PcaA, an *S*-adenosyl methionine methyltranferase. Mutants in *pcaA* are attenuated and produce less severe immunopathology in mice. Here, Rao *et al.* have focused on trehalose dimycolate (TDM), an inflammatory glycolipid, to monitor the effects of cyclopropyl modification on the earliest part of *M. tuberculosis* infection.

In the first week after aerosol inoculation of mice, titres of an *M. tuberculosis pcaA* mutant in the lungs were markedly reduced — 50-fold lower than the wild type — but growth of the mutant was comparable with the wild type by 2 weeks post-infection. This growth defect only occurred in the presence of tumour necrosis factor (TNF), which implicated cyclopropane modification of glycolipids in TNF induction. The *pcaA* mutants also induced reduced amounts of TNF in macrophages *in vitro* compared with wild-type *M. tuberculosis*, which indicates that they were hypo-inflammatory. Delipidation of bacilli, which removes 90% of TDM, markedly reduced the induction of TNF by the wild-type bacteria, and lipid-swapping experiments between the wild-type and *pcaA* mutants confirmed that *pcaA* mutant mycolates were hypo-inflammatory. Finally, TDM purified from the wild type was a far more potent inducer of TNF in macrophages compared with TDM purified from the *pcaA* mutant.

These results implicate mycolic acids as effector molecules that modulate the innate immune response to *M. tuberculosis*. It is possible that induction of TNF by virulent *M. tuberculosis* might be an important pathogenic strategy, and understanding how different cell-wall components function in mycobacterial pathogenesis should allow improved rational drug design against this major global pathogen.

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References and links

ORIGINAL RESEARCH PAPER Rao, V. *et al.* *Mycobacterium tuberculosis* controls host innate immune activation through cyclopropane modification of a glycolipid effector molecule. *J. Exp. Med.* 14 Feb 2005 (doi:10.1084/jem.20041668)