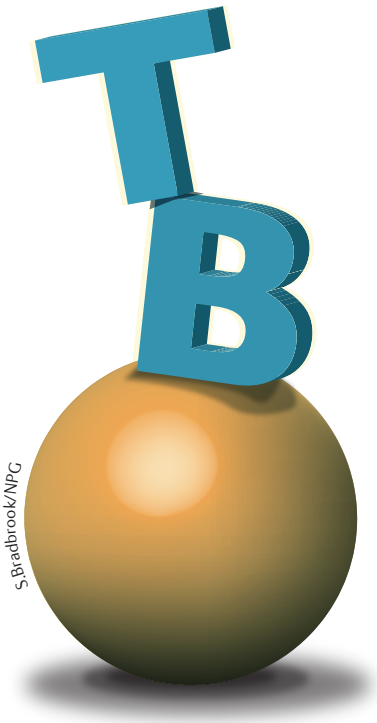
INFECTIOUS DISEASES

Tipping TB off balance

> suppression of type I IFNs is … key to the ability of IL-1 and PGE2 to confer resistance to *M. tuberculosis*

In the face of a growing global epidemic of tuberculosis (TB), the results of a study by Mayer-Barber *et al.* provide proof of concept that manipulating the host eicosanoid balance might offer a long-awaited alternative therapeutic approach to combat *Mycobacterium tuberculosis*.

That mice lacking the interleukin-1 (IL-1) receptor type 1 (*Il1r1*$^{-/-}$ mice) were highly susceptible to *M. tuberculosis* infection was nothing new to the authors. More intriguing was their discovery that levels of the eicosanoid prostaglandin E2 (PGE2) — which is generated by cyclooxygenase 2 (COX2; also known as PTGS2) — were reduced, whereas those of lipoxygenase-dependent eicosanoid products were increased, in bronchoalveolar lavage fluid from infected *Il1r1*$^{-/-}$ mice compared with wild-type mice. Details subsequently emerged of how IL-1 normally promotes the synthesis of PGE2 by COX2, enabling macrophages to restrict *M. tuberculosis* growth during infection.



S. Bradbrook/*NPG*

The authors noted that PGE2 synthesis also increased alongside levels of IL-1 in the absence of type I interferon (IFN) signalling, which is consistent with their previous findings that type I IFNs antagonize the IL-1 pathway during *M. tuberculosis* infection. Notably, this ability of type I IFNs to inhibit IL-1 production correlates with increased virulence in certain *M. tuberculosis* strains, prompting Mayer-Barber *et al.* to explore whether IL-1 and PGE2 could counter-regulate type I IFNs to influence bacterial growth. Indeed, the levels of type I IFNs correlated inversely with those of IL-1 and PGE2, and with their associated influence on bacterial control, such that inhibiting IFN signalling markedly decreased the susceptibility of *Il1r1*$^{-/-}$ mice to infection. The suppression of type I IFNs is, therefore, key to the ability of IL-1 and PGE2 to confer resistance to *M. tuberculosis*.

Knowing that a type I IFN gene signature is associated with active TB, the authors explored the relevance of these findings to human disease and, based on the results of two independent study cohorts, they discovered that the IL-1, eicosanoid and IFN pathways could distinguish patients with active pulmonary TB from healthy controls or those with latent disease. So, might targeting host eicosanoids prove to be effective against active disease, which is associated with high type I IFN responses? Under such conditions (that is, in mice lacking IL-1 or in those treated with an IFN inducer), increasing PGE2 levels by clinically approved means enhanced the survival of *M. tuberculosis*-infected mice. These data ultimately provide the proof of concept that tipping the eicosanoid balance in favour of PGE2 constitutes an effective strategy against TB.

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ORIGINAL RESEARCH PAPER Mayer-Barber, K. D. *et al.* Host-directed therapy of tuberculosis based on interleukin-1 and type I interferon crosstalk. *Nature* **511**, 99–103 (2014)