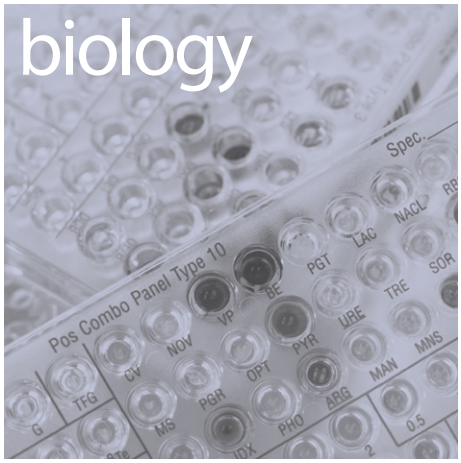

MICROBIOLOGY

Inhibition of essential enzymes in *Mycobacterium tuberculosis*

Current therapies of mycobacterial infections require multiple drugs and treatment for six months or more. Patient non-adherence and acquired drug resistance contribute to frequent failure to eradicate the bacteria. Further knowledge of how *M. tuberculosis* grows and persists within the lung is essential for the development of new therapeutic strategies. Previous studies have suggested that in contrast to many bacterial pathogens mycobacterial mainly use fatty acids as nutrients during infections.

Therefore, Muñoz-Elías *et al.* [1] investigated how *M. tuberculosis* enzymes involved in utilization of fatty acids influence growth and persistence. Mutants in one or both of the isocitrate lyases (ICL1 and ICL2) were analyzed for growth *in vitro*, growth in macrophages, and for virulence in mice. This revealed that ICL1 and 2 were jointly required for utilization of fatty acids, but not glucose, *in vitro*. The ICL double mutant (Δicl1Δicl2) could not grow in mice, bacteria were rapidly eliminated from spleen and lungs, and no lung or spleen pathology could be observed. Furthermore, Δicl1Δicl2 could not replicate in immunodeficient mice and did not survive within murine macrophages. Finally, the ICL inhibitor 3-nitropropionate (3-NP) completely inhibited growth of *M. tuberculosis* in both murine and human macrophages. Due to neurotoxicity 3-NP could not be used in an animal model.

This study reveals that two isocitrate lyases are jointly required for growth and persistence of *M. tuberculosis*, and that an enzyme inhibitor could block bacterial growth within cells. These very promising findings could lead to the development of a new class of mycobacterial drugs targeting these essential enzymes.

1 Muñoz-Elías, E.J. (2005) *Mycobacterium tuberculosis* isocitrate lyase 1 and 2 are jointly required for *in vivo* growth and virulence. *Nat. Med.* 11, 638–644

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PRION DISEASES

No anchor, no scrapie

Misfolded prion protein (PrPSc) is responsible for devastating brain-wasting diseases such as Creutzfeld-Jakob disease in human, scrapie in sheep and mad cow disease. These prion diseases, or transmissible spongiform encephalopathies (TSE), present some similar pathology to other encephalopathies such as Alzheimer and Parkinson disease. By contrast, TSE is distinct from other encephalopathies as they are transmissible by prion inoculation or ingestion. Although the mechanism for prion-mediated cell death remains poorly understood, the glycosylphosphatidylinositol (GPI) anchor of PrP has been hinted to be involved in the cycling between cell surface and endosomes, suggesting that GPI might be important in the infectivity of PrPSc.

In their study using a transgenic animal model, Chesebro *et al.* provided great insight into the role of GPI moiety of PrP in the pathogenesis of prion diseases. Transgenic mice were engineered to express a GPI-negative, anchorless, secreted version of the normal PrPc. When these mice were infected with PrPSc by intracerebral inoculation, in spite of the fact that secreted PrPc was converted into PrPSc, these animals did not exhibit signs of clinical scrapie. As assessed by light and electron microscopy, formation of amyloid plaques was prevalent in the brains of these animals. These results demonstrate that GPI is critical for prion toxicity, but it is dispensable for prion replication and the formation of PrPSc plagues.

The findings from this study strongly support the contention that the binding of PrPSc to cell surface is required for neurotoxic signal. Although the observation time of >600 days should have been sufficient for clinical symptoms to appear, it remains possible that prion-induced lesions might be developed at a later time. The normal functions of PrPc remain unclear, although there is some indication that it functions as a protease and a signal-transduction molecule. If PrPSc induces brain damage by disrupting normal signaling of PrPc, the answer to the riddle of how infectious prion causes mayhem in the brain might indeed lies in the normal functions of PrPc.

2 Chesebro, B. *et al.* (2005) Anchorless prion protein results in infectious amyloid disease without clinical scrapie. *Science* 308, 1435–1439

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  PII: S1359-6446(05)03545-2