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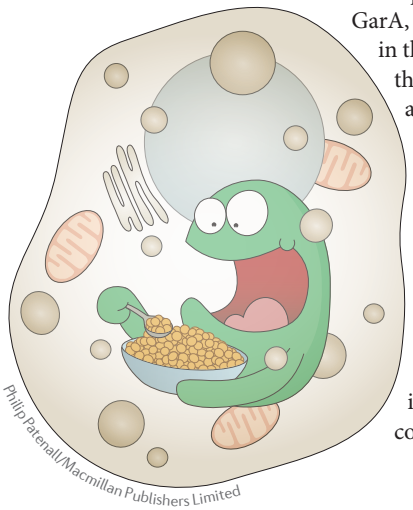
BACTERIAL PHYSIOLOGY

An inside job on metabolism

> *M. tuberculosis* adapts to environmental stresses that are associated with an intracellular lifestyle

Mycobacterium tuberculosis, the causative agent of tuberculosis, is an intracellular pathogen that has adapted to a life inside of host macrophages. Metabolic adaptations to changes in environmental conditions are thought to be crucial for the virulence and survival of *M. tuberculosis* during pathogenesis; for example, by adapting to host responses that starve intracellular bacteria of amino acids and adapting to hypoxic environments. Two new studies reveal how *M. tuberculosis* adapts to environmental stresses that are associated with an intracellular lifestyle.

In the first study, Rieck *et al.* investigated the role of the mycobacterial serine/threonine kinase PknG and its substrate GarA in contributing to the virulence of *M. tuberculosis*. PknG phosphorylates GarA, and this results in the regulation of the tricarboxylic acid (TCA) cycle and glutamate synthesis. The authors found that GarA is required for the efficient growth of *M. tuberculosis* in macrophages and for virulence in mice, and confirmed that phosphorylation sites on the protein were required for efficient growth. Next, the authors observed that disruption of *garA* and *pknG* caused specific and opposing effects on nutrient requirements for growth. Specifically, disruption of *garA* led to a dependence on glutamate and asparagine, whereas disruption of *pknG* led to a defect in the utilization of these amino acids.



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The authors then investigated the environmental signals that alter the phosphorylation status of GarA and found that it is unphosphorylated only during starvation conditions. The addition of amino acids that can restore growth in Δ*garA* mutants resulted in the phosphorylation of GarA. Furthermore, metabolome analyses showed that amino acid metabolism is the main target of regulation by GarA and PknG. Together, these observations provided strong evidence that *M. tuberculosis* may sense amino acid levels inside host cells to control amino acid metabolism.

In a second study, Eoh *et al.* investigated the response of *M. tuberculosis* to hypoxic conditions. Using an *in vitro* hypoxia model, the authors found that hypoxia results in the accumulation of intermediates of the early stages of glycolysis and the pentose phosphate pathway, which were linked to hypoxia-dependent decreases in a downstream glycolytic intermediate, phosphoenolpyruvate, and an upstream glucose disaccharide, trehalose, which can act as a carbon store. After exposing *M. tuberculosis* to hypoxic conditions in the presence of ^{13}C-labelled glucose or acetate, metabolites predominantly accumulated in the unlabelled fraction, which suggests the metabolism of a pre-existing store, such as trehalose. As trehalose is a major component of the cell surface mycolyl glycolipids of *M. tuberculosis*, the authors hypothesized that hypoxia induced the catabolism of these lipids, which was confirmed using lipidomics. The authors then observed that these accumulated metabolic intermediates were used for growth after re-aeration. In summary, this study indicates that *M. tuberculosis* responds to hypoxic environments by mounting a metabolic response in anticipation of ultimately re-entering the cell cycle.

Together, these two studies provide strong evidence that sensing and responding to environmental changes are essential for bacteria that adopt intracellular lifestyles.

Ashley York

ORIGINAL ARTICLES Rieck, B. *et al.* PknG senses amino acid availability to control metabolism and virulence of *Mycobacterium tuberculosis*. *PLoS Pathog.* **13**, e1006399 (2017) | Eoh, H. *et al.* Metabolic anticipation in *Mycobacterium tuberculosis*. *Nat. Microbiol.* **2**, 17084 (2017)