ANTIMICROBIALS

New drugs for an old scourge?

Tuberculosis (TB) remains a serious problem worldwide. The causative agent, *Mycobacterium tuberculosis*, is difficult to treat, in part because it can persist under hypoxic (low oxygen) conditions in a dormant form that has reduced sensitivity to many antibiotics. Rao and colleagues report that *de novo* synthesis of ATP and maintenance of energized membranes are required for *M. tuberculosis* to survive in the dormant state. These findings could lead to the use or development of new drugs that target recalcitrant, dormant bacteria.

TB requires long treatment regimens, in part owing to the survival of dormant *M. tuberculosis* under hypoxic conditions. Rao *et al.* found that the intracellular concentration of ATP dropped by more than fivefold as the bacteria adjusted to hypoxic conditions *in vitro*, which makes the bacteria particularly sensitive to drugs that target ATP synthesis. Indeed, dormant bacteria were up to 50-fold less sensitive to antibiotics that target growth and division, but up to eightfold more sensitive to drugs that target the synthesis of ATP, than actively growing bacteria.

Because ATP generation depends on the formation of a proton motive force (PMF) across the plasma membrane, disruption of the PMF is likely to kill dormant bacteria. The authors showed that both components of the PMF (the membrane potential and the transmembrane proton gradient) are actively maintained in dormant bacteria and that disruption of either with specific inhibitors decreased ATP concentrations in the bacteria and bacterial viability.

The electron transport chain is usually required for establishing the PMF. Inhibition of Ndh2, the electron donor that is used in the electron transport chain under hypoxic conditions, affected both viability and ATP concentrations in *M. tuberculosis* cells. The authors speculate that cells die owing to a loss of oxidizing power in the form of NAD^+, which is regenerated from NADH during ATP synthesis, rather than because of a lack of ATP.

These results indicate that inhibitors of *de novo* ATP synthesis and NAD^+ regeneration can kill dormant *M. tuberculosis*. Proof of principle of this approach is that the drug R207910, which inhibits another component of the ATP-synthesis pathway, the F_0F_1 ATPase, is efficacious against *M. tuberculosis in vivo* and is well tolerated by humans.

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ORIGINAL RESEARCH PAPER Rao, S. P. S. *et al.* The proton motive force is required for maintaining ATP homeostasis and viability of hypoxic, nonreplicating *Mycobacterium tuberculosis*. *Proc. Natl Acad. Sci. USA* **105**, 11945–11950 (2008)

FURTHER READING Sacchettini, J. C., Rubin, E. J. & Freundlich, J. S. Drugs versus bugs: in pursuit of the persistent predator *Mycobacterium tuberculosis*. *Nature Rev. Microbiol.* **6**, 41–52 (2008) | Andries, K. *et al.* A diarylquinolone drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* **307**, 223–227 (2005)