AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Bacteriology

ARTICLES
15 August 2012 Volume 194 Issue 16
https://doi.org/10.1128/jb.00585-12

Mycobacterium tuberculosis Protein Kinase K Enables Growth Adaptation through Translation Control

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ABSTRACT *Mycobacterium tuberculosis* serine/threonine protein kinases (STPKs) are responsible for orchestrating critical metabolic and physiological changes that dictate mycobacterial growth adaptation. Previously, we established that PknK participates in regulatory pathways that slow the growth of *M. tuberculosis* in a variety of *in vitro* stress environments and during persistent infection in mice. In the present study, we have elaborated on the mechanism of PknK-mediated regulation. Through transcription profiling of wild-type H37Rv and a Δ*pknK* mutant strain during logarithmic and stationary growth phases, we determined that PknK regulates the expression of a large subset of tRNA genes so that regulation is synchronized with growth phase and cellular energy status. Elevated levels of wild-type *M. tuberculosis* PknK ($PknK_{Mtb}$), but not phosphorylation-defective $PknK_{Mtb}$, in *Mycobacterium smegmatis* cause significant retardation of the growth rate and altered colony morphology. We investigated a role for PknK in translational control and established that PknK directs the inhibition of *in vitro* transcription and translation processes in a phosphorylation-dependent manner. Increasing concentrations of ATP or PknK exert cooperative effects and enhance the inhibitory function of PknK. Furthermore, truncation and mutational analyses of PknK revealed that PknK is autoregulated via intramolecular interactions with its C-terminal region. Significantly, the invariant lysine 55 residue was only essential for activity in the full-length PknK protein, and the truncated mutant proteins were active. A model for PknK autoregulation is proposed and discussed.

Received 7 April 2012 **Accepted** 23 May 2012 **Accepted manuscript posted online** 1 June 2012 **Published** 27 July 2012
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