Title: Evaluating the sensitivity of *Mycobacterium tuberculosis* to biotin deprivation using regulated gene expression

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Abstract

In the search for new drug targets, we evaluated the biotin synthetic pathway of *Mycobacterium tuberculosis* (*Mtb*) and constructed an *Mtb* mutant lacking the biotin biosynthetic enzyme 7,8-diaminopelargonic acid synthase, BioA. In biotin-free synthetic media, Δ*bioA* did not produce wild-type levels of biotinylated proteins, and therefore did not grow and lost viability. Δ*bioA* was also unable to establish infection in mice. Conditionally-regulated knockdown strains of Mtb similarly exhibited impaired bacterial growth and viability *in vitro* and in mice, irrespective of the timing of transcriptional silencing. Biochemical studies further showed that BioA activity has to be reduced by approximately 99% to prevent growth. These studies thus establish that *de novo* biotin synthesis is essential for *Mtb* to establish and maintain a chronic infection in a murine model of TB. Moreover, these studies provide an experimental strategy to systematically rank the *in vivo* value of potential drug targets in Mtb and other pathogens.