

Structure-function properties of Mycobacterium tuberculosis WhiB1

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Summary

Mycobacterium tuberculosis is the causative agent of human tuberculosis (TB), which claimed 1.8 million lives in 2015 (WHO, 2016). A key component of TB pathogenesis is the ability of *M. tuberculosis* to enter a non-replicating persistent state following colonization of the human lung. Emergence from the persistent state upon immunosuppression, sometimes decades after the initial infection, results in an active infection (reactivation TB) that can be fatal if untreated. The fundamental role of Wbl proteins in developmental processes in actinomycetes suggested that they could play a role in entry into and emergence from the non-replicative persistent state that is characteristic of *M. tuberculosis* infections. *M. tuberculosis* possesses seven genes encoding Wbl proteins and several of these have been implicated in features of tuberculosis pathogenesis. The *M. tuberculosis whiB1* gene is essential and encodes a DNA-binding protein with an NO-sensitive [4Fe-4S] cluster. Nitric oxide is an important component of the host response to *M. tuberculosis* infection; high concentrations of NO generated by activated macrophages can kill the bacilli but low NO levels promote transition to the dormant non-replicating state. Here, the WhiB1 [4Fe-4S] cluster is shown to be essential for forming a complex with SigA and that reaction with NO disassembles the complex, indicating the role of reprogramming gene expression. Until now the structure of a Wbl protein had not been solved. An NMR structural model of WhiB1 is presented, revealing a core of three α -helices held together by the [4Fe-4S] cluster. The structure suggests that loss of the iron-sulfur cluster (by nitrosylation) frees a fourth C-terminal helix permitting positively-charged residues therein to engage in DNA-binding. The sensitivity of WhiB1 to nitric oxide, the ability to interact with SigA, and the structure characterization of the protein suggest the protein role in regulating the pathogenicity of *M. tuberculosis* during infection.