REVIEW ARTICLE

The sigma factors of *Mycobacterium tuberculosis*: regulation of the regulators

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Keywords
Mycobacterium; post-translational regulation; sigma factor; tuberculosis

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(Received 8 September 2009, revised 27 October 2009, accepted 4 November 2009)

doi:10.1111/j.1742-4658.2009.07479.x

One of the important determinants of virulence of *Mycobacterium tuberculosis* is adaptation to adverse conditions encountered in the host cells. The ability of *Mycobacterium* to successfully adapt to stress conditions is brought about by the expression of specific regulons effected by a repertoire of σ factors. The induction and availability of σ factors in response to specific stimuli is governed by a complex regulatory network comprising a number of proteins, including σ factors themselves. A serine–threonine protein kinase-mediated signaling pathway adds another dimension to the mycobacterial σ factor regulatory network. This review highlights the recent advances in understanding mycobacterial σ factors, their regulation and contribution to bacterial pathogenesis.

Introduction

The causative agent of tuberculosis (TB), the intracellular bacterial pathogen *Mycobacterium tuberculosis*, latently infects about one-third of the world's population and claims one life every 15 s. Although the World Health Organization-recommended treatment strategy for the detection and cure of TB, the 'Directly Observed Treatment, Short-course' (DOTS), has reduced the burden of TB to a great extent, the incidence of TB has shown an increase in recent years as a result of the emergence of drug-resistant TB and co-infection with the human immunodeficiency virus (http://www.who.int/tb/en/). Despite global efforts, no new drugs for the treatment of TB have been developed successfully for more than four decades.

The success of *M. tuberculosis* as a highly adapted pathogen rests upon its ability to establish a persistent infection in the hostile environment of the host cell through mechanisms involving transcriptional reprogramming, ensuring metabolic slowdown and the upregulation of virulence and stress-response pathways [1]. In the course of a successful infection, the bacterium copes with numerous stresses (reviewed previously [2]) and modulates host responses through coordinated regulation of its gene expression in response to signals encountered in the host body. Gene expression in bacteria is regulated primarily at the level of transcription initiation, which is mediated by the RNA polymerase (RNAP) holoenzyme. The

Abbreviations
ECF, extracytoplasmic function; *imp*, immunopathology; *M. bovis* BCG, *Mycobacterium bovis* Bacille Calmette–Guérin; PPE, proline-proline-glutamate; RNAP, RNA polymerase; STPK, serine–threonine protein kinase; Tat, twin-arginine translocation; TB, tuberculosis; TCS, two-component system; TSP, transcription start point; ZAS, zinc-associated anti-σ factor.

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