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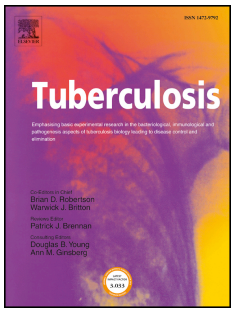

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Proteomic analysis reveals that Sulfamethoxazole induces oxidative stress in *M. tuberculosis*

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Summary

The emerging resistance of tuberculosis (TB) to current first line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) warrants alternative treatment approaches with broad-spectrum efficacy. Previously, we have shown that sulfamethoxazole (SMX) has synergestic activity with rifampicin against *Mycobacterium tuberculosis*. The primary target of SMX is *folP1* in mycobacteria; however, SMX may affect other secondary targets in *M. tuberculosis*. This study investigated the potential additional targets of SMX in a clinical isolate of *M. tuberculosis* using Orbitrap mass spectrometry to identify differentially expressed proteins following treatment with a sub-lethal concentration of SMX. Raw data have been deposited as ProteomeXchange accession PXD009315. Our proteomic analysis identified approximately 1500 proteins in total of which 46 proteins were differentially regulated as a result of SMX treatment. These included 25 upregulated and 21 downregulated proteins. The oxidative stress proteins (Rv2428, AhpC and Rv2394, GgtB) and an enzyme from the electron transport chain (Ndh-II, Rv1854c) were found to be upregulated. Gene expression analysis correlated with the observed proteomic changes. In conclusion our results show that SMX treatment of a drug sensitive *M. tuberculosis* clinical isolate resulted in the regulation of proteins involved in the oxidative stress response, indicating the induction of oxidative stress by SMX in mycobacteria.

Keywords: *Mycobacterium tuberculosis*, Sulfamethoxazole, Proteomics, Oxidative stress.

Introduction

Mycobacterium tuberculosis is a highly infectious pathogen causing tuberculosis (TB) in 10.4 million people worldwide with 1.5 million deaths including 0.4 million individuals with HIV-TB co-infection [1,2]. Thus, new and effective drugs are urgently needed to combat MDR (multi drug-resistant) and XDR (extensively drug-resistant) tuberculosis, however new drug development is extremely expensive and time consuming.