Gene Expression Mechanism of Alternative Sigma Factors SigE and SigB Inducing Rifampicin Resistance in Mycobacterium Smegmatis

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Tuberculosis, an infectious respiratory disease caused by Mycobacterium tuberculosis, is estimated to have infected more than a quarter of the world's population. It was the second leading cause of death in 2020 only after COVID-19. Upon diagnosis, strong antibiotics such as Rifampicin and Isoniazid are used in conjunction. However, M. tuberculosis has especially strong resistance to antibiotics during its dormant state, leading to the need of long treatment time. It is known that some alternative sigma factors, which regulate RNA polymerase during transcription, are closely related to the expression of resistance-related genes. In this research, we used various approaches to find the mechanism of rifampicin resistance by studying sigma factors SigB and SigE in model organism Mycobacterium smegmatis. We analyzed the RNA sequencing data of aa3 cytochrome C, sigB and sigE deletion mutants and discovered a strong correlation relationship between differentially expressed genes that we defined. To confirm the sequencing data and find the exact order of mechanism, we conducted beta-galactosidase assay and qRT-PCR on these mutants. Both experimental results were in line with RNA sequencing data, and we concluded that respiratory stress caused by aa3 cytochrome C mutation leads to overexpression of sigE, and the expressed SigE sigma factor causes overexpression of SigB, which we found to regulate several Rifampicin resistance related genes. Finally, zone inhibition assay on SigB-regulated gene overexpressed strains showed increased resistance to Rifampicin, supporting our proposed mechanism of resistance during latent state.

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