Elucidating the Metabolism and Toxicity of Host-Derived Toxin Methylglyoxal in Mycobacterium Tuberculosis and Mycobacterium Smegmatis

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In the past decade, tuberculosis has become the most significant global health challenge due to co-infection with HIV/AIDS, antibiotic resistance and the ineffectiveness of BCG. Methylglyoxal (MG) is a host-derived toxin produced as a result of carbon metabolic imbalance in many organisms, including Mycobacterium tuberculosis (Mtb). MG can be implemented in a therapeutic agent that target problems including persistence and antibiotic resistance through inducing self-poisoning. However, the metabolism and toxicity of MG are entirely unstudied in mycobacteria and such fundamental knowledge is crucial for creating such a therapeutic agent. Through this study, we were able to isolate spontaneous Mycobacterium smegmatis mutants that displayed 4-fold resistance to MG. A full genomic sequencing of 9 mutants showed 3 non-synonymous mutations in MSMEG_3197, MSMEG_4262 and MSMEG_6092. Tuberculosis homologs exist for all 3 genes: Rv1592c, QcrA and Lsr2 respectively and all genes have been implicated in antibiotic response and reactive oxygen species in previous studies. We were able to begin the process of characterizing these genes through glucose toxicity assays as well as aerobic and anaerobic MICs. We were also able to isolate 2 susceptible M. smeg transposon mutants and are continuing to study these mutants as well as isolating and verifying additional mutants. Finally, we were able to conduct a microarray analysis of transcription response of Mtb to 1mM MG. All genes isolated from the microarray represent excellent candidates for future research that we are currently conducting. Through this study, we are making significant advances into creating a novel therapeutic agent against tuberculosis as this study is the first to begin studying MG metabolism and toxicity within Mtb.

Awards Won:
Third Award of $1,000