Knockdown of the Essential 23S rRNA Methyltransferase, rv3579c, Increases the Susceptibility of Mycobacterium Tuberculosis to Macrolides

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According to the CDC, in 2018, 1.7 billion people were infected with Mycobacterium tuberculosis (Mtb). To treat tuberculosis (TB) infections, there has been interest in using macrolides, a family of drugs that includes clarithromycin, as they are well-tolerated by most individuals. However, Mtb possesses intrinsic resistance to macrolides, rendering macrolide drugs ineffective. The basis for this resistance is little understood; however, we previously identified rv3579c, a predicted 23S rRNA methyltransferase, to be a novel macrolide-resistance factor in Mtb. Using ms6073, the homologous gene to rv3579c in M. smegmatis (a non-lethal model of Mtb), I showed that, with genetic knockdown of ms6073, M. smegmatis becomes more susceptible to clarithromycin, thereby highlighting a mechanism that could potentially facilitate successful treatment and elimination of TB in affected individuals. Here, I expanded my earlier work by individually mutating several conserved residues in these proteins to better elucidate their functions. Moreover, I tested the susceptibility of ms6073 knockdown in M. smegmatis to 14 additional ribosome-targeting antibiotics to identify if ribosome function was impaired. Interestingly, only fusidic acid and clarithromycin were able to prevent growth. I also found that knockdown of ms6073 and rv3579c is bacteriostatic, not bactericidal. Thus, I determined that a combination therapy of genetic knockdown with drug treatment is necessary to effectively treat TB infections. With these additional pivotal findings, I have laid the groundwork for further research to determine whether or not rv3579c can be targeted by chemical compounds to both inhibit Mtb growth and render the bacteria sensitive to macrolides.

Awards Won:

Third Award of $1,000