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Contribution ID: **109** Type: **Invited Talk**

Evaluating the mycobacterial proteostasis system as a drug target in tuberculosis

Thursday, 1 December 2022 13:45 (30 minutes)

Tuberculosis (TB) is a chronic lung disease caused by infection with Mycobacterium tuberculosis (Mtb). TB is the leading global cause of infectious disease-related deaths and disproportionately affects populations in the Global South. While TB can be treated with combination antibiotic therapy, there remain substantial therapeutic challenges. The extended duration of treatment for TB results in compliance issues which has led to the development of drug resistance. Therefore, new strategies to shorten treatment duration and combat resistance are required. Drug resistance is driven by mutations in specific Mtb proteins targeted by antibiotics. Therefore, one strategy to circumvent resistance is to inhibit the bacterial proteostasis system, as mutated protein variants may be less stable than the wild type variants. In the context of rifampicin resistance, we studied the effect of drug-resistance mutations in the target protein RpoB. We show that RpoB is a client protein of the major Hsp70 proteostasis complex in Mtb and that Hsp70 can protect RpoB from stress inactivation. Molecular dynamics simulations using GROMACS suggested that drug-induced mutations alter the stability of the RpoB protein. Specifically, RpoB drug resistant mutations D435V, D435V-H445Y, D435V-H445Y-S450L, H445Y, and G442A-S450L led to reduced protein stability, while S450L led to a more stable RpoB phenotype. The in silico predictions were compared to in vitro biochemical assays in which the thermal stability and Hsp70 interaction were compared. Taken together, our data suggest that RpoB drug-induced mutations alter protein stability and Hsp70 interaction, and may predict the reliance of these proteins on the Mtb Hsp70 proteostasis system. Consequently, inhibition of Hsp70 is being evaluated as a strategy to sensitise bacteria to rifampicin.

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Session Classification: HPC Applications

Track Classification: Bioinformatics and Biological Sciences