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Newer molecular targets and therapeutic strategies for intervention against *Mycobacterium tuberculosis*

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*M. tb*), takes one human life every 15-20 seconds globally. We have been focusing on the functional biology of this pathogen with a view to design innovative interventions against TB. We identified and characterized several virulent proteins of *M. tb* that help in intracellular survival by modifying host cellular machinery. Phylogenetic analysis of *M. tb* methyltransferases (MTases) pointed to an evolutionary relationship of *M. tb* with halotolerant organisms, notably in the context of their ability to withstand the host osmotic stress, thus highlighting their likely role in pathogenesis, virulence and niche adaptation. Some of the MTases exhibit antigenic patches and regulate transmembrane transport proteins. Another class of proteins, the sigma factors and their target genes, has been shown to move from non-pathogenic to pathogenic Mycobacteria. The *M. tb* PE_PGRS subfamily has unusually high levels of disordered stretches compared to any other family in the proteome and was highly enriched in average number of anchor binding sites, eukaryotic linear motifs (ELMs) and has highly biased amino acid composition rich in disorder promoting alanine and glycine residues and play roles in molecular mimicry. One member of this protein family causes activation of Unfolded Protein Response as evident from increased expression of GRP78/GRP94 and CHOP/ATF4, leading to disruption of intracellular Ca2+ homeostasis and increased NO and ROS production. The consequent activation of effector caspase-8, resulted in apoptosis of macrophages. In other series of investigations, comparative proteomic and genomic analyses revealed the exclusive presence of 'Signature sequences' in *M. tb* genome, some of which have potential utility in TB diagnosis based on limited clinical validation. Hypothetical proteins coded by one such 'Signature sequences' was found to be a functional S-adenosyl dependent DNA methyltransferase and binds DNA non-specifically and protects DNA from oxidative stress by scavenging iron thereby, preventing generation of free radicals and by physically binding DNA and providing a physical barrier. Using drug re-purposing strategies we also identified existing US FDA approved drugs that inhibit *M. tb* by disrupting the pathogen's biofilm forming ability and thus have the potential to act as a new TB drug and to reduce the duration of treatment. My presentation will cover some of these findings from our group.

Speaker Biography

Seyed Ehtesham Hasnain is a Professor and the Head of Jamia Hamdard-Institute of Molecular Medicine and Invited Professor at Indian Institute of Technology, Delhi. He has received his PhD from JNU (1980), Post-doctoral training in Canada/USA, and was a Staff Scientist at National Institute of Immunology, New Delhi and the Vice Chancellor (President) of Jamia Hamdard. He is associated with editorial boards of national/international journals and has authored more than 250 publications/patents and recipient of many national and international awards including S S Bhatnagar Prize, Ranbaxy Research Award, J C Bose National Fellow, Humboldt Research Prize and Robert Koch Fellow (Berlin). He is an Elected Fellow of German Academy of Sciences, Leopoldina and American Academy of Microbiology, etc. He has received Germany's highest recognition DasVerdienstkreuz, 1. Klasse in 2014. His research area includes functional molecular epidemiology and biology, *Mycobacterium tuberculosis*, transcriptional regulation of gene expression, genetic hyper-variability, molecular pathogenesis and disease intervention.

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