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PDIM and SL1 accumulation in *Mycobacterium tuberculosis* is associated with *mce4A* expression

Pooja Singh[1,5], Rajesh Sinha[1,2], Gaurav Tyagi[1], Naresh kumar Sharma[1], Neeraj k Saini[3], Amita Chandolia[1], Ashok Kumar Prasad[4], Mandira Varma-Basil[1], Mridula Bose[1#]

[1]Department of Microbiology, V. P. Chest Institute, University of Delhi, Chatra Marg, Delhi, India
[2]Department of Biochemistry, V. P. Chest Institute, University of Delhi, Chatra Marg, Delhi, India.
[3]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY, USA.
[4]Department of Chemistry, Bioorganic Laboratory, University of Delhi, Delhi 110007, India.
[5]Public Health research Institute, New Jersey Medical School - Rutgers, The State University of New Jersey, Newark, NJ, USA.

[#] Corresponding Author: Professor Mridula Bose
Telephone: +91-11-27667441
Fax: +91-11-27666549
Email-id: bosemridula@yahoo.co.in

ABSTRACT

Lipid metabolism forms the heart and soul of *Mycobacterium tuberculosis* life cycle. Starting from macrophage invasion at cholesterol rich micro-domains to a sustainable survival for infection by utilizing cholesterol, *Mycobacterium* displays the nexus of metabolic pathways around host derived lipids. *mce4* operon acts as cholesterol import system in *M. tuberculosis* and here we demonstrate role of *mce4A* gene of this operon in cholesterol catabolism. Here *M. tuberculosis* H37Rv overexpressing Rv3499c (*mce4A*) recombinant was used as a model to decipher the metabolic flux during intake and utilization of host lipids by mycobacteria. We analysed the impact of *mce4A* expression on carbon shift initiated during cholesterol utilization necessary for long term survival of mycobacterium. Through transcriptional analysis, upregulation in methylcitrate cycle (MCC) and methylmalonyl pathway (MMP) genes was observed in Rv3499c overexpressing recombinants of *M. tuberculosis* H37Rv. Up-regulation of methylmalonyl pathway associated enzyme encoding genes increased accumulation of virulence associated mycobacterial lipids phthiocerol dimycocerates (PDIM) and sulfolipid (SL1). We demonstrate that MCC and MMP associated enzyme encoding genes are upregulated upon *mce4A*