Gut microbiota regulate lung immunity against *Mycobacterium tuberculosis* by signaling through mincle receptor

Various factors and mechanism behind gut microbiota mediated control of immune response during tuberculosis (TB) is still unknown. Gut microbiota regulates the host immunity to infection at distant mucosal sites, such as the lung. But the involvement of bacterial products and their mechanism of modulating lung immunity in TB are still elusive. Gut microbial components serve as ligands for the activation of immune cells through various pattern recognition receptors (PRRs). In the present study, we have demonstrated the importance of signaling through mincle receptor in imparting lung immunity against *Mtb*. Administration of TDB (glycolipid analogue) and *Lactobacillus plantarum* to gut disrupted mice restored the mincle receptor expression, compromised lung dendritic cell function and inefficient T cell effector/memory generation in the lungs. Further, significant changes in different bacterial species (*Bacteriodes* and *Lactobacillus* genus) correlated well with the protective immune response observed against *Mtb* on triggering through mincle receptor. This study delineates the significance of gut microbiota derived glycolipids as cues to boost lung immunity against *Mtb*.

Summary

Gut dysbiosis impairs the efficacy of isoniazid against *Mycobacterium tuberculosis*

TB continues to remain a global threat owing to the generation of drug resistant *Mtb* strains, lengthy drug treatment and toxicity associated with TB-drugs. Isoniazid (INH) is the first line of drug employed for TB treatment, but factors affecting INH efficacy, remained unexplored. Gut microbes are known to affect the host immune response. In the current study, we have studied the role of gut microbiota on INH efficiency to kill *Mtb*. Employing *in vivo* model of experimental TB, we found that gut dysbiosis suppresses INH mediated *Mtb* clearance through alteration of gut microbes composition. Moreover, gut dysbiosis in INH treated mice, significantly elevated the lung *Mtb* burden, reduced T cell activation, proliferation and memory generation. Further, compromised intestinal barrier integrity and immunity was observed in these mice. Interestingly, Abx treatment did not affect the INH mediated apoptosis of T cells but rather it diminished the innate immune response, as seen by the impairment of dendritic cells activation, down-regulation of pro-inflammatory cytokines and PRRs expression. This study elucidates the importance of gut microbiota in modulating INH efficacy. In future, supplementation of beneficial gut microbes with anti-TB drugs may considerably aid in TB treatment.

Signaling through dectin-1 enables effective clearance of *Mycobacterium tuberculosis*

Dectin-1 is an innate receptor expressed on macrophages, DCs, monocytes, etc. Curdlan is a beta-1, 3-glucan polysaccharide, component of bacteria, yeast and fungi cell wall, which signals through dectin-1. This study characterized the immunomodulatory effect of curdlan in triggering dectin-1 against *Mtb* infection. Dectin-1 signaling using curdlan enhanced the antigen presentation, proinflammatory cytokines release, *Mtb* uptake and killing activity of macrophages. Furthermore, curdlan immunotherapy in mouse model of TB significantly reduced the *Mtb* burden in the lungs and spleen. This immunotherapy further augmented protective Th1 and Th17 response and boosted *Mtb* specific central and effector memory CD4 T cell response. The mechanism deciphered in dectin-1 mediated *Mtb* killing was found to be through nitric oxide release and autophagy induction. Taken together, signaling through dectin-1 employing curdlan exerts effective innate and adaptive immune response against *Mtb*. These findings suggest that immunotherapy involving curdlan can be novel strategy to effectively treat TB.