Chasing the functions of Mycobacterium Tuberculosis Glycolipids during Infection using Membrane Biophysics and Chemical Proteomics

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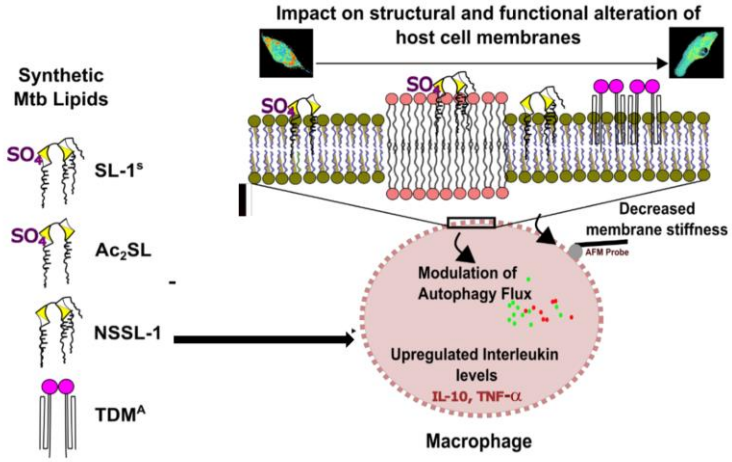
Abstract: Microbial lipids play a critical role in the pathogenesis of infectious diseases.[1] Mycobacterium tuberculosis (Mtb)—causative agent of Tuberculosis—synthesizes chemically distinct glycolipids that are exposed on its outer membrane and interact with the membranes of host macrophages.[2-3] However, the effects of the structurally diverse Mtb glycolipids on the host cell membrane properties to fine-tune the host cellular response is unknown. In this work, we combined membrane biophysics, cell biology and chemical synthesis to assess the effects of different Mtb lipids on cell membrane mechanics, lipid diffusion, and cytoskeleton of THP-1 macrophages.[4-6] We found that Mtb lipids are transferred to macrophage membranes in a lab infection model, followed by modulation of macrophage membrane biophysical properties, and actin cytoskeleton. Physicochemical assays with Mtb lipid analogs revealed insights into their structure-function relationships highlighting specific roles of lipid acyl chains and head group along with effects on membrane-associated autophagy signalling. Chemical proteomics based affinity pull down using clickable Mtb lipid probes revealed potential Mtb lipid-binding host proteins. These observations provide a novel lipid-centric paradigm of Mtb pathogenesis that is amenable to pharmacological inhibition and could promote the development of robust biomarkers of Mtb infection and pathogenesis.



References and notes:

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