Phenolic Glycolipid I confers advantage to *M. leprae* for invasion of the Peripheral Nerve System allowing modulation of Pattern Recognition Receptors and metabolism in Schwann cells favoring bacterial survival.

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Peripheral nerve damage is the more severe consequence of leprosy that occurs in all clinical forms of the disease. It results from the capacity of *Mycobacterium leprae*, an obligate intracellular bacillus, to infect Schwann cells (SC), the glial cells of the peripheral nervous system. These cells show remarkable plasticity and contribute to the regeneration capacity of the adult PNS even after severe injury. In-depth investigation aiming *M. leprae*-nerve interaction to develop new strategies for nerve impairment prevention and treatment is therefore of great importance. Previous studies have shown that *M. leprae* induces the production of insulin-like growth factor 1 favoring SC survival as well as drastic changes in SC lipid and glucose metabolism that promote bacterial persistence. Moreover, recent publications have shown the capacity of *M. leprae* to induce reprogramming of SC to a stage of progenitor/stemlike cells probably contributing to dissemination of infection. However the molecular mechanisms underlying these events and the contribution of *M. leprae* main glycolipid, such as PGL I, need to be better understood. Thus, to better decipher the role of this glycolipid in leprosy neuropathogenesis, besides *M. leprae*, a genetically engineered *M. bovis* BCG strain producing PGL I (BCG PGL I) was used as an alternative tool. In this work we have managed to show the critical role of PGL I on *M. leprae* adhesion and internalization in SC. We provide evidence that PGL I production and bacterial viability are determinants for mycobacterial internalization into SC. Furthermore, we propose that live PGL I producing mycobacteria modulate the expression of phagocytic receptors that specifically recognize cell wall envelope components expressed by pathogenic or slow growing mycobacteria. We demonstrate the engagement of CD206 that contributes to internalization and bacterial survival of live PGL I producing mycobacteria in SC. Additionally; we propose an active crosstalk between CD206 and the transcription factor PPARγ modulating downstream immune functions in SC. PPARγ is a member of the lipid-activated nuclear receptor family and has been demonstrated to function as a key transcriptional regulator in inflammation and lipid metabolism in macrophages and dendritic cells. We observed that the signaling pathway involving CD206 recognition followed by PPARγ expression and activation lead to induction of IL-8 and prostaglandin E 2. In fact, while other proinflammatory cytokines may be reduced in anergic lepromatous patient, the host innate response involving the leucocyte attractant IL-8 seemed to be vigorous and could be involved in neuroinflammation.

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