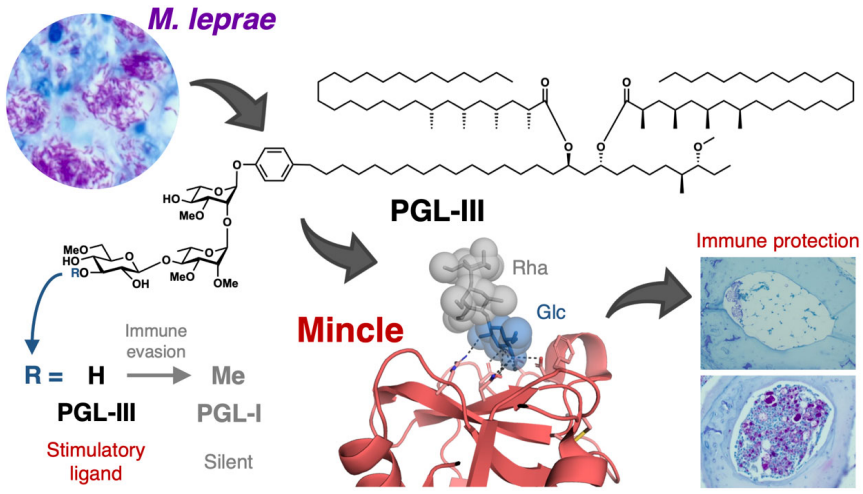
How does *M. leprae* disrupt macrophages?

Keywords: *Mycobacterium leprae*, Hansen's disease, innate immunity, antimicrobials

Although leprosy (Hansen's disease) is one of the oldest known diseases, the pathogenicity of *Mycobacterium leprae* (*M. leprae*) remains enigmatic. Indeed, the cell wall components responsible for the immune response against *M. leprae* are as yet largely unidentified. The research group of Sho Yamasaki (Molecular Immunology, IFReC/RIMD/CiDER Osaka University) revealed phenolic glycolipid-III (PGL-III) as a *M. leprae*-specific ligand for the immune receptor Mincle. PGL-III is a scarcely present trisaccharide intermediate in the biosynthetic pathway to PGL-I, an abundant and characteristic *M. leprae* glycolipid. Using activity-based purification, we identified PGL-III as a Mincle ligand, that is more potent than the well-known *M. tuberculosis* trehalose dimycolate. The co-crystal structure of Mincle and a synthetic PGL-III analogue revealed a unique recognition mode, implying that it can engage multiple Mincle molecules. In Mincle-deficient mice infected with *M. leprae*, increased bacterial burden with gross pathologies were observed. These results show that PGL-III is a non-canonical ligand recognized by Mincle triggering protective immunity.



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Title: "PGL-III, a rare intermediate of Mycobacterium leprae phenolic glycolipid biosynthesis, is a potent Mincle ligand"

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