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Research on vaccine candidates, and immune-stimulating and -suppressive compounds derived from various pathogens

Outline

In this research, we evaluate *in vitro* activities of protective antigens derived from known and unknown components of various pathogens. We select vaccine seeds, evaluate *in vivo* activities, and develop promising candidates as vaccines or immune-stimulating or -suppressive agents. As the specific aim 1, we aim to clarify the structural basis of immune-stimulating and –suppressive activities of mycobacterial glycolipids. As the specific aim 2, we plan to establish an inexpensive, cross-protective pneumococcal surface protein A (PspA) nasal vaccine using TLR ligand as an adjuvant, and aim to demonstrate its protective effect.

Expected Outcome

Specific Aim 1: We intend to clarify the structural basis and physiological significance of mycobacterial glycolipids that are thought to be critical for immune modulation. In future, this research may lead into the development of vaccines, drugs, and immune-modulatory agents.

Specific Aim 2: Selection of family and clade of PspA, TLR ligand, and ratios of PspA to TLR ligand, may lead to the development of an inexpensive and cross-protective PspA nasal vaccine with a high protective activity in the future.

Purpose

To identify promising seeds of vaccines and adjuvants by screeining constituents of various pathogens having immune-stimulating and -suppressive abilities.

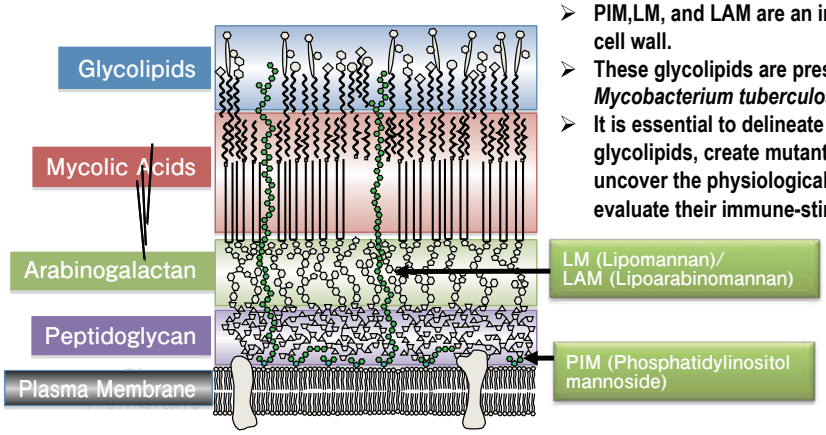
Specific Aims

1. Evaluation of immune-stimulating and -suppressive activities of mycobacterial glycolipids
2. Application of various TLR ligands for pneumococcal intranasal vaccine

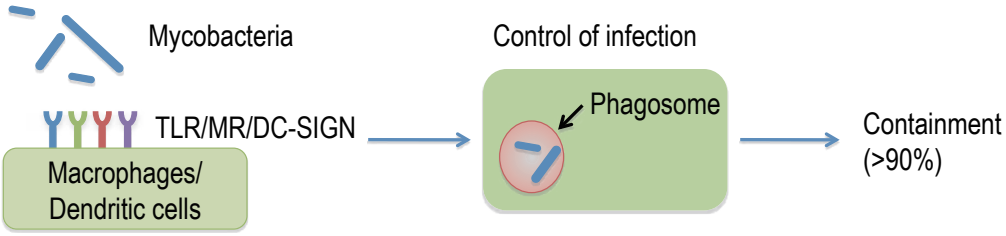
Mycobacteria and Pneumococci

1. Mycobacteria cause various diseases such as tuberculosis and leprosy. They survive in the host for a long time, evading from host immunity. Many cell wall glycolipids possess immune-stimulating and –suppressive activities, but detailed molecular mechanisms of immune evasion remain elusive.
2. *Streptococcus pneumoniae cause pneumonia, meningitis, and sepsis in infants and elderly. Currently available vaccines are indicated for infants and adults, and are effective against invasive infections. However, its effect is serotype-specific, and its production is costly. Thus, the development of an inexpensive vaccine with broad coverage is needed.*

Mycobacterial Cell Wall: Components and Immune Responses



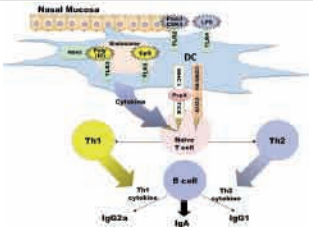
- PIM,LM, and LAM are an important component of mycobacterial cell wall.
- These glycolipids are present in all mycobacteria, including *Mycobacterium tuberculosis.*
- It is essential to delineate the biosynthetic pathways of these glycolipids, create mutants defective in the biosynthetic steps, uncover the physiological significance of these glycolipids, and evaluate their immune-stimulating and –suppressive activities.



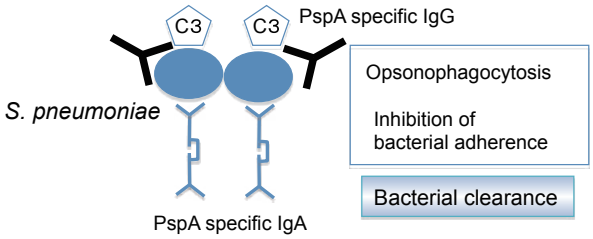
- PIM/LM/LAM are recognized by Toll-like receptor (TLR), mannose receptor (MR), and DC-SIGN, and stimulate immune reactions.
- Initial infection is controlled by the immune system, but phagocytosed mycobacteria survive in the host macrophages.

Development of PspA nasal vaccine using TLR ligand

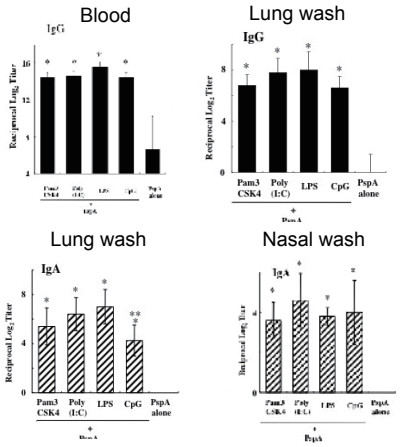
TLR ligand stimulates dendritic cells through TLR and enhances PspA-specific antibodies



Possible mechanisms of antibacterial actions by specific antibodies



Induction of PspA-specific antibodies by PspA nasal vaccine



Accumulated results

PspA nasal vaccine induced PspA-specific IgG and IgA in the airway as well as in blood, and demonstrated an increased bacterial clearance in the airways against different serotype of *S. pneumoniae*. (Oma K, et al. Vaccine, 27: 3181-3188, 2009)。

A basic structure of a human divalent PspA nasal vaccine which is applicable for clinical practice will be established under a good manufacturing practice (GMP) guideline.