23. Synthetic study of glycoconjugates for elucidation of their biological functions

Koichi Fukase (Osaka University)

Innate immunity is a phylogenetically ancient defense system against micro-organisms. The innate immune response is activated by receptors that recognize microbial components such as bacterial peptidoglycan (PGN) and lipopolysaccharide (LPS).

LPS is a cell surface glycoconjugate of Gram-negative bacteria. The active entity of LPS is its lipophilic part designated lipid A. Various structural analogues, including radio and fluorescence labeled derivatives, were synthesized to elucidate the mechanism of immunostimulation. Recent studies have revealed that the complex of toll like receptor 4 (TLR4)/MD-2 is the receptor of LPS and lipid A. Binding study of TLR4/MD-2 with the radio-labeled lipid A clearly demonstrated that TLR4/MD-2 directly binds to lipid A.

PGN, a major component of cell wall, is an alternating β(1,4) linked *N*-acetylmuramyl-*N*-acetylglucosaminyl glycan whose residues are cross-linked by short peptides. We previously demonstrated that the minimum structure required for the immunostimulation of PGN is muramyl dipeptide (MDP). MDP and various PGN partial structures (mono-, tetra- and octasaccharides having di-, tri-, tetra- or pentapeptides) showed the activity via TLR2 independent pathway, although TLR2 was reported to be a PGN receptor. An intracellular receptor, NOD2, was then found to recognize MDP as well as these partial structures.