Structural Specificities of beta-Glucans on Receptor-Binding and Immunostimulatory Activity

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β-glucan is a natural abundant constitutive component in the cell wall of fungi, plant, algae and some bacteria. These beta-glucans have structural variety depending on the primary structure and molecular weight. The difference of the physicochemical properties of beta-glucans substantially affect the solubility and the immunobiological activity. This diversity on the structural difference results in difficulties to understand the activation mechanisms of beta-glucans as immunostimuli. Host defense system recognizes the structural difference of the beta-glucans via multiple molecules including soluble plasma proteins, glycosphingolipids, and transmembrane receptors. In this talk, I would like to introduce the structural characteristics of biologically active beta-glucan, especially (1,3)-β-D-glucans, from fungi, and the structure-activity relationship on the recognition by several beta-glucan binding molecules and receptors.

Molecular Basis for Innate Immune Recognition of (1,3)-b-D-Glucan as a Pathogen-Associated Molecular Pattern

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Recognition of pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) of innate immunity underlies self/nonself discrimination by multicellular organisms. Despite their biological significance, the analyses of molecular recognition of PAMPs via PRRs remain largely untouched. Hemolymph of horseshoe crabs (also called limulus), an arthropod species, rapidly makes a clot to engulf invading microorganisms. This reaction is very sensitive to lipopolysaccharide and (1,3)-β-D-glucan on Gram-negative bacteria and fungi, respectively, and hence utilized as assay reagents that detect and quantitate these PAMPs with a name of "limulus test". In this seminar, I will briefly summarize molecular cascades that constitute the coagulation system and focus on recognition of (1,3)-β-D-glucan by the

serine protease zymogen factor G. Molecular dissection and detailed kinetic analyses have revealed that binding with a strong avidity between factor G and (1,3)-β-D-glucan is accomplished by multivalent binding of a binding unit with a very weak affinity to a (1,3)-β-D-glucoside linkage. The multivalent binding to polymers of a simple target structure would be one of the principles that allows stable and specific recognition of PAMPs by PRRs in innate immunity.

(1, 3)-ß-D-Glucan: Recent Development as a Diagnostic Analyte and Biological Response Modifier

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(1,3)-β-D-glucan (BG) is widely distributed across phylogenetic divisions, including fungi, plants, algae, and bacteria, but is absent in animals. BG's near pan-fungal presence as a cell wall structural material has made it a useful analyte in fungal infection detection, and its properties as an elicitor of innate immunity have generated applications as a general immune stimulant and in anti-tumor immunotherapy. BG's diagnostic utility is dependent upon the biological specificity of the Horsehoe Crab hemocyte recognition protein, Factor G, and downstream elements of the Limulus (LAL) and Tachypleus (TAL) cascades. Exquisitely sensitive in vitro diagnostics based upon these factors received marketing clearance in Japan (in the mid-1990s) and, recently, in the US. The availability of BG detection reagents has permitted the characterization of unplanned human exposure to BG. Numerous medicines and medical devices have been shown to be contaminated with BG, leading to inadvertent exposure, with, in addition to potential false positive diagnostic results, unknown biological consequences. Animal models of BG exposure have demonstrated catastrophic sequelae, in sub-lethal challenge models using endotoxin or NSAIDS. Toxicologically relevant exposure levels, experienced through contaminated parenterals or medical devices, are unknown. Evaluation of the biological consequences of such exposure can draw upon the endotoxin exposure model.