Elucidation of immunity and pathogenesis through glycosciences

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There are numerous unsolved mysteries in immunity and pathogenesis. Deciphering these mysteries should provide new concepts and tools useful in diagnosis and therapy of diseases incurable by current medical and pharmaceutical technologies. Glycoscinces are unconventional and unique ways to attack these problems. Carbohydrate-recognition proteins, lectins, and a group of glycoproteins heavily *O*-glycosylated through their serine and threonine residues, mucins and mucin-like molecules, have been the focus of my investigations in the last 20 years as summarized below.

Cancer progression and metastasis: Cancer progression and metastasis are regulated by the interactions between tumors and host microenvironments, which is composed of lectins and mucins together with other glycoconjugates. By the use of a large number of surgical specimens, increased quantity a mucin with sialylated carbohydrate chains were shown associated with advanced colorectal carcinomas. This mucin turned out to be Mucin 1 (MUC1) and our monoclonal antibody specific for MUC1 with sialyl-T residues were shown to be useful to identify tumors at the advanced stages in colon, pancreas, gal bladder, and kidney carcinomas. Based on these findings, development of MUC1-DNA vaccine to eradicate micrometastases and residual diseases is underway. Mouse mammary carcinoma-associated mucin, epiglycanin/Mucin 21(MUC21), was originally identified in 1975 and re-discovered, cloned and named as MUC21 in 2005. This mucin was shown to be capable of antagonizing with cell adhesion promoting cell migration.

Hypersensitivity and inflammatory diseases: Calcium-dependent (C-type) lectins widely distribute on the surfaces of vertebrate cells in the immune system, particularly of antigen-processing dendritic cells and macrophages. MGL/CD301 is a unique C-type lectin for its carbohydrate specificity to galactose as a monosaccharide. By the use of MGL1-KO mice, this molecule was strongly implicated with inflammatory bowel diseases at the intestine and with inflammation of subcutaneous tissue through macrophage functions to produce cytokines. Cells expressing MGL2 in the skin was proven to be conventional dermal dendritic cells, which are dominant antigen presenting cells in contact dermatitis. These findings should prove that lectins and mucins serve as targets of diagnosis and therapy.

Use of mutated lectin libraries in cell therapy and serum diagnosis: *Maackia amurensis* hemagglutinin was mutated at their carbohydrate recognition loops and libraries of mutated lectins with distinct individual specificity were generated. The libraries were used to classify cells with a variety of stages of differentiation. The libraries were also useful to distinguish IgA from healthy individuals and that from IgA nephropathy.

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