Current perspectives

Glycans and glycan-binding proteins in immune regulation: A concise introduction to glycobiology for the allergist

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Cells are endowed with a rich surface coat of glycans that are carried as glycoproteins and glycolipids on the outer leaflets of their plasma membranes and constitute a major molecular interface between cells and their environment. Each cell's glycome, the sum of its diverse glycan structures, comprises a distinct cellular signature defined by expression levels of the enzymes responsible for glycan biosynthesis. This signature can be read by complementary glycan-binding proteins (GBPs) that translate glycan recognition into function. Nowhere is this more evident than in the immune system, where glycans and GBPs are integral to pathogen recognition and control of inflammatory responses. Glycobiology, the study of glycan structures and their functions, increasingly provides insight into immunoregulatory mechanisms and thereby provides opportunities for therapeutic intervention. This review briefly examines the makeup of the human glycome and the GBPs that translate glycan recognition into function and provides examples of glycan recognition events that are responsible for immune system regulation to promote wider appreciation of this rapidly expanding area of research. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Glycome, lectin, selectin, galectin, siglec, sialic acid, inflammation*

Abbreviations used
GBP: Glycan-binding protein
iNKT: Invariant natural killer T
Siglec: Sialic acid–binding immunoglobulin-like lectin
TCR: T-cell receptor

Cells are composed of 4 major classes of molecules: nucleic acids, proteins, glycans, and lipids. Among these, glycans inhabit a special niche at cell surfaces, where they are involved in intermolecular and cell-cell recognition events that define and control cell interactions and functions.[1,2] Glycan recognition is often mediated by complementary glycan-binding proteins (GBPs), each of which carries a specific carbohydrate recognition domain that confers glycan-binding specificity.[3] Other functional domains on GBPs translate glycan binding into appropriate cellular responses. Nowhere is this more evident than in the immune system, where glycans and GBPs on the surfaces of immune cells are involved in an evolutionary chess match of immune activation and regulation within a dynamic pathogen landscape.[2,4-6]

Humans have more than 80 different GBPs (also known as lectins) in at least 12 structural families (see http://www.imperial.ac.uk/research/animallectins). Knowledge of the glycans and GBPs that underlie and regulate immune function provides previously unanticipated opportunities for rational design of targeted therapies for immune dysfunction, some of which show promise in the clinic.[7,8] This review introduces the key players in human glycobiology: the human glycome (the totality of human glycan structures) and GBP families that decipher the glycan code. Examples of the roles of glycans and GBPs in infectious disease, inflammation, and control of immune responses follow. An accompanying review in this issue of the *Journal* provides a more focused perspective of the roles of glycans and GBPs in patients with allergic diseases.[9]

THE HUMAN GLYCOME

Every cell in nature has a rich and diverse surface glycan coat that constitutes its interface with the environment.[2] Although the complexity and diversity of glycans throughout nature are truly daunting, human glycans are more circumscribed and amenable to structure-function studies using rapidly improving analytic techniques. A basic understanding of the building blocks, major structural themes, and general biosynthetic machinery of the human glycome provides the context for understanding glycomic regulation in the immune system.

The human glycome is built primarily from just 9 monosaccharide building blocks (Fig 1),[10] each of which is a 6-membered ring (5 carbons and oxygen) further defined by the identity and stereochemistry of the molecular constituents on each ring carbon (mostly hydroxyl groups). Monosaccharides are enzymatically linked to form linear and branched oligosaccharides on protein and lipid carriers. Because each monosaccharide can link to any of up to 4 hydroxyls on another monosaccharide in one of 2 configurations (α or β) and in either linear or branched arrays, an impressive diversity of distinct structures can be created from just a few building blocks. Whereas 3 different amino acids can combine to form 6 distinct tripeptides, 3 different monosaccharides can combine to form more than a thousand distinct trisaccharides. The diversity of glycan

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Supported by a program project grant from the National Institutes of Health/National Heart, Lung, and Blood Institute (P01 HL-107151).

Disclosure of potential conflict of interest: R. L. Schnaar's institution has received funding from the National Institutes of Health, as well as the National Institutes of Health/National Heart, Lung and Blood Institute.

Received for publication October 23, 2014; accepted for publication October 28, 2014.

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0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2014.10.057

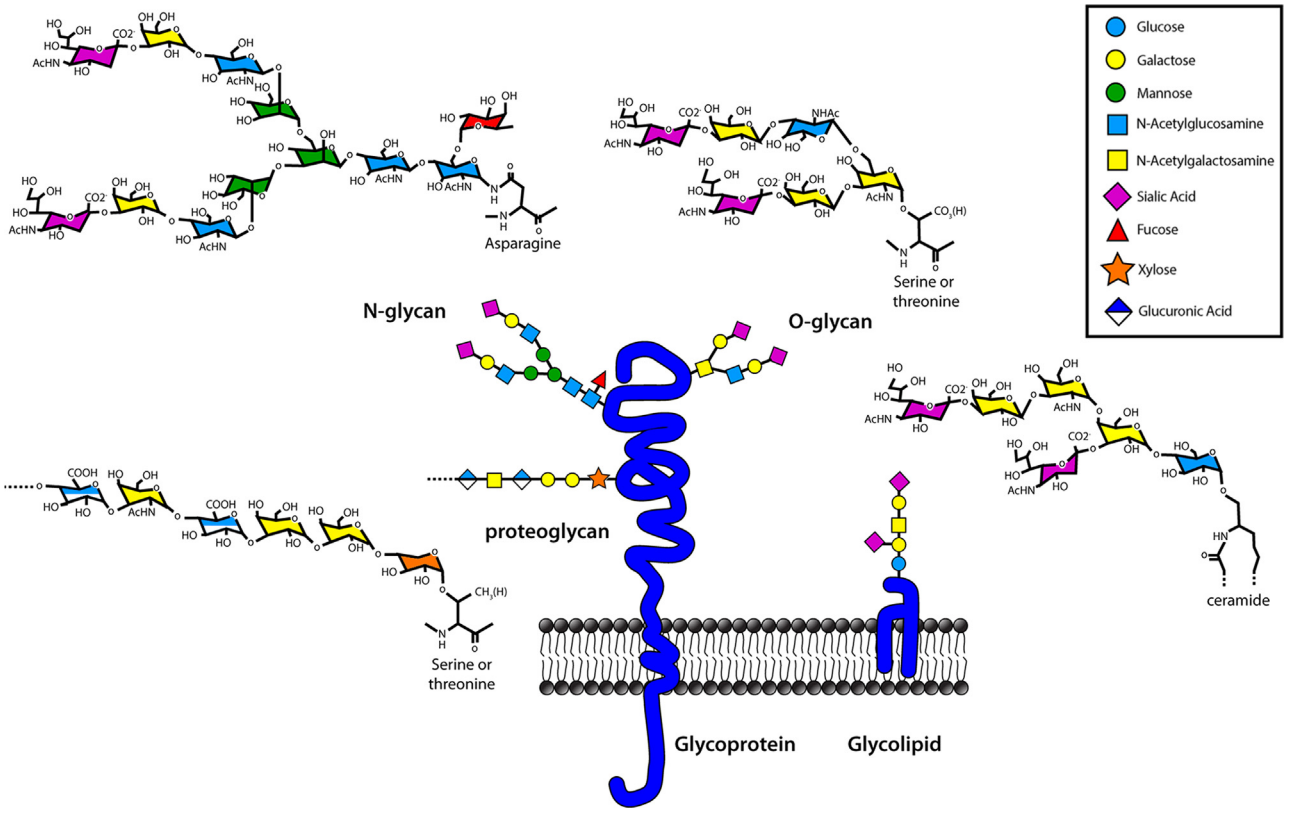

FIG 1. Cell-surface glycans. All mammalian cells are endowed with a dense and diverse surface coat of glycans comprised of glycoproteins, proteoglycans, and glycolipids. They are built primarily from just 9 different monosaccharide building blocks, each of which is a 6-membered ring with distinct structural substituents. A color-coded symbol nomenclature for these (see the key in the illustration) has been agreed upon by the field.[10] N-linked glycans are attached to protein asparagine residues and are invariably branched structures that display varied termini. O-linked glycans are attached to protein serine or threonine residues and typically consist of shorter branched or unbranched structures. Proteoglycans are also attached to protein serine or threonine residues but are notable for their long disaccharide repeats, most of which are highly charged because of the abundance of sugar acids and sulfates. Mammalian glycolipids primarily consist of glycans attached to a ceramide lipid moiety. Together, these glycans comprise the glycome of each cell, providing it with the diverse surface structures required for that cell's functions.

structures found on cells is not random but is carefully controlled by gene expression. Each cell's glycome is defined by the expression of the genes responsible for glycan biosynthesis.[11] These include genes coding glycosyltransferases (approximately 200 in the human genome), glycosidases, glycan precursor biosynthetic enzymes, and transporters that together represent more than 3% of all human genes. Cell-specific expression of a distinct suite of glycan biosynthetic genes generates each cell's glycan "persona," a face to the world that regulates its intracellular and intercellular molecular interactions. The cell's glycome varies among cell types, during differentiation, and in response to outside stimuli, providing a rich layer of regulation of cellular functions.

It is estimated that human glycosyltransferases create approximately 7000 potential terminal glycan-binding determinants, the basic unit of glycan recognition by GBPs (up to 5-6 sugars in a specific grouping).[12] Because oligosaccharide chains are hydrophilic and often charged, they spread out in space, and even minor changes, such as linkage position, linkage configuration, or even the stereochemistry of a single hydroxyl group, provide the basis for the specificity of GBP recognition and downstream functional consequences. The interplay between glycan biosynthetic gene expression, glycan structure, GBP recognition, and biological function is the focus of the field of glycobiology.

Glycans at cell surfaces are classified as glycolipids or glycoproteins (Fig 1). Glycolipids have their hydrophobic lipid tail firmly embedded in the outer leaflet of the plasma membrane, with their hydrophilic oligosaccharide chain extending out into the extracellular space. In most cells glycolipids comprise a small percentage of total plasma membrane lipids. In contrast, nearly all proteins at the cell surface are glycoproteins, including single- and multiple-pass transmembrane and secreted proteins. Glycans on proteins are classified based on their covalent linkage to the polypeptide: an asparagine (N-linked) or a serine or threonine (O-linked). N-linked protein glycosylation is initiated during protein translation in the endoplasmic reticulum, whereas O-linked glycosylation occurs after translation in the Golgi apparatus. In both cases the glycans are further modified and elaborated in the Golgi apparatus on their way to the cell surface. Whereas O-linked glycans are built stepwise and can be as small as a single sugar, N-linked glycans are prebuilt on a special lipid carrier and transferred as a characteristic 14-sugar block onto the nascent polypeptide, where the block is trimmed and then further elaborated. Most mature O-linked oligosaccharides are small, whereas

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