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Roles for Glycosylation in Receptor-Ligand Interactions in the Immune System



profile

Pauline M. Rudd

Dr. Pauline Rudd obtained a degree in Chemistry from the University of London and a PhD from the Open University. She is currently a University Reader in Glycobiology in the University of Oxford and in 1998-9 was a visiting research scientist at The Scripps Research Institute in San Diego, CA. Her group focuses on both structural and recognition roles for glycans attached to glycoproteins in the immune system and inflammation. These include immunoglobulins, the molecules involved in the T-cell response to MHC I antigen presenting cells, the complement system and the matrix metalloproteases. Together with her colleagues, she has pioneered the development of novel technology for the rapid, sensitive analysis of both N- and O-linked sugars attached to glycoproteins and this has enabled the glycan analysis of microgram quantities of scarce biological materials such as tapasin, prion protein and neutrophil gelatinase B.

On the T cell surface, CD48 and CD2 provide a molecular spacer between T cells and antigen presenting cells. The oligosaccharides attached to this cell adhesion pair orient binding faces, provide protease protection and restrict non-specific lateral protein-protein interactions. The glycosylation of CD3 and the TCR play a role in the assembly and organisation of the TCR complex (4). In CD8, which is anchored to the T cell but binds MHC I on APCs, four O-glycans attached to the membrane distal stalk region are likely to play a critical role in the geometry of co-receptor interactions that span the nascent immunological synapse (5).

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Almost all of the key molecules involved in antigen recognition, presentation and the adaptive immune response are glycoproteins (1). The glycans have two distinct roles: in the first case the sugars confer stability on the proteins to which they are attached, protecting them from proteases and non-specific protein-protein interactions. In the second, specific regions of the oligosaccharide chains provide recognition epitopes. A major issue that must be addressed when proposing carbohydrate ligands is that individual monosaccharides have low affinity for protein receptors, usually in the mM range. For example, in the endoplasmic reticulum, specific glycoforms of MHC I that contain $\text{Glc}_1\text{Man}_9\text{-}_7\text{GlcNAc}_2$ bind the lectin chaperones calnexin and calreticulin. In both cases, the proposed glycan recognition epitope that can provide the necessary affinity is the tetrasaccharide (Glc_1Man_3) on the $\alpha 1,3$ arm of $\text{Glc}_1\text{Man}_9\text{-}_7\text{GlcNAc}_2$ (2).

In a dynamic cycle in which the terminal Glc residue is alternately removed and replaced, membrane bound calnexin, releases and binds unfolded proteins until they achieve their properly folded conformation. This pathway, available to all N-glycosylated proteins, enables the efficient folding of MHC I heavy chains. However, after incorporation of $\beta 2m$, MHC I binds to the soluble lectin calreticulin and is incorporated into the peptide loading complex which also contains tapasin, transporter of antigenic peptide (TAP) and ERp57 (a member of the protein disulphide isomerase family). The interaction of calreticulin with MHC I stabilizes the multimolecular complex and retains MHC I in the ER until the antigenic peptide is loaded into the groove (pMHC I). The presence of the $\text{Glc}_1\text{Man}_9\text{-}_7\text{GlcNAc}_2$ glycoforms of MHC I in this complex is consistent with the hypothesis that the class I loading process is an adaptation of the quality control mechanism involving calreticulin and ERp57 (3). At the end of a dynamic cycle of de- and re-glycosylation, during which the peptide is loaded, the terminal Glc residue is finally removed. The complex dissociates, freeing the pMHC I to be transported to the Golgi and then to the surface of the antigen presenting cell (APC) for recognition by the T cell receptor (TCR) complex.

On the T cell surface, CD48 and CD2 provide a molecular spacer between T cells and antigen presenting cells. The oligosaccharides attached to this cell adhesion pair orient binding faces, provide protease protection and restrict non-specific lateral protein-protein interactions. The glycosylation of CD3 and the TCR play a role in the assembly and organisation of the TCR complex (4). In CD8, which is anchored to the T cell but binds MHC I on APCs, four O-glycans attached to the membrane distal stalk region are likely to play a critical role in the geometry of co-receptor interactions that span the nascent immunological synapse (5).

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(6), in which most of the components are glycosylated (7). The high affinity required for functional recognition of agalactosyl IgG is provided by the multiple presentation of sugars on aggregated IgG to the multiple carbohydrate recognition domains of the lectin. In the inflammatory pathway terminal galactose residues on sugars attached to gelatinase B bind up to 4 molecules of galectin 3. Multiple presentation of glycan epitopes is also a feature of the innate immune system. For example, secretory IgA1 contains multiple terminal $\text{Gal}\beta 1,3\text{GalNAc}$ epitopes on its oligosaccharides (8) through which it can attach to pathogenic bacteria in the gut, thus preventing bacterial adhesion to potential host cells.

A novel carbohydrate antigenic epitope that may represent a new paradigm for antibody-antigen recognition has been defined on the human immunodeficiency virus (HIV) type-1 (9). 2G12 is a broadly neutralizing human monoclonal antibody against HIV-1 that binds to a carbohydrate-dependent epitope on gp120, the surface coat protein of the virus. This epitope is formed from two 'self' oligomannose sugars that are presented in such close proximity that their terminal sugars form a high affinity, contiguous 'non-self' epitope.

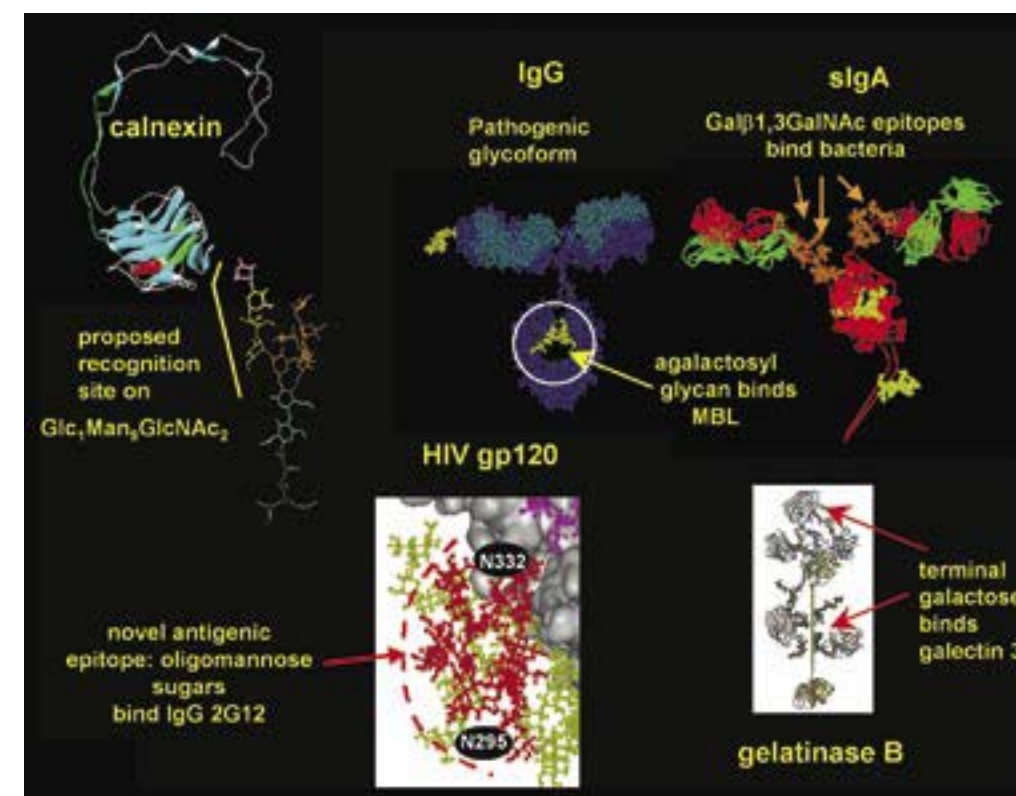


Figure 1. Oligosaccharide presentation and recognition. Physiological recognition involves either multiple monosaccharide sub-sites (eg calnexin, gp120) or multiple presentation of glycan epitopes (eg IgG, IgA, gelatinase B).

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