Introduction for the Special Issue on Glycosylation and Immunity

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Received: 2 May 2012 / Accepted: 3 May 2012 / Published online: 6 June 2012
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Introduction

This issue of Seminars in Immunopathology focuses on recent advances in understanding how innate and adaptive immune responses may be modulated by glycosylation of molecules relevant to the mammalian immune system. Eight prominent investigators who have made major contributions to specific components of this field have kindly contributed comprehensive reviews of the literature in their areas of expertise. It is important to note in this Introduction that glycosylation in this context does NOT refer to non-enzymatic protein glycation characteristic of proteins in humans with diabetes mellitus and elevated blood and tissue glucose levels. By contrast, glycosylation in the articles in this series does refer to the complex enzymatic processes that elaborate covalent modification of proteins with glycans at certain asparagine or serine/threonine moieties. The biochemistry and genetics of mammalian glycosylation have been reviewed in a comprehensive monograph devoted to providing an overview of these subjects [1], and in-depth in reviews published in the literature [2–4]. The reader is encouraged to consult these sources for broad overviews of the field of glycosylation. Happily, each of the eight articles in this issue of Seminars in Immunopathology provides an excellent overview and details of the glycosylation pathways specifically relevant to the subject of the article. These will be sufficient for the non-expert to understand

these pathways and how they intersect with and contribute to immune function.

It is important to note that there are literally hundreds of distinct glycan structures known in any given mammalian species. This complexity is made even more formidable by the fact that for any given glycoprotein, the glycoprotein is typically not homogeneous with respect to the glycan structures that decorate the protein. Specifically, when evaluating the glycan structures at any specific glycosylation site on a specific glycoprotein, individual glycoprotein molecules may differ by displaying distinct structural variants of the glycan. Further combinatorial complexity is introduced when a glycoprotein has more than a single glycosylation site. Thus, for any given glycoprotein, there is typically a spectrum of glycoforms, both in the asparagine-linked glycans and in the serine/threonine-linked glycans [3, 4], for instance, thus complicating efforts to understand how glycosylation contributes to the function of any specific glycoprotein. Additional complexity obtains because glycan structures are dictated by the glycosylation machinery expressed in the cell type where the glycoprotein is expressed. This machinery includes especially the repertoire of glycosyltransferases and glycohydrolases that elaborate glycan structure. This repertoire typically varies, qualitatively and quantitatively, among cell types within a mammalian organism, often in a lineage-specific manner, and can vary with the physiology or pathophysiology of the cell or organism. Consequently, it is always necessary to consider that the glycan structures identified on a specific mammalian glycoprotein may vary depending on origin of the cell type and its physiological status, and thus may complicate conclusions about the function of a glycoprotein identified only in a specific cellular or physiological context. The authors of the articles in this series are well aware of these issues and address them where this has been investigated to

This article is published as part of the Special Issue on Glycosylation and Immunity [34:3]

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a relevant extent, or in a speculative manner, where experimental data are not available.

There is also daunting complexity with respect to the hundreds of glycan-binding proteins (lectins) expressed by any given mammalian species. An overview of this subject is provided in reference [1], and is dealt with in more detail in reference [5], where a specific immune cell perspective is brought to bear on these proteins. As with glycan structures, expression of mammalian lectins is often lineage-specific, and can vary with the physiology of a cell, tissue, or the whole organism. Additional complexity derives from the observation that mammalian lectins can bind glycan structures in *trans* (i.e., a lectin expressed by one cell type binds a glycan expressed by another cell type), or in *cis* (i.e., a lectin expressed by a cell type binds a glycan also expressed by the same cell), and both. A final aspect of complexity derives from studies disclosing that some mammalian lectins have apparently evolved to recognize glycans expressed by microbial species but not by the mammalian host, whereas other lectins can bind both mammalian glycan structures and microbial glycans.

In general, studies of the genetics and biochemistry of mammalian glycans and glycosylation pathways have unveiled two general mechanisms whereby protein glycosylation contributes to the function of a protein. The first of these general mechanisms represent those whereby the glycan itself is a ligand, or a component of a ligand, directly recognized by a receptor, where the receptor is typically a glycan binding protein (lectin) but can be another glycan in some as-yet rare instances. The second of these general mechanisms represent those whereby the glycan modulates the structure of the glycoprotein, likely via allosteric mechanisms, to enable or disable a binding interaction of the glycoprotein with another protein, such binding interaction required for the function of the glycoprotein. In this second mechanism, the glycan itself does not directly contribute to ligand activity. There are of course circumstances where it is clear that aberrant expression of a specific glycan structure (loss or gain) has a causal relationship to disease, but through mechanisms that are largely hypothetical at the current stage of investigation.

The articles in this series address glycan functions in the immune system that are representative of each known mechanism, and in some instances provide examples where possible mechanisms can be inferred but are not yet fully defined at a molecular level.

With respect to mechanisms where the glycan itself is a ligand or a component of a ligand, six of the articles in this series turn on this paradigm. Kobayashi et al. review the formidable wealth of data identifying a sialylated, sulfated, fucosylated glycan that decorates specific glycoproteins, elaborated by specialized microvascular endothelial cells, and which serves as an adhesive receptor for L-selectin

expressed by lymphocytes. Kobayashi et al. review how this ligand-receptor couple functions to enable recruitment of lymphocytes to sites of inflammation, and recruitment of lymphocytes to peripheral lymph nodes and other non-inflamed lymphoid organs.

Lühn and Wild provide a review and perspective on a similar paradigm, involving the fucosylation component of the glycan ligand discussed by Kobayashi et al. Their review summarizes data supporting a role for such fucosylated ligands in mediating adhesion and recruitment of neutrophils and other myeloid lineage cells, as well as some types of polarized T lymphocytes, via the adhesion molecules E-selectin and P-selectin. This data includes studies forthcoming from humans with informative inactivating mutations in loci that encode components of the glycosylation pathways required for the synthesis of such glycan ligands. Lühn and Wild also discuss how genetic deficiency in sialyltransferase expression “uncovers” the expression of a galactosylated glycan ligand expressed by blood platelets. The consequence of such “unmasking” is an enhanced interaction between platelets and a liver-specific lectin termed the asialoglycoprotein receptor, leading to enhanced sequestration of platelets in the liver and thrombocytopenia.

Schwab et al. review and interpret the data identifying the molecules and mechanisms underlying the longstanding mystery about how intravenously administered IgG can be an effective anti-inflammatory treatment in a number of diseases that have a prominent pro-inflammatory component. The literature reviewed by Schwab et al. show that sialic acid, on the glycans that decorate immunoglobulin G, is an essential component of part of the ligand “activity” exhibited by IgG for a lectin termed DC-SIGN which is expressed on human dendritic cells and macrophages. When DC-SIGN is liganded by sialic acid-rich IgG, signal transduction events are thought to elicit the elaboration of IL-33 by myeloid lineage cells, which in turn causes the elaboration of IL-4 by basophils and likely other cellular components of the innate immune system. IL-4 is then proposed to act on effector macrophages to up-modulate expression of the inhibitory Fc receptor FcγRIIB, down-modulate expression of activating FcγRs on innate immune effector cells, and together desensitize effector cells to the pro-inflammatory effects of immune complexes.

Grigorian et al. provide a perspective on how a large number of genetic and environmental factors can dysregulate Golgi-derived asparagine-linked glycosylation in the autoimmune disease multiple sclerosis. This perspective is then framed in the context of other work demonstrating that members of the galectin family of galactose binding proteins, expressed by T lymphocytes, can interact in *cis* with branched asparagine-linked glycans on the T cell receptor to modulate the sensitivity of T cells to activating signals.

Ryan and Cobb provide a focused summary of how asparagine-linked glycans are assembled. This summary is a prelude to discussing the state of the literature on asparagine-linked glycosylation of MHC Ia, MHC Ib, and MHC II molecules, including what is known, and not yet known, about the functions of such modifications. Their article includes a summary of the current state of understanding of how a novel class of T cell-dependent bacterial-derived zwitterionic polysaccharide antigens interacts with and is presented by MHC II molecules. These studies, largely carried out by the Cobb group, indicate that these polysaccharide antigens interact with a combination of the MHC II protein backbone and the complex N-glycans that modify this backbone. Their studies provide strong support for the exciting hypothesis that glycan–glycan interactions contribute to binding, and function, in this context.

Novak and colleagues review the literature and their own studies that have sought to understand the mechanistic relationship between galactose-deficient IgA1 and a disease known as IgA nephropathy, which is the most common primary glomerulonephritis in the world. This relationship establishes a paradigm for autoimmune-mediated tissue damage, which turns on the hypothesis that autoimmunity against galactose-deficient IgA1 leads to the formation of IgA1-containing immune complexes. These complexes in turn accumulate in the mesangial region of the kidney and in that location promote mesangial cell proliferation, extracellular matrix secretion, glomerular sclerosis and interstitial fibrosis, and loss of filtration function. Novak and colleagues provide the reader with a comprehensive understanding of the glycobiology of normal and galactose-deficient IgA1, and discuss interesting hypotheses about mechanisms that account for loss of galactose moieties, and for the generation of autoantibodies directed against the resulting galactose-deficient IgA1 glycoforms.

Klaas and Crocker provide a review and perspective on the structure, expression, and function of a sialic acid binding protein termed Sialoadhesin, a member of the family of sialic acid binding Ig-like lectins or siglecs. Their article summarizes the wealth of data implicating Sialoadhesin as an endocytic receptor, with roles in regulating the immune responses to viral, bacterial, and parasite pathogens. Klaas and Crocker also review the data supporting the hypothesis that Sialoadhesin participates in the uptake and processing of sialylated self-antigens in contexts that include antigen cross-presentation in antitumor immunity, and the promotion of self-tolerance.

Each of the articles briefly summarized above has a focus, major or tangential, on pathogenic mechanisms dictated completely or partially by direct participation of the glycan in a binding activity that reflects function. By contrast, the article by Zhou reviews molecules and mechanisms that are perhaps most appropriately characterized as models of *indirect* participation by the glycan in protein–protein interactions. In this article, Zhou summarizes a substantial body of work, much of it her own, identifying a key functional role for an unusual set of O-fucosylated glycans that decorate the Notch family of transmembrane signaling receptors. The literature and work she reviews indicates that these glycans are essential to enable Notch–Notch ligand interactions, and thus essential to the elicitation of effective Notch-dependent signal transduction activities and subsequent downstream development or differentiation events. Importantly, the data she summarizes and/or cites indicates that the O-fucosylated glycans borne by Notch family members modulate the strength and quality of binding by Notch ligands via mechanisms that indirectly modulate the strength of the protein–protein interactions characteristic of Notch–Notch ligand interactions, but not via mechanisms whereby the glycan moieties participate directly at the interface between Notch and its ligands.

These recent perspectives on roles of glycans in the immune system provide an up-to-date and representative sample of some of the most mechanistically driven insights into how glycans function to maintain a normal immune system, and how immune dysfunction can derive from aberrant glycan structure.

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