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MEETING REPORT

State of the Union: Glycobiology and Immunology in the Canadian Rockies

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This March nearly 150 investigators attended the first international meeting focused solely on the role of glycans within the immune system. This Keystone Symposia meeting entitled "New Frontiers at the Interface of Immunity and Glycobiology" took place at Lake Louise, Alberta, Canada and was organized by Brian Cobb, Gabriel Rabinovich, and Yvette van Kooyk. We are pleased to report that the state of this union is strong and growing.

"Glycoimmunology" includes both the immunology and glycobiology communities and is a rapidly expanding field as the involvement of carbohydrates in host responses rises to prominence. This growing awareness is visible within the Consortium for Functional Glycomics, led by the meeting's keynote speaker Jim Paulson of the Scripps Research Institute in La Jolla, CA, in which more than half of the 540 participating investigators have a stated interest in understanding the role of glycans and glycan-binding proteins within the immune system. Although the society-oriented meetings for glycobiology and immunology do touch on some of the areas of convergence, it is clear that they do not adequately cover the diverse areas of active investigation at this interface. As a result, the two underlying goals of this meeting were to bring those investigators together to better define the glycoimmunology field and to raise awareness of the importance of glycans in the immune system.

The undeniable truth of the broad and profound impact carbohydrates and their binding partners have in the immune response was brought to crystal clear relief over the four and a half days of presentations. It is becoming obvious that there is essentially no area of immunology that is not directly affected by protein glycosylation, lipid glycosylation, or microbial glycans. The audience heard about the latest findings on the mechanism, immunogenicity, and adaptive effector responses to glycan-based antigens, whether through the traditional B cell receptor or T cell-dependent pathways such as CD1 presentation of glycolipids or MHCII presentation of polysaccharides. As time goes on, it is becoming more and more clear that carbohydrates can do many of the things that were previously thought to be restricted to proteins.

One area that finds itself in a rather peculiar state is the topic of pattern recognition receptors (PRRs), their ligands, and the effect binding has on the innate and adaptive response. There are many laboratories around the world that study the Toll-like receptor (TLR) family, and this line of research has been a hot topic in immunology for the last decade. However, the fact that essentially every TLR ligand is a carbohydrate or carbohydrate conjugate, including LPS, peptidoglycan, and even the nucleic acids which are merely complex polymers of ribose and deoxyribose, seems to be quite understudied. This was on display at this conference through highlighting other PRRs that play key roles in regulating the immune system, such as the C-type lectin (*e.g.*, DC-SIGN) and Siglec (*e.g.*, CD22) families. As the names imply, all of these molecules are carbohydrate-binding proteins that play diverse and critical roles ranging from activation of macrophages to fine-tuning inflammatory responses.

Another lectin family, the galectins, was also a topic of much interest. Galectin-1 and galectin-3 were the focus at the meeting, highlighting the complex problem of how these ubiquitous carbohydrate-binding proteins exert differential effects (*e.g.*, pro-inflammatory vs. anti-inflammatory) through interactions with similar ligands on different cells. It is clear that this area of study is rapidly evolving and may hold the key to understanding many of the regulatory pathways within immune cells that are critical not only for immune homeostasis, but appropriate effector responses under the right conditions.

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The audience was treated to the latest information about how glycans are absolutely necessary for the maintenance of hematopoiesis and leukocyte differentiation and trafficking as well as controlling many aspects of cell-cell and microbe-host adhesion and communication. It is remarkable to note that nearly every one of the key proteins responsible for cellular homing to sites of inflammation, infection or damage are carbohydrate-binding proteins, as exemplified by the selectins which mediate leukocyte rolling and adhesion. Infectious agents as diverse as parasite, bacterial, fungal, and viral microbes were discussed in terms of the use of microbial and host glycans during host-pathogen interactions and how these structures affect disease outcome. This included a session on the difficulties of utilizing the envelope protein GP120 on HIV and how its glycosylation pattern might be used as a novel target for vaccines in our fight against AIDS.

Since glycans can allow for the discrimination between self and non-self, aberrant glycosylation can sometimes indicate cancer or lead to autoimmunity. One example discussed at the conference was how under-glycosylated forms of the mucin proteins (*e.g.*, MUC1) are strongly associated with many cancers and how this "altered self" form of MUC1 has captured our imaginations as a cancer vaccine target. In contrast, changes in collagen glycosylation have now been linked to the onset of rheumatoid arthritis, raising exciting possibilities for better understanding the role of protein glycosylation in autoimmune diseases.

As always, there were some topics omitted from the sessions that should be covered in future glycoimmunology meetings. One in particular was the role of O-GlcNAc in cellular signaling pathways and how this glycosylation pathway interacts with and modulates the canonical phosphorylation pathways in immune cells. The NFκB cascade is the central player in both innate and adaptive immune responses and the role of O-GlcNAc on that pathway deserves much attention.

In total, this Keystone Symposia conference effectively consolidated many of the ways that carbohydrates influence the immune system into a single meeting. This included antigen presentation and recognition; regulation of immune cells and responses by C- and F-type lectins, Siglecs, and other surface receptors; the influence of galectin and selectin binding to glycans on cell surfaces in immune regulation and homing respectively; the role of glycosylation in dissecting the difference between self and non-self and the breakdown of this pathway during cancer and autoimmunity; and how protein glycosylation is a key factor in cellular development and differentiation. As a means to connect these areas of investigation, the meeting also included a workshop which updated the attendees on the latest strategies of glycomics and glycoproteomics for the identification of glycan structures associated with different cells, tissues, and disease states.

It was reported that a number of participants formed collaborations within the context of the week at Lake Louise, and many participants agreed that a recurring glycoimmunology meeting is highly warranted. We certainly felt that the meeting was a major success and, if nothing else, it demonstrated that the time has come to push for better integration of carbohydrate research and immunology.