Glycosylation and disease mechanisms

PI
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Group members;
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There are four major lines of research projects that have been lately developing in the group; all projects relate to biomedical impact of variations of glycosylation being involved in infectious diseases, in congenital muscular dystrophies, in transfusion medicine and finally in developing novel methods for characterization of glycoproteins in biological fluids, cells and tissues.

Winter vomiting disease and its agent Norovirus (NoV family of Calicivirus), is nowadays recognized as the dominating cause of non bacterial gastroenteritis worldwide. NoV, a small single stranded RNA virus, is an increasing threat to individuals in both developing countries (200,000 deaths/year) and in closed settings throughout the world (hospitals, nursing homes, day-care centres, cruise ships etc.). Within the last five years our group has, in collaboration with prof. Lennart Svensson, Linköping, substantially contributed to the understanding of the carbohydrate binding specificities of NoV virus-like particles to human histo-blood group antigens giving explanations to outbreak variations in individual’s susceptibility to NoV, both at the molecular and at the genetic level (allelic variations in glycosyltransferase genes) [1, 5, 6, 8, 13, 14]. In addition we have identified novel, NoV strain specific, binding specificities to both glycoproteins and to glycosphingolipids [10, 12] and are now, in close collaboration with prof. Fredrik Höök, Chalmers, studying the dynamic mechanisms of virus binding to glycosphingolipids in bilayer membranes [16]. By homology modelling and molecular dynamic simulations [18], together with Per-Georg Nyholm and his group at Biognos AB, were are also in the process of screening for and designing appropriate inhibitors of virus adhesion, using binding techniques that are now well established in our laboratory.

A major concern in viral diseases is how pathogens manage to evade the immune response after propagation and subsequent release from the host cell. In collaboration with prof. Sigvard Olofsson, Inst of Biomedicine, Göteborg, we have studied the effect of the latent virus Herpes simplex type 1 (HSV1) on glycosyltransferase expression in human cells. Interestingly, there is an early gene induction of specific fucosyltransferases [2] leading to expression of the Sialyl Lewis x antigen [2, 7, 11], a common mammalian receptor structure of the selectin family used by leukocytes to evade the blood circulation and get into sites of inflammation (through E-selectin binding) or into lymph nodes (L-selectin binding). The biosynthesis of this carbohydrate based receptor structure has been the object of several studies from our own group some of which during the last five years [3, 4]. We are now
collaborating with prof. Olofsson on the structurally characterization of specific glycans and glycosylation attachment sites of glycoproteins of HSV-1.

Glycosylation is generally recognized as the most complex post translational modification of proteins and due to its structural variability two separate methodologies, essentially based on mass spectrometry, for characterizing glycoproteins have evolved; glycomics for released glycans and proteomics for proteins. A few years ago we set out to fuse these two techniques in order to map the specific glycans while still attached to the amino acid residues of the protein backbone. A first publication came out 2009 in Nature Methods [17] where we introduced a capture-and-release technology to specifically enrich and characterize sialylated glycoproteins. The technique allowed us to define 36 $N$-linked and 44 $O$-linked glycosylation sites on glycoproteins of human cerebrospinal fluid. In parallel, we have employed the technique for mapping unique $O$-glycosylation sites of $\alpha$-dystroglycan prepared from human skeletal muscle [19], of platelet surface glycoproteins [15] released during storage in medium, and of glycoproteins prepared from human serum [9] and urine samples. The technology is now being refined for higher sensitivity, better primary and secondary ion fragmentation and applicability to characterize also membrane bound glycoproteins. Structural information on glycosylation and attachment sites of defined glycoproteins are continuously being added to the SwissProt database and thus made publicly searchable through Mascot database searches.

References


CV for Knut GÖRAN Iwo LARSON

Academic degrees/positions:
MD, University of Gothenburg (GU) 1977
Licensed physician (läkarlegitimation) 1984
Medical specialist, Clinical Chemistry 1988
PhD, GU 1982
Associate professor (docent), Med Biochemistry, GU 1984
Associate professor (docent), Clinical Chemistry, GU 1989
Senior physician, Sahlgrenska sjukhuset 1995
Professor, Human toxicology, Linköping University 1996
Professor, Laboratory Medicine/Glycobiology, GU 1998

Postdoc at the Biomembrane Institute, Department of Pathobiology, University of Washington, Seattle 1991-1992
Senior Research Fellow, NIH Fogarty Fellow 1995

Present Position
Dept of Clinical Chemistry and Transfusion Medicine, Inst. of Biomedicine, GU
Professor/senior physician, chief executive 1998
Sambio Core facilities, Sahlgrenska academy, GU
Head (prefekt) 2009

Scientific publications
I am author or co-author on about 120 peer-reviewed scientific publications.

Research Grants
I receive fundings as PI from the Swedish Research Council and from the Swedish Governmental grants to Sahlgrenska University Hospital to about 2 Mn SEK per year. I am also a core collaborator in a grant from VINNOVA on “Innovations for health” with PI prof Fredrik Höök, Chalmers, with a funding of 12.5 Mn SEK for 2009-014 on “Generic Sensor Devices for Diagnostics and Drug Screening”

Academic Supervisor
I have had the responsibility as main supervisor for 7 PhD students (Per Falk, dissertation 1991; Anders Elmgren, 1998; Robert Kronstrand, 2001; Karin Wåhlander, 2002; Ammi Grahn, 2003; Gustaf Rydell, 2009; Viktoria Rumjantseva, 2009) and as co-supervisor for 2 PhD students (Ragnar Lindstedt, 1993; Per Bengtson, 2003). I am presently main supervisor for 2 PhD students (Adnan Halim, Waqas Nasir) and co-supervisor for one (Johanna Nilsson).

External Academic engagements
I have served as the Faculty opponent at the Universities of Uppsala and Lund and as scientific reviewer in the committee of Biochemistry for the National Research Council between the years 2000-2005. I have served as member of the faculty committee on several dissertations and predissertations at the Sahlgrenska academy but not as a regular member. I have reviewed several manuscript but not as a regular member of an editorial board.

Leadership
I headed the Sahlgrenska University Hospital Division of Laboratory Medicine (Clinical chemistry, bacteriology, virology, pathology and cytology, immunology and transfusion medicine) covering a yearly budget of more than 500 Mn SEK, 650 employees and a production of about 5.5 million analyses per year between the years 1998-2007.