1952nd Conference

Glycobiology Conference 2018

5th International Conference on

Glycobiology & Glycoproteomics

&

3rd International Conference on

Molecular Biology & Nucleic Acids

August 27-28, 2018 | Toronto, Canada

Keynote Forum

Day 1

5th International Conference on
GLYCOBIOLOGY & GLYCOPROTEOMICS
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MOLECULAR BIOLOGY & NUCLEIC ACIDS
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Richard N Sifers

Baylor College of Medicine, USA

Different populations of endoplasmic reticulum mannosidase I/Man1b1 play distinct roles in the proteostasis network of the vertebrate secretory pathway

Statement of Problem: Although inherited information exists within a genetic material, defects in the encoded proteins are responsible for manifestations associated with abnormal biology. Therefore, a need exists to mechanistically define the proteostasis systems responsible for managing the cellular proteome as a means to eventually identify novel therapeutic sites for disease intervention. To this end, we have monitored the fates of newly synthesized proteins that are translocated into the secretory pathway, many of which are subjected to asparagine(N)-linked glycosylation. In addition to facilitating proper protein folding, modification of the appendage flags misfolded N-glycoproteins for elimination by "ER-associated Degradation" (ERAD). The currently accepted flagging mechanism involves the opportunistic cleavage of alpha-1,2-mannose units. Although this crucial event was initially thought to involve ER mannosidase I (Man1b1), recent evidence indicates that the protein is not a component of the mammalian glycoprotein quality control interactome, localizes to post-ER compartments, and does not require enzymatic activity to promote N-glycoprotein degradation.

Methodology & Theoretical Orientation: The present study sought to define the contribution of Man1b1 to the operation of an apparently "unconventional" ERAD client recruitment system. The effects of wildtype and selectively mutated forms of recombinant human Man1b1 on the fates of selected ERAD clients were monitored through the use of pharmacologic inhibitors, metabolic radiolabeling, immunoprecipitation, and western blotting.

Findings: Distinct populations of Man1b1 have identified that exhibit different intracellular trafficking patterns, unique functional partners, and unique client specificities.

Conclusion & Significance: An unexpected level of functional plasticity exists in the proteostasis network of the secretory pathway, extending the role of a specific mannosidase beyond that of limits of Glycobiology.

Biography

Sifers helped pioneer the initial mechanistic analysis of the biological systems that manage glycoprotein homeostasis (i.e. glycoproteostasis) in the mammalian secretory pathway. Using alpha1-antitrypsin deficiency as a medically relevant paradigm and client, his lab characterized the processes of chaperone-assisted glycoprotein folding as a means of conformation-based intracellular retention and proposed and characterized the mannose timer hypothesis as an initial step in N-glycan-targeted proteolysis (quality control). Subsequently, his team identified the underlying contribution of the unfolded protein response (UPR) and elucidated how compromised quality control can function as an etiologic agent of infantile liver cirrhosis.

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Albert M Wu

Chang-Gung University, Taiwan

Roles of polyvalency of glycotopes in the mechanism of protein-glycan interactions-one of the most potential directions for the transforming glycosciences

Lectins are Glycan-Binding Proteins (GBP). On cell surfaces, they mediate cell-cell interactions by combining with complementary carbohydrates on opposing cells. They play a key role in the control of various normal and pathological processes in living organisms, such as fertilization, embryogenesis, cell migration, organ formation, immune defense, and microbial infection. Improper function of cell recognition may cause disease. (Sharon and Lis, Science, 1989 246,227) The hallmark of lectins is the ability to bind carbohydrates specially and reversible. To provide a more valid and satisfactory depiction of the carbohydrate specificity (RFs, Recognition Factors) of lectins in order to elucidate their functional roles and to optimize their biomedical applications, the following RFs have to be defined— (i) Sub-monosaccharide RFs (epimers and anomers of monosaccharides); (ii) Monosaccharide specificity (Gal, GalNAc, GlcNAc, Man, LFuc, and Sialic acid from mammalian glycans); (iii) Expression of a lectin reactivities toward structural units by decreasing order; (iv) the most active ligand; (v) simple multivalent or cluster forms of carbohydrate structural units; (vi) complex polyvalent structural units and/or glycotopes as well as their resulting conformational features present in macromolecules. These RFs can be divided into two forms for different functions- the Mono- forms are the weak RFs and provide mainly essential and basic structures for lectin identification and classification, while their polyvalent forms and resulting conformation features play a critical role in recognition intensities. The Roles of Polyvalency of Glycotopes in the Mechanism of Protein-Glycan interactions- should be one of the most advanced achievements in the field of Glycoimmunology since 1980.

Biography

Wu obtained his PhD degree with W Pigman, who is one of the pioneers in glycoproteins, at New York Medical College; and had his postdoctoral training at EA Kabat's Lab for quantitative immunochemistry, Columbia University Medical Center, New York. He joined as a faculty position at Texas A&M University in 1982; promoted as a full professor at Chang-Gung University since 1989; and as Emeritus Professor after 2011. Dr Wu published over 120 glycoprotein and polyvalent glycotopes related papers. He is the chief editor for three volumes of Molecular Immunology of Complex Carbohydrates 1 to 3 in Adv. Exp. Med. Biol. 228, 451, 705 (Springer Publisher). His major interests are (i) Glycan purification and characterization; (ii) recognition factors of glycans; (iii) combining sites of lectins and antibodies. He received many Outstanding Research Awards from government agents in Taiwan and USA.

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Myron R Szewczuk

Queen's University, Canada

Neuraminidase-1 and its role in multistage tumorigenesis

Neuraminidase-1 (Neu1) has recently emerged as a central target in the sialidase-mediated regulation of tumorigenesis. Recent evidence indicates that Neu1 plays a much more profound role in human cancers than previously expected. In clinical setting its being essential that targeted therapies are to circumvent multistage tumorigenesis, which includes genetic mutations at the different growth factor receptors, tumor neovascularization, chemoresistance, immune-mediated tumorigenesis and the development of tissue invasion and metastasis. Firstly, the cell-surface molecular signaling platform will be described as controlling Neu1 sialidase activity, and discuss its relevance in cancer cell signaling. Second, the current understanding of Neu1 activity associated with cancer development will be summarized, and outline the key roles of Neu1 during various stages of tumorigenesis, including regulation of growth factor receptor signaling, control of Toll-like receptor (TLR) signaling and immune-mediated tumorigenesis, regulation of epithelial-mesenchymal transition (EMT), metastasis and acquired chemoresistance, and regulation of tumor vascularization.

Biography

Myron R Szewczuk is Full Professor of Immunology and Medicine, Queen's University, Kingston, Ontario Canada for the past 37 years. Dr Szewczuk's recent research has focused on the role of glycosylation in receptor activation with a particular focus of Toll-like, nerve growth factor Trk, eGFR and insulin receptors. He has discovered a novel receptor-signaling platform and its targeted translation in multistage tumorigenesis.

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Jun-ichi Kadokawa

Kagoshima University, Japan

Enzymes as powerful biocatalysts for precision synthesis of oligo and polysaccharides

Oligo- and polysaccharides have complicated structures because of the structurally different monosaccharide units and differences in stereo- and rearrangements of glycosidic bonds. Various structures of such substances in nature exhibit several functions in host organisms, and a subtle change in the monosaccharide structure and the type of glycosidic linkage exerts a profound effect on their properties and functions. Accordingly, the synthesis of well-defined non-natural oligo- and polysaccharides has attracted significant attention. Enzymes are identified as powerful biocatalysts to precisely synthesize oligo- and polysaccharides because enzymatic reactions using glycosyl substrates are progressed with regio- and stereocontrolled fashions in glycosidic linkage formation without the use of protective groups. Phosphorylase, which catalyzes phosphorolysis of α-(1→4)-glucans at a non-reducing end in the presence of inorganic phosphate, producing α-D-glucose 1-phosphate (Glc-1-P), is one of the enzymes that are practically used as the catalyst for synthesis of oligo- and polysaccharides with a well-defined structure. Because by means of the reversibility of the phosphorolytic reaction, phosphorylase catalyzes successive glucosylation using Glc-1-P as a glycosyl donor (monomer) and a maltooligosaccharide as a glycosyl acceptor (primer) as the polymerization to produce -(1→4)-glucans, that is, amylose with liberating inorganic phosphate (Fig1). As this enzyme shows loose specificity for the recognition of substrates, it recognizes several analogue substrates of Glc-1-P as glycosyl donors in glycosylations to give non-natural oligo- and polysaccharides. For example, α-D-glucosamine (GlcN-1-P) and α-D-glucuronic acid 1-phosphates have been used as glycosyl donors in phosphorylase-catalyzed enzymatic glucosaminylation and glucuronidation to give non-natural basic and acidic oligosaccharides having glucosamine and glucuronic acid residues at the non-reducing end, respectively. Phosphorylase isolated from thermophilic bacteria, *Aquifex aerolicus* VF5, catalyzes enzymatic polymerization of GlcN-1-P as a monomer from maltotriose primer. The enzymatic reaction was accelerated in ammonia buffer containing Mg2+ ion, owing to the precipitation of inorganic phosphate, giving non-natural amino polysaccharide, which corresponded to chitosan stereoisomer.

Biography

Jun-ichi Kadokawa received his Ph.D. in 1992. He then joined Yamagata University as a Research Associate. From 1996 to 1997, he worked as a visiting scientist at the Max-Planck-Institute for Polymer Research in Germany. In 1999, he became an Associate Professor at Yamagata University and moved to Tohoku University in 2002. He was appointed as a Professor of Kagoshima University in 2004. His research interests focus on polysaccharide materials. He received the Award for Encouragement of Research in Polymer Science (1997) and the Cellulose Society of Japan Award (2009). He has published more than 200 papers in academic journals.

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Myron R Szewczuk

Queen's University, Canada

Aberrant sialoglycan patterns facilitate 3D multicellular spheroid and xenograft tumor formation

Multicellular tumor spheroids are now at the forefront of cancer research, designed to mimic tumor-like developmental patterns in vitro. Tumor growth *in vivo* is known to be highly influenced by aberrant cell surface specific sialoglycan structures on glycoproteins. Aberrant sialoglycan patterns that facilitate spheroid formation are not well defined. Here, matrix-free spheroids from human breast, pancreatic and prostate cancer cell lines and their respective chemoresistant variants were generated using a unique cyclic Arg-Gly-Asp-D-Phe-Lys peptide modified with 4-carboxybutyl-triphenylphosphonium bromide (cyclo-RGDfK (TPP)) induced self-assembly platform. The cyclo-RGDfK(TPP) peptides mimic the natural extracellular matrices (ECM) protein's ability to induce cell aggregation via α5β1 integrin. We used the cyclo-RGDfK (TPP) approach to biochemically induce cell aggregation and compaction, transmogrifying monolayer cancer cells into tumor spheroids. MCF-7 and PANC-1 cells, and their drug-resistant cancer cell lines (MCF-7 TMX, PANC1-GemR) express different sialic acid content, which influenced their ability to form spheroids under cyclo-RGDfK (TPP)-induced self-assembly. Cancer cell aggregation and compaction correlate with the presence of α-2.3- and α-2,6-sialic acid cell surface residues to form spheroids under cyclo-RGDfK (TPP)-induced self-assembly and xenograft tumors. Removal or blockage of SA inhibited cell aggregation. Neuraminidase inhibitor, oseltamivir phosphate, enhanced cell aggregation and promoted compaction of cell aggregates. Future studies should build upon these findings and explore alternate and novel methods to target the cancer cell glycome and the unique sialylation patterns of the adhesion molecules involved in the spheroid formation and tumor progression.

Biography

For the past 37 years, Dr Szewczuk is Full Professor of Immunology and Medicine, Queen's University, Kingston, Ontario Canada. Dr Szewczuk's recent research has focused on the role of glycosylation in receptor activation with a particular focus of Toll-like, nerve growth factor Trk, EGFR and insulin receptors. He has discovered a novel receptor-signaling platform and its targeted translation in multistage tumorigenesis.

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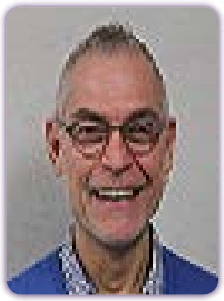

Jose Kovensky

University of Picardie Jules Verne, France

Multivalent sugar-lectin interactions from glycoclusters on oligosaccharide scaffolds to self-assembling structures

Carbohydrates play an essential role in several biological functions associated with selective interactions with cellular proteins that govern a wide variety of life processes. In living organisms, these high-affinity carbohydrate-protein interactions occur through multivalent contacts, characterized by an enhancement of the affinity when the sugar ligand is presented in a cluster rather than alone. Several biomimetic approaches have been developed in order to prepare synthetic multivalent neoglycoconjugates to interfere with a series of pathological events such as infections due to viruses and bacteria, tumor progression and migration, and inflammation processes. We constructed multivalent glycoconjugates on oligosaccharide scaffolds, to obtain structures with improved hydrophilicity and pharmacokinetics, as compared to peptidic, aromatic, or polymeric scaffolds. We were able to perform regioselective oxidation of mono-, di-, trisaccharides and cyclodextrins. We started preparing multimannosides, galactosides, and lactosides, synthesized by coupling the corresponding alkynyl glycosides to the azido modified oligosaccharides by CuAAC. We obtain a considerable gain in affinity to model lectins as Concanavalin A and PNA. Some of our glycoclusters were able to inhibit galectins 1 and 3. Afterward, we synthesized other glycoclusters exposing thiosugars, showing higher stability towards glycosyl hydrolases than O-glycosides. S-galactosides, S-lactosides, 3-deoxy-S-lactosides, and analogs of dithiogalactoside (a commonly used galectin inhibitor) afforded new multivalent probes to analyze sugar-lectin interactions. We finally explored a supramolecular approach for the construction of multivalent architectures, able to interact with proteins, through the design and synthesis of thiolactose-based amphiphiles. Interestingly, two compounds which only differ in the length of the spacer connecting the sugar fragments to the scaffold showed different properties. In this presentation, we will present the synthesis and affinities of different glycoclusters, and we discuss the influence several parameters as the triazole moiety, the length of the spacer, the ability for crosslinking of our glycoclusters, and the self-assembling properties of sugar-based amphiphiles.

Biography

Professor Jose Kovensky has PhD from the Universidad de Buenos Aires (Argentina, 1992). He did his postdoctoral research at the Ecole Normale Superieure (Paris, France, 1994-1995). After being Professor of Organic Chemistry in Argentina, he got a Full Professor position in Amiens in 2002. He has been the principal investigator of several projects financed by the Regional Council or Picardie Region, binational projects France-Germany, France-Argentine, and partner in European Projects. He has directed or co-directed 12 PhD theses. He is a co-author of more than 80 publications (articles, book chapters, patents). He has a wide experience in the synthesis and modification of oligosaccharides, in particular, uronic acid containing oligosaccharides, sulfonated oligosaccharides, glycosaminoglycans, multivalent glycoclusters, and sugar-based surfactants.

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Jean-Yves Masson

Laval University Cancer Research Center, Canada

Roles of PARP-1 and PALB2 in controlling DNA resection and strand invasion during DSB repair

Endogenous DNA double-strand breaks (DSBs) are extremely hazardous for a cell. If left unrepaired, DSBs can drive cells to genomic instability and tumor development. Our laboratory focuses on the intricate network of homologous recombination (HR) enzymes responsible for repairing DSBs. This seminar will focus on two key aspects of HR, DNA resection and strand invasion. Following the formation of DSBs, PARP-1 is rapidly recruited and activated through its binding to free DNA ends. PARP-1 synthesizes a structurally complex polymer composed of ADP-ribose units that facilitates local chromatin relaxation and the recruitment of DNA repair factors. Here, we identify a novel function for PARP-1 in DNA double-strand break resection. Remarkably, inhibition of PARP-1 leads to hyperresected DNA double-strand breaks. We show that loss of PARP-1 and hyper resection are associated with loss of Ku, 53BP1 and RIF1 resection inhibitors from the break site. Furthermore, PARP-1 abrogation leads to an increase of homologous recombination in vivo. Our work has direct implications for the clinical use of PARP inhibitors. Inherited mutations in PALB2 are associated with a predisposition for ovarian, breast and pancreatic cancers. PALB2 was identified BRCA2 interacting protein, essential for BRCA2 anchorage to nuclear structures and strand invasion. We will present our work in deciphering the functions of PALB2 in HR. Predicting the functional consequences of PALB2 mutations or variants has been challenging as they can lead to different biological effects. Using a novel CRISPR/Cas based homologous recombination assay, biochemical and cellular assays, we performed a structure-function analysis of PALB2 using PALB2 truncated mutants (R170fs, L531fs, Q775X and W1038X). These studies allowed us to uncover a PALB2 regulation mechanism by which cancer cells could drive genomic instability. The assays presented here will be valuable tools for the functional assessment of PALB2 variants, or other homologous recombination genes, in cancer etiology.

Biography

Jean-Yves Masson is an internationally recognized expert in DNA repair mechanisms. Throughout his career, Dr Masson focused on radiation and chemicals that impede DNA replication to induce DNA double-strand breaks (DSBs). Failure to remove these breaks leads to cell death, genetic mutations, gross chromosome rearrangements, and to cell transformation and cancer. He is one of the few world experts on PALB2, a protein which is getting scientific and public attention as PALB2 mutations increase breast cancer by 6-8 fold. He established that PALB2 deficient cells are very sensitive to PARP inhibitors, a very promising therapeutic avenue for breast/ovarian cancer. Dr Masson was recently inducted as a Canadian Academy of Health Sciences fellow.

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Hamid Mirzaei

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Hydralazine induces stress resistance and extends Caenorhabditis elegans lifespan by activating the NRF2/SKN-1 signaling pathway

Advances in modern medicine have led to increased life expectancy. As an aging population increases, finding a cure for an age-related cognitive decline is becoming more and more important. A hallmark of neurodegenerative diseases, one of the main pathologies underlying age-related dementia, is the deposition of insoluble proteins in cells of the neuromuscular system causing proteotoxicity. Substantial literature suggests that the primary inducer of proteotoxicity in aging is chronic deterioration of defense machinery including antioxidant, heat shock, and degradation systems. Deterioration of defense machinery create imbalances in aggregation and clearance pathways leading to proteotoxicity by altering aggregate dynamics, localization and aberrant interactions. One of the main targets of toxic proteins aggregates is mitochondria resulting in mitochondrial dysfunction and increased oxidative stress. Nuclear factor (erythroid-derived 2)-like 2 and its Caenorhabditiselegans ortholog, SKN-1, are transcription factors that have a pivotal role in the oxidative stress response, cellular homeostasis, and organismal lifespan. Similar to other defense systems, the NRF2-mediated stress response is compromised in aging and neurodegenerative diseases. Here, we report that the FDA approved drug hydralazine is a bona fide activator of the NRF2/SKN-1 signaling pathway. We demonstrate that hydralazine extends healthy lifespan (~25%) in wild-type and tauopathy model *C. elegans* at least as effective as other anti-aging compounds, such as curcumin and metformin. We show that hydralazine-mediated lifespan extension is SKN-1 dependent, with a mechanism most likely mimicking calorie restriction. Using both *in vitro* and *in vivo* models, we demonstrate that hydralazine has neuroprotective properties against endogenous and exogenous stressors. Our data suggest that hydralazine may be a viable candidate for the treatment of age-related disorders.

Biography

Dr Hamid Mirzaei's research is focused on finding the target of novel and FDA approved compounds using a combination of proteomics, computational biology, and biochemistry. Many FDA approved drugs are currently in use without the clear understanding of their mechanism of action. On the other hand, there are quite a few well-characterized natural products with unknown targets. Dr Mirzaei uses systems biology to understand the drug's mechanism of action by identifying the target of the drugs and their cellular and organismal phenotypes.

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