Göteborg, 2017

Glycoproteomics incursions into the realm of proteoglycans

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Jubileumsaulan, Sahlgrenska Universitetssjukhuset, Göteborg, måndagen den 6 mars 2017 kl. 13:00

av **Alejandro Gómez Toledo**

Fakultetsopponent:
Henrik Clausen, Professor
University of Copenhagen, Denmark

Avhandlingen baseras på följande delarbeten

I. Noborn F, Gomez Toledo A, Sihlbom C, Lengqvist J, Fries E, Kjellén L, Nilsson J, Larson G. *Identification of chondroitin sulfate linkage region glycopeptides reveals prohormones as a novel class of proteoglycans*. Mol Cell Proteomics. 2015 Jan; 14(1):41-9.

II. Gomez Toledo A, Nilsson J, Noborn F, Sihlbom C, Larson G. *Positive mode LC-MS/MS analysis of chondroitin sulfate modified glycopeptides derived from light and heavy chains of the human inter-α-trypsin inhibitor complex*. Mol Cell Proteomics. 2015 Dec; 14(12):3118-31.

III. Nasir W, Toledo AG, Noborn F, Nilsson J, Wang M, Bandeira N, Larson G. *SweetNET: A Bioinformatics Workflow for Glycopeptide MS/MS Spectral Analysis*. J Proteome Res. 2016 Aug 5; 15(8):2826-40.

IV. Noborn F, Gomez Toledo A, Green A, Nasir W, Sihlbom C, Nilsson J, Larson G. *Site-specific identification of heparan and chondroitin sulfate glycosaminoglycans in hybrid proteoglycans*. Sci Rep. 2016 Oct 3; 6:34537.

V. Gomez Toledo A, Pereira MA, Clausen TM, Simonsson S, Salanti A and Larson G. *The expression of placental-type chondroitin sulfate A is associated with a heterogeneous group of CSPGs in human cancer and IPS cells*. Manuscript

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Glycoproteomics incursions into the realm of proteoglycans

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Abstract

The proteoglycans are acidic and heavily modified glycoproteins that are essential for development, tissue organization and cell hemostasis. They are linked to pathogenesis by modulating microbial infection, cancer behavior and cardiovascular dysfunction. To assess their impact on human health and disease, a deep understanding of their structure and function relationships is required. Unfortunately, this has been severely hampered by analytical difficulties related to their glycosaminoglycan (GAG) chains.

In this PhD thesis, we developed analytical workflows for the structural characterization of human proteoglycans from body fluids and cells. We combined enzymatic degradation steps, chromatographic separation and high-resolution mass spectrometry. Additionally, we developed SweetNET, a bioinformatics platform to cope with the large amounts of data generated from these high-throughput experiments.

In addition to the structural characterization of known human proteoglycans, we conducted detailed analysis of 21 novel core proteins carrying GAG modifications. They included several human prohormones, defining them as a novel class of proteoglycans. The results suggested that the acidic sugars might be important for hormone processing and packing within intracellular vesicles. We also identified unique GAG modifications with a potential regulatory role and redefined the consensus sequence for sugar attachment. Finally, we discovered the presence of oncofetal GAG modifications on induced pluripotent stem cells, using a unique malaria protein probe. These modifications displayed a stage-specific dependence, which we propose may have an impact on stem cell self-renewal and differentiation capacity.

Keywords: proteoglycans, glycosaminoglycans, mass spectrometry, VAR2CSA, iPS cells, inter-alpha trypsin inhibitor, bioinformatics, glycopeptides, prohormones

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