CRG Centre de Regulació Genòmica

ABSTRACTS

CRG Core Facility Technology Symposium: "Applying proteomics to life sciences: from ions to biology"

21 November 2014
PRBB Auditorium, Barcelona

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Integrated structural analysis of the human nuclear pore complex

The nuclear transport system defines the composition of the nuclear compartment in eukaryotic cells. Selective transport occurs through nuclear pore complexes that interact with nuclear transport factors of various transport pathways. We have combined cryo electron microscopy with cross-linking mass spectrometry, targeted proteomics and structural modeling to investigate the scaffold architecture of the human nuclear pore. Using an integrated structure determination approach, we determined the structure of a major scaffold motif, the Nup107 subcomplex, in isolation and when integrated into the NPC. Our data suggest that 32 copies of the Nup107 subcomplex assemble into two reticulated rings, one each at the cytoplasmic and nuclear face of the NPC. This arrangement explains how changes of the diameter are realized that might accommodate transport huge cargoes. We used targeted proteomics to measure the stoichiometry of all nuclear pore complex components and have investigated the extent of stoichiometric variations that occur across different cancer cell types. Our data point to a compositional fine-tuning the nuclear transport system that goes along with cell differentiation and is reflected in structural adjustments of peripheral components of the nuclear pore complex.

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Defining the oligomer form/s responsible for amyloid-β neurotoxicity in Alzheimer´s disease

Amyloid-β (Aβ) oligomers are considered the pathogenic form of Aβ in Alzheimer´s disease (AD). However, their heterogeneous and transient nature have precluded definition of the term *neurotoxic Aβ oligomer*, thus preventing the development of therapeutic strategies that target them. Inspired by functional and structural changes associated to AD, such as oxidative stress and membrane disruption, we have developed strategies, namely chemical cross-linking and the use of detergent micelles, to prepare Aβ oligomers with well-defined properties. Using these samples, we are obtaining crucial information on the chemical and structural features that define *Aβ oligomer neurotoxicity*, critical to treat AD.

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Decoding Network Dynamics in Cancer

Biological systems are composed of highly dynamic and interconnected molecular networks that drive biological decision processes. The goal of network biology is to describe, quantify and predict the information flow and functional behavior of living systems in a formal language and with an accuracy that parallels our characterization of other physical systems such as Jumbo-jets. Decades of targeted molecular and biological studies have led to numerous pathway models of developmental and disease related processes. However, so far no global models have been derived from pathways, capable of predicting cellular trajectories in time, space or disease. The development of high-throughput methodologies has further enhanced our ability to obtain quantitative genomic, proteomic and phenotypic readouts for many genes/proteins simultaneously. Here, I will discuss how it is now possible to derive network models through computational integration of systematic, large-scale, high-dimensional quantitative data sets. I will review our latest advances in methods for exploring phosphorylation networks. In particular I will discuss how the combination of quantitative mass-spectrometry, systems-genetics and computational algorithms (NetworKIN [1], NetPhorest [4] and KinomeXplorer [10]) made it possible for us to derive systems-level models of JNK and EphR signaling networks [2,3]. I shall discuss work we have done in comparative phospho-proteomics and network evolution[5-7]. Finally, I will discuss our most recent work in analyzing genomic sequencing data from NGS studies and how we have developed new powerful algorithms to predict the impact of disease mutations on cellular signaling networks [8,9]. I shall illustrate the power of these approaches in a recent study where we have identified colon cancer metastasis cell signaling networks.

References:

http://www.lindinglab.org

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Understanding Cellular Proteolysis With Proteomic Approaches

Proteolysis affects every protein through limited processing, N- or C-terminal truncation, or degradation. Unlike other post−translational modifications, proteolysis is irreversible and occurs intra− and extracellularly. Limited proteolysis regulates cytokine function, zymogen activation, membrane shedding, and assembly of structural proteins. The large number of genetically encoded proteases in man (> 560) illustrates the involvement of proteolysis in most physiological and pathological processes. However, the *in vivo* substrate profiles of most proteases have remained elusive; presenting a major hurdle to understanding and therapeutically exploiting protease function in health and disease.

System−wide, unbiased identification of protease substrates has long been inaccessible but is now enabled by recently developed proteomic strategies for the quantitative determination of neo N− and C−termini together with high-content screening of *in vitro* protease specificity.

I will introduce these novel techniques and highlight how they can be applied to better understand proteolytic processing in the cellular context.