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Monitoring protein structural changes on a proteome-wide scale

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Protein structural changes induced by external perturbations or internal cues can profoundly influence protein activity and thus modulate cellular physiology. Mass spectrometry (MS)-based proteomic techniques are routinely used to measure changes in protein abundance, post-translational modification and protein interactors, but much less is known about protein structural changes, owing to the lack of suitable approaches to study global changes in protein folds in cells. In my talk, I will present a novel structural proteomics technology developed by our group that enables the analysis of protein structural changes on a proteome-wide scale and directly in complex biological extracts. The approach relies on the coupling of limited proteolysis (LiP) tools and an advanced MS workflow. LiP-MS can detect subtle alterations in secondary structure content, larger scale movements such as domain motions, and more pronounced transitions such as the switch between folded and unfolded states or multimerization events. The method can also be used to pinpoint protein regions undergoing a structural transition with peptide-level resolution. I will describe selected applications of the approach, including 1. The identification of proteins that undergo structural rearrangements in cells due to a nutrient shift; 2. The analysis of *in vivo* protein aggregation; 3. The cell-wide analysis of protein thermal unfolding; and 4. The identification of protein-small molecule interactions (e.g. drug-target deconvolution). I will discuss the power and limitations of the method and possible new directions in structural biology enabled by this emerging approach to protein structure analysis.

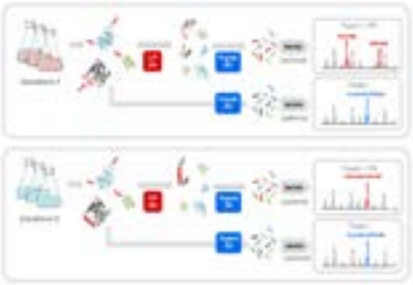

Figure1: *LiP-MS approach. A native proteome extract is incubated with a broad-specificity protease for a short time. Red arrows indicate LiP sites. Protease activity is quenched by shifting the proteome to denaturing conditions and complete trypsin digestion is then performed. A fraction of the same sample is only subjected to the trypsin step. The samples are analyzed by MS and levels of the resulting fully tryptic (FT) and half-tryptic (HT) peptides are compared. A FT peptide containing a LiP cleavage site will be detected in the trypsin control and replaced by two HT halves in the sample subjected to LiP. N and D indicate native and denaturing conditions, respectively.*

Biography

Paola Picotti completed her PhD at the University of Padua (Italy) and then joined the group of Ruedi Aebersold at ETH Zurich (Switzerland), where she developed novel targeted proteomic techniques. In 2011, she was appointed Assistant Professor at ETH Zurich. Her group develops structural and chemoproteomics methods and uses them to study the consequences of intracellular protein aggregation. Paola Picotti's research was awarded an ERC Starting grant, a Professorship grant from the Swiss National Science Foundation, the Latsis Prize, the Robert J Cotter Award, the SGMS Award and the EMBO Young Investigator Award. Main contributions of her group are the development of a structural method to analyze protein conformational changes on a system-wide level, the discovery of novel allosteric interactions, the analysis of the determinants of proteome thermostability and the identification of a novel neuronal clearance mechanism for a protein involved in Parkinson's disease.

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