Proteomes in 3D

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. In my talk, I will present a structural proteomics method that enables 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 MS. 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. I will describe how we are applying this approach to study the molecular bases of protein aggregation diseases and to the identification of protein-small molecule interactions (e.g. drug targets). I will also propose that monitoring protein structural states on a proteome-wide scale can serve as a new powerful readout to pinpoint altered protein functional states and the (de)regulation of biochemical pathways. Last, I will discuss the power and limitations of the new approach.