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 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 approach and possible new directions in structural biology enabled by this emerging approach to protein structure analysis.