Toward large-scale differential interactomics with cross-linking mass spectrometry

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Cross-linking mass spectrometry-based proteomics (XLMS) comprises the art of shortlisting amino acids that are in proximity (~20 Armstrong) within the same protein or from different (interacting) proteins. This is typically accomplished using bifunctional chemical reagents of known length that covalently link in each end to specific amino acids; the system is then tryptically digested and the linked peptides are identified by high-resolution tandem mass spectrometry with the aid of computational tools. To date, most applications aimed for aiding to unveil the structure of protein complexes. Under this context, we introduced the first fully graphical search engine for this purpose, SIM-XL, worked together with PRIDE to define community standards for sharing data, and performed the first characterization of the coupling of a homodimer (APOA1) using XLMS. Recently, a new class of crosslinker reagents, that are cleavable during the dissociation in the mass spectrometer, has unlocked new possibilities to tackle even more complex problems such as, say, aiming toward the study of differential interactomics. Do we have the software to face such challenges? What are the experimental limitations? In my talk, I will bring you up to speed on the latest developments in the realm of cleavable cross-linking mass spectrometry and then share some of our latest accomplishments and benchmarking that are paving the way toward enabling large-scale differential interactomics.

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