

## **Protein-Protein Interaction Studies by Chemical Cross-Linking and High-Resolution Mass Spectrometry**

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During the past few years, tremendous progress has been made in mapping interface regions between interacting proteins, which is crucial for understanding signal transduction pathways and regulation of proteins. High-resolution structural analysis of proteins is currently accomplished by NMR spectroscopy and X-ray crystallography. These techniques, however, are time- and material-consuming methods and moreover, they are not applicable to all proteins or protein complexes. A promising strategy with the potential to obtain low-resolution structural information on minute amounts of proteins is based on a combination of chemical cross-linking and mass spectrometry. After the cross-linking reaction, cross-linked complexes are enzymatically digested and the created peptide mixtures are analyzed by high-resolution mass spectrometry (nano-HPLC/MALDI-TOF/TOF-MS and nano-HPLC/nano-ESI-LTQ-Orbitrap-MS). Based on the distance restraints derived from the chemical cross-linking data we are able to generate three-dimensional structure models of the protein-protein and protein-ligand complexes using computational docking methods. Currently, we are studying a number of protein complexes, such as different calmodulin/target protein complexes, complexes between laminin N-terminal domains (ca. 150 kDa) as well as complexes between the peroxisome-proliferator activated receptor alpha (PPAR $\alpha$ ) and low-molecular weight ligands. Our integrated approach possesses the potential to be employed for structural studies of a wide range of protein complexes, which are difficult to be analyzed by other 3D protein structure determination methods, namely very large protein complexes or membrane proteins.