The Power of Chemical Cross-Linking and Mass Spectrometry to Study Protein Complexes

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Detailed knowledge of three-dimensional protein structures is critical for understanding cellular processes at the molecular level. However, applying conventional methods of structural biology is challenging when analyzing membrane proteins, transient complexes or very large protein assemblies. Chemical cross-linking in combination with mass spectrometry (MS) and computational modeling has emerged as an alternative strategy to obtain three-dimensional structural information of proteins and protein complexes [1]. The chemical cross-linking/MS approach can be used in combination with complementary low-resolution structural methods to study proteins and protein assemblies, which are otherwise not amenable to the high-resolution structural techniques of X-ray crystallography or NMR spectroscopy. Chemical cross-linking relies on the introduction of a covalent bond between functional groups of amino acids within one protein, to gain insight into the conformation of a protein, or between interaction partners to elucidate interfaces in protein complexes. Based on the distance restraints derived from the chemical cross-linking data, 3D-structural models of proteins and protein complexes can be constructed.

We employ the chemical cross-linking/MS strategy to study proteins and protein complexes covering a wide range of biological activities. Currently, we are exploring the incorporation of unnatural photo-reactive amino acids into the proteins of interest followed by UV-induced cross-linking and MS analysis. In my talk I will give an overview of the cross-linking strategies that can be employed to derive 3D-structural information of proteins. With the continual improvements in mass spectrometric equipment and bioinformatics tools, the chemical cross-linking strategy can be expected to contribute valuable structural information of proteins that are otherwise not amenable to analysis.

References

[1] Sinz, A., *Exp. Rev. Proteomics* **2014**, *16*, 733; Rappsilber, J., *J. Struct. Biol*. **2011**, *173*, 663.