(Supra)molecular modulation of protein interactions
Nuclear Receptors and Caspases as case studies

Chemical biology is the study of biological phenomena with an approach originating from chemistry combining and integrating chemistry and biology. As such chemical biology can address biological problems with molecular techniques not accessible via biology alone. This lecture will focus on the application of chemical biology approaches for the study and modulation of two types of protein interactions: the nuclear receptor-coactivator interaction and caspase dimerization. Specific focus will be on the role supramolecular chemistry can play is this respect.

The nuclear receptor – cofactor interaction is the key protein-protein interaction that transfers ligand induced changes in the nuclear receptor conformation to the transcriptional machinery. A molecular understanding of this process and its regulation is necessary to fully control and predict the effects of nuclear receptor modulation, either via classical ligands or via direct modulation of this interaction. Chemical biology strategies to elucidate this protein-protein interaction at the molecular level are discussed.

Supramolecular chemistry has primarily found its inspiration in biological molecules, such as proteins and lipids, and their interactions. Currently the supramolecular assembly of designed compounds can be controlled to great extent. This provides the opportunity to combine these synthetic supramolecular elements with biomolecules for the study of biological phenomena. Supramolecular elements can for example be ideal platforms for the recognition and modulation of proteins and cells. Caspase homodimerization is a key step in the activation of their enzymatic activity. Control over protein homodimerization allows investigating the molecular processes underlying this activation mechanism. We have generated a so-called supramolecular inducer of dimerization that can act as an allosteric modulator of caspase dimerization and allows highly efficient and reversible activation of caspase activity.

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