Structural biology of small-molecule stabilization of protein-protein interactions

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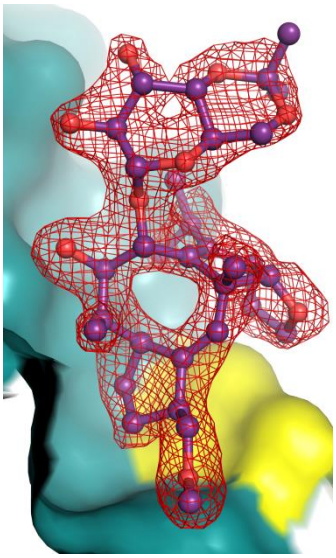
Targeted pharmacological modulation of Protein-Protein Interactions (PPIs) is a promising strategy in Chemical Biology and Drug Development. However, in the vast majority of cases this concept has been realized only for inhibition of PPIs despite the fact that in many biomedical contexts stabilization of PPIs would be desirable [1]. The natural product fusicoccin A (FC-A) is stabilizing the binding of 14-3-3 adapter proteins to the plant H^+-ATPase PMA serving as proof-of-principle molecule for the possibility to address the widespread interactome of 14-3-3 proteins [2, 3]. In humans, these proteins interact with partner proteins implicated for example in cancer (Raf, p53, YAP/TAZ, β-catenin) or neurodegenerative diseases (Tau, α-Synuclein, LRRK2). We have devised a fusicoccin-derivative (FC-THF) that stabilizes the interaction of 14-3-3 with the K^+ channel TASK-3 [4]. A similar concept can be applied for the enhancement of CFTR plasma membrane localization, an important aspect for the treatment of cystic fibrosis [5]. In a possible new strategy for cancer therapy we have shown how the fusicoccin class of natural products can stabilize the inhibitory interaction of 14-3-3 proteins with the estrogen receptor (ER), the protein kinase C-RAF, and the adapter protein Gab2 [6,7,8]. Together with the demonstration that 14-3-3 PPI stabilizers can be identified by screening conventional compound libraries [9,10] these studies support the concept of small-molecule PPI stabilization for biomedical research. In addition, we have also contributed to small-molecule inhibition of 14-3-3 PPIs, targeting for example the pathogenicity protein ExoS from *Pseudomonas aeruginosa* [11,12] or Tau, implicated in Alzheimer's Disease [13,14].



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Talk Summary

In this talk I will advertise the use of small-molecule stabilization of 14-3-3 protein-protein interactions (PPIs) for chemical biology and drug discovery. X-ray protein crystallography is key to understand the mode-of-action of these rim-of-the-interface binding molecules.