Title: Expanding the ligandable proteome with diverse electrophiles

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Abstract:

Existing approaches to profile the ligandable proteome utilize electrophiles that exploit the enhanced nucleophilicity of Cys residues. Though covalent profiling of Cys has been successful, Cys is one of the least abundant amino acids with ~2% occurrence in the human proteome. Therefore, exploring reactive functionalities that enable robust capture of an expanded set of amino acids can increase the coverage of the ligandable proteome and help identify novel pharmacologically accessible pockets on proteins of interest. One such residue is Trp which plays a variety of functional roles in protein structure and biochemistry but lacks electrophilic approaches for direct profiling due to its low abundance and modest nucleophilicity. Herein, I highlight the chemoproteomic characterization of novel chemistries for direct ligation of Trp and its utility to expand ligandability mapping beyond Cys. Furthermore, I discuss the utility of privileged electrophiles, such as sulfur (VI) fluoride exchange (SuFEx) chemistries, for the development of novel covalent inhibitors that engage WDR5 to disrupt interactions with its binding partner MYC. Moreover, I explore covalent chemoproteomic approaches to monitor WDR5 target engagement and site occupancy directly and indirectly in complex proteomes using a variety of SuFEx-bearing probes. Taken together, by exploring a diverse array of reactive functionalities along with covalent chemoproteomic profiling we can better understand covalency for residues beyond Cys and for next-generation covalent therapeutics.