BIOCHEMISTRY SEMINAR

Fluorine-Displacement Probes to Interrogate Post-Translational Modification (PTM)-related Protein-Protein Interactions

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Abstract: Post-translational modifications (PTMs) modify existing proteins with additional chemical functionalities, resulting in the mediation of signaling events underlying various cellular processes. The dysregulation of PTMs has been closely related to the onset and/or relapse of human diseases. Yet, many PTM-related non-histone proteins and enzymes remain to be elucidated in terms of their identity, functions, and roles in cellular activities such as activation, proliferation, and migration, simply due to the lack of effective tools for efficient labeling and global profiling.1-3 Despite the development of bioorthogonal chemical reactions such as “click chemistry”, few research programs have explored protein labeling or tagging with reduced sterics. Towards this end, my group has invented a series of steric-free bioorthogonal reactions (fluorine displacement reactions (FDR))2-3 and has developed a novel class of FDR-based imaging and proteomics probes aimed at a complete dissection of substrate proteins and protein-protein interactions of acetylation and glycosylation that are featured in diseased cell lines; which for now cannot be systematically profiled due to limitations in the current chemical labeling approach that heavily relies on sterically hindered ‘click chemistry’ tags and the current biological approach that relies on unrobust antibodies.2-3

Concurrently, to facilitate the studying and targeting of any new protein-protein interactions (PPIs) to be revealed by the aforementioned research investigations in PTM signaling, we also exploited other tool probes4-5 such as peptide stapling based on the FDR reaction. The resulting peptides possessed improved folding, stability, and on-target affinity, but also displayed enhanced cell penetration than the peptides stapled by traditionally used ring-closing metathesis.4-5 As an on-going effort, my group has been applying this new class of peptide mimetics to interrogate Axin-β-catenin interactions, p53-MDM2, and estrogen receptor α-coactivator interactions that are key to the onset and relapse of breast cancers, leukemia, and lymphoma, etc, as well as novel PPIs of protein tyrosine phosphatases that are important to neuron regeneration.

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References:

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