Selective labeling of glycoside hydrolases using ligand-directed protein profiling

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Small molecules selectively interacting with proteins and thereby modulating enzyme activity are of great interest for chemical biology and chemical medicine. Altering the intrinsic catalytic activity, either through enzyme activation or inhibition, leads to decisive effects on the biological system.[1]

With the development of activity-based protein profiling (ABPP), detection of actually active enzyme rather than the expression level of the protein became feasible. [2-3]

In ligand-directed chemistry (LDC), a variation of ABPP, profiling of enzymes without losing their intrinsic activity was achieved.[4-5] In this approach, a small molecule based probe features a reversible inhibitor as ligand (A) and a cleavable electrophilic group (B) which can be attacked by a nucleophilic amino acid residue, nearby, but outside the active site forming a covalent bond. Subsequently, the consequently truncated probe can depart from the ligand-binding site, thus the enzyme's activity is maintained (Figure 1).

Here we report the design, synthesis, and biological evaluations of iminosugar based probes for selective profiling of glycoside hydrolases, applying the ligand-directed chemistry (LDC) approach. Experimental details and results will be presented.

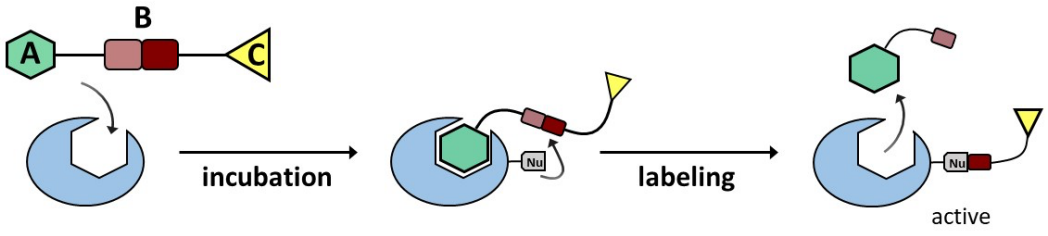

Figure 1: Principle of ligand-directed chemistry. (A) reversible inhibitor as ligand; (B) linker with electrophilic reactive group; (C) reporter tag.

Bibliographic references:

[1] A. L. Hopkins and C. R. Groom (2002), Nat. Rev. Drug Discov. (1) 727-730.
[2] H. S. Overkleeft et al. (2014) Bioconjugate Chem. (25) 1181-1191.
[3] H. Deng et al. (2020) Eur J Med Chem. (191) 112151.
[4] S. Tsukiji et al. (2009) Nat. Chem. Biol. (5) 341-343.
[5] T. Tamura and I. Hamachi (2019) J. Am. Chem. Soc. (141) 2782-2799.