Ligand-Directed Site-Selective Cysteine Bioconjugation of the KELCH Domain of KEAP1 with Hypervalent Iodine Reagents

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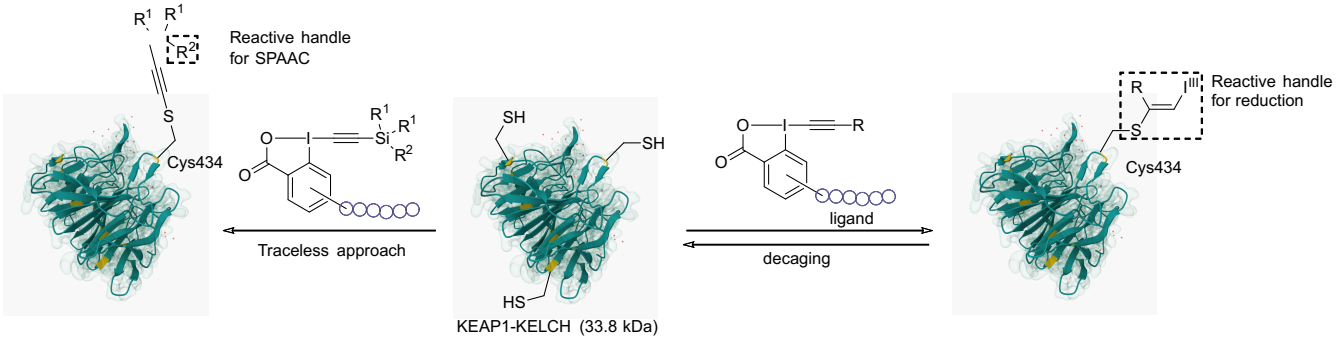
Site selective labelling of proteins is essential to improve diagnostics and therapeutics tools. While many site-selective labelling methods have been developed, they often require genetic modification of the protein of interest (POI). In contrast, affinity-driven reactions have allowed the site-selective labeling of native, nontagged proteins with chemical probes in physiological contexts.[1]

Our group reported the use of hypervalent iodine-based Ethynylbenziodoxolones (EBXs) reagents for bioconjugation on cysteine on native protein.[2,3] We present here a strategy for single site-selective bioconjugation on native protein with ligand-directed EBXs reagents.[4] Specifically, we successfully labelled Cys 434 in the KELCH domain of KEAP1, a key protein in the regulation of oxidative stress. EBXs could be used either as traceless reagents with release of the peptide ligand to introduce reactive handles such as azides or alkynes or as covalent reagents leading to the formation of peptide-protein adducts, which could be cleaved in a separated step.



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