Chemical decaging in living systems

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General applicable tools for manipulation of biomolecule functions under living conditions are highly desired in the post-genomic era. Bioorthogonal chemistry has revolutionized our ability to label and visualize various biomolecules inside living cells \cite{1}. However, efforts have been traditionally focused on developing bioorthogonal conjugating reactions, which, in many cases, are limited for function investigations of many biomolecules and biological processes. Recently, Professor Peng Chen’s laboratory in the Department of Chemical Biology at Peking University has begun to address this challenge by inventing bioorthogonal elimination reactions triggered by small molecules in a series of innovative work \cite{2–4} (Fig. 1a).

Chen laboratory started their attempts in developing bioorthogonal elimination reactions to manipulate intracellular proteins two years ago. In the first work, they coupled the genetic code expansion strategy with the palladium-mediated deprotection chemistry for chemical rescue of protein functions in living cells \cite{2} (Fig. 1a and b). Bio-compatible palladium catalysts allowed chemical decaging of propargyloxycarbonyl (Proc)-caged lysine side-chain on intracellular proteins, permitting gain-of-function study of protein functions (e.g. bacterial toxins) under their native cellular environment (Fig. 1b). This work represents the first example in which an elimination chemistry catalyzed by a transition metal is used for manipulating biomolecules inside cells. They have recently developed an elegant bioorthogonal elimination strategy based on a Diels–Alder (DA) reaction for chemical decaging of proteins \cite{3} (Fig. 1a and c).

Their approach converted an inverse electron demand DA reaction, a widely used bioorthogonal conjugation reaction, into a decaging reaction by triggering the elimination of trans-cyclooctene-masked ε-amine on lysine residue, a modified lysine that can be incorporated using unnatural amino acid strategy. Chemically caged firefly luciferase were constructed and were shown to be activated by this strategy within 10 min, offering a rapid and facile method for turning ‘ON’ protein activity within the complex intracellular signaling networks (Fig. 1a and c).

Although similar strategies have been developed via the use of light (known as photo-decaging) instead of small molecules as the triggering element, the chemical decaging strategy provides unique advantages for biological studies that cannot be achieved with photo-decaging. Chen group has extended the chemical decaging strategy to glycans on live cells (Fig. 1a and d) \cite{4}. Through collaboration with Professor Xing Chen in the same department, they utilized palladium nanoparticles to effectively eliminate the Proc-group on metabolically incorporated N-Proc-neuraminic acid into neuraminic acid (Neu5Ac) on cell surface glycans. Their Pd-mediated chemical conversion mimics the enzymatic de-N-acetylation of N-acetylneuraminic acid (Neu5Ac), which is a proposed mechanism for the natural occurrence of...
Neu on cell-surface glycans. They show that this strategy can be used to modulate cell clustering status via manipulation of cell-surface charge by unmasking the free amine on Neu5Ac to neutralize its negatively charged carboxyl group (Fig. 1d).

The Chen group successfully extended the bioorthogonal chemistry from ligation to elimination reactions, which could find facile applications in real biological settings. Their work will inspire the expansion of the definition and utilization of bioorthogonal chemistry to diverse chemical transformations in living systems [5].

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