(SD2020-497) Light-activated tetrazines enable live-cell spatiotemporal control of bioorthogonal reactions

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BACKGROUND

Bioorthogonal ligations encompass coupling chemistries that have considerable utility in living systems. Among the numerous bioorthogonal chemistries described to date, cycloaddition reactions between tetrazines and strained dienophiles are widely used in proteome, lipid, and glycan labeling due to their extremely rapid kinetics. In addition, a variety of functional groups can be released after the cycloaddition reaction, and drug delivery triggered by in vivo tetrazine ligation is in human phase I clinical trials.

While applications of tetrazine ligations are growing in academia and industry, it has so far not been possible to control this chemistry to achieve the high degrees of spatial and temporal precision necessary for modifying mammalian cells with single-cell resolution.

TECHNOLOGY DESCRIPTION

Researchers from UC San Diego have now demonstrated visible light-activated formation of tetrazines from photocaged dihydrotetrazines, which enables live-cell spatiotemporal control of rapid biorthogonal cycloaddition reactions between tetrazines and dienophiles such as trans-cyclooctenes (TCOs). Photocaged dihydrotetrazines are stable in conditions that normally degrade tetrazines, enabling efficient early-stage incorporation of bioorthogonal handles into biomolecules such as peptides. Photocaged dihydrotetrazines allow the use of non-toxic visible light to trigger tetrazine ligations on live mammalian cells. By tagging reactive phospholipids with fluorophores, the researchers demonstrate modification of HeLa cell membranes with single-cell spatial resolution.

APPLICATIONS

In the cited publication, the inventors demonstrated a methodology for the photoactivation of tetrazines that enables biomolecular labeling, spatiotemporal modification of live-cell membranes with single-cell precision, and photopharmacology (and precision drug delivery) when combined with “click to release” strategies.

STATE OF DEVELOPMENT

Tetrazine instability is a well-recognized obstacle to their use, and the inventors have found that photocaged tetrazine precursors are highly stable, even in the presence of strong bases which rapidly degrade tetrazines. Given the stability of photocaged dihydrotetrazines, this invention is expected to find broad application as a

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OTHER INFORMATION

KEYWORDS
diagnostics, materials, therapeutics, tetrazine ligation, bioorthogonal chemistry, tetrazine photoactivation, photopharmacology, click to release

CATEGORIZED AS
- Medical
  - Delivery Systems
  - Disease: Cancer
  - Research Tools
  - Therapeutics

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general tetrazine protecting group. Photocaged dihydrotetrazines would be especially useful in conditions known to degrade tetrazines, such as those encountered during the installation of 18F radionuclides for PET imaging or for live-cell pulse-chase experiments where tetrazine reactivity would be required to be maintained for an arbitrary amount of time before reaction. Indeed, preliminary results indicate that photocaged dihydrotetrazines, unlike tetrazines, are very stable under the conditions typically used for fluorination. Since this new method directly activates tetrazine precursors, high spatiotemporal precision is achievable. By modifying phospholipids on cell surfaces, the inventors showed that single-cell activation is feasible. The technique could enable monitoring of lipid trafficking and dynamics in live cells by controlling where and when caged tetrazines on lipids are activated and following their transport by post-labeling with dienophile modified fluorophores.

Light activated release of the chemotherapeutic doxorubicin was carried out by combining photoactivation of tetrazine formation with “click to release” strategies. The photocaged tetrazine precursor and light alone showed negligible toxicity, demonstrating the biocompatibility of the technique. Such optically controlled drug release may have practical application in image guided surgery and photodynamic therapy.

This invention might be extended to other amine caging functionalities capable of masking dihydrotetrazines, allowing rapid biorthogonal ligation in response to additional stimuli such as enzymatic activity, pH, or the presence of metal complexes.

INTELLECTUAL PROPERTY INFO

UC San Diego is offering to license patent rights for companies pursuing commercial products or services of this technology.

RELATED MATERIALS

► Luping Liu, Dongyang Zhang, Mai Johnson, Neal K. Devaraj. Light-activated tetrazines enable live-cell spatiotemporal control of bioorthogonal reactions. bioRxiv 2020.12.01.405423 - 12/02/2020

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