MOLECULAR ENGINEERING

Time-resolved protein activation

Blocking the active sites of proteins with a photocaged tyrosine allows for temporally precise photoactivation of a wide range of proteins of interest.

Current methods of genetic and pharmacological manipulation of protein activity are not sufficiently specific for a protein of interest and do not allow for precise temporal control of the manipulation without perturbation of normal protein function. Furthermore, these methods need to be adapted for each protein of interest, which limits their broader applicability.

Chu Wang, Peng Chen, and colleagues from Peking University, in China, have now developed a generalizable approach for protein activation without genetic fusion in living systems. Building on previous work on genetically incorporated 'caged' amino acids, they blocked protein activity by introducing a photocaged tyrosine, coupled with a group that can be cleaved by light, close to the functional site of a protein. The overall structure of the modified protein is not altered by the insertion of the caged tyrosine, so apart from the selective block of enzyme activity, its biological activity closely resembles that of the wild-type protein. To reactivate the protein, photo-decaging is used to remove the tyrosine block from the functional site.

The researchers developed a computational algorithm to determine the optimal site in which to insert the modified tyrosine. A calculation involving geometry and energy-based parameters identified fewer than ten potential sites for the proteins studied in the paper that needed to be tested experimentally.

Wang, Chen, and colleagues demonstrated their approach, 'computationally aided and genetically encoded proximal decaging' (CAGE-prox), on a range of proteins and enzymes, such as KRAS and even proteins with complicated or undefined active sites.

Other applications of CAGE-prox shown in the paper are the temporally precise photoactivation of caspase-3 to identify its proteolytic substrates within 30 minutes after its decaging, and targeted activation of the anthrax toxin component lethal factor in cancer cells to inhibit the proliferation of MAPK-dependent cells.

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Research papers
Wang, J. et al. Time-resolved protein activation by proximal decaging in living systems. *Nature* **569**, 509–513 (2019).