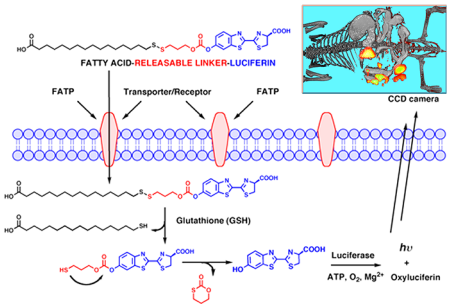
ACS chemical biology

In This Issue

pubs.acs.org/acschemicalbiology

ILLUMINATING FATTY ACID UPTAKE

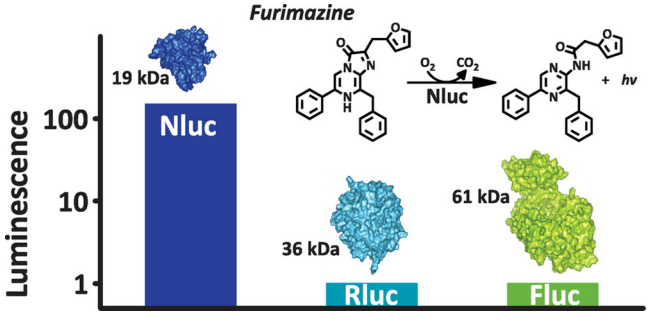
Fatty acids are important sources of energy for most cell types and play key roles in diverse normal and pathological processes. Cellular uptake of these long hydrocarbon chains topped with carboxylic acids is affected and altered by numerous factors in the biological milieu, but monitoring fatty acid location has proved technologically challenging. Now, Henkin *et al.* (DOI: 10.1021/cb300194b) use bioluminescence imaging to enable real-time, quantitative visualization of fatty acid uptake in cells and animal models.



Key to their strategy was the synthesis of a bioactivatable fatty acid derivative conjugated *via* disulfide bond to the bioluminescent compound luciferin, which emits light upon oxidation by the enzyme luciferase. The conjugate is stable outside cells, but upon disulfide cleavage in the reducing environment of the cytoplasm, luciferin is released. This innovative probe enabled visualization of fatty acid uptake in two cell types, adipocytes and fibroblasts, and also in several organs in mice genetically engineered to express luciferase.

A BRIGHT FUTURE FOR ENGINEERED SHRIMP LUCIFERASE

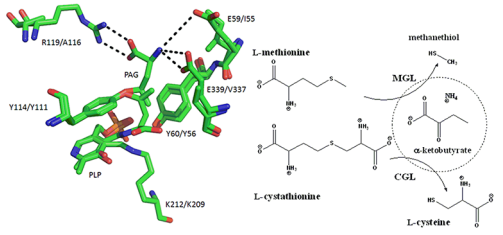
A variety of microbes, insects, and marine organisms produce light for a variety of purposes including to attract prey, to repel predators, as a means of communication, or as a light source. They use enzymes called luciferases to oxidase a small molecule substrate called luciferin to generate such bioluminescence, and these enzyme–substrate pairs have become invaluable molecular tools for exploring biological processes. Now, Hall *et al.* (DOI: 10.1021/cb3002478) report the engineering of an engineered luciferase-luciferin-derived system with superior light emitting and physicochemical properties.



As a starting point, the researchers looked to the luciferase from the deep sea shrimp *Oplophorus gracilirostris*, which emits bright clouds of blue light to defend itself from predators. They manipulated the structure of the small subunit of this heteromeric enzyme to increase its stability and simultaneously tweaked the structure of its substrate to create a molecule called furimazine. This novel enzyme–substrate pair generates much brighter luminescence than the traditional pair and is highly stable in culture medium and cells, suggesting it as an improved bioluminescence system for biological discovery and analysis.

ENGINEERED AMINO ACID DEGRADATION

Cancer cells are more dependent on the amino acid L-methionine than are normal cells, a property that has fuelled investigation of L-methionine depletion as an anticancer strategy. Treatment of animal models with the bacterial enzyme methionine-γ-lyase, which degrades L-methionine, has demonstrated promising activity in reducing tumor growth, but the enzyme is not very stable and is highly immunogenic in primate disease models. Now, Stone *et al.* (DOI: 10.1021/cb300335j) report the manipulation of a human cystathionine-γ-lyase to generate an enzyme capable of degrading L-methionine.



Using scanning saturation mutagenesis and rational design, the investigators identified just 3 amino acid substitutions that transformed cystathionine-γ-lyase to an enzyme that could degrade L-methionine. The mutant enzyme exhibited increased stability over the bacterial methionine-γ-lyase and demonstrated toxicity against numerous cancer cell lines. Moreover, administration of the enzyme to mice resulted in decreased levels of L-methionine in the serum and reduced tumor growth in mice with neuroblastoma xenografts. Notably, because the enzyme is derived from a human enzyme, chances are good that it will not be immunogenic.

Published: November 16, 2012