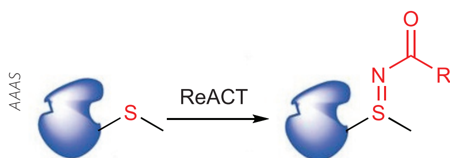
BIOCONJUGATION

Methionine's time to shine

Science **355**, 597–602 (2017)



Methionine is one of the rarest amino acids in proteins, making it a potentially attractive handle for highly selective protein modification. However, because of a lack of robust bioorthogonal reactions for targeting methionine, it has historically been overlooked in favor of the other sulfur-containing residue, cysteine, which is more nucleophilic. Lin *et al.* have now developed a modification strategy that utilizes methionine's redox activity for conjugation under physiological conditions. This method, redox-activated chemical tagging (ReACT), relies on an oxaziridine reagent that converts the methionine side chain to a sulfimide conjugation product while reducing the reagent to an aldehyde. This reaction is selective for methionine over other nucleophilic amino acids and does not denature proteins, and the product is stable when exposed to reducing reagents or elevated temperatures for up to one hour. To demonstrate its utility, the authors applied the ReACT method to label proteins with alkyne- or azide-containing tags for further click chemistry and to synthesize antibody–drug conjugates. Furthermore, as methionine sulfoxide is insensitive to ReACT, the probe was applied to selectively label reactive methionines for activity-based protein profiling, leading to the identification of hyperreactive residues in enolase that have redox-active functions *in vivo*. With methionine now a viable choice for chemoselective bioorthogonal tagging, the options for bioconjugation are wider than ever. *CD*

DEVELOPMENT

Marking the transition

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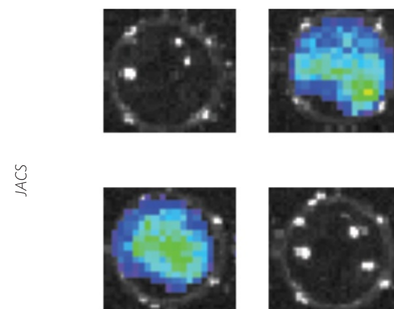
N^6-Methyladenosine (m^6A) is an mRNA post-translational modification that is recognized by the RNA-binding protein YTHDF2, which regulates mRNA stability. In order to understand the dynamics of m^6A modification during embryonic development, Zhao *et al.* performed m^6A sequencing of zebrafish maternal transcripts and found that 36% were m^6A modified. Given that these maternal transcripts decreased in abundance during the maternal–zygotic transition (MZT), with a corresponding increase in zygotic transcription, the authors hypothesized that YTHDF2 might be involved in maternal mRNA clearance. Injection of GFP-labeled mRNA with and without the m^6A modification into maternal *ythdf2* zebrafish mutants revealed that m^6A-modified RNA exhibited a slower rate of degradation during the MZT in these mutants relative to wild-type embryos. Consistent with this result, maternal *ythdf2* zebrafish mutants exhibited an upregulation of maternal transcripts involved in cell cycle and reproduction and lowered levels of zygotic transcripts along with developmental delay and cell cycle progression defects, indicative of a defective MZT. Overall, these findings indicate that the m^6A modification has a key role in transcriptome switching during early embryo development. *GM*

IMAGING

Luciferase matchmaker

J. Am. Chem. Soc. **139**, 2351–2358 (2017)



Bioluminescence imaging techniques use luciferase to catalyze the oxidation of a luciferin substrate, producing light. While natural and artificial variants of both enzyme and substrate enable imaging with different wavelengths of light, the poor selectivity of luciferases for their cognate luciferins (over other structurally similar luciferins) hampers their use in multicomponent imaging. To address this shortcoming, Jones *et al.* targeted both sides of the luciferase–luciferin pair to engineer orthogonality. First, the authors designed and synthesized a panel of luciferin analogs with increased steric bulk that weakened their binding to the wild-type luciferase while retaining their intrinsic potential for light emission. The authors then generated libraries of luciferase variants by targeted mutagenesis at residues predicted to be important for substrate binding. Screening this mutant library for enzymes that were active with luciferin analogs also enabled iterative rounds of library diversification, and a secondary screen rated all of the pairwise combinations of enzyme and substrate for orthogonality. From these screens, three luciferases were identified that were capable of orthogonal activation by select luciferin analogs *in vitro* and in cell culture. These new luciferase–luciferin pairs are themselves potentially useful contributions to the bioluminescence toolbox, and this approach to their generation could be applied to future efforts in developing selective imaging probes. *CD*

DRUG DISCOVERY

Uncoupling coupled transport

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The human malaria parasite *Plasmodium falciparum* has developed resistance to most existing drugs, so drugs with new mechanisms of action are urgently needed. One parasite pathway that is underexplored as a potential therapeutic target is that involved in the generation of ATP. The parasite takes up glucose and converts it via glycolysis to lactate, generating ATP in the process. The lactate end product is exported from the parasite via a proton-coupled (pH-dependent) transporter. Hapuarachchi *et al.* screened a curated collection of antiplasmodial compounds for their effect on parasite pH and identified 15 compounds that acidified the parasite. Monitoring the acidification under conditions in which glycolysis was either active or turned off revealed that 2 of the 15 hits exerted their effect on pH through the inhibition of proton-coupled lactate efflux. Parasites selected for resistance to one of these two compounds that were also resistant to the otheR had a mutation in the lactate–H^+ transporter *Pf*FNT. The compounds inhibited lactate transport both in isolated parasites and in *Xenopus* oocytes expressing the *Pf*FNT transporter. The resistance-associated mutation in *Pf*FNT reduced inhibition of transport in both systems. This study highlights the potential of the lactate transporter *Pf*FNT as an antimalarial drug target. *MB*

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