METABOLISM

First aid for flavin

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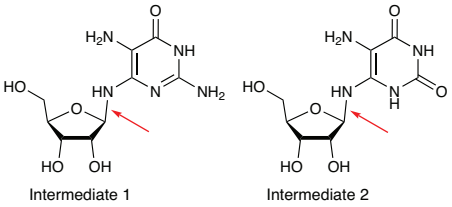

Cellular metabolism is typically described in terms of specific pathways that work together to provide the cell with energy and biomolecular precursors. However, increasing evidence suggests that the metabolic map contains a variety of detours and dead ends, with associated clean-up crews to resolve the problems. For example, directed overflow systems divert chemicals produced in excess, whereas metabolite damage preemption or repair systems prevent or correct chemical and enzymatic damage involving reactive small molecules. Frelin *et al.* suspected that the undefined COG3236 domains fused to or associated with enzymes involved in riboflavin biosynthesis might serve in one of these protective functions, as this pathway has no known post-transcriptional regulatory mechanisms and the pathway intermediates are highly reactive. To test this hypothesis, the authors monitored the fate of riboflavin intermediates in the presence of one of several COG3236 homologs, observing that the first two intermediates (shown) but not the third were converted into new compounds in the presence of the COG3236 domains. Computational analysis, genomic relationships and chemical characterization confirmed that the COG3236s cleave the N-glycosidic bond (red arrows), yielding products distinct from those generated by spontaneous decomposition and confirming that the COG3236 enzymes serve an active role in directing compound degradation to innocuous byproducts. Enzyme specificity agreed with the anticipated need for the COG3236 domain: the *Vibrio vulnificus* COG3236 fused to an earlier enzyme in the pathway was more active on intermediate 1, whereas a plant COG3236 fused to a later enzyme preferred intermediate 2. Finally, analysis of literature data along with a two-hybrid experiment suggested that the enzymes in this pathway form a metabolon, or multienzyme complex, explaining how these COG3236 domains would have privileged access to the reactive intermediates to prevent cellular damage as well as why the overexpression of COG3236s did not influence flavin levels in *Arabidopsis* or *Escherichia coli*. *CG*

RNA METABOLISM

With or without U

Cell **159**, 1365–1376 (2014)

Terminal uridylyl transferases (TUTs) catalyze the template-independent addition of uridine to the 3′ ends of many types of RNAs, but the physiological function of mRNA uridylation is not entirely clear. By employing a recently developed method called TAIL-seq, Lim *et al.* have now shown that two human TUTs—TUT4 and TUT7—catalyze mRNA uridylation globally. Follow-up experiments indicated that TUT4 and TUT7 preferentially act on mRNAs with short poly(A) tails (5–25 nucleotides) *in vitro* and in cells. The authors then determined that poly(A) binding protein C1 (PABPC1) binds to longer poly(A) tails (>25 nucleotides), preventing TUT4 and TUT7 from uridylating the 3′ ends of those mRNAs. Additional experiments revealed that the half-lives of most mRNAs were increased by an average of ~30% when TUT4 and TUT7 were both depleted in HeLa cells, indicating that uridylation is a general mechanism by which the stabilities of mRNAs are altered. The authors also showed that knockdown of several 5′–3′ and 3′–5′ mRNA decay factors, including the 5′ revealed that the half-lives of m-DCP2 decapping complex, and a core subunit of human exosome, led to the accumulation of uridylated mRNAs with short poly(A) tails. On the basis of these results, the authors proposed a new model for uridylation-dependent mRNA decay: when mRNA decay is initiated by deadenylation, PABPs disassociate from that mRNA, enabling TUT4 and TUT7 to carry out the uridylation reaction; the nascent oligo(U) tails are detected by 5′–3′ and/or 3′–5′ mRNA decay factors, which then degrade the mRNA. Further experiments are needed to determine whether uridylation-dependent mRNA decay provides a fundamental role in the eukaryotic mRNA decay pathway. *JMF*

ALZHEIMER'S DISEASE

Bound with Aβ

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The assembly of amyloid-β peptides (Aβ) into oligomers and fibrils is a hallmark of Alzheimer's disease (AD) pathology. It is thought that the toxic species, which include oligomers and protofibrils, are soluble aggregates rather than the end product of aggregation, which are fibrils found in extracellular plaques in diseased brain. The toxicity of these intermediates is most likely due to their interactions with other biomolecules, including proteins and cell membranes. Indeed, several essential proteins have been shown to coaggregate with Aβ, leading to cytotoxicity due to loss of function. Other Aβ-binding proteins could cause toxicity by initiating aberrant signaling processes or by targeting the various Aβ species (and any coassociated proteins) for internalization, thereby mislocalizing them. Binding events may also reflect protective mechanisms to limit Aβ toxicity. To characterize Aβ protofibril interactions at a global level, Rahman *et al.* performed pulldown experiments with an Aβ variant that forms stable protofibrils that are indistinguishable in structure and function from those generated from wild-type Aβ. They identified proteins that bind the protofibrils in serum and in cerebrospinal fluid, where Aβ levels are known to reflect brain amyloid load. The authors identified 101 proteins, including known Aβ-binding proteins and proteins involved in the complement system, inflammation and hemostasis as well as lipid transport and metabolism. Among the known binders, apolipoproteins apolipoprotein E (ApoE) and clusterin as well as immunoglobulins were identified. ApoE, the Aβ binder that they found at the greatest abundance and that binds at high affinity (K_D = 3 nM, as measured by surface plasmon resonance), is a major genetic risk factor associated with AD that has been shown to modulate Aβ aggregation and promote its clearance from the brain. Further study will be required to dissect the rich collection of interactions revealed here to define potential new mechanisms for modulating Aβ structure and function. *MB*