METALS

Zinc stores

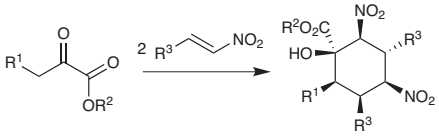
Cell Metab. **15**, 88–99 (2012)

Myriad cellular processes depend on zinc, and organisms require homeostatic mechanisms to regulate this metal. Although zinc storage organelles have been identified in eukaryotic cells, how cellular storage contributes to homeostasis at the organismal level remains unclear. To investigate this question, Roh *et al.* used the zinc-specific fluorescent dye FluoZin-3 and lysosome-specific markers in *Caenorhabditis elegans* to show that zinc was concentrated in gut granules in intestinal cells and that the level of labile zinc in these granules responded to the concentration of dietary zinc. Mutation of *glo* genes important for lysosome biogenesis or of the gene encoding the cation diffusion facilitator protein cdf-2, which concentrates zinc in organelles, reduced zinc content in both the gut granules and the entire worm. The relative growth of wild-type worms or *glo*- or *cdf-2*-mutant worms in response to dietary zinc supplementation, but not that of other metals, suggested that the gut granules may have a role during zinc toxicity. Zinc deficiency similarly coincided with a loss of FluoZin-3 signal from gut granules. Under zinc-deficient conditions, worms pre-fed zinc showed a growth advantage over those that were not presupplemented, and mutation of *cdf-2* abrogated this advantage. Together, these data suggest that worms depend on *cdf-2* to store excess labile zinc in lysosome-related organelles in intestinal cells and that these stores can be mobilized during dietary deficiency. *AD*

DOMINO REACTIONS

Chiral cycloaddition

Angew. Chem. Int. Ed. **51**, 1248–1251 (2012)

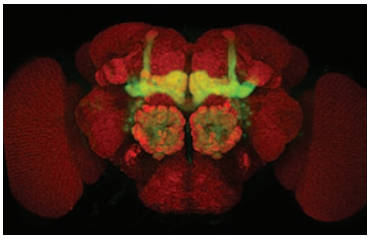


Domino reactions offer facile access to complex molecular architectures, often with exquisite stereochemical control. Shi *et al.* provide an elegant example of this approach in a new [2+2+2] cycloaddition reaction combining Michael and Henry reactions to access a cyclohexane product with stereochemically defined substituents at each ring carbon. In particular, the authors used an α-ketoester as a latent reactive enolate with two nitroalkene electrophiles to extend and finally join the carbon chain. The first step of the reaction—formation of a metal enolate—was critical to direct the stereochemistry of the entire sequence. As a result, the authors synthesized a series of rigid chiral ligands intended to similarly induce chirality in the metal complex, identifying a single Cu–diamine complex as providing excellent yields and enantioselectivity. With their catalyst in hand, the authors demonstrated the versatility of the reaction by varying both ketoester and nitroalkene starting materials: divergent ketoesters were well tolerated, as were a range of aromatic nitroalkenes, though aliphatic nitroalkenes were not applicable and a single nitroalkene modified with an *ortho*-substituted benzaldehyde proved problematic. The reaction proceeds at room temperature and gram scale using only 0.1 mol% catalyst, and so it should provide straightforward entry into a variety of complex synthetic routes. *CG*

RNA EDITING

Following ADAR

Nat. Methods, published online 25 December 2011, doi:10.1038/nmeth.1827



JAMES JEPSON

Adenosine deaminase that acts on RNA (ADAR) regulates neuronal functions by catalyzing the conversion of adenosine to inosine in target codons of double-stranded RNAs. Now, Jepson *et al.* develop a method to monitor *Drosophila* ADAR (dADAR) activity *in vivo* at the level of single neurons. The authors generated a GFP reporter (GFP^{edit}), which consists of the GFP coding sequence fused to a previously identified ADAR target sequence. They detected GFP fluorescence—and therefore dADAR activity—in distinct regions of the mushroom body and the antennal lobes of the *Drosophila* nervous system, depending on developmental stage. Next, the authors identified the regions in which dADAR activity was physiologically repressed by taking advantage of an autoediting mechanism by which dADAR inhibits its own activity. They introduced mutations at the endogenous dADAR locus to express a noneditable and constitutively active variant and compared the regions of activity in these flies to those in the wild type. They detected an increase of GFP^{edit} fluorescence only in specific cell types of the mushroom bodies of adult flies, indicating a well-defined spatial regulation of dADAR activity. Using the same reporter system, the authors observed variations in dADAR activity between individuals of the same population, potentially accounting for differences in behavior. This approach may be used to follow alterations in RNA editing *in vivo* and relate them to neuronal functions and neurological diseases. *AC*

POST-TRANSLATIONAL MODIFICATIONS

Sulfhydration switch

Mol. Cell **45**, 13–24 (2012)

Nuclear factor κB (NF-κB) is a transcription factor that acts downstream of tumor necrosis factor-α (TNF-α) and regulates antiapoptotic gene expression. Sen *et al.* now show that TNF-α signaling induces sulfhydration (R-SSH) of NF-κB and that this modification is critical for transcriptional activation. Hypothesizing that NF-κB activity may be linked to H_2S—a second messenger produced by cystathionine γ-lyase (CSE)—the authors showed that TNF-α treatment led to enhanced CSE and H_2S levels in cells and that DNA binding by NF-κB was dependent on CSE activity. Cysteine tagging and MS revealed that Cys38 within the DNA-binding p65 subunit of NF-κB underwent sulfhydration by H_2S. Cys38 had previously been identified as a site for S-nitrosylation that inhibits NF-κB activity, so the authors used a two-color tagging approach to show that Cys38 sulfhydration peaks shortly after TNF-α activation and that the amount of *S*-nitrosylcysteine is maximal at later times. The transcriptional activation profile of TNF-α–treated cells showed a similar time course, and additional biochemical analysis revealed that p65 sulfhydration enhances NF-κB binding to ribosomal protein S3 (RPS3), a known transcriptional coactivator. These results outline a time-dependent transcriptional regulatory mechanism by NF-κB that involves TNF-α induction of H_2S biosynthesis, selective p65 sulfhydration and transcriptional activation in collaboration with RPS3, which is followed by nitrosylation-dependent deactivation of gene expression. *TLS*

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