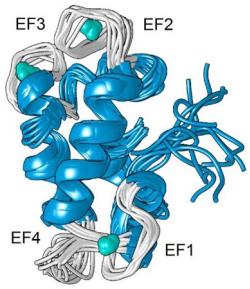
METALS

Lanthanide lover

J. Am. Chem. Soc. **140**, 15056–15061 (2018)
Biochemistry https://doi.org/10.1021/acs.biochem.8b01019 (2018)



Credit: *ACS*

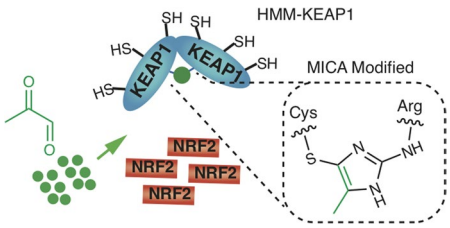
Certain methylotrophic bacteria use lanthanides as cofactors in methanol dehydrogenase and other metalloenzymes. While studying how these enzymes selectively incorporate lanthanides, Cotruvo et al. identified a new type of lanthanide-binding protein, lanmodulin (LanM), in *Methylobacterium extorquens*. LanM contains four carboxylate-rich EF hand motifs similar to those found in the eukaryotic calcium-binding protein calmodulin, but with additional aspartate and proline residues. An NMR solution structure of LanM bound to yttrium, determined by Cook et al., also revealed that adjacent EF hands are unusually fused. In vitro, metal-free LanM is relatively disordered, but lanthanide binding induces a conformational change to a more ordered state. By contrast, LanM's response to calcium is much weaker, indicating ~10^8-fold selectivity. Mutation of the proline residues in the EF hands made LanM more sensitive to calcium, indicating the importance of these residues in selecting for lanthanides over a more abundant metal. Although the role of this protein in bacteria has yet to be determined, the characterization of LanM and its homologs may help to understand how methylotrophic bacteria process these uncommon metals. *CD*

https://doi.org/10.1038/s41589-018-0196-z

POST-TRANSLATIONAL MODIFICATIONS

Playing KEAP1-away

Nature **562**, 600–604 (2018)



Credit: *Nature*

NF-E2-related factor 2 (NRF2) is a key regulator of oxidative stress and is normally sequestered in the cytoplasm by the Kelch-like ECH associated protein 1 (KEAP1). Covalent modification of reactive cysteines on KEAP1 by electrophiles alters the NRF2–KEAP1 interaction, resulting in NRF2 accumulation and pathway activation. Although covalent small-molecule inhibitors of KEAP1 have been described, Bollong et al. sought find an alternative means of activating NRF2, identifying the nonelectrophilic small molecule CBR-470-1 from a high-throughput screen. Target identification studies revealed that CBR-470-1 directly inhibits the glycolytic enzyme phosphoglycerate kinase 1 (PGK1), resulting in accumulation of metabolites including methylglyoxal (MGO). Interestingly, CBR-470-1 treatment or PGK1 knockdown resulted in the appearance of a high-molecular-mass form of KEAP1 that was associated with NRF2 activation and dependent on MGO. Finally, direct interaction of KEAP1 with MGO resulted in a new post-translational modification: a methylimidazole cross-link between C151 and R135 of KEAP1. Overall, these findings reveal a unique interplay between glucose metabolism, KEAP1 function and the cellular antioxidant response. *GM*

https://doi.org/10.1038/s41589-018-0197-y

DNA MODIFICATION

N^6-mA condenses chromatin

Cell **175**, 1228–1243 (2018)

Although the N^6-methyladenine (N^6-mA) DNA modification has been shown to exist within human genomic DNA, its biological function remains unclear. To investigate the role of N^6-mA in glioblastoma, Xie et al. first showed that N^6-mA was upregulated in human patient-derived glioblastoma stem cells (GSCs) and primary human tumor specimens. Genomic profiling revealed that N^6-mA is distributed in intergenic regions and overlaps with heterochromatic histone modifications. Deletion of the N^6-mA demethylase ALKBH1 increased N^6-mA levels and decreased chromatin accessibility in GSCs. Sites with increased N^6-mA modifications were found in ALKBH1-regulated genes associated with K3K9me3-containing heterochromatin regions, suggesting that ALKBH1 depletion promotes heterochromatin formation by increasing N^6-mA levels to repress gene expression. Silencing ALKBH1 inhibited proliferation and the self-renewal ability of GSCs, as well as tumor growth in mice xenograft models. This study revealed the relationship between N^6-mA and chromatin status and provided a potential therapeutic target for glioblastoma therapy. *YS*

https://doi.org/10.1038/s41589-018-0199-9

MICROBIOLOGY

The bacteria that move me

Nature **563**, 402–406 (2018)

The intestinal microbiota regulates various biological functions such as communication between the gut and the nervous system, though the mechanistic details are incomplete. Now, Schretter et al. find a role for the microbiota in coordinated locomotion in the fruit fly *Drosophila melanogaster*, first showing that adult female flies lacking commensal bacteria exhibited increased walking speeds and daily activity. Introduction of one of the two dominant resident species, *Lactobacillus brevis*, or a cell-free supernatant of these bacteria restored the temporal patterns of locomotion to that of conventionally raised flies. A combination of biochemical analysis of these supernatants, a screen of a mutant *Escherichia coli* strain library, and rescue and deletion experiments identified xylose isomerase (Xi) as a determinant of the *L. brevis*–mediated locomotor effects. Supplementation of flies with Xi substrates and products identified trehalose as mediating the locomotor effects of Xi, while activation of individual neuronal populations implicated signaling pathways downstream of the neurotransmitter octopamine. These results point to specific microbiota products in regulating *D. melanogaster* octopaminergic pathways to modulate locomotion. *MB*

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