Activation of methylmalonyl-Coenzyme A mutase by MeaB

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In mammalian cells, only two enzymes are known to require vitamin B_{12} (cobalamin, Cbl) derivatives as a cofactor: methionine synthase, a cytosolic enzyme, which uses methylcobalamin, and methylmalonyl-coenzyme A mutase (MCM), a mitochondrial enzyme, which uses 5'-deoxyadenosylcobalamin (AdoCbl) (1). The latter enzyme has a broad distribution among living organisms and is found in both bacteria and in animals (2). In mammals, MCM serves to funnel catabolites of odd-chain fatty acids, cholesterol and branched-chain amino acids to a useful metabolite, succinyl-CoA, which can be utilized in the Krebs cycle. In contrast, in bacteria, the mutase is involved in the reverse metabolic direction, linking the production of propionate to succinate (3).

In mammals, inherited defects that impair the activity of MCM lead to methylmalonic aciduria. Such a disorder can result from mutations in the gene encoding MCM or from mutations that impair AdoCbl metabolism. A newly described gene, MMAA (for ***m***ethyl***m***alonic ***a***cidemia linked to the cbl***A*** complementation group), involved in the conversion of methylmalonyl-CoA to succinyl-CoA has been identified in humans and a role for it in the transport of vitamin B_{12} into mitochondrion has been speculated (4). A homolog of MMAA, meaB, has been recently characterized in *Methylobacterium extorquens* AM1 (5). A role for MeaB in the MCM dimer stabilization and AdoCbl cofactor protection has been proposed (6). However, the exact function and the mechanism by which MeaB interacts with MCM remain unclear.

In order to address the role of MeaB, we undertook the biochemical characterization of the MCM/MeaB interaction. In contrast to what has been proposed (6), our results suggest that MeaB is not involved in protection against inactivation of MCM during turnover but acts as an activator of MCM activity by apparently decreasing the rate-limiting step of the MCM-catalyzed reaction, *i.e.*, the product release.

References:

1. Chemistry and Biochemistry of B12 (R. Banerjee, Ed.) Wiley & Sons, New York, 1999.
2. Banerjee, R., and Ragsdale, S.W. (2003) *Annu. Rev. Biochem.* **72**, 209-247.
3. Retey, J. in B12 (B. Dolphin, Ed.) pp 357-380, Wiley & Sons, New York, 1982.
4. Dobson, C.M., Wai, T., Leclerc, D., Wilson, A., Wu, X., Doré, C., Hudson, T., Rosenblatt, D.S., and Gravel, R.A. (2002) *Proc. Natl. Acad. Sci. USA* **99**, 15554-15559.
5. Korotkova, N., Chistoserdova, L., Kuksa, V., and Lidstrom, M.E. (2002) *J. Bacteriol.* **184**, 1750-1758.
6. Korotkova, N., and Lidstrom, M.E. (2004) *J. Biol. Chem.* **279**, 13652-13658.