Radical Enzymes and their Escorts

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Methylmalonyl-CoA mutase is the only coenzyme B_{12} enzyme that is found in humans and resides in the mitochondrion. It catalyzes the interconversion of methylmalonyl-CoA to succinyl-CoA using radical intermediates. Mutations in this enzyme result in methylmalonic aciduria. Howerver, in addition to methylmalonyl-CoA mutase there are at least two other loci, which when impaired also lead to methylmalonic aciduria. These encode adenosyltransferase and a GTPase of unknown function. Our studies on adenosyltransferase indicate that it binds its cofactor in a novel 4-coordinate form in the cob(II)alamin oxidation state and suggest that it may be involved in the direct delivery of the product, coenzyme B_{12} to the target enzyme, to methylmalonyl-CoA mutase. The role of the GTPase is not known. Our studies with a bacterial ortholog, MeaB reveal that it increases the kcat of the mutase reaction and appears to do so by hastening the rate-limiting step, product release. The roles of these proteins in mitochondrial B_{12} trafficking will be discussed.