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Biochem J. 2007 Feb 22; : 17313371 (P,S,E,B)

Phosphoethanolamine N-methyltransferase (PMT-1) catalyzes the first reaction of a new pathway for phosphocholine biosynthesis in Caenorhabditis elegans.

Katherine Brendza, William Haakenson, Rebecca Cahoon, Leslie Hicks, Lavanya Palavalli, Brandi Chiapelli, Merry McLaird, James McCarter, D Williams, Michelle Hresko, Joseph Jez

The development of nematicides targeting parasitic nematodes of animals and plants requires the identification of biochemical targets not found in host organisms. Recent studies suggest that Caenorhabditis elegans synthesizes phosphocholine through the action of phosphoethanolamine methyltransferases (PEAMT) that convert phosphoethanolamine to phosphocholine. Here we examine the function of a PEAMT from C. elegans (gene: pmt-1; protein: PMT-1). Our analysis shows that PMT-1 only catalyzes the conversion of phosphoethanolamine to phospho-monomethylethanolamine, which is the first step in the PEAMT-pathway. This is in contrast to the multifunctional PEAMT from plants and Plasmodium that perform multiple methylations in the pathway using a single enzyme. Initial velocity and product inhibition studies indicate that PMT-1 uses a random sequential kinetic mechanism and is feedback inhibited by phosphocholine. To examine the effect of abrogating PMT-1 activity in C. elegans, RNA-mediated interference (RNAi) experiments demonstrate that pmt-1 is required for worm growth and development and validate PMT-1 as a potential target for inhibition. Moreover, providing pathway metabolites downstream of PMT-1 reverses the RNAi phenotype of pmt-1. Because PMT-1, is not found in mammals, is only distantly related to the plant PEAMT, and is conserved in multiple parasitic nematodes of humans, animals, and crop plants, inhibitors targeting it may prove valuable in human and veterinary medicine and agriculture.

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Donald Danforth Plant Science Center, St. Louis, Missouri 63132, Departments of Medicine and Cell Biology & Physiology, Washington University School of Medicine, St. Louis, Missouri 63110, and Department of Biology, University of Missouri, St. Louis, Missouri 63121.

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