



Metabolic Insights from murine knockouts in hepatic phospholipid biosynthesis

We have developed mouse models in which either the gene that encodes phosphatidylethanolamine *N*-methyltransferase (PEMT) or hepatic CTP:phosphocholine cytidyltransferase (CT) has been disrupted.

The *Pemt*^{-/-} mice appear normal and breed normally. However, when challenged with a choline-deficient diet, the *Pemt*^{-/-} mice experience liver failure in 3 days. When challenged with a high fat/high cholesterol diet, there was a ~ 40% decrease in the levels of plasma cholesterol and phosphatidylcholine in the *Pemt*^{-/-} mice. The mice displayed a sexual dimorphism since males showed a large decrease in plasma triacylglycerol and apolipoprotein B whereas females did

not. The decrease appears to be due to a defect in secretion of very low density lipoproteins from hepatocytes. Also of medical interest, the levels of plasma homocysteine, an independent risk factor for cardiovascular disease, were decreased in *Pemt*^{-/-} mice due to a 50% decrease in secretion from hepatocytes. Homocysteine is derived from the other product of the PEMT pathway, S-adenosylhomocysteine.

Using the cre/lox technique we have constructed mice that lack CTa only in the liver. These mice survive and appear to be normal. The amount of CT activity is decreased by 85%; the residual CT activity is due to expression of CTβ. The expression of PEMT is increased by 2-fold in the livers of CTa knockout mice. The levels of plasma cholesterol, phosphatidylcholine and apolipoprotein A1 were decreased by 50% in these mice. In contrast to the *Pemt*^{-/-} mice, the male hepatic CTa^{-/-} mice had only a small decrease in plasma triacylglycerol whereas the decrease in female mice was 50%. In line with the increase in PEMT activity in the hepatic CTa^{-/-} mice, there was an increase in the level of plasma homocysteine compared to wildtype mice.

In conclusion, inhibition of PC biosynthesis by either pathway results in decreased levels of PC and cholesterol (HDL). Elimination of the PEMT pathway can limit TG and apo B100 secretion from livers of male mice whereas elimination of CTa particularly limits TG secretion from female mice. PEMT has a major role in the regulation of plasma homocysteine



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Date: 19 Mar 2004, Fri

Time: 4 pm

Venue: LT 20

Host: Prof Hew C L

All are welcome

Structural Biology & Functional Genomics Lecture Series

Seminar Announcement

(Department of Biological Sciences & Office of Life Sciences, NUS)