MECHANISMS UNDERLYING FATTY LIVER DISEASE IN EARLY POSTNATAL MALNUTRITION

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Background: Malnutrition causes acute liver damage and hepatic dysfunction. Children with severe acute malnutrition and adolescents with anorexia nervosa develop steatosis. Additionally, small-for-gestational-age newborns are at increased risk of non-alcoholic fatty liver disease (NAFLD) in early childhood. Mechanisms by which malnutrition causes fatty liver disease, and general mechanisms underlying NAFLD pathogenesis, are poorly understood. Phospholipids play major roles in the structure and function of lipid membranes, helping package lipids and VLDL cholesterol into droplets for export. More than half of the liver’s total phospholipid content occurs as phosphatidylcholine (PC) and phosphatidylethanolamine (PE). PC and PE levels are tightly regulated through three complex enzymatic pathways: biosynthesis of PC or PE, degradation of choline (the substrate for PC synthesis), and conversion of PE into PC. In healthy liver tissue, the molar ratio of PC/PE is maintained strictly between 1.5 and 2.0. Molar ratios outside of this range are found in NAFLD. The aim of this study is to characterize abnormal lipid accumulation and phospholipid regulatory pathways in our mouse model of early-life malnutrition.

Materials/Methods: C57BL/6 mice were weaned to a low-protein low-fat chow or isocaloric control chow; at 8 weeks of age liver was harvested. Steatosis was visualized with oil red O staining and expression levels of enzymes participating in the three pathways that regulate PC and PE levels were assessed by western blot.

Results: Livers from malnourished mice demonstrated profound macrovesicular steatosis (Figure). Malnourished livers contained reduced quantities of one or more proteins in each of the three enzymatic pathways. These included the PC-synthesizing enzyme CTP:phosphocholine cytidyltransferase (28% decrease, p=0.009); the choline-degrading enzymes ALDH7A1 (45% decrease, p=0.007), BHMT (48% decrease, p=0.004), and GNMT (39% decrease, p=0.04); and the PE-to-PC converting enzyme PE-methyltransferase (67% decrease, p=0.007).

Conclusions: Macrovesicular steatosis forms by 8 weeks of life in mice undergoing early postnatal malnutrition. There is decreased expression of multiple enzymes that regulate PC and PE concentrations in malnourished livers, suggesting that the PC/PE ratio may be abnormal. Restoration of PC and PE homeostasis should be explored as a potential therapeutic avenue to ameliorate malnutrition-induced fatty liver disease.

Images / Graph / Table