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Soluble isocitrate dehydrogenase plays a key role in obesity and hyperlipidemia

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NADPH is an essential co-factor for fat and cholesterol biosynthesis. However, the role of cytosolic $NADP^+$-dependent isocitrate dehydrogenase (IDPc), a putative NADPH producer, in the control of the fat and cholesterol metabolism has not been assessed. Here we report that increased or decreased IDPc expression in 3T3-L1 fat cells promoted or retarded adipogenesis, respectively. Furthermore, overexpression of IDPc in transgenic mice exhibited fatty liver, hypertriglyceridemia, hypercholesterolemia and obesity by increasing NADPH production leading to subsequent stimulation of acetyl-coenzyme A and malonyl-coenzyme A consumption. In contrast, administrations of a synthetic IDPc inhibitor, DA11004, to *ob/ob* mice effectively reduced body weight with lowering cholesterol and triglyceride levels. In addition, a positive relationship ($r = 0.69$, $P<0.01$) between plasma IDPc activity and body mass indexes was observed in 98 randomly-selected human volunteers. Our findings strongly indicate that NADPH produced by IDPc plays an important role in controlling body fat and lipid biosynthesis.

NADPH is an essential co-factor for numerous enzymes in fatty acid and cholesterol biosynthesis. For instance, 3-L-hydroxylacyl-coenzyme A dehydrogenase and enoyl-coenzyme A reductase in fatty acid synthesis and hydroxymethylglutaryl-coenzyme A reductase, a rate-limiting enzyme in cholesterol biosynthesis, require NADPH. The latter enzyme is a critical target of the well-established cholesterol-lowering "statin" drugs.

It has been demonstrated that glucose 6-phosphate dehydrogenase (G6PDH), 6-phosphogluconate dehydrogenase and malic enzyme are significant cytosolic NADPH producers responsive to diet. However, activities of these enzymes were markedly lower than that of cytosolic $NADP^+$-dependent ICDH (IDPc) in the rat liver , thus suggesting a possibility that NADPH-producing IDPc may play crucial role in controlling the metabolisms of body fat and lipid synthesis. In mammals, three classes of isocitrate dehydrogenase (ICDH) isoenzymes exist: mitochondrial NAD^+-dependent ICDH (IDH) (EC 1.1.1.41), mitochondrial $NADP^+$-dependent ICDH (EC 1.1.1.42) (IDPm) and IDPc. Among these three isoenzymes, IDH has been thought to play a major role in the oxidative decarboxylation of isocitrate in the tricarboxylic acid cycle. However, exact functions of IDPc and IDPm, which produce α-ketoglutarate, CO_2 and NADPH from isocitrate in the cytosol and mitochondria, respectively, have not been well established. Recently, we have demonstrated that IDPm and IDPc play important roles in cellular defense against oxidative damage by providing NADPH required for the regeneration of reduced glutathione in the mitochondria and the cytosol, respectively. IDPc was also demonstrated to be a major NADPH supplier in the ovary. Taken together, these reports suggested the possibility that IDPc is a major producer of cytoplasmic NADPH required for fat and cholesterol biosynthesis.

Here we show that increased expression of IDPc promoted adipogenesis of 3T3-L1 fat cells, whereas decreased IDPc expression retarded adipogenesis. In addition, transgenic mice overexpressing IDPc display hyperlipidemia, fatty liver and obesity by the increased NADPH production leading to the activation of fatty acid and cholesterol synthesis. Consistent with these results, the plasma IDPc activity positively correlated with body mass index and plasma cholesterol content in 98 randomly selected human subjects. The administration of DA11004, a chemical inhibitor of IDPc, to *ob/ob* mice successfully reduces body weight, cholesterol and triglyceride levels. We conclude that IDPc is a major NADPH producer required for fat and cholesterol biosynthesis, and that IDPc may be a novel and promising therapeutic target for abnormal lipid synthesis and obesity.