Acat-2, A Second Mammalian Acyl Coa:Cholesterol Acyltransferase That Is Involved In Cholesterol Metabolism

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Technology description

Investigators at UCSF and their collaborators have identified a second Acyl-COA: cholesterol acyl transferase, named ACAT-2. The cDNA sequence of mouse acat-2 is described and the deduced polypeptide sequence of ACAT-2 is 44% identical to the original ACAT enzyme, now renamed ACAT-1. The mouse acat-2 gene maps to chromosome 15 and encodes a 46kDa protein that is associated with cell membranes and demonstrates high levels of cholesterol esterification activity. Mouse ACAT-2 is primarily expressed in the mouse liver and small intestine, supporting a model in which ACAT-2 participates in the esterification of cholesterol in these tissues.

Acyl-COA: cholesterol acyl transferases or ACAT is an enzyme that catalyzes the esterification of cholesterol to form cholesteryl ester. Minimally, ACAT-mediated formation of cholesteryl ester from cholesterol prevents the toxic accumulation of excess cholesterol in a cell and maintains a free diffusion gradient across the cell membrane, particularly in the small intestine. In addition, the assembly and secretion of Apolipoprotein-B containing lipoproteins in the liver and intestines is thought to be dependent on the ACAT-mediated formation of cholesteryl esters from cholesterol. In steroidogenic tissue such as the adrenal glands, ACAT activity produces cytosolic droplets loaded with cholesteryl esters from which they can be mobilized as cholesterol substrates for the generations of steroids. Furthermore, macrophages that accumulate cholesteryl ester in cytosolic lipid droplets as a result of ACAT activity appear foamy and are a characteristic early indicator of atherosclerotic lesions. Animal models that completely lack ACAT protein are viable, albeit with tissue-specific reductions in cholesteryl ester, suggesting that another ACAT enzyme is present in these animals.

Additional Information

Related Materials

Cases S et al. ACAT-2, A Second Mammalian Acyl-CoA: Cholesterol Acyltransferase, Its cloning, expression, and characterization. J Biol Chem. 273, Vol. 41, 26755–64, 1998.

Buhman K et al. Resistance to diet-induced hypercholesterolemia and gallstone formation in ACAT2-deficient mice. Nature Medicine, Vol. 6, No. 12, 1341-47, 2000.

Application area

More recent studies suggest that the targeted depletion of ACAT-2 in the liver and intestines in acat-2 conditional knockout mice ameliorates diet-induced hepatic accumulation of cholesteryl ester and hypercholesterolemia. Moreover, loss-of ACAT-2 activity prevents the formation of cholesterol gallstones in certain strains of mice that are fed a diet high in cholic acid. Therefore, inhibitors of ACAT-2 have potential use in preventing or treating diet-induced hepatic accumulation of cholesteryl ester, hypercholesterolemia, and cholesterol gallstones. In addition, inhibitors of ACAT-2 have the potential to counter the deleterious accumulation of cholesteryl ester in macrophages and hence are candidates for preventing or treating atherosclerotic lesions.

Potential Uses:
Diagnostic screening
Therapeutic agent identification
Treatment of diseases associated with ACAT-2 activity

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