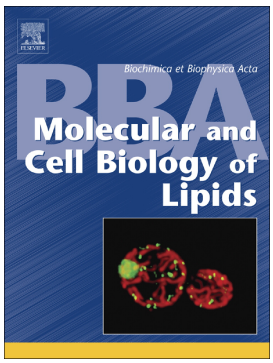

EP4 emerges as a novel regulator of bile acid synthesis and its activation protects against hypercholesterolemia

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EP4 emerges as a novel regulator of bile acid synthesis and its activation protects against hypercholesterolemia

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Abstract

Prostaglandin E receptor subtype 4 (EP4) knockout mice develops spontaneous hypercholesterolemia but the detailed mechanisms by which EP4 affects cholesterol homeostasis remains unexplored. We sought to determine the cause of hypercholesterolemia in EP4 knockout mice, focusing on the role of EP4 in regulating the synthesis and elimination of cholesterol. Deficiency of EP4 significantly decreased total bile acid levels in the liver by 26.2% and the fecal bile acid content by 27.6% as compared to wild type littermates, indicating that the absence of EP4 decreased hepatic bile acid synthesis and their subsequent excretion in stools. EP4 deficiency negatively regulate bile acid synthesis through repression of phosphorylated extracellular signal-regulated kinase 1/2 (ERK)-mediated cholesterol 7α-hydroxylase (CYP7A1) expression and that the hypercholesterolemia in EP4 knockout mice is due to a defect in cholesterol conversion into bile acids. Deficiency of EP4 also increased *de novo* cholesterol synthesis and altered cholesterol fluxes in and out of the liver. Treating high fat diet-challenged mice with the pharmacological EP4 agonist, CAY10580 (200μg/kg body weight/day *i.p*) for three weeks effectively prevented diet-induced hypercholesterolemia, enhanced endogenous bile acid synthesis and their fecal excretion. In summary, EP4 plays a critical role in maintaining cholesterol homeostasis by regulating the synthesis and elimination of bile acids. Activation of EP4 serves as an effective novel strategy to promote cholesterol disposal in the forms of bile acids in order to lower plasma cholesterol levels.

Key words: EP4, hypercholesterolemia, bile acids, CYP7A1, cholesterol homeostasis.