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Abstract 4363116: HEPATIC DELIVERY OF MICRORNA-30C ANALOG C2 REDUCES PLASMA CHOLESTEROL IN MICE AND MONKEYS AND ATHEROSCLEROSIS IN MICE WITHOUT CAUSING LIVER INJURY

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Abstract

Background: Despite the availability of many drugs, cardiovascular disease (CVD) remains a major cause of premature mortality worldwide. High plasma cholesterol (chol) levels are risk factors for CVD. Previously, we showed that hepatic expression of microRNA-30c (miR-30c) reduces plasma chol and atherosclerosis (athero) in mice without causing steatosis.

Hypothesis: MiR-30c analog, C2, will reduce hypercholesterolemia and athero in mice and hypercholesterolemia in African Green monkeys.

Methods: Male and female C57BL/6J (n=6/group, 2-month-old) mice were fed a Western diet (WD) for 2 months and injected IV with C2, miR-30c (100-500 mg/kg/week) or PBS. For athero studies, male *Ldlr*$^{-/-}$ mice were fed a WD (n=30, 2-month-old). After 3 months, 10 mice were used for baseline. The remaining mice were switched to a chow diet and received PBS or C2 (500 mg/kg/week, n=10) for 2 months. Male FRG-humanized liver (FRG) mice were fed WD and injected with C2 or miR-30c (500 mg/kg/week) for 1 month. Four (15–20 years old) female monkeys were injected once with 40 and thrice with 80 mg/kg/week of C2 or miR-30c.

Results: Hepatic delivery of C2 reduced plasma chol levels in WD-fed hypercholesterolemic C57BL/6 mice and in diabetic hyperlipidemic monkeys. In FRG mice, C2 prevented development of WD-induced hypercholesterolemia. In WD fed *Ldlr*$^{-/-}$ mice, C2 significantly reduced plasma chol and athero plaque size and composition indicating that the chol-reducing effects of C2 do not rely on LDL receptors. C2 reduced plasma apoB and IDL/LDL chol, hepatic MTP and triglyceride production, and enhanced hepatic fatty acid (FA) oxidation and fecal chol excretion. C2 had no effect on hepatic TG and chol, plasma TG, CK-MB, ALP, ALT, AST, IL-6, TNF- alpha, and INF-gamma indicating absence of cellular lipid

accumulation, inflammatory and immune responses. Hepatic RNA-Seq analysis showed downregulation of FA biosynthesis and upregulation of FA degradation, bile acid (BA) synthesis and BA secretion pathways in the C2 compared to PBS group. C2 increased ileal BA transporters suggesting enhanced enterohepatic circulation. C2 also enhanced jejunal ABCG5/8 with no effect on NPC1L1 and ABCA1 expression indicating transintestinal cholesterol excretion may enhance fecal excretion.

Conclusions: C2 reduces plasma chol without causing liver injury or inflammation in mice and monkeys. C2 could be the first-in-class miR therapeutic drug that reduces plasma chol without causing hepatic steatosis in humans.