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Commentary

LDL Receptor Gene-Ablated Hamsters: A Rodent Model of Familial Hypercholesterolemia with Dominant Inheritance and Diet-Induced Coronary Atherosclerosis

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Familial hypercholesterolemia (FH) is a genetic disorder arising from a mutation in the low density lipoprotein receptor (LDLR) gene, and is characterized by severe elevations in LDL cholesterol (LDLc) levels and circulating triglyceride (TG). FH is among the most prevalent hereditary metabolic disorders in the world, and results in advanced atherosclerotic plaque deposition, coronary artery disease (CAD), and death. Current animal models of FH poorly characterize the rapid, and lethal progression of CAD in these patients. Moreover, as an autosomal dominant disorder, the clinical severity of this disease varies between homozygous and heterozygous individuals; with this genotypic heterogeneity also failing to be faithfully reproduced in previous animal models of FH. The current article by Guo et al. addresses these issues by introducing a breakthrough LDLR knockout (KO) hamster model. This LDLR-KO hamster reproduces the phenotypical divergence seen between hetero- and homozygous individuals, and displays a dyslipidemic and atherosclerotic profile similar to humans.

In the study of lipoprotein metabolism, the Syrian Golden hamster offers several clinical advantages over other rodent models of disease. Like humans, they express cholesterol ester transfer protein (CETP), and exhibit intestine-specific editing of apoB lipoproteins; whereas, the lipoprotein profile of mice differs significantly from human due to non-specific lipoprotein editing and lack of CETP expression. Since the overproduction of apoB-containing lipoproteins is a proponent to the development of atherosclerosis and CAD – the primary mortality-associated risk factor in FH – it is essential that animal models closely mimic a human lipoprotein profile. Comparison of FPLC analysis between WT hamster and humans confirms this similarity, whereas, WT mice exhibit a divergent profile with markedly reduced LDL. Importantly, the phenotypic parallels seen between hamsters and humans are preserved when comparing hetero- and homozygous populations of either species; with both showing an exaggerated increase in plasma cholesterol, and overproduction of LDL as the predominant lipoprotein. Thus, the hamster LDLR-KO model represents a more physiologically applicable model for atherosclerosis research compared to other contemporary rodent models.

Laboratories studying the implications of dyslipidemia in other disease states may also benefit from this model. Notably, there has been significant interest in the overproduction of intestine-derived apoB48-containing chylomicrons in insulin resistant type II diabetics (T2D). Insulin resistance has been linked to elevations in postprandial lipoprotein levels, and this dyslipidemia is now emerging as a major contributor to the development of CVD and atherosclerosis (Higgins and Adeli 2017; Patsch et al. 1992). The hamster LDLR-KO model may be particularly applicable to this research as postprandial TG levels were higher in $Ldlr^{-/+}$ and $Ldlr^{-/-}$ hamsters, indicating delayed chylomicron clearance in mutants. In contrast, VLDL secretion was unchanged between mutant and WT hamsters, which suggests that a sustained accumulation of postprandial chylomicrons is proponent to atherosclerotic plaque deposition. This is emphasized by the fact that intestinally-derived apoB48 is able to bind to proteoglycans on the arterial wall with similar affinity as liver-derived apoB100 (Flood et al. 2002); and subendothelial retention of apoB lipoproteins is considered to be the initiating event in atherosclerosis (Proctor et al. 2002). Furthermore, $Ldlr^{-/-}$ hamsters showed a high degree of mortality on a high cholesterol high fat (HCHF) diet, which was associated with advanced atherosclerosis in the aorta and coronary arteries.

This relationship is further evidenced by the discovery that ezetimibe - a selective inhibitor of cholesterol absorption from the intestine - was the only pharmacological intervention able to successfully lower total plasma cholesterol and TG in mutant hamsters. This finding is of particular importance since the average adult in western society is commonly in the postprandial state, and that cell surface expression of the LDL receptor is decreased by 41% in type II diabetic individuals (Duvillard et al. 2003). Therefore, this model may provide novel insight into the mechanisms of both postprandial and fasting dyslipidemia. Moreover, it has already demonstrated value in determining the efficacy of new and existing pharmacological therapies which target plasma LDLc.

Currently, LDLR-KO mice are among several animal models utilized in the study of non-alcoholic fatty liver disease (NAFLD). However, this hamster model may prove to be a more appropriate model for several reasons. Firstly, LDLR-KO mice require several months of HCHF feeding to initiate a sustained inflammatory and fibrotic response in the liver (Bieghs et al. 2012); with high fat diet alone being insufficient

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to induce inflammatory infiltrate (Kong et al. 2009). Whereas, when fed a HCHF diet for two weeks, $Ldlr^{-/+}$ hamsters showed significant increases in plasma triglyceride and total cholesterol, suggesting that the hamster model is more susceptible to dyslipidemia. Second, the development of NAFLD and non-alcoholic steatohepatitis (NASH) is characterized by elevations in plasma TG and hepatic overproduction of LDL paired with diminished HDL (Fon Tacer and Rozman 2011). Mice, however, lack CETP and are therefore HDL heavy, with even LDLR-KO mice showing meagre rises in LDL plasma levels, and no changes in HDL. Thus, the lipoprotein mechanics in the KO hamster model is far better suited to model this disorder.

Overall, the LDLR-KO hamster described here heralds a breakthrough for the study of lipid metabolism. Specifically, it produces a far more clinically relevant model in which to study dyslipidemia, as it relates to several metabolic disorders, including atherosclerosis, NAFLD, and T2D.

Conflict of Interest

The authors declare no conflict of interest.

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