Mouse Models of Coronary Heart Disease
Technology #18863

Applications
Scavenger receptor class B type I (SR-BI)-ΔCT mice in combination with apoE KO or LDLR KO or HypoE allele can be used as a fertile model of rapid onset and fatal occlusive coronary arterial atherosclerosis and coronary heart disease (CHD) in place of combinations with SR-BI KO mice. In addition, the SR-BI-ΔCT mouse alone or in combination can also be used as a mouse model for hypercholesterolemia, macrocytic anemia, hepatic and splenic extramedullary hematopoiesis, massive splenomegaly, reticulocytosis, thrombocytopenia, vascular disease, stroke, arterial thrombosis, deep vein (venous) thrombosis, Addison’s disease, infectious diseases, and atherothrombosis.

Problem Addressed
Good preclinical mouse models of atherosclerotic CHD are essential to understand the pathophysiology of the disease as well as test efficacy of therapeutic options. Currently, the mouse models of atherosclerotic CHD combine co-mutations in SR-BI, apoE, LDLR, or, in some cases PDZK1, with administration of either normal chow or atherogenic diet. These mouse models exhibit occlusive coronary artery disease, myocardial infarction (MI) and premature death, thus, mimicking human disease fairly well. However, these mice, except PDZK1, also exhibit abnormally high ratio of unesterified to total cholesterol (UC:TC), resulting in infertility. This makes the mouse model difficult to raise or produce and very costly. Even though PDZK1 mice are fertile, these mice in combination with apoE knockout (KO) develop CHD that is substantially less severe than other models. Thus, there is a huge need to develop a mouse model of atherosclerotic CHD that captures all the phenotype but is still fertile.

Technology
This technology combines learning from PDZK1 KO mice to preserve fertility in SR-BI KO mice. PDZK1 binds to the carboxyl terminal PDZ domain in SR-BI and post-transcriptionally controls expression and function of SR-BI in hepatocytes but not in steroidogenic cells. In this technology, a SR-BIΔCT knock-in mouse was generated, which introduced a stop codon before the last 3 amino acids of the C-terminus, effectively resulting in deletion of the PDZ binding region of SR-BI. These mice do not have severely high UC:TC ratio, thus, preserving fertility. They, however, mimic SR-BI KO mice in terms of plasma lipoprotein composition and size, atherosclerosis, and CHD susceptibility. When combined with either apoE KO or LDLR KO, these mice develop early-onset fatal atherosclerotic CHD on standard chow-diet or atherogenic diet respectively. Thus, this technology describes a new mouse model for atherosclerotic CHD that have severe disease phenotype but are fertile, thus, will be cheaper to raise and produce compared to previous alternatives. At least one additional variant model using the SR-BIΔCT knock-in mouse is also undergoing testing.

Advantages
SR-BIΔCT are fertile unlike SR-BI KO mice, thus, are cheaper and easier to raise.
SR-BIΔCT/apoE double KO and SR-BIΔCT/LDLR double KO mice provide a new atherosclerotic CHD model that mimic previous models while avoiding shortcomings of infertility.

Categories For This Invention:
- Life Sciences
- Clinical Applications
- Cardiovascular
- Research Tools
- Transgenic

Intellectual Property:
Mouse models having a knockin scavenger receptor class B type I
PCT
2018-049162
Mouse models having a knockin scavenger receptor class B type I
US Patent Pending
2019-0289835

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Publications:
Carboxy-terminal deletion of the HDL receptor reduces receptor levels in liver and steroidogenic tissues, induces hypercholester
Am J Physiol Heart Circ Physiol

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