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PRECLINICAL RESEARCH

Apolipoprotein E Deficiency Increases Remnant Lipoproteins and Accelerates Progressive Atherosclerosis, But Not Xanthoma Formation, in Gene-Modified Minipigs

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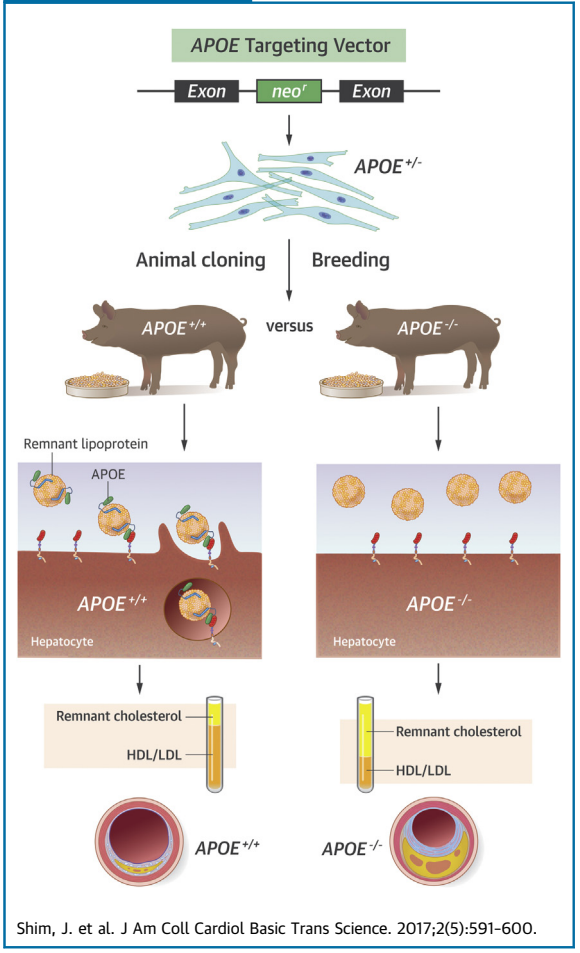
VISUAL ABSTRACT



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HIGHLIGHTS

- ***APOE*-deficient Yucatan minipigs were created by recombinant adeno-associated virus mediated gene targeting in porcine fibroblasts followed by somatic cell nuclear transfer.**
- ***APOE*$^{-/-}$ minipigs displayed increased plasma cholesterol and accumulation of APOB48-containing chylomicron remnants on low fat-diet, which was significantly accentuated upon feeding a high-fat, high-cholesterol diet.**
- ***APOE*$^{-/-}$ minipigs showed accelerated progressive atherosclerosis but not xanthoma formation indicating that remnant lipoproteinemia does not induce early lesions but is atherogenic in pre-existing atherosclerosis.**

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ABBREVIATIONS AND ACRONYMS

APOB = apolipoprotein B

APOE = apolipoprotein E

cDNA = complementary DNA

HFHC = high-fat high-cholesterol

IDL = intermediate-density lipoprotein

LAD = left anterior descending (coronary artery)

LDL = low-density lipoprotein

LDLR = low-density lipoprotein receptor

LF = low-fat

Neo = neomycin

rAAV = recombinant adeno-associated virus

SMC = smooth muscle cell

VLDL = very-low-density lipoprotein

SUMMARY

Deficiency of apolipoprotein E (APOE) causes familial dysbetalipoproteinemia in humans resulting in a higher risk of atherosclerotic disease. In mice, APOE deficiency results in a severe atherosclerosis phenotype, but it is unknown to what extent this is unique to mice. In this study, *APOE* was targeted in Yucatan minipigs. *APOE*$^{-/-}$ minipigs displayed increased plasma cholesterol and accumulation of apolipoprotein B-48–containing chylomicron remnants on low-fat diet, which was significantly accentuated upon feeding a high-fat, high-cholesterol diet. *APOE*$^{-/-}$ minipigs displayed accelerated progressive atherosclerosis but not xanthoma formation. This indicates that remnant lipoproteinemia does not induce early lesions but is atherogenic in pre-existing atherosclerosis. (J Am Coll Cardiol Basic Trans Science 2017;2:591–600) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The most efficient animal model of experimental atherosclerosis is the apolipoprotein E (APOE)-deficient mouse (1) which develops severe hypercholesterolemia and rapid, fibroatheromatous atherosclerosis on normal chow diet. APOE is synthesized in hepatocytes and several other cell types, and serves as a ligand for low-density receptor-related protein 1-mediated clearance of apolipoprotein B-48 (APOB-48)-containing chylomicron remnants and low-density lipoprotein receptor (LDLR)-mediated clearance of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) (2). Due to hepatic editing of *Apob* mRNAs, mice secrete APOB-48-containing VLDLs, making them particularly dependent on APOE-mediated clearance mechanisms (3). However, loss of several other APOE-mediated functions may contribute to the severe atherosclerosis phenotype of the *Apoe*$^{-/-}$ mice. APOE has been shown to dampen inflammation, inhibit smooth muscle cell (SMC) proliferation and migration, and to be involved in reverse cholesterol transport (4). Lipoproteins from *Apoe*$^{-/-}$ mice also more readily produce foam cells in vitro for reasons that are not well understood (5). In humans, genetic variants that increase remnant lipoproteins similar to those seen with APOE-deficiency not only increase the risk of ischemic heart disease but also the plasma level of C-reactive protein (CRP). This is not seen with gene variants that increase low-density lipoprotein (LDL); possibly reflecting a pro-inflammatory effect of remnant lipoproteins in the arterial wall (6).

Several lines of hypercholesterolemic minipigs exist with spontaneous or genetically engineered defects in LDLR-mediated hepatic LDL uptake (7). These include familial hypercholesterolemia-Bretoncelles-Meishan pigs with a spontaneous *LDLR* mutation (8), human *D374Y* gain-of-function proprotein convertase subtilisin/kexin type 9 (PCSK9) transgenic Yucatan minipigs (9), and most recently, *LDLR* knockout Yucatan minipigs (10). When fed a high-fat high-cholesterol diet, these lines accumulate LDL-sized and larger APOB-100-containing lipoproteins and they develop fibroatheromatous atherosclerotic plaques in major arteries. These lines are useful for many purposes, but rates of plaque progression are modest,

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

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