VSMC in response to growth factor stimulation, supporting our previous findings that TRPC6$^{-/-}$ VSMC are modulated from a contractile to a proliferative phenotype.

Conclusions: TRPC6 depletion is associated with decreased myocardin and the emergence of pathogenic VSMC behavior. TRPC6-dependent signaling may, therefore, be a therapeutic target to promote myocardin expression and stabilize the VSMC contractile phenotype after arterial injury.

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Periadventitial Delivery of Simvastatin from Microparticles Attenuates Arteriovenous Fistula Outflow Vein Neointimal Hyperplasia

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Background: Venous neointimal hyperplasia (VNH) is vexing problem to maintain arteriovenous fistula (AVF) patency in end-stage renal disease patients. The available drug delivery systems to prevent VNH formation are limited. VNH is characterized with increased expression of transforming growth factor-β1 (TGF-β1), vascular endothelial growth factor-A (VEGF-A), and monocyte chemoattractant protein-1 (MCP-1). We sought to determine whether periadventitial delivery of microparticles coated with simvastatin (MP-SIM) could prevent VNH formation via inhibition of gene expression of TGF-β1, VEGF-A, and MCP-1 in a murine AVF model with chronic kidney disease.

Methods: At day −28, 8-week-old C57BL/6J male mice were randomly grouped into control group (MP alone) or MP-SIM group and nephrectomy was used to induce chronic kidney disease. At day 0, an AVF was created. A volume of 20 μL of phosphate-buffered saline with 16.6 mg/mL of either MP or MP-SIM was applied to the periadventitia of the proximal AVF outflow vein at the time of AVF creation. Fistula patency was assessed weekly using Doppler ultrasound examination. Mice were humanely killed at day 3 and 28 for gene expression and immunohistochemistry staining respectively.

Results: At day 3, the gene expression of TGF-β1, VEGF-A, and MCP-1 was significantly decreased in MP-SIM group. At day 28, there was a significant increase in the peak systolic velocity and decrease in the average neointimal area and cell density in MP-SIM group. At day 28, as assessed using immunohistochemistry staining, there was a significant increase in apoptosis and a decrease in the smooth muscle cell, fibroblasts, macrophages, fibrosis, and cellular proliferation in MP-SIM group.

Conclusions: Our study indicates that periadventitial delivery of MP-SIM attenuates VNH at 4 weeks after AVF creation. Further studies using a porcine animal model to confirm these findings are recommended. The potential clinical applicability of controlled release simvastatin to decrease expression of TGF-β1, VEGF-A, and MCP-1 while increasing apoptosis and decreasing cellular proliferation is encouraging.

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ABSTRACT SESSION II: ATHEROSCLEROSIS AND THE ROLE OF THE IMMUNE SYSTEM

Absence of Cpla2 in Lrp1 Smooth Muscle Cell-Deficient Mice Promotes Severe Aortic Atherosclerotic Disease

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Smooth muscle cell targeted deficiency of low-density lipoprotein (LDL) receptor-related protein 1 (LRP1) in a mouse model (smLRP1$^{-/-}$) results in accelerated aortic atherosclerosis through activation of cytoplasmic phospholipase A2 (cPLA2), leading to reduced ABCA1 expression in vascular smooth muscle cells, and increased intracellular cholesterol accumulation. We therefore hypothesized that deficiency of cPLA2 would impede atherogenesis in the smLRP1$^{-/-}$ mouse model.

Methods: Adult male smLRP1$^{-/-}$;cPLA2$^{-/-}$;LDLR$^{-/-}$ (triple knockout) mice were placed on a high cholesterol diet for 16 weeks and compared with age- and diet-matched sibling control smLRP1$^{+/+}$;cPLA2$^{-/-}$;LDLR$^{-/-}$ mice. Histologic analysis was performed using en face whole aorta Oil red O (ORO) staining, as well as a cross-sectional analysis of the aortic root with ORO, Picro Sirius red, Alizarin red, and immunofluorescence. Immunoblot protein analysis was performed using lysed whole aortas. Data are presented as mean ± standard error of the mean. Statistical analysis was performed using one- and two-way analysis of variance with Tukey's correction.

Results: En face ORO analysis revealed increased lipid accumulation in triple knockout mice as compared with controls (60 ± 3% vs 13 ± 2%; $P <$ .001) (Fig). Uniquely, triple knockout mice develop extensive necrotic cores and thin fibrous caps in atherosclerotic lesions in the aortic root (Fig). ABCA1 is paradoxically increased both in whole aorta lysate as well as in immunofluorescence staining of the aortic root.

Conclusions: Deficiency of cPLA2 in the smLRP1$^{-/-}$ mouse model rescued ABCA1 expression, but unexpectedly increased lipid accumulation within the plaque and generated more vulnerable plaque. Future studies will underpin the mechanisms that guide severe disease development in our triple knockout mice via regulation of ABCA1.

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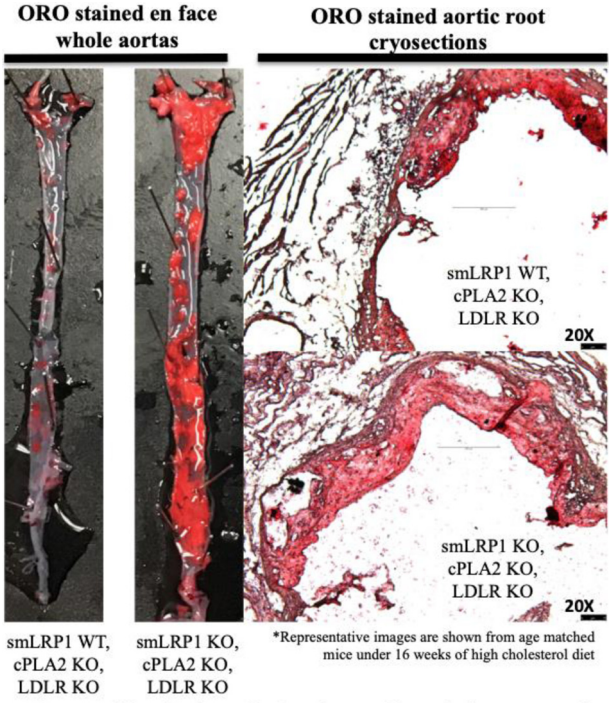

Fig. Histologic analysis using en face whole aorta and aortic root cryosection Oil red O (*ORO*) staining for atherosclerotic lesions.

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Serum Circulating Fatty Acid Synthase as a Diagnostic Biomarker for Chronic Limb-Threatening Ischemia

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Objectives: Circulating fatty acid synthase (cFAS), a de novo lipogenesis enzyme, is elevated in the serum of patients with diabetes mellitus (DM)