Mechanism and Targeting of Host-Microbial Trimethylamine Pathway to Reduce Neointimal Hyperplasia after Injury
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INTRODUCTION Each year, 7.4 million Americans with CVD undergo procedures. However, up to 50% of treated vessels exhibit restenosis. This is due to neointimal hyperplasia, a pathologic response of the blood vessel to vascular intervention. The pathologic neointima is composed of cells from multiple possible sources, including resident smooth muscle cells, adventitial fibroblasts, and endothelial cells that transform into myofibroblasts via endothelial-to-mesenchymal transition (endoMT). Major gaps exist in our understanding of the complex process of pathologic neointima formation after injury.

Gut microbiota exposed to a Western diet rich in compounds such as choline generate trimethylamine (TMA) via the enzyme TMA lyase, which is converted to trimethylamine N-oxide (TMAO). Elevated TMAO is associated with endothelial injury and the promotion of fibrotic cellular phenotypes.

We propose a novel pathway for neointimal hyperplasia that links gut microbiota, a TMAO produced by gut microbiota from dietary nutrients, and neointimal hyperplasia after vascular surgery.

METHODS In vivo experiments: 15-week-old C57BL/6 mice were given control drinking water with 1% choline for 3 weeks prior to left carotid ligation. Morphometric analysis of arteries 4 weeks after injury to quantify the extent of injury was performed. In a subset of mice microbial TMA lyase activity was blocked using iodomethylcholine (IMC) and levels of TMA and TMAO were measured.

In vitro experiments: Human umbilical vein endothelial cells (HUVEC) were treated with TMAO and measurements of endoMT including cell morphology and mesenchymal-specific cell marker expression were examined.

RESULTS

CONCLUSIONS Our preliminary findings strongly implicate a novel diet-microbe-host driving neointimal hyperplasia development after vascular surgery.