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Gut Microbiota–Derived Trimethylamine N-Oxide Contributes to Abdominal Aortic Aneurysm Through Inflammatory and Apoptotic Mechanisms

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Originally published 3 Apr 2023 | <https://doi.org/10.1161/CIRCULATIONAHA.122.060573> | Circulation. 2023;147:1079–1096

Abstract

Background:

Large-scale human and mechanistic mouse studies indicate a strong relationship between the microbiome-dependent metabolite trimethylamine N-oxide (TMAO) and several cardiometabolic diseases. This study aims to investigate the role of TMAO in the pathogenesis of abdominal aortic aneurysm (AAA) and target its parent microbes as a potential pharmacological intervention.

Methods:

TMAO and choline metabolites were examined in plasma samples, with associated clinical data, from 2 independent patient cohorts (N=2129 total). Mice were fed a high-choline diet and underwent 2 murine AAA models, angiotensin II infusion in low-density lipoprotein receptor–deficient (*Ldlr*^{−/−}) mice or topical porcine pancreatic elastase in C57BL/6J mice. Gut microbial production of TMAO was inhibited through broad-spectrum antibiotics, targeted inhibition of the gut microbial choline TMA lyase (*CutC/D*) with fluoromethylcholine, or the use of mice genetically deficient in flavin monooxygenase 3 (*Fmo3*^{−/−}). Finally, RNA sequencing of in vitro human vascular smooth muscle cells and in vivo mouse aortas was used to investigate how TMAO affects AAA.

Results:

Elevated TMAO was associated with increased AAA incidence and growth in both patient cohorts studied. Dietary choline supplementation augmented plasma TMAO and aortic diameter in both

mouse models of AAA, which was suppressed with poorly absorbed oral broad-spectrum antibiotics. Treatment with fluoromethylcholine ablated TMAO production, attenuated choline-augmented aneurysm initiation, and halted progression of an established aneurysm model. In addition, *Fmo3*^{-/-} mice had reduced plasma TMAO and aortic diameters and were protected from AAA rupture compared with wild-type mice. RNA sequencing and functional analyses revealed choline supplementation in mice or TMAO treatment of human vascular smooth muscle cells–augmented gene pathways associated with the endoplasmic reticulum stress response, specifically the endoplasmic reticulum stress kinase PERK.

Conclusions:

These results define a role for gut microbiota–generated TMAO in AAA formation through upregulation of endoplasmic reticulum stress–related pathways in the aortic wall. In addition, inhibition of microbiome-derived TMAO may serve as a novel therapeutic approach for AAA treatment where none currently exist.

Footnotes

*T.W. Benson and K.A. Conrad contributed equally.

Supplemental Material is available at

<https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.060573>.

For Sources of Funding and Disclosures, see page 1094.

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