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Commentary

Intestinal Microbiome and Atherosclerosis

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The understanding of the role of nutrition in atherosclerosis has been revolutionized by the recognition of effects of the intestinal microbiome. Intestinal bacteria ferment nutrients into metabolic products, with profound effects on atherosclerosis and on cardiovascular risk.

Carnitine from red meat (~4 times as much as in chicken or fish) and choline, including phosphatidylcholine from egg yolk, are converted by the intestinal microbiome into trimethylamine (Wang et al., 2011; Koeth et al., 2013), the compound that causes the fishy odor in uremic breath. Trimethylamine is oxidized in the liver to trimethylamine *N*-oxide (TMAO), which causes atherosclerosis in an animal model (Wang et al., 2011), and markedly increases cardiovascular risk.

That the TMAO results from fermentation by intestinal bacteria was shown in animal model and in human subjects by giving antibiotics to eliminate the intestinal bacteria. Perhaps the most interesting thing about these studies was that vegans given carnitine did not product TMAO, apparently lacking the "meat-eating" bacteria that do so (Koeth et al., 2013). This suggests that it may be possible to modify the intestinal microbiome, by a process similar to "repopulation" commonly used to treat clostridium difficile.

Among patients referred for coronary angiogram, TMAO levels were measured after a test dose of two hard-boiled eggs. Patients with TMAO in the top quartile had 2.5 times higher three-year risk of stroke, myocardial infarction or vascular death compared to those in the lowest quartile (Tang et al., 2013).

The metabolic products of the intestinal microbiome are to a great extent eliminated by the kidneys; they therefore accumulate in patients with renal failure, and may be termed gut-derived uremic toxins (GDUT). Homocysteine, a leading candidate to explain high cardiovascular risk in uremia, appears to account for only ~20% of the excess carotid atherosclerosis in renal failure (Spence et al., 2016). Levels of TMAO are high in renal failure, and besides increasing cardiovascular risk, also accelerate decline of renal function (Tang et al., 2015). Besides TMAO from carnitine and phosphatidylcholine, there are a number produced from proteins/amino acids.

In patients with CKD, plasma levels of indoxyl sulfate (IS) and p-cresyl sulfate (PCS) are 54 and 17 times higher, respectively, than in healthy individuals. Both IS and PCS are associated with accelerated progression to dialysis and cardiovascular risk among pre-end-stage renal disease (ESRD) patients (Lin et al., 2014; Lin et al., 2015a). Indoxyl sulfate is also associated with increased all-cause mortality, and with glycation end products (Lin et al., 2015b).

Cardiovascular risk is very high in patients with renal failure (Gansevoort et al., 2013), so for patients with renal failure it is particularly important to avoid red meat and egg yolks.

Besides the metabolic products of the intestinal microbiome, it seems that there are other non-metabolic pathways by which "gut microbes can also signal to the host to regulate innate immunity through metabolism-independent pathways, where constituents of the microbial cell wall are sensed by host cells through pattern recognition receptors to further impact CVD progression."

In this issue of the journal *EBioMedicine*, Chen et al. (2016) report what appears to be a metabolism-independent mechanism by which the intestinal microbiome can affect atherosclerosis. They found that effects of the intestinal microbiome resulted in recruitment and ectopic activation of B2 cells in perivascular adipose tissue and an increase in circulating IgG, increasing development of atherosclerosis. This was prevented by antibiotic elimination of the intestinal microbiome, and also by depletion of B2 cells with antibodies.

There is more to be discovered about this story, but already it is clear that the intestinal microbiome has important effects on atherosclerosis and cardiovascular risk. Learning how to mitigate these effects will be an important field of research in the coming years.

Disclosure

The author declared no conflicts of interest.

References

Chen, L., Ishigami, T., Nakashima-Sasaki, R., et al., 2016. Commensal microbes-specific activation of B2 cell subsets contribute to atherosclerosis development independent of lipid metabolism. EBioMedicine 13, 237–247.

Gansevoort, R.T., Correa-Rotter, R., Hemmelgarn, B.R., et al., 2013. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 382 (9889), 339–352.

Koeth, R.A., Wang, Z., Levison, B.S., et al., 2013. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat. Med. 19 (5), 576–585.

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http://dx.doi.org/10.1016/j.ebiom.2016.10.033

Lin, C.J., Pan, C.F., Chuang, C.K., et al., 2014. P-cresyl sulfate is a valuable predictor of clinical outcomes in pre-ESRD patients. Biomed. Res. Int. 2014, 526932.
Lin, C.J., Wu, V., Wu, P.C., Wu, C.J., 2015a. Meta-analysis of the associations of p-cresyl sulfate (PCS) and indoxyl sulfate (IS) with cardiovascular events and all-cause mortality in patients with chronic renal failure. PLoS One 10 (7), e0132589.
Lin, C.J., Lin, J., Pan, C.F., et al., 2015b. Indoxyl sulfate, not p-cresyl sulfate, is associated with advanced glycation end products in patients on long-term hemodialysis. Kidney Blood Press. Res. 40 (2), 121–129.
Spence, J.D., Urquhart, B.L., Bang, H., 2016. Effect of renal impairment on atherosclerosis: only partially mediated by homocysteine. Nephrol. Dial. Transplant. 31 (6), 937–944.
Tang, W.H.W., Wang, Z., Levison, B.S., et al., 2013. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N. Engl. J. Med. 368 (17), 1575–1584.
Tang, W.H., Wang, Z., Kennedy, D.J., et al., 2015. Gut microbiota-dependent trimethylamine *N*-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ. Res. 116 (3), 448–455.
Wang, Z., Klipfell, E., Bennett, B.J., et al., 2011. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 472 (7341), 57–63.