The French Paradox: Is it all in the gut?

Daniel Bikle, MD, PhD January 2017

A recent publication by Ming-liang Chen et al. entitled Resveratrol attenuates trimethylamine-N-oxide (TMAO)-induced atherosclerosis by regulating TMAO synthesis kand bile acid metabolism via remodeling of the gut microbiota in mBIO 7: e02210-15 puts a new twist on the resveratrol (RSV) story. As is well known, RSV and other polyphenols are in relatively high concentrations in the skins and seeds of grapes, especially red grapes. Red wine contains levels of RSV on the order of 2-8 mg/liter. Drinking red wine is associated with a lower risk of cardiovascular disease, and at least part of this protective effect has been attributed to its RSV content. Although a number of mechanisms have been proposed for this potential beneficial effect of RSV on health in general and cardiovascular disease in particular, no previous study has considered its role on the gut microbiome despite the poor intestinal absorption of RSV and other phenolic phytochemicals. This study directed its attention to the gut microbiome and its production of trimethylamine (TMA), which is converted to TMAO in the liver. TMAO appears to promote the development of atherosclerosis (AS) in part by reducing hepatic bile acid synthesis leading to increased cholesterol levels.

The authors used a mouse model, ApoE-/-, known to be susceptible to the early development of AS. On a chow diet the gut flora of these mice metabolize choline to TMA, which is then metabolized to TMAO in the liver. Feeding these mice choline resulted in a rapid increase in TMAO in the blood, an effect markedly reduced when the diet also contained 0.4% RSV. This was associated with a reduction in cholesterol levels and an increase in bile acid synthesis and fecal excretion, all effects blocked by antibiotics. Moreover, RSV blocked the increase in aortic plaque development following choline administration. That the gut flora were responsible was demonstrated by showing that antibiotics, presumably non absorbable, (not specified in publication) abolished TMAO production. RSV administration altered the gut microbiome most notably by increasing bacteroidetes at the expense of Firmicutes, although a number of other species were affected as well. This shift was associated with a reduction in the ability of the cecal content from RSV-ingesting mice to metabolize choline to TMA.

So what are we to make of all this. As noted above, red wine contains around 2-8mg/L. The mice were fed a diet containing 0.4% RSV. A mouse eats 3-5gm chow/day, so the RSV ingested was 12-20mg/day, or what the mouse would have consumed drinking 1-2 gallons of red wine per day. So the bottom line is that we should enjoy our red wine in moderation, but not get too concerned that it is having a major effect on our gut microbiome and its ability to produce compounds contributing to atherosclerosis. That said, maybe a moderate amount of red wine would be enough to alter our gut microbiomes toward a profile less likely to produce metabolites that adversely affect cholesterol metabolism, but this will require testing in humans—any volunteers?