Editorial

A Gut Feeling About Developmental Programming Mechanisms

Trimethylamine-N-Oxide May Enhance Atherosclerosis in Offspring of Hypercholesterolemic Mice

Wulf Palinski

It is now widely recognized that perinatal exposure to maternal dysmetabolic conditions may influence cardiovascular diseases in offspring.[1] Maternal hypercholesterolemia, in particular, increases the susceptibility to atherosclerosis in humans and experimental models. The translational relevance of developmental programming is obvious. If safe interventions in hypercholesterolemic mothers before or during pregnancy can attenuate pathogenic programming, atherogenesis may be reduced throughout adult life.[1] Although the consequences of maternal hypercholesterolemia in humans are increasingly evident,[2] the mechanisms involved remain largely unknown.

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In this edition of the journal, Trenteseaux et al[3] identify a novel mechanism that may promote atherosclerosis in apoE$^{-/-}$ mice. In their study, homozygous female offspring of hypercholesterolemic (apoE$^{-/-}$) mothers developed greater lesions in the aortic root than offspring of normocholesterolemic (apoE$^{+/-}$) mothers, consistent with increased aortic atherosclerosis observed in LDL$^{-/-}$ mice or rabbits. Remarkably, maternal hypercholesterolemia was associated with higher plasma levels of trimethylamine-N-oxide (TMAO) and increased hepatic gene expression of flavin-containing monooxygenase 3, which contributes to the formation of TMAO. TMAO levels were highly correlated with aortic root atherosclerosis, and recent reports on the atherogenic role of TMAO in mice and humans[4,5] support the assumption that it also enhanced atherosclerosis in the offspring of hypercholesterolemic mothers. In male offspring, TMAO levels were several-fold lower than in females and no effect of maternal hypercholesterolemia on the much smaller aortic lesions was detected.

These findings raise the intriguing possibility that the gut microbiota may be involved in developmental programming. In fact, intestinal microbiota generate TMA, the precursor of TMAO, from phosphatidylcholine-rich nutrients, and TMA formation is influenced by the composition of the microbiota as well as the diet. Both maternal hypercholesterolemia and altered microbiota may lead to extensive epigenetic changes, but methylation of *Fmo3* promotor regions was not significantly affected by maternal hypercholesterolemia, so other mechanisms are likely to be involved. Interestingly, hypercholesterolemia did not raise the maternal TMAO levels. This confirms that programming of offspring atherogenesis was driven by maternal hypercholesterolemia, rather than by maternal TMAO, but does not rule out effects mediated by altered maternal microbiota.

Several other atherogenic mechanisms have been described previously in offspring of hypercholesterolemic mothers, including impaired endothelial function and vascular reactivity, increased blood pressure, changes in cholesterol, glucose and insulin metabolism, altered mRNA and protein expression of genes influencing cell growth and proliferation, decreased activities of antioxidant enzymes, and increased generation of proinflammatory eicosanoids.[1] The involvement of TMAO (Figure) constitutes an important addition to our knowledge of developmental programming mechanisms, because TMAO levels are unlikely to be confounded by the extent of offspring atherosclerosis. However, establishing that any particular mechanism is indeed programmed in the perinatal period and that it provides a significant contribution to offspring atherogenesis is difficult. Potential confounders include the degree of maternal and offspring hypercholesterolemia, the effects of the underlying genetic defect on lipoprotein profiles and immune mechanisms, the age of offspring and the extent of their atherosclerosis. Sex differences may also be considerable, in particularly in murine models, less so in models with diet-induced hypercholesterolemia.

Although the main approach to preventing atherogenic programming would be to reduce maternal hypercholesterolemia, establishing the relevance of proposed mechanisms, including TMAO, will be valuable, because it may indicate additional targets for interventions after birth. To establish relevance of a putative mechanism in developmental programming, 2 conditions should be fulfilled. First, that the mechanism be evident in more than one model, preferably in different animal species. Second, that it be reduced in offspring by pre- or perinatal interventions that protect against atherogenic programming without affecting maternal cholesterol levels. Some interventions in animal models have been able to do so,[6,7] but the proposed mechanism could also be selectively inhibited in offspring.

In this endeavor, it is important to remember that developmental programming of atherosclerosis may be latent, that is, only become apparent in the presence of atherogenic cofactors.[8]

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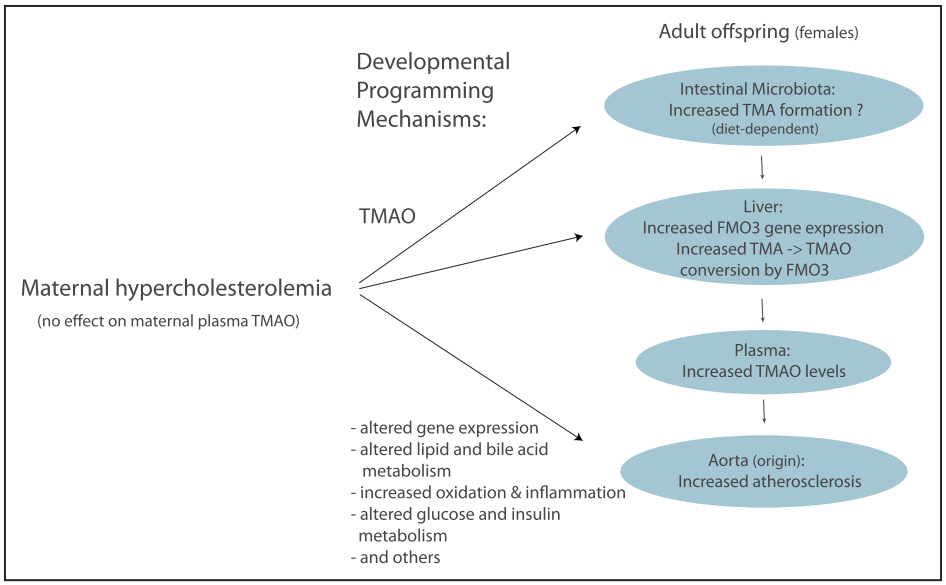

Figure. Proposed role of trimethylamine-N-oxide (TMAO) in developmental programming of atherosclerosis. FMO3 indicates flavin-containing monooxygenase 3.

This also stands in the way of another requirement one would otherwise make, ie, that the putative mechanism should be evident in offspring before the onset of significant atherosclerosis.

Verification in humans will obviously be most important. In the past, the limited availability of cholesterol data during pregnancy has hindered retrospective investigation in offspring of mothers with perinatal hypercholesterolemia in most counties.[9,10] Fortunately, recent data from the Framingham Study have shown a markedly increased cardiovascular risk in offspring of mothers who were hypercholesterolemic both sometime before and after pregnancy, and thus presumably also during pregnancy.[2] This opens new opportunities to determine the atherogenic effects and mechanisms of maternal hypercholesterolemia using large multigenerational databases.

Disclosures

None.

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