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EDITORIAL COMMENT

Arginine and Old MACE

Small Molecules in Atherogenesis Support the Concept of Coronary Artery Disease as a Complex Trait*

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In the final years of the last century, the noted epidemiologist Meir Stampfer proclaimed that over 90% of coronary artery disease (CAD) could be prevented. This was not an idle rumination but a prediction based on his own work (1,2) and the remarkable development of knowledge on atherogenesis and acute coronary syndromes (ACS) since World War II. Coronary artery disease had been demonstrated to be an inflammatory illness, due to chronic vascular exposure to oxidized lipids and other endothelial toxins, whose plaques could rupture and trigger thrombosis, acutely impeding myocardial blood flow and causing ACS (3–5). At the same time that surgical and percutaneous interventional approaches were being perfected, the field was being focused on biologic interventions that would reduce vascular inflammation and prevent complications if not cure atherosclerosis. The unified theory is the basis for Stampfer's prediction, and it is likely true.

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But at the beginning of the "Century of Biology," atherosclerosis might not be your father's steak, eggs, and an early morning smoke. Hyperlipidemia and inflammation might play a duet, each leading to atherogenesis (6) with the effective treatment of either, for example, in the setting of "normal" low-density lipoprotein cholesterol levels (<130 mg/dl), improving outcomes (7). The pathology and clinical expression also might be binary, with thick-capped, lipid-poor, constrictive plaques causing chronic ischemia and thin-capped, lipid-rich, less-intrusive plaques causing ACS (8). And the importance of family history for "premature" ACS (9) might not lie in genes for atherogenesis but in genes for myocardial infarction itself (10,11). The concept that there could be separate inheritance for atherosclerosis on the one hand and myocardial infarction on the other is one of the foundation-crumbling wonders of the genomic age, as shocking as the tiny number of human protein-encoding genes and the Lamarckian appearance of epigenetics.

Modern molecular biology has also enhanced knowledge of atherosclerosis along more exotic pathways. In the 1950s, a notion was popularized that atherosclerosis was due to "slow metabolism," perhaps on the basis of the theory that slow clearance of postprandial lipids allowed fatty arterial deposits to grow (12). Metabolism and small molecular modifications outside of the traditional risk factors—although all operating along the inflammatory-atherogenic-thrombotic axis—now have been identified as important in atherosclerosis as well. These moieties cover quite a spectrum and include advanced glycation end products and their receptor (13,14), arginase I in macrophages (15), and protein carbamylation (16). The latter work of Wang et al. (16), some of whom are coauthors on the present study (13), is an important set of observations linking smoking and uremia to atherogenesis through inflammation induced by homocitrulline modification of proteins by cyanate (13).

It is in this remarkable and heightened environment of discovery that Tang et al. (17) at the Cleveland Clinic describe a possible role for the catabolism of the amino acid arginine in both atherosclerosis and major adverse cardiovascular events (MACE). Arginine is the sole source of nitrogen for the synthesis of nitric oxide (NO), a former molecule of the year (18), which has broad biologic signaling activities, is a potent vasodilator, and is protective of the vasculature (19). The authors hypothesized that a sensitive approach to measuring arginine and its catabolites, ornithine and citrulline, in the NO synthetic pathway (see Fig. 1 in Tang et al. [17]) would show that atherosclerosis and MACE are related to decreased arginine bioavailability. Decreased bioavailability could limit NO, and this in turn could diminish its protection of the vasculature, allowing atherogenesis to flourish. They measured the "global arginine bioavailability ratio" (GABR), defined as arginine/(ornithine + citrulline), as that sensitive measure, more sensitive than measuring arginine levels alone. The study used 1,010 consecutive subjects undergoing elective cardiac catheterization who had been enrolled in a sophisticated tissue-banking protocol that included plasma, serum, and deoxyribonucleic acid. They discovered, after adjusting for confounders, that both decreased GABR and higher concentrations of citrulline were correlated with the prevalence of CAD (with adjusted odds ratios of 3.93 and 5.98, respectively) and the development of MACE (with adjusted hazard ratios of 1.98 and 2.40, respectively) (17). The relationships are strong, the study is interesting, and the authors have described another small molecule that might have atherogenic and plaque-disrupting potential.

We do not know, on the basis of this first analysis focusing on the substrates of the NO synthetic pathway,

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whether GABR or citrulline alone will prove to be either mechanistically important in atherogenesis or predictive of MACE as a biomarker. The kinetics and compartmentalization of NO synthesis (20) make the significance of a low GABR or a high citrulline concentration uncertain, in the important terms of whether they result in poor or inadequate or inappropriate synthesis of NO, which in turn could lead to atherogenesis and MACE. As for the establishment of GABR as a prognostic factor, as the authors point out, a prospective study across a broader population will be necessary.

Nonetheless, this work adds importantly to the rich understanding of CAD as a "complex trait," defined rather nicely by a workshop at the National Institutes of Health as "determined by many factors, including genetic and environmental components, which interact in often unpredictable ways [wherein. . .] the whole is not only greater than the sum of its parts, it might be different from the sum of its parts" (21). We still do not know whether, if the population had a low-density lipoprotein cholesterol level of 70 mg/dl, around which endothelial-dependent relaxation reaches a maximum, or one even lower, there would be any atherosclerosis at all. Whereas CAD might become the leading cause of death in the world in a few years, the secrets of its complexity will continue to unfold, and ultimately Stampfer's prediction will prevail.

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REFERENCES

1. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. N Engl J Med 1991;325:373–81.
2. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000;343:15–22.
3. Ross R, Glomset JA. The pathogenesis of atherosclerosis (first of two parts). N Engl J Med 1976;295:369–77.
4. Ross R, Glomset JA. The pathogenesis of atherosclerosis (second of two parts). N Engl J Med 1976;295:420–5.
5. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation 2005;111:3481–8.
6. Steinberg D. Atherogenesis in perspective: hypercholesterolemia and inflammation as partners in crime. Nat Med 2002;8:1211–7.
7. Ridker PM, Danielson E, Fonseca FA, et al., for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
8. Davies MJ. Stability and instability: the two faces of coronary atherosclerosis: the Paul Dudley White Lecture, 1995. Circulation 1996;94:2013–20.
9. Breslow JL, Dammerman M. Genetic determinants of myocardial infarction. Adv Exp Med Biol 1995;369:65–78.
10. Wang Q, Rao S, Shen G-Q, et al. Premature myocardial infarction novel susceptibility locus on chromosome 1p34-36 identified by genome-wide linkage analysis. Am J Hum Genet 2004;74:262–71.
11. Topol EJ. The genomic basis of myocardial infarction. J Am Coll Cardiol 2005;46:1456–65.
12. Zilversmit DB. Atherogenesis: a postprandial phenomenon. Circulation 1979;60:473–85.
13. Schmidt AM, Yan SD, Wautier JL, Stern D. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. Circ Res 1999;84:489–97.
14. Ramasamy R, Yan SF, Schmidt AM. Stopping the primal RAGE reaction in myocardial infarction. Capturing adaptive responses to heal the heart. Circulation 2008;117:3165–7.
15. Teupser A, Burkhardt R, Wilfert W, et al. Identification of macrophage arginase I as a new candidate gene of atherosclerosis resistance. Arterioscler Thromb Vasc Biol 2006;26:365–71.
16. Wang Z, Nicholls SJ, Rodriguez ER, et al. Protein carbamylation links inflammation, smoking, uremia and atherogenesis. Nat Med 2007;13:1176–84.
17. Tang WHW, Wang Z, Cho L, Brennan DM, Hazen SL. Diminished global arginine bioavailability and increased arginine catabolism as metabolic profile of increased cardiovascular risk. J Am Coll Cardiol 2009;53:2061–7.
18. Koshland DE. The molecule of the year. Science 1992;258:1861.
19. Cooke JP, Dzau VJ. Nitric oxide synthase: role in the genesis of vascular disease. Annu Rev Med 1997;48:489–509.
20. Getz GS, Reardon CA. Arginine/arginase NO NO NO. Arterioscler Thromb Vasc Biol 2006;26:237–9.
21. National Institutes of Health. National Institute of General Medical Sciences. Report: The Genetic Architecture of Complex Traits Workshop. Available at: http://www.nigms.nih.gov/News/Reports/genetic_arch.htm. Accessed February 18, 2009.

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