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EDITORIAL COMMENT

Interleukin-1 Revisited

Further Insights Into its Role in Atherosclerosis and as a Potential Therapeutic Target for Treatment*

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Stable obstructive coronary artery disease (CAD) and acute coronary syndromes (ACS) result from the complex interplay between genetic factors and environmental exposures over time. However, few studies have provided clarity around the interactions between different genes and environmental exposures and the resultant effects on cardiovascular (CV) phenotype. Even the model of gene–environment interaction is likely oversimplistic as there are likely to be multiple genes involved in: 1) the initiation of atherosclerosis; and 2) modification of the subclinical course, interplaying with different environmental factors to influence the timing and the type of clinical presentation (Fig. 1). In this issue of the *Journal,* Tsimikas et al. (1) link for the first time the potential interactions between genetic factors influencing inflammation and exposure to modified lipids, and how this may influence the development of CAD and CV events.

See page 1724

Cholesterol carried within apolipoprotein B-100 (apoB)-containing lipoproteins is continuously associated with the risk for fatal and nonfatal myocardial infarction (MI) (2). Furthermore, oxidized phospholipids (OxPLs), and in particular OxPLs associated with apoB (OxPL/apoB), predict the risk for cardiovascular events and reclassify about 30% of patients considered at intermediate risk (3). In part, higher OxPL may reflect higher absolute levels of apoB-containing lipoproteins and higher non–high-density lipoprotein cholesterol levels, but also could be enhanced among those with a higher inflammatory burden. The latter could be driven via principally genetic factors or via environmental factors associated with higher oxidative states, such as diabetes or chronic kidney disease. A substantive body of classic epidemiology and Mendelian randomization studies now implicates lipoprotein (LP) (a) as a causal factor in cardiovascular disease, although the relationship with risk does not appear to be continuous but rather curvilinear, with greatest risk observed in the highest quintile (4). Previously, Taleb et al. (5) demonstrated that OxPLs are preferentially carried by Lp(a) compared with other apoB-containing lipoproteins. Thus, in part, the risk related to higher Lp(a) levels could result from its relationship with OxPLs.

OxPLs are pro-inflammatory and destabilize atherosclerotic plaques, further amplifying any intrinsic inflammatory potential within patients. It is plausible, therefore, that the interplay between OxPLs and inflammation results in the severest cardiovascular phenotypes, whether that is the presence of angiographic CAD or acute CV events. Tsimikas et al. (1) studied 499 consecutive patients undergoing clinically indicated coronary angiography who were genotyped for common variants in the IL-1 locus that influence the pro-inflammatory cytokine IL-1β; specifically, *IL1A* (+4,845), *IL1B* (+3,954 and −511) and 4 specific haplotypes (IL-1[+]) known to be associated with higher levels of the inflammatory cytokine IL-1β were compared with haplotypes associated with lower levels of IL-1β (IL-1[−]). The pro-inflammatory haplotypes studied have also been previously associated with high circulating levels of C-reactive protein (CRP), presumably via IL-1β–mediated stimulation of IL-6, which is the main driver for CRP production. Using a definition of CAD as diameter stenosis >50%, Tsimikas et al. (1) assessed the relationship between IL-1(+) status and the presence or absence of CAD across quartiles of OxPL/apoB and Lp(a) using cross-sectional data and essentially a case–control design. Interestingly, IL-1(+) and IL-1(−) subjects were well-matched and did not differ in the presence or absence of CAD or in the extent of CAD, OxPL/apoB, or Lp(a).

In their analyses (for simplicity described here as) focusing on quartile 4 (Q4) versus quartile 1 (Q1) of lipid parameter, OxPL/apoB was associated with an increased risk for CAD (odds ratio [OR]: 1.96) overall, which among IL-1(+) patients was even stronger (OR: 2.84) but was absent among the IL-1(−) cohort. If genetic influences play a significant role in modulating phenotype, we would expect the impact of these to occur in younger patients. This is exactly what the authors observed, with a rather impressive significant OR of 7.03 among the <60-year age strata when assessing the risk of IL-1(+) genotype among those with OxPL/apoB Q4 versus Q1. By contrast, there was no significant association with CAD among those age <60 years who were IL-1(−); and among those >60 years of age, there was no significant association between OxPL/apoB and risk irrespective of genotype, suggesting that the risk from elevated levels of OxPL/apoB is greatest among those who are younger and who have an IL-1(+) inflammatory haplotype (p for

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From the Cardiovascular Sciences Research Centre, St. George's University, London, United Kingdom. Dr. Ray has received honoraria (modest) for consulting and is a member of the speaker's bureaus and advisory committees from Pfizer Inc., AstraZeneca Pharmaceuticals LP, Merck Sharp & Dohme, Abbott Laboratories, Roche Therapeutics Inc., Regeneron Pharmaceuticals, Inc., Aegerion Pharmaceuticals, Inc., The Sanofi-Aventis Group, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Eli Lilly and Co., Daiichi-Sankyo, Inc., Amgen Inc., and Bristol-Myers Squibb Co. Steven Nissen, MD, served as Guest Editor for this paper.

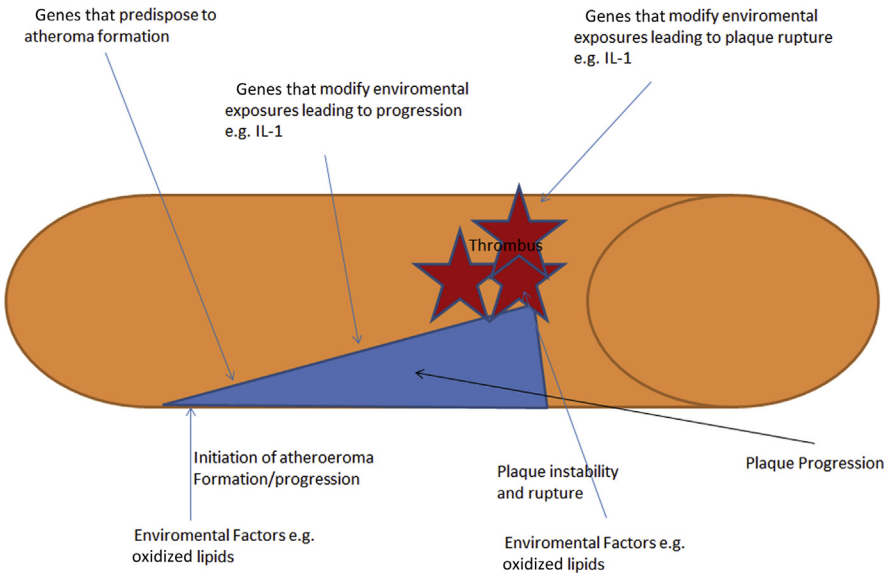

Figure 1 **Schematic of the Interaction Between Multiple Genes and Multiple Exposures to Influence Coronary Artery Disease and Acute Coronary Syndromes**

IL = interleukin.

interaction = 0.007). Similarly, when the risk associated with higher Lp(a) was assessed (Q4 vs. Q1), the results were qualitatively similar (OR: 9.0 in the <60-year age stratum for IL-1[+] status), with evidence of increased risk particularly among younger subjects with a pro-inflammatory IL-1(+) haplotype (p for interaction = 0.019). Further data to support this potentially biologically relevant interaction were also provided by the authors in the form of data that showed that patients with IL-1(+) haplotype and OxPL/apoB levels greater than median presented for clinically warranted cardiac catheterization 3.9 years earlier, with the corresponding figure for Lp(a) being 3.5 years. This interaction was not only relevant for the presence of angiographic disease, but as the authors show with longitudinal data, the same consistent interactions were observed with risk for future acute CV events. For instance, when IL-1(+) and IL-1(−) genotype were compared crudely, no real trend emerged with longitudinal risk. However, when data were stratified by haplotype and OxPL/apoB exposure, then 4-year risk for death, MI, stroke, and/or need for revascularization were greatest among those with IL-1(+) haplotypes with OxPL/apoB greater than median (p = 0.002 vs. all other groups), with evidence of an interaction (p for interaction = 0.002). Qualitatively similar results were observed for Lp(a), with the greatest risk observed among IL-1(+) genotype when Lp(a) was greater than median compared with all other combinations (p = 0.034; p for interaction = 0.014). Tsimikas et al. (1) is the first study to provide compelling evidence that inflammation modulates oxidized lipids to influence the presentation of CAD.

So how might the IL-1 locus influence CAD? Firstly, inflammation is known to be integral to the pathophysiology of coronary atherosclerosis and ACS, and histopathologic data indicate that the pro-inflammatory cytokine IL-1 is abundant in atherosclerotic tissue compared with healthy controls and that levels are particularly increased within the vessel wall in subjects with ACS. The naturally occurring antagonist of IL-1, IL-1 receptor antagonist (IL-1Ra), is also found in atherosclerotic tissue (specifically the endothelium), and the balance between these 2 cytokines may determine a number of cellular responses. Indeed, in diseases known to have an inflammatory etiology, such as inflammatory bowel disease, a relative excess of IL-1 to IL-1Ra has been associated with chronicity and severity of symptoms. The IL-1 locus on chromosome 2 (2q13) contains 3 important genes (*IL1A, IL1B,* and *IL1RN*) coding for 2 pro-inflammatory cytokines, IL-1α and IL-1β, and their antagonist, IL-1Ra, in partial linkage disequilibrium. These genes appear to be functional with genetic variants associated with differences in levels of CRP as well as IL-1α, IL-1β, and IL-1Ra in both plasma and within the endothelium (6). Furthermore, genetic variations at the IL-1 locus, specifically, *IL1A* (−889 or +4,845), *IL1B* (−511 or +3,953), and *IL-1RN* (+2,018), have been associated with a number of diseases that have an inflammatory etiology, including CAD (7,8), and this risk is further increased in the presence of environmental factors such as *Chlamydia pneumonia* (9). Among patients with diabetes, genetic variations in *IL1RN*(+2,018) (known to be associated with lower circulating levels of