Editorial

Polymorphism of the Lipopolysaccharide Receptor (CD14) and Myocardial Infarction

New Evidence for a Role of Gram-Negative Bacterial Infection?

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The idea that an inflammatory response directed at microorganisms might contribute to the atherogenic process is not new. In the last century, Virchow noted histopathological parallels between bacterial infection and atheromata. Recent reports have rekindled interest in the possibility that infection, particularly by Gram-negative bacteria, may contribute to the inflammatory component of atherosclerosis (including the major acute event of myocardial infarction) and that activation of monocytes may contribute to myocardial infarction as well as atherogenesis. Two European groups have now independently tested the hypothesis that genetic variations in the receptor for lipopolysaccharides (LPSs; endotoxins) produced by Gram-negative bacteria, CD14, may be a risk factor for myocardial infarction. Each group, one from Germany and the other from the Czech Republic, found a common polymorphism in the upstream, untranslated region of the CD14 gene. At the polymorphic site, cytosine or thymine polymorphism in the promoter region of the CD14 gene by Spl transcription factor binding site known to have a major influence on CD14 expression. Moreover, each group has reported evidence that expression of the T allele may be a risk factor for myocardial infarction.

The designs of the 2 studies were distinct. The German study of 2228 patients in Giessen and Bad Nauheim, all of whom had undergone diagnostic coronary angiography for suspected coronary heart disease (CHD), was reported this year. The genotype (CC, TC, or TT) was assessed by single-strand conformation or restriction fragment length analysis, and in some cases by both methods. The overall distribution was 28% CC, 50% CT, and 22% TT. No evidence for variation in this distribution was found according to extent or severity of disease or between those who had a history of myocardial infarction and those who did not. Moreover, the allele expression was unrelated to a number of established CHD risk factors. However, among normotensive TT homozygotes, the relative risk of past myocardial infarction was 1.4, and for normotensive nonsmokers it was 1.6, the latter value being statistically significant in both univariate and multivariate regression analysis. The relative risk (3.8) was highly significant for normotensive nonsmokers >62 years old but not for younger patients. The results of the subgroup analysis involving a small fraction of the total population in this study must be interpreted cautiously. Moreover, as noted by the authors, the T allele was overrepresented only in a subgroup of older patients and could therefore be a negative rather than positive risk factor.

The Czech report in this issue of Circulation was a case-control study involving 178 men (average age, 56 years) with myocardial infarction admitted to 2 coronary care units in 2 districts of central Bohemia. Controls were all from a nearby Czech district and represented a randomly selected 1% population sample: 135 men with an average age of 55 years. The Czech investigators identified the same common polymorphism in the promoter region of the CD14 gene by restriction fragment length analysis. Among patients, the frequency of the 3 genotypes was similar to that of the total group of Germans (29% CC, 43% CT, and 27% TT), but among controls the distribution was strikingly different (45% CC, 39% CT, and 16% TT). The differences in genotype and T allele frequency were highly significant. As in the German study, the CD14 polymorphism was unrelated to a number of established CHD risk factors, but surprisingly, none of these conventional risk factors differed significantly between the Czech patient and control groups.

The Czech investigators also found that the density of CD14 among 38 healthy young men was significantly higher (by ≈40%) on blood monocytes from TT homozygotes than from the other 2 genotypes.
Taken alone, each study is suggestive that the T allele may be a new risk factor for myocardial infarction, and the Czech study provides a possible mechanism (increased CD14 expression) involving the Spl promoter site in the CD14 gene. The T allele is sufficiently common to exert a significant influence on the course of CHD in these 2 populations. That the German and Czech populations studies are genetically distinct is suggested by the location of the latter in central Bohemia. In some parts of Bohemia, German admixture may be substantial. In a northern Bohemian district, for example, the insertion/deletion polymorphism of the ACE gene is consistent with considerable German admixture. In central Bohemia, by contrast, the allele frequencies of this polymorphism differ and resemble those of some other Slavic countries (R. Poledne, personal communication, 1999). Thus, despite obvious differences in design, the findings suggest association of the T allele of CD14 with myocardial infarction in 2 European ethnic groups.

What possible mechanistic connection can be made between a receptor for bacterial endotoxins and clinical coronary disease? Clearly there is a large inflammatory component in atherogenesis. Furthermore, the decreased plaque stability that underlies acute occlusive coronary syndromes is attributed chiefly to the inflammatory response of macrophages. LPSs present a protopathic threat to vertebrates, against which a complex system of defense has evolved. LPSs are bound in plasma by the LPS binding protein (LBP), a structural homologue of the plasma phospholipid transfer protein. A soluble splice variant of CD14 (sCD14) occurs in plasma. The binding of LPS to sCD14 is greatly accelerated by LBP. LPS can be transferred directly to HDLs by LBP, but the transfer from sCD14 is much faster. This reaction may serve to damp the activation by endotoxins. Two soluble splice variants of CD14 (sCD14) occur in plasma. The binding of LPS to sCD14 is much faster. This reaction may serve to damp the LPS-induced release of tissue factor by macrophages and endothelial cells would have procoagulant activity. The further finding that the LPB is capable of transferring phospholipids to sCD14 suggests that these proteins could affect the structure and speciation of HDLs in addition to changes in the lipoproteins that may attend their uptake of LPS. Thus, if the C(−260)→T polymorphism indeed leads to differences in the density of the mCD14 on cells as described by Hubacek et al., it could influence several inflammatory and other processes that might be involved in a contribution by bacterial endotoxins to atherogenesis. It will also be important to determine the effect of the polymorphism on the content of sCD14 in plasma.

The data from Czech and German populations clearly call for confirmation in other ethnic groups as well as in prospective studies. It could be of particular interest to test the association of the T allele with myocardial infarction in more isolated and genetically homogeneous ethnic groups known to be at high risk. In Finns, a recent study of Y chromosome haplotypes indicates a dual origin. Many Finns descended from early Asian immigrants have a common Y haplotype. Such an analysis among Finns might thus be concentrated on this distinctive genetic isolate, which predominates in northern Karelia and certain other provinces.

References


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