Gene polymorphisms of pro- (or anti-) inflammatory cytokines and vascular disease

In this issue, Humphries and colleagues furnish new evidence that a polymorphism in the interleukin-6 gene is associated with coronary artery disease\(^1\). This paper indicates that inflammation has an important role both in the development of atherosclerotic plaques and in their clinical expression. The data further suggest that gene polymorphisms in genes coding for pro- (or anti-) inflammatory cytokines may be useful markers of an increased vascular risk.

Inflammation and vascular disease

The role of inflammation in vascular disease has attracted widespread interest; atherosclerosis is a chronic inflammatory disease of the arterial wall characterized by progressive accumulation of lipids, cells (macrophages, lymphocytes, and smooth muscle cells), and extracellular matrix proteins\(^2\). Inflammatory cells, which are present in arterial lesions, are considered to be key players in various processes such as plaque progression, plaque rupture, and vessel thrombosis\(^3\); inflammation has also been linked with aneurysm formation, another clinical manifestation of atherosclerosis. Studies that evaluated serum markers of inflammation such as C-reactive protein have provided important information on the relationship between inflammation and vascular disease: elevated levels of C-reactive protein have been associated with a higher risk of future coronary events and with a worse clinical outcome in patients with unstable coronary syndromes.

Although the mechanisms of the inflammatory vascular response to atherosclerosis are still the subject of intensive investigations, various cytokines have been implicated. The pro-inflammatory cytokine interleukin-6 is a central mediator of the acute-phase response and a primary determinant of hepatic production of C-reactive protein\(^4\). Interleukin-6 gene transcripts are expressed in human atherosclerotic lesions\(^5\). Elevated levels of interleukin-6 have been reported among patients with acute coronary syndromes\(^6\) and are associated with increased risk of future myocardial infarction in apparently healthy men\(^6\). Other pro-inflammatory cytokines such as interleukin-1 or tumour necrosis factor alpha may act via stimulation of the production of interleukin-6\(^7\); plasma concentrations of tumour necrosis factor alpha are persistently elevated among post-myocardial infarction patients at increased risk for recurrent coronary events. Less information is available regarding the role of anti-inflammatory cytokines in atherosclerosis; it has, however, recently been demonstrated that the anti-inflammatory cytokine interleukin-10 may act as a protective factor in atherosclerosis. Interleukin-10 is expressed both in early and in advanced human atherosclerotic plaques\(^8\) and inhibits many cellular processes, such as metalloproteinase production or tissue factor expression that may potentially play a role in the clinical expression of atherosclerotic plaque rupture or erosion.

Genetics of inflammation and vascular diseases

Numerous studies have underlined the importance of genetic variations as susceptibility factors for atherosclerosis: polymorphisms in genes coding for proteins involved in the regulation of lipid metabolism, thrombosis, proteolysis, or in the control of neurohormonal activation have been associated with an increased risk of atherosclerosis. Insights into the important role of inflammation in the pathogenesis of vascular diseases have led to the hypothesis that gene polymorphisms in pro- (or anti-) inflammatory cytokines may also be markers of increased vascular risk. In the present paper by Humphries et al., the C allele of the \(-174 G>C\) polymorphism in the promoter of interleukin-6 was found to be associated with significantly higher systolic blood pressure and with higher risk of coronary artery disease in healthy men. Although further work needs to be done to clarify...
the relationship between the increased levels of interleukin-6 during the course of atherosclerosis and the interleukin-6 –174 G>C polymorphism, these results demonstrate that genetic variations in the inflammatory system are potentially important modulators of vascular risk.

Apart from these new data on interleukin-6, other polymorphisms in the inflammatory system have previously been described and may also be relevant to the control of vascular inflammation. The interleukin-1 receptor antagonist gene polymorphism has been associated with coronary artery disease\(^9\) and with restenosis after coronary stent implantation\(^10\). Polymorphisms in tumour necrosis factor alpha and interleukin-10 genes\(^11,12\) may partly determine cytokine production and thus also be involved in the genetic regulation of vascular inflammation. Combinations of different polymorphisms may permit us to define groups of patients according to their susceptibility to inflammation and thus to provide a better estimate of the risk of atherosclerosis (as it has already been reported for prediction of the risk of heart transplant rejection\(^13\)). Such hypotheses would have to be tested in large prospective studies with clinical end-points. However, smaller, carefully designed, studies will also be useful to test for associations between genotypes and intermediate phenotypes; the pathogenesis of vascular diseases reflects a complex interaction of diverse mechanisms such as plaque progression, plaque rupture, extra-cellular matrix remodelling, or thrombosis; the impact of a given genotype may vary according to the mechanism considered. This can be illustrated by previously published studies on the 5A/6A polymorphism in the gene of the metalloproteinase stromelysin-1 (MMP3). While the more active (5A) allele has been associated with acute coronary syndromes or aneurysmal disease\(^14\) (two situations in which increased proteolysis may be important), the less active (6A) allele has been associated with angiographic progression of coronary artery disease\(^15\) or restenosis after balloon angioplasty (two situations in which decreased proteolysis and subsequent matrix deposition may play a role).

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References


