Editorial

CMV endothelitis as a factor in the pathogenesis of atherosclerosis

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See article by Guetta et al. [8] (pages 538–546) in this issue.

Although many factors that contribute to the development of atherosclerosis are known, major parts of its etiology need still to be elucidated. Since the 1970’s a link between infectious disease and atherosclerotic disease has been hypothesized [1–3]. Infectious agents that are implicated in the pathogenesis of atherosclerosis include bacterial pathogens, such as Helicobacter pylori or Chlamydia pneumoniae, but also viruses are thought to play an important role [4]. Cytomegalovirus (CMV) is one of the most intense studied viruses as related to its potential role as a causative infectious agent that may contribute to the development of atherosclerosis [5]. There are several lines of evidence that CMV may be involved in atherogenesis. Firstly, more than 20 epidemiological studies show a relationship between the presence of CMV antibodies in serum and atherosclerotic disease. The odds ratio for atherosclerosis in CMV antibody positive patients in most of these studies is around 2. Although many of these studies had a relatively small sample size, may have been influenced by confounding factors, and were performed in patients with secondary atherosclerotic changes rather than primary atherosclerosis, the picture is quite consistent [3]. A second bit of evidence comes from another series of studies, in which detection of (parts of) the virus or pieces of the CMV genome are related to the presence of atherosclerotic plaques [6]. CMV can be found in vascular smooth muscle cells, endothelial cells and mononuclear cells that are involved in the atheromatous plaque. Although the difference between the presence or absence of CMV in vessels with or without atherosclerosis is relatively small, an important part of the effect may be obscured by detection failures. Thirdly, prospective studies show that accelerated atherosclerosis is more common in coronary arteries of transplanted hearts of patients that are CMV positive as compared with CMV negative patients [7]. Taken together, there may be some, though not yet convincing, indication that CMV infection is implicated in the pathogenesis of atherosclerosis.

The molecular mechanism, by which CMV infection may interfere in the pathogenetic pathways leading to atherosclerosis, is only partly understood. CMV infection is common and about 50% of adults has experienced a (usually asymptomatic) infection in their life. Hereafter, the virus remains present in cells in a latent state. Viral replication may be ongoing at a low level and involves the expression of different sets of genes. The first viral genes expressed are immediate early genes, which may mediate promoter activity of subsequent sets of genes. Proteins that are encoded by these genes exert transcriptional modulation of other viral genes and may affect host cell regulation. From this perspective, CMV infection of endothelial cells may indeed affect endothelial cell properties and may contribute to changes that lead to the development of atherosclerosis. In this issue of Cardiovascular Research, Guetta et al. provide more insight in the role of immediate early gene products on endothelial cell gene activity and adhesive properties of endothelial cells [8]. In particular, the authors describe the effect of CMV immediate early gene products IE72 and IE84 on relative promoter activities of cellular growth factor and adhesion molecule genes. Furthermore, they demonstrate that CMV immediate early gene expression leads to an increase in monocyte adhesion to endothelial cells. These observations contribute importantly to the knowledge on the potential mechanisms by which CMV infection may lead to vascular atherosclerotic changes. Most of the previous work focused on the role of CMV in vascular smooth muscle cells, showing an enhancement of cell proliferation, elevated growth factor expression (particularly platelet-derived growth factor), apoptosis and increased uptake of oxidized LDL by these cells [9,10]. The present observation is related to the effect of CMV infection of endothelial cells, which may indeed experience important modulation due to CMV infection and viral replication. Earlier studies showed that endothelial cells that were infected with CMV
were more procoagulant, were more capable of leukocyte adhesion, and showed inhibition of nitric oxide-driven vasomotor response [11]. In addition, acute and chronic infection with CMV after carotid artery injury in rats caused increased neointimal accumulation [12]. In the present report, the focus is again on endothelial cells as a target of CMV infection. The endothelial cells that were challenged with immediate early gene products of CMV replication indeed showed changes that are compatible with the development of atherosclerosis. Interestingly, Guetta et al. also demonstrate a modulatory effect of thrombin on the CMV immediate early gene-induced changes in endothelial cells. Cross-talk between coagulation proteases, infectious agents, and inflammatory responses is indeed thought to occur in the complex mechanisms leading to atherosclerosis and acute atherothrombotic events [13,14].

In conclusion, there are biological and epidemiological indications that CMV infection of endothelial cells and the subsequent endothelial cell response (‘CMV endothelitis’) may play a role in the pathogenesis of atherosclerosis. Much more proof, however, will be needed before the existence of this putative link can be firmly established. In addition, at this stage the relative clinical importance of CMV infection for the occurrence of atherosclerotic disease is completely unclear. Nevertheless, studies such as the present report of Guetta et al. [8] will be helpful in assessing the role of CMV as an etiologic factor in the development of atherosclerosis.

References


