Chlamydia pneumoniae and Endothelial Activation
The Smoke That Precedes the Fire of Atherosclerosis?

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Exactly 100 years ago, the physician Sir William Osler suggested an important role for infection, in the pathogenesis of atherosclerosis. Indeed, it is now well accepted that atherosclerosis is a disease with a large inflammatory component. In addition to traditional risk factors, such as hypertension, hyperlipidemia, diabetes, and smoking, previous, as well as chronic or recurrent, infection has emerged as a novel risk factor for atherosclerosis. Cytomegalovirus, herpes simplex virus, Helicobacter pylori, and hepatitis A are a few examples of pathogenic agents that have been, in 1 form or another, associated with atherosclerosis. However, no association appears to have garnered more attention, or plausibility, than that between Chlamydia pneumoniae (formerly Chlamydia pneumophila) infection and atherosclerosis.

C pneumoniae is an obligate intracellular and Gram-negative bacterium and is primarily a pathogen of the respiratory system. Based on serological studies, the prevalence of C pneumoniae, has been estimated to be ~50% in young to middle-aged adults and can reach as high as 70% with advanced age, suggesting that C pneumoniae exposure is not only common but is also recurrent during one’s lifetime. C pneumoniae accounts for nearly 10% of all community-acquired bacterial pneumonias and is categorized among the “atypical pneumonias,” including that caused by Mycoplasma pneumoniae and Legionella pneumophila, and is capable of causing chronic as well as subclinical infection.

The first evidence linking C pneumoniae infection and atherosclerosis was obtained from the finding that individuals with coronary heart disease and acute myocardial infarction were found to posses significantly higher titers of C pneumoniae–specific IgG antibodies than that in individuals without cardiovascular disease. Subsequent studies found that C pneumoniae infection is resident among arterial fatty streaks, as well as in advanced atherosclerotic plaques. Moreover, a cadre of approaches and advanced technologies, including immunohistochemistry, RT-PCR, electron microscopy, and tissue microarray technology, have confirmed the presence of C pneumoniae in atherosclerotic lesions as well as in vascular tissue. Based on such approaches, it has been estimated that C pneumoniae is present in approximately 50% to 60% of atheromatous tissue, whereas the prevalence in samples from patients without evidence of atherosclerosis is less than 5%. It is also possible to isolate and culture the bacterium from atherosclerotic lesions, indicating that the pathogen is not only viable but is also capable of active replication. Thus, the present body of evidence is highly suggestive of a causal role for C pneumoniae infection in atherosclerosis.

Although the evidence suggests a role of C pneumoniae in atherosclerosis, what is not clear, however, is exactly what role C pneumoniae plays in the initiation of the atherosclerotic process. One possibility involves C pneumoniae in endothelial activation. Endothelial activation has been defined as a phenotypic change in endothelium involving increases in leukocyte adherence and transmigration accompanied by activation of the inflammatory response and is considered one of the early events in the atherosclerotic process (Figure). C pneumoniae can be found to infect all of the major cellular players involved in the pathogenesis of atherosclerosis, including endothelium, smooth muscle, and monocytes/macrophages. When cocultured, C pneumoniae–infected macrophages can infect endothelium and smooth muscle cells, thereby demonstrating a mode of transference of a respiratory pathogen to the vasculature.

Among the antigenic determinants of infection, both C pneumoniae–derived heat shock protein 60 and lipopolysaccharide have been implicated as likely mediators of endothelial activation in response to C pneumoniae infection. C pneumoniae–derived heat shock protein 60 and lipopolysaccharide mediate their effects, in part, through activation of nuclear factor (NF)-κB, a major transcription factor involved in the regulation of a large array of inflammatory gene products, such as E-selectin, P-selectin, interleukin (IL)-6, IL-8, platelet activator inhibitor-1, basic fibroblast growth factor, and tumor necrosis factor-α. Alterations in the inflammatory gene expression profile are important, because they have been shown to contribute to vascular injury, including endothelial dysfunction. For example, IL-6 expression in the vascular wall plays an important role in mediating the endothelial dysfunction produced by inflammatory stimuli, such as angiotensin II. Thus, examination of the molecular mechanisms involved in C pneumoniae–induced endothelial activation and dysfunction are critical in unraveling the contribution of this pathogen to cardiovascular disease.

In this issue of Circulation Research, Schmeck et al present convincing evidence for a role of C pneumoniae–induced histone modification in the inflammatory activation of endothelium. Using an in vitro model of direct C pneumoniae infection of human endothelial cells, they were able to provide insight into the effects of C pneumoniae on endothelial activation without the confounding influence of...
C. pneumoniae infection has been associated with the pathogenesis of atherosclerosis. C. pneumoniae is capable of infecting the cells of the vasculature, including endothelium. Perhaps more important, C. pneumoniae infection can produce a phenotypic change in endothelial cells, often referred to as endothelial activation. Alterations in inflammatory gene products have been associated with endothelial activation in response to C. pneumoniae infection, including genes associated with activation of the transcription factor NF-κB (NFκB). In addition, histone modification, including acetylation and phosphorylation, has emerged as a key regulator of transcription. The findings by Schmeck et al suggest that histone modification plays an important role in endothelial activation in response to C. pneumoniae infection, including increases in endothelial cytokine release. G-CSF indicates granulocyte colony-stimulating factor; ICAM, intercellular adhesion molecule; IL, interleukin; MIP, macrophage inflammatory protein; VCAM, vascular cell adhesion molecule.

Among their many pleiotropic effects, hydroxymethylglutaryl coenzyme A reductase inhibitors have been shown to possess antioxidant and antiinflammatory properties that are independent of their cholesterol-lowering effects. Antiinflammatory actions of simvastatin may be mediated, in part, through inhibition of small GTP-binding Rho protein family members, including Rac1. Consistent with such effects, cytokine secretion could be reduced with simvastatin, as well as the specific Rac1 inhibitor NSC23766, in the present study, suggesting a role for small Rho/GTPases in this response. Cells treated with NSC23766, as well as simvastatin, were found to associated with reductions in global histone acetylation, as well as phosphorylation, of specific histone residues. Moreover, inhibition of histone deacetylase with trichstatin A or suberoylanilide hydroxamic acid served to synergistically enhance the C. pneumoniae–mediated increase in cytokine release.

To demonstrate that the observed increase in global histone acetylation had specific functional effects on gene transcription, the authors selected to further examine the degree of acetylation of the IL-8 gene promoter on IL-8 gene expression. Consistent with the concept that acetylation of promoter regions is key element in the transcriptional regulation of chromatin, the authors found acetylation of the IL-8 gene promoter region increased in response to C. pneumoniae infection and was associated with enhanced recruitment of NFκB (p65/RelA) as well as RNA polymerase II. Moreover, the activation of NFκB as well as RNA polymerase II could be blocked in cells treated with the hydroxymethylglutaryl coenzyme A reductase inhibitor simvastatin.
The present data clearly demonstrate that Rac1-mediated histone modification plays a critical role in C pneumoniae-mediated endothelial activation, as well as in inflammatory gene expression and release. How do such findings translate to humans with previous or chronic C pneumoniae infection, specifically in terms of vascular function? Preliminary data suggest that patients who are seropositive for C pneumoniae IgG antibodies do not demonstrate any alterations in endothelial-dependent responses. Interestingly, however, patients who are seropositive for other infectious agents, such as cytomegalovirus, in addition to C pneumoniae, are found to display reductions in endothelial function. Such findings support the concept that it may be the total pathogen burden (as opposed to any single microorganism) that influences the degree of vascular dysfunction associated with infection. In contrast, repeated C pneumoniae exposure is capable of inducing endothelial dysfunction in apolipoprotein E–deficient mice. Although alterations in nitric oxide signaling have been suggested, the exact contribution of inflammatory mediators, as well as increases in oxidative stress to C pneumoniae–induced reductions in nitric oxide–mediated signaling and endothelial dysfunction, is presently unclear. In addition to impairment of endothelial function, the degree of aortic lipid accumulation can be markedly enhanced in mice following infection with C pneumoniae, suggesting that alterations in inflammatory gene expression following C pneumoniae infection may be exacerbated by the intracellular accumulation of lipids, which may also contribute to endothelial dysfunction. In conclusion, the findings by Schmeck et al suggest that alterations in inflammatory gene expression following C pneumoniae infection may serve to promote endothelial activation, the proverbial kindling for the fire of atherosclerosis.

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References


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