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Commentary

Heat shock proteins and atherosclerosis

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Stress proteins or heat shock proteins (hsps) are a group of families of approximately two dozen proteins and cognates showing highly homologous sequences between different species, from bacteria to man. Increased hsp expression, induced by different types of stress, such as infections, high temperature, free radicals or mechanical stress, provides the cells with protection from environmental insults [1–3]. Endothelial cells, macrophages and smooth muscle cells localized in atherosclerotic lesions express hsp at high levels [4], which is subjected to various stresses. Interestingly, hsp60, recognized as a mitochondrial protein, was identified as appearing on the cell surface [5,6]. It has also been demonstrated that hsp60 is present as a soluble form in circulation and correlated with severity of atherosclerosis [7,8]

There is evidence that both chlamydial and human hsp60 have a cytokine-like activity and induce tumour necrosis factor- (TNF-) alpha and matrix metalloproteinase (MMP-9) production by human and mouse macrophages [9,10]. Importantly, both chlamydial or human hsp60 induced E-selectin, ICAM-1, and VCAM-1 expression and IL-6 production on endothelial cells [11]. These findings suggest that hsp60 directly stimulates vascular endothelial cells and macrophages, leading to an inflammatory response, which could contribute to the pathogenesis of atherosclerosis.

In this issue of *European Journal of Clinical Investigation*, Prohaszka and colleagues [12] provide novel data that indicate an even stronger correlation between autoantibodies against human hsp60 and atherosclerosis, although a difference in anti-mycobacterial hsp65 or GroEL antibody titers between healthy donors and patients with severe atherosclerosis exists. What can we learn from such studies about the pathophysiology of atherosclerosis?

Growing evidence indicates associations between infections and vascular disease [13]. How infections are involved in vascular disease remains to be elucidated. Increased blood viscosity, hypercoagulability and alterations of the serum lipid profile are postulated mechanisms. *C.pneumoniae*, *H.pylori* or cytomegalovirus infections may contribute to local inflammation by cytokine induction or antigen stimulation [13]. However, immune reactions to bacterial hsp65 may be a possible link between the various incriminated microorganisms and atherogenesis [14]. Abundant bacterial hsp65 may evoke an anti-self immune response in susceptible individuals due to its high sequence homology with the human homologue, as hypothesized by Wick *et al.* [15]. Indeed, circulating hsp65 antibodies are absent in specific pathogen-free animals. Likewise, Prohaszka *et al.* [12] confirmed the association of anti-*H.pylori* antibodies with antibacterial hsp65 or GroEL antibodies in humans, suggesting that induction of hsp65 antibodies primarily depends on infections.

On the other hand, Prohaszka *et al.* [12] demonstrated that autoantibodies against human hsp60 are independent of *H.pylori* infections and weakly correlated with the presence of antibodies to bacterial hsp65 or GroEL. They also found that autoantibodies to human hsp60 and antibodies to mycobacterial hsp65 present in the sera of patients with atherosclerosis have different epitope specificity and complement activating ability [16]. According to this hypothesis, the production and the pathogenic involvement of antibacterial hsp65 antibodies and anti-human hsp60 autoantibodies in atherosclerosis are different. Support for this notion is the coexistance of circulating soluble hsp60 antigen and antimycobacterial hsp65 antibodies in subjects with atherosclerosis [17], indicating that these antibodies may not bind to soluble hsp60 in circulation. However, Western blot analysis provided solid evidence that antimycobacterial hsp65 antibodies did bind to human hsp60 [18]. The contradictory phenomena observed *in vivo* and *in vitro* might reflect the difference between native and denatured hsp60.

Schett *et al.* [19] demonstrated that antimycobacterial hsp65 antibodies mediate endothelial cytotoxicity via cross-reactivity to human hsp60, implicating that endothelial cell injury might be induced *in vivo* [15]. If autoantibodies to human hsp60 are also a predictive

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parameter for atherosclerosis and independently exist in patients with severe atherosclerosis, it would be interesting to further study the mechanisms of the autoantibody production and how they are involved in the pathogenesis of atherosclerosis. I believe that search for the answer of these questions could enhance our understanding of the pathophysiology of atherosclerosis.

Added in proof

During the process of the manuscript, a similar study showing an association of anti-human hsp60 antibodies and coronary artery disease has been published in *Circulation* 2001; **103**: 1071–1075.

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