Editorial

The Heat Is on
Heat-Shock Proteins and Atherosclerosis

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It is common knowledge that atherosclerosis is a multifactorial disease, and the disease-promoting role of classic risk factors for atherosclerosis, such as high serum cholesterol levels, diabetes, hypertension, smoking, and various types of infections, has been proven in innumerable clinical studies. Despite the fact that we are dealing with a chronic disease, however, there is a surprising scarcity of reports dealing with the very first stages of atherogenesis, ie, those that are not yet leading to clinical symptoms. It is now evident that inflammatory/immunologic processes play a major role in the development of atherosclerosis. The correlation between the presence and amount of inflammatory surrogate markers and the occurrence of sonographically demonstrable early arterial changes becomes more significant the earlier in the course of the disease that these analyses are performed. Although complicated atherosclerotic lesions, as the name implies, are composed of many different cellular and extracellular constituents, the earliest lesions are characterized by intimal infiltration by mononuclear cells often still without the presence of foam cells, especially in those instances in which risk factors other than high serum cholesterol levels are operative. In this context, it is important to remember that the first intima-infiltrating cells in early, clinically nonapparent lesions are lymphoid cells, followed by blood-borne monocytes, and finally smooth muscle cells immigrating from the media.1 Later, both the scavenger receptor–expressing macrophages and smooth muscle cells may transform into foam cells accompanied by fibroblast and myofibroblast proliferation with collagenous and noncollagenous extracellular matrix protein deposition leading to the paradigmatic hardening of the arterial wall. The antigenic specificity of early intima-infiltrating lymphoid cells is still to be determined.

In this issue of Circulation, Park et al2 address the possible role of heat shock protein (HSP) 27 in atherogenesis. HSPs have risen to prominence in atherosclerosis research for 2 reasons: (1) They represent the response of cells of the vessel wall to various stressors, notably classic atherosclerosis risk factors, and (2) they are targets for innate and adaptive immune reactions initiating and perpetuating the vascular inflammatory process. HSPs are classified into various families according to their molecular weight, ranging from large (90 to 100 kDa) to very small (<10 kDa) forms. HSPs are among the phylogenetically most conserved molecules showing a high-sequence homology from prokaryotes to humans. Thus, there is a >97% homology of HSP60 between different bacterial species, and bacterial and human HSP60 still display a >55% overall homology, amounting to >70% at certain molecular domains. Under physiological conditions, HSPs fulfill important roles for intracellular protein folding, transport, and degradation. Under stress conditions, they also act as chaperones, ie, they associate with other cellular proteins and protect them from denaturation.3

HSP60 and HSP70 have received increasing attention in atherosclerosis research, whereas little has been published on HSP27 on this context. Thus, immobilization or surgical stress leads to an upregulation of inducible HSP70 and HSP27 in rats on both RNA and protein levels. The greatest abundance of HSP70 expression was observed in the adrenal system, followed by the vascular system, notably in the aorta.4

On being subjected to atherosclerosis risk factors, both HSP60 and HSP70 are expressed by endothelial cells at those territories of the arterial vessels that are subjected to turbulent rather than laminar shear stress flow conditions, ie, at the vascular branching points. Venous endothelial cells usually do not express HSP60 or HSP70. However, when they come under arterial blood pressure and flow conditions, eg, when used as arterial-venous bypass conduits, endothelial HSP60 expression and intimal mononuclear cell infiltration, which follows, are the first events that later lead to restenosis.5

HSP60 has attracted interest not only as a stress response and chaperone molecule but also as an important microbial and autoantigen, the latter representing biochemically modified autologous HSP60 released after cellular necrosis. Because during her or his lifetime every normal human being has mounted an immune response against microbial HSP60 and has developed bona fide autoimmunity against biochemically altered autologous HSP60, this protective defense may have to be “paid for” by a cross-reactivity with HSP60 expressed on stressed endothelial cells at the mentioned predilection sites for the development of atherosclerotic lesions. HSP70 does not seem to play a triggering role for the immunologic autoreactive process because in experimental animals only immunization with HSP60 but not HSP70 leads to the development of the first inflammatory stage of atherosclerosis.6
HSP27 forms dimers and tetramers that after phosphorylation associate with cytoskeletal actin and act as filament stabilizers under stress conditions. Furthermore, HSP27 is able to interfere with the apoptotic pathway, eg, by interacting with Daxx and Fas. It can also inhibit the release of the proapoptotic molecule Smac/Diablo and block the intrinsic pathway by increasing the retention of cytochrome c.

HSP27 has also been described to play an important role in promoting tumor genesis and growth, affording cellular protection in the central nervous system and exerting a chaperone function in the epidermis. In regard to the cardiovascular system, HSP27 expression has been found to be altered in congestive heart failure and is upregulated in stressed or vascular endothelial cell growth factor–activated human endothelial cells. It has also been reported that proinflammatory mediators (C-reactive protein) and cytokines (interleukin-6, tumor necrosis factor-α) are able to upregulate HSP27 expression.

The possible role of HSP27 in atherogenesis has been addressed only recently. In this issue of Circulation, Park et al studied the expression of HSP27 in human atherosclerotic plaques as well as the increased plasma levels of HSP27 in patients with acute coronary syndrome. Using 2-dimensional gel electrophoresis and Western blotting, the investigators analyzed 3 types of arterial tissues for the expression of HSP27, ie, atherosclerotic plaques, nearby normal-appearing areas from the same vessels, and nonatherosclerotic reference arteries. Of the list of many differentially expressed proteins, only HSP27 was studied in depth.

Interestingly, the authors found significantly increased HSP27 expression in the adjacent normal-appearing vessel areas compared with unaffected reference vessels. However, the phosphorylation of HSP27 was most pronounced in the normal reference arteries, intermediate in the adjacent normal-appearing areas, and lowest in the plaque core. In addition, in the lesional core region a lower degree of HSP27 expression emerged compared with areas adjacent to plaques. These findings were corroborated by immunohistological staining of the respective regions.

Analysis of the HSP27-containing area of 2-dimensional gels showed a surprisingly high number of spots, probably indicating posttranslational modification of the molecule. It would be interesting to investigate whether autoantibodies against these modified forms or fragments of HSP27 are formed during atherogenesis. That these various spots were indeed HSP27 was corroborated by matrix-assisted laser desorption-ionization time-of-flight mass spectrometry. In contrast to the increased expression of HSP27 in the normal-appearing adjacent areas, the phosphorylation of HSP27 was decreased at this site, entailing a significantly lower phospho-HSP27/total HSP27 expression ratio in the adjacent area compared with normal arterial tissue. In the plaque core areas, phospho-HSP70 was barely detectible. The expression of HSP70 was higher in both the plaque core areas and the adjacent normal-appearing areas compared with the normal reference tissue. The expression of β-actin was not different in any of the 3 types of specimens.

The fact that the highest degree of HSP27 expression was observed in the still normal-appearing area adjacent to the atherosclerotic plaque seems plausible because this is where the action is, ie, where inflammatory processes are most prominent. HSP27 has to be phosphorylated before fulfilling its chaperone function, and again the gradation in the degree of phosphorylation from normal reference arteries over the adjacent normal-appearing area toward the plaque supports this course of events.

The decrease of HSP27 expression toward the atherosclerotic core may be explained by the inversely increased proteolytic activity: Atherosclerotic plaques contain ample amounts of proteases, and extracellular HSP27 will therefore be degraded, whereas intracellularly located HSP27 in the adjacent still normal-appearing area is protected from this proteolytic process.

Can HSP27 be used as a diagnostic serum parameter similar to soluble HSP60? The authors show that there is no difference in HSP27 serum levels between a normal healthy reference group and a group having risk factors for coronary artery disease. In contrast to the known situation with HSP60 and HSP70, circulating levels of HSP27 do not seem to be correlated with risk factors for coronary artery disease, but significantly higher levels are seen in patients with acute coronary syndrome. Again, it would be interesting to also determine anti-HSP27 antibodies and perhaps HSP27-reactive peripheral blood T cells as additional parameters.

In summary, this article supports the notion that the stress response of the various cellular components of the vessel wall is an important trigger of atherogenesis, especially the earliest inflammatory stages that may still be accessible to modern diagnostic, preventive, and therapeutic measures. In addition to its chaperoning function during this process, it may be of interest to also address the possible role of HSP27 as an antigen recognized by the innate and/or adaptive immune system.

Disclosures

None.

References


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