Response: Is Low-Heat Shock Protein 70 a Primary or a Secondary Event in the Development of Atherosclerosis?

We thank Dr Philip Hooper and Dr Joanna Hooper for their comments on our recent article.1 Their question as to whether Hsp70 levels are low as a result of atherosclerosis or whether low Hsp70 levels are the primary event leading to atherosclerosis is clearly an important one. Our previous study in which we reported there to be no relationship between serum levels of Hsp70 and the presence of atherosclerosis in subjects with established hypertension, as determined on the basis of carotid intima-media thickness,2 would argue against the proposition that Hsp70 levels are low as a result of atherosclerosis. However, another study has reported Hsp70 levels to be lower in patients at the time of diagnosis of coronary artery disease by coronary angiography.3 In Zhu et al’s study, individuals exhibiting Hsp70 levels below the median had twice the risk of coronary artery disease than individuals with levels above the median, and disease severity (number of diseased vessels) was also inversely associated with circulating Hsp70 levels.3

As the Hoopers indicate, Hsp70 is a cytoprotective molecule, and a deficiency in its presence might increase the vulnerability of cardiovascular tissue to environmental and physical stressors. The majority of work in this area has focused on Hsp70 as an intracellular molecule, and little is known about its ability to protect cells when present in the extracellular environment. One study has addressed this issue and demonstrated that extracellular Hsp70 protects stressed aortic cells in culture by a mechanism that appears to involve cell surface binding, but not internalization.4 However, the mechanism by which this effect is achieved has never been elucidated.4

Key issues will be to identify the source of Hsp70 in the peripheral circulation and to determine the mechanism by which Hsp70 is released and whether extracellular levels reflect intracellular levels. Were the origin of circulating Hsp70 to be the endothelium, then it might be reasonable to assume that levels are influenced by endothelial dysfunction, either directly or via the compromised generation of nitric oxide. However, Hsp70 induces nitric oxide production from macrophages,5 and if it is similarly capable of inducing nitric oxide production from endothelial cells, then it might be difficult to distinguish the primary event and evaluate its significance to endothelial dysfunction.

Another mechanism by which Hsp70 might modify the establishment and/or progression of atherosclerosis is via an anti-inflammatory effect. Intracellular Hsp70 has been shown to attenuate inflammatory responses, because elevating intracellular levels of Hsp70 in the vasculature reduces leukocyte adhesion at inflammatory sites.6 Immunization with Hsp70 has also been shown to prevent disease in experimental models of autoimmunity.7–9 Although purely speculative at this time, it might be that elevated serum Hsp70 levels reflect an antiinflammatory and/or an antiatherogenic state.

In summary, the presence of heat shock proteins in the peripheral circulation is a relatively recently reported phenomenon10,11 and its biological and clinical significance has yet to be elucidated. The basis for the apparent relationship between high-serum Hsp70 levels and protection against atherosclerosis is currently unknown, and further work is required to understand the influence of extracellular Hsp70 on the pathogenesis of inflammatory disease.

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