Published in final edited form as:
J Am Coll Cardiol. 2013 October 15; 62(16): 1455–1456. doi:10.1016/j.jacc.2013.05.040.

Cooling the Fire of Atherosclerosis With Heat Shock Protein 27*

Neal L. Weintraub, MD and **Jack Rubinstein, MD**
Division of Cardiovascular Diseases, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

Abstract

Decades of research have increased our understanding of the role and interplay between serum cholesterol, inflammation, and oxidative stress in the pathogenesis of atherosclerosis (1). Uptake and retention of low-density lipoprotein (LDL) by macrophages in the intima is dependent on adhesion molecules and inflammatory cytokines and amplified by oxidative stress. This hostile environment is toxic to endothelial and smooth muscle cells, which further hampers vascular homeostasis. These interrelated steps provide potentially fruitful therapeutic targets for the prevention and treatment of atherosclerosis.

Keywords

apoptosis; estrogen receptor; inflammation; macrophage

Heat shock proteins (HSPs) may lie at this juncture, as they modulate immune responses, cytotoxicity, and oxidative stress. This class of proteins was discovered in the 1960s and initially described as inducing transient resistance to cell death in response to increasing temperature (2). Subsequently, subtypes were discovered and found to play unique biological roles as molecular chaperones, with some shown to protect cells from apoptosis induced by ischemia and energy depletion (reviewed by Kregel [3]).

HSP27 was found in the 1980s to play a predominantly antiapoptotic role (4) via modulating cytochrome C–mediated cytosolic activation of caspases (5). Its potential role in atherosclerosis subsequently emerged from basic investigations and studies of human vascular tissues. Martin-Ventura et al. (6) demonstrated that high levels of HSP27 were present in healthy vessels and decreased in atherosclerotic plaques, with circulating HSP27 being decreased in patients with carotid artery disease compared with healthy controls. A follow-up in vitro study suggested that HSP27 may induce plaque stability through modulation of plasmin and other mediators of apoptosis (7). Moreover, an electrophoretic analysis of human carotid endarterectomy specimens demonstrated that HSP27 was

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

Reprint requests and correspondence: Dr. Neal L. Weintraub, Division of Cardiovascular Diseases, Department of Internal Medicine, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, Ohio 45267. weintrnl@ucmail.uc.edu.

Dr. Rubinstein has reported that he has no relationships relevant to the contents of this paper to disclose.

increased in the normal portions of the vessel compared with nearby atherosclerotic plaques, implying that the presence and/or production of HSP27 confers plaque stability (8).

Sex-specific atheroprotective effects of HSP27 were described by Rayner et al. (9), who demonstrated in an ApoE knockout mouse model of atherosclerosis that female mice with transgenic HSP27 overexpression exhibited reduced atherosclerotic plaque area, concomitant with increased circulating HSP27 levels. Mechanistic studies demonstrated that estrogen receptor beta stimulation induces the expression and release of HSP27 in macrophages, which prevent the uptake of modified LDL and inflammatory cytokine release (10). Although these studies in genetically modified mouse models are informative, investigations using approaches that are more analogous to clinical practice are required to advance the field toward the bedside.

In the present study, Seibert et al. (11) advance our understanding of both the clinical and basic science implications of HSP27's role in atherosclerosis. The authors obtained data prospectively from a human cohort demonstrating that decreased serum HSP27 correlates with the presence of anatomic coronary artery disease and the incidence of major adverse cardiac events (MACE). The findings regarding the former are consistent with published data showing that serum HSP27 levels are higher in healthy subjects compared with those with carotid artery stenosis (6). Regarding the latter, data are conflicting, with 1 previous study reporting an increase in serum HSP27 in patients with acute coronary syndrome (8), and a prospective study (in women) failing to find a correlation between increased serum levels of HSP27 and reduced incidence of MACE (12).

The authors further report that patients with higher levels of HSP27 (dichotomously separated) are more likely to be female, which is also consistent with published data demonstrating that HSP27 is linked to circulating estrogen levels, although it should be emphasized that the subgroup of patients with higher levels of HSP27 also appears to be generally healthier (younger with a lower prevalence of comorbidities). Nevertheless, the study is intriguing and provides evidence of the feasibility of measuring HSP27 in the serum and its potential use as a novel biomarker of cardiovascular disease. It does not, however, demonstrate the potential for HSP27 to identify high-risk patients independently of other risk factors. This and other issues would need to be resolved to determine the overall utility of HSP27 as a biomarker for cardiovascular risk.

The authors proceed to present data confirming a modulatory role for HSP27 in the development of atherosclerosis in a mouse model. They first demonstrate that over-expression of HSP27 in bone marrow–derived cells is sufficient to elicit atheroprotection, consistent with the macrophage mechanism of action proposed in previous publications by this group. Histology of the atherosclerotic plaque in mice with bone marrow–derived HSP27 over-expression demonstrated reduced plaque size and lesional apoptosis. As a next step toward clinical translation, the authors tested whether recombinant HSP (rHSP27) can effectively modulate the progression of atherosclerosis. Mice treated with rHSP27 exhibited reduction in plaque formation. Interestingly, mice treated with exogenous rHSP27, but not those with bone marrow–derived HSP27 over-expression, exhibited lower serum cholesterol

levels, implying that rHSP27 may also modulate atherosclerosis by favorably affecting the lipid profile.

The enthusiasm for HSP27 as a potential therapeutic target in atherosclerosis should be tempered by our lack of knowledge of the precise mechanism of action of HSP27, whether its efficacy is sex specific, and how cholesterol levels might be affected by the recombinant protein. Moreover, administration of the recombinant protein could lead to the development of antibodies that over time might hamper therapeutic efficacy. Furthermore, HSP27 may affect the development and/or progression of estrogen-dependent cancers because it has been associated with both favorable and adverse prognosis in estrogen-positive breast cancers and the degree of tumor differentiation in endometrial carcinomas (13). Moreover, blockade of HSP27 has been used to interrupt the growth of other types of cancers, suggesting that rHSP27 could have opposite effects (14). Even if data continue to accumulate to support beneficial effects of HSP27 in atherosclerosis, extensive preclinical studies would be required to document an acceptable safety profile.

In summary, Seibert et al. (11) have advanced our understanding of HSP27 as a putative biomarker and therapeutic target in atherosclerosis. The authors are to be congratulated for their work, which answers many important questions. As to be expected, however, their study also raises many new questions that will need to be addressed to continue advancing this area of research to the bedside.

Acknowledgments

This work was supported by National Institutes of Health grants HL076684 and HL112640 (to Dr. Weintraub).

References

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005; 352:1685–95. [PubMed: 15843671]
2. Gerner EW, Schneider MJ. Induced thermal resistance in HeLa cells. Nature. 1975; 256:500–2. [PubMed: 1160994]
3. Kregel KC. Invited review: Heat shock proteins: modifying factors in physiological stress responses and acquired thermotolerance. J Applied Physiol. 2002; 92:2177–86. [PubMed: 11960972]
4. Landry J, Chretien P, Lambert H, Hickey E, Weber LA. Heat shock resistance conferred by expression of the human HSP27 gene in rodent cells. J Cell Biol. 1989; 109:7–15. [PubMed: 2745558]
5. Bruey JM, Ducasse C, Bonniaud P, et al. Hsp27 negatively regulates cell death by interacting with cytochrome C. Nat Cell Biol. 2000; 9:645–52. [PubMed: 10980706]
6. Martin-Ventura JL, Duran MC, Blanco-Colio LM, et al. Identification by a differential proteomic approach of heat shock protein 27 as a potential marker of atherosclerosis. Circulation. 2004; 110:2216–9. [PubMed: 15249501]
7. Martin-Ventura JL, Nicolas V, Houard X, et al. Biological significance of decreased HSP27 in human atherosclerosis. Arterioscler Thromb Vasc Biol. 2006; 6:1337–43. [PubMed: 16574891]
8. Park HK, Park EC, Bae SW, et al. Expression of heat shock protein 27 in human atherosclerotic plaques and increased plasma level of heat shock protein 27 in patients with acute coronary syndrome. Circulation. 2006; 114:886–93. [PubMed: 16923754]
9. Rayner K, Chen YX, McNulty M, et al. Extracellular release of the atheroprotective heat shock protein 27 is mediated by estrogen and competitively inhibits acLDL binding to scavenger receptor-A. Circ Res. 2008; 103:133–41. [PubMed: 18566345]

10. Rayner K, Sun J, Chen YX, et al. Heat shock protein 27 protects against atherogenesis via an estrogen-dependent mechanism: role of selective estrogen receptor beta modulation. Arterioscler Thromb Vasc Biol. 2009; 29:1751–6. [PubMed: 19729610]

11. Seibert TA, Hibbert B, Chen YX, et al. Serum heat shock protein 27 levels represent a potential therapeutic target for atherosclerosis: observations from a human cohort and treatment of female mice. J Am Coll Cardiol. 2013; 62:1446–54. [PubMed: 23764828]

12. Kardys I, Rifai N, Meilhac O, et al. Plasma concentration of heat shock protein 27 and risk of cardiovascular disease: a prospective, nested case-control study. Clin Chem. 2008; 54:139–46. [PubMed: 18024525]

13. Ciocca DR, Oesterreich S, Chamness GC, McGuire WL, Fuqua SA. Biological and clinical implications of heat shock protein 27,000 (Hsp27): a review. J Natl Cancer Inst. 1993; 85:1558–70. [PubMed: 8411230]

14. Zoubeidi A, Zardan A, Wiedmann RM, et al. Hsp27 promotes insulin-like growth factor-I survival signaling in prostate cancer via p90Rsk-dependent phosphorylation and inactivation of BAD. Cancer Res. 2010; 70:2307–17. [PubMed: 20197463]