Heat Shock Protein 47
A Chaperone for the Fibrous Cap?
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According to The American Heritage College Dictionary,1 a chaperone is “a guide or companion whose purpose is to ensure propriety or restrict activity.”

The term “molecular chaperone” is applied to proteins that control the proper folding of nascent polypeptides into the correct 3D structure (ensure propriety) or maintain polypeptides in an inactive state (restrict activity) until they have been transported to their ultimate intracellular or extracellular destinations and assembled into functional multiprotein complexes.2 Many of the proteins that function as molecular chaperones were originally identified as “heat shock proteins” (Hsps), because their abundance increased in cells subjected to thermal stress. Individual members of the extended Hsps are usually identified by reference to their molecular mass (eg, Hsp70, Hsp90, etc). The terminology can be misleading because not all Hsps are heat-inducible, not all chaperones are called Hsps, and diverse forms of cellular stress other than elevated temperature lead to transcriptional and post-transcriptional regulation of chaperone synthesis.

Many of the molecular chaperones of the extended Hsp family are highly conserved across evolution (ie, very similar in bacteria, yeast, and humans) and are expressed in virtually all cell types.3 Such proteins function in fundamental cellular housekeeping activities to maintain homeostasis with respect to protein folding and sorting among intracellular compartments and the assembly of macromolecular complexes. Several of these ubiquitously expressed Hsps also serve cytoprotective functions during metabolic stresses, as was demonstrated by several groups who studied Hsp70 and other Hsps in hypoxic and ischemic cells and tissues.4–6

Other molecular chaperones are restricted to certain cell types and seem to have more specialized functions. An interesting example of this latter class of chaperones is a protein called αB-crystallin, a small (22 kDa) Hsp that is the major protein of the lens of the eye and is highly abundant within the myocardium. In the heart, αB-crystallin is thought to function as a chaperone for the assembly and remodeling of sarcomeres,7 a concept supported by the recent identification of a missense mutation in αB-crystallin that segregates with the disease phenotype in a large family afflicted with cardiomyopathy.8

Hsp47 is another example of a Hsp with specialized functions. Under unstressed conditions, Hsp47 is expressed selectively within the endoplasmic reticulum of cells that synthesize and secrete type I or type III collagen.9 A transient physical association between Hsp47 and procollagen molecules within the endoplasmic reticulum10 serves to stabilize procollagen monomers, to prevent their premature aggregation into oligomeric forms, and to modulate their transfer to the Golgi apparatus before export from the cell.11 Steady-state levels of Hsp47 and type I collagen are increased coordinately in tissues undergoing pathological fibrosis,9 and the production of type I collagen is decreased if Hsp47 expression is inhibited.10

Returning to the dictionary definition of chaperone1 and extending the metaphor from a molecular to a tissue level, it is difficult to imagine any entity in greater need of a chaperone to ensure its propriety than the atherosclerotic plaque. The breakdown of the fibrous cap that overlies the lipid-rich core of advanced atherosclerotic lesions is almost always the event that precipitates acute myocardial infarction or unstable angina.12 Because the fibrous cap of human atheroma is rich in type I collagen, the molecular chaperone function of Hsp47 with respect to procollagen becomes pertinent, in principle, to the pathogenesis of acute coronary syndromes.

The article by Rocnik et al13 provides direct evidence that Hsp47 is expressed in atherosclerotic, but not normal, human arteries. The expression of Hsp47 is most clearly evident in the superficial layers of atheroma comprising the intima and fibrous/collagenous cap. The authors further demonstrate that all cells expressing type I collagen also express Hsp47, although Hsp47 is, interestingly, also expressed in some cells in which type I procollagen could not be detected by immunohistochemical methods. In human smooth muscle cells maintained in culture, the expression of Hsp47 is regulated by peptide growth factors of the transforming growth factor-β and fibroblast growth factor families, as well as by oxidized low-density lipoprotein, which provides a regulatory link to extracellular signaling molecules known to modulate cellular and molecular characteristics of the vessel wall.

Although this article13 falls short of defining a functional role for Hsp47 in the natural history of atherosclerotic vascular disease, these new data raise some interesting questions that should be addressed in future studies. To what degree do variations in procollagen synthesis, processing, and maturation influence the mechanical stability of atheroma?
Will it prove possible to stabilize plaques and prevent vascular occlusion by interventions that modulate the expression of Hsp47 and/or specific procollagen genes? Such questions seem approachable using genetic manipulations of animal models, and the answers could conceivably suggest novel approaches to modify the risk of catastrophic plaque rupture.

Complex interactions among many factors influence the mechanical stability of atheroma, and it would not be surprising if other cellular and molecular events overwhelm efforts to stabilize plaques by the manipulation of collagen biosynthesis or post-translational processing. Nevertheless, the role of Hsp47 within the diseased vessel wall merits further exploration. Any chaperone capable of tempering the unruly and unpredictable behavior of nonocclusive atheroma would surely find gainful employment in cardiovascular medicine.

References

KEY WORDS: Editorials | atherosclerosis | stress
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Circulation. 2000;101:1227-1228
doi: 10.1161/01.CIR.101.11.1227
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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