Cytoskeletal Abnormalities in the Failing Heart
Out on a LIM?

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The “modern” era in our understanding of heart failure began around 1990, when unexpected results from clinical trials indicated that maladaptive growth, rather than depressed contractility, is the major cause of the poor prognosis in patients with this syndrome, and that the long-term benefits of angiotensin-converting enzyme inhibitors are due to inhibition of proliferative signaling rather than vasodilation. The potential importance of molecular abnormalities in the failing heart was further highlighted in 1990 by the discovery that myosin heavy-chain mutations cause hypertrophic cardiomyopathy. Many additional sarcomeric protein abnormalities are now known to cause hypertrophic cardiomyopathy, and between a quarter and a third of idiopathic dilated cardiomyopathies appear to be associated with familial disease. In contrast to hypertrophic cardiomyopathy, most of the abnormal proteins thus far linked to dilated cardiomyopathy are cytoskeletal, rather than sarcomeromic.

The most important signaling function of the cytoskeleton is to modify proliferative responses, such as growth, differentiation, and cell cycling, when cells adhere to the extracellular matrix or when they contact other cells. Signals generated by cell deformation can activate a panoply of proliferative responses that modify cell size and shape. Central to this signaling function is a family of plasma membrane proteins called adhesion molecules that, when bound to surrounding structures, activate tyrosine kinases that participate in signal transduction cascades. In terms of the “wired building” analogy, this ability of adhesion molecules to modify cell function in response to mechanical perturbations at the cell surface is analogous to having sensors on the surface of a building generate signals that modify the occupants’ behavior.

The LIM proteins (named for lin-11 and mec-3, regulatory proteins found in the roundworm Caenorhabditis elegans, and the insulin binding protein Isl-1) make up a diverse family of regulatory and cytoskeletal proteins. The defining features of the LIM motif are 2 adjacent zinc fingers, which form homodimers and heterodimers that serve both mechanical and signaling functions. Some LIM proteins link cytoskeletal elements to one another and contribute to the mechanical connections between myocardial cells at the intercalated disc. Other members of this family are coupled to DNA-binding homeodomains that allow these zinc finger proteins to function as transcription factors, or to protein kinases that participate in signal transduction cascades. One group of LIM proteins, called LIM-only proteins, consists almost entirely of the LIM motif. Although these LIM-only proteins do not contain DNA-binding homeodomains or protein kinases, many regulate proliferative responses. One LIM-only protein, called ACT (activator of CREM in testis), regulates transcription factors (CREM and CREB) that are also controlled by cAMP-dependent protein kinases, and so may stimulate proliferative responses similar to those initiated by β-adrenergic receptor agonists.

MLP (muscle LIM protein), a LIM-only protein expressed in striated muscles, regulates muscle differentiation. When overexpressed in myoblasts, this protein promotes myogenesis, while suppression of MLP expression inhibits differentiation. In skeletal muscle, MLP is present during development and is down-regulated in the adult phenotype, whereas in the heart, MLP levels are high in both fetal and adult myocytes. Because the LIM-only protein lacks DNA binding and protein kinase moieties, its myogenic actions occur when it binds to other proteins, most likely other members of the LIM family. MLP, for example, is associated with the actin cytoskeleton, where interactions with other actin-binding LIM-proteins appear to regulate myofilament assembly.

A role for MLP in the pathogenesis of clinical heart failure was suggested in 1997, when Arber et al found that transgenic MLP-deficient mice develop a dilated cardiomyopathy characterized not only by chamber enlargement, but also by a 2- to 4-fold increase in heart weight. Further evidence that MLP abnormalities are important in the failing heart is provided by Zolk et al, who report that MLP mRNA and protein levels are abnormally low in the hearts of patients with dilated cardiomyopathies. The significance of this abnormality is not clear, however, because MLP protein and

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The cytoskeleton, like the beams and girders in a modern building, maintains a highly organized structure within cells. Cytoskeletal proteins imbedded in the plasma membrane connect this intracellular matrix with extracellular connective tissue proteins and adjacent cells. In addition to these mechanical functions, the cytoskeleton plays a major role in communication. Cytoskeletal proteins, therefore, do more than maintain cell architecture; their participation in cell signaling is analogous to using the steel framework of a building as the phone system.

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mRNA levels in many apparently normal hearts are similar to those in the failing hearts. There is, however, no reason to suspect that the abnormality is a marker for a familial cardiomyopathy, because reductions of MLP mRNA and protein levels in ischemic cardiomyopathy are similar to those in idiopathic dilated cardiomyopathy.

This early report cannot tell us whether low MLP levels contribute to the pathophysiological process responsible for the progression of dilated cardiomyopathies, are part of a compensatory response, or are an epiphenomenon. The low levels of this LIM-only protein in failing hearts may represent an example of the “reversion to the fetal phenotype” seen in overloaded hearts because down-regulation of this protein, which promotes differentiation, could be part of the process that returns cell phenotype to the less differentiated fetal state.

Whatever the explanation, the finding of a new cytoskeletal abnormality in human dilated cardiomyopathy adds acquired disease to the familial dilated cardiomyopathies in which cytoskeletal proteins are abnormal. One of the more fascinating implications of the decreased MLP levels described by Zolk et al. is the possibility that LIM-only protein abnormalities participate in the progressive dilatation (remodeling) of failing hearts. Additional knowledge of this cytoskeletal abnormality, therefore, could lead to the development of new means to improve prognosis in these patients by slowing, or even reversing, this maladaptive growth response.

References


Key Words: Editorials | heart failure | signal transduction | remodeling | cytoskeleton | cardiomyopathy | cell adhesion molecules
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Circulation. 2000;101:2672-2673
doi: 10.1161/01.CIR.101.23.2672

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