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The heart of autophagy: Deconstructing cardiac proteotoxicity

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Abstract

The heart is capable of robust structural remodeling, sometimes improving performance and sometimes leading to failure. Recent studies have uncovered a critical role for autophagy in disease-related remodeling of the cardiomyocyte. We have shown previously that hemodynamic load elicits a maladaptive autophagic response in cardiomyocytes which contributes to disease progression. In a recent study, we went on to demonstrate that protein aggregation is a proximal event triggering autophagic clearance mechanisms. The ubiquitin-proteasome-dependent pathways of protein clearance are similarly activated in parallel with processing of stress-induced protein aggregates into aggresomes and clearance through autophagy. These findings in the setting of pressure overload contrast with protein aggregation occurring in a model of protein chaperone malfunction in myocytes, where activation of autophagy is beneficial, antagonizing disease progression. Our findings situate heart disease stemming from environmental stress in the category of proteinopathy and raise important new questions regarding molecular events that elicit adaptive and maladaptive autophagy.

Keywords

cardiac hypertrophy; heart failure; cardiomyocyte; cardiac remodeling

A striking feature of the heart is its capacity for structural remodeling in response to environmental demands.[1] Indeed, the heart is a remarkably plastic organ, capable of growing or shrinking in the setting of a variety of physiological or pathological stimuli. In some instances, cardiac growth is beneficial, facilitating the organism's response to exercise, postnatal development or pregnancy. In other instances, such as the stress of hypertensive disease or infarction, cardiac remodeling is maladaptive, predisposing to arrhythmia and heart failure. In yet other situations, such as prolonged bedrest or weightlessness, the heart actually shrinks. There is great interest in developing therapeutic strategies that promote physiological cardiac remodeling and minimize the pathological variety.

Autophagy Contributes to Cardiac Remodeling

Growth and remodeling of the adult heart occur through changes in the balance between protein synthesis and protein degradation, as well as through the death (or survival) of individual myocytes. During hypertrophic growth, enhanced protein synthesis leads to an increase in the size of individual myocytes and heightened organization of intracellular force-generating units (sarcomeres). With time, decompensation ensues as the ventricular walls thin through a

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combination of proteolysis and/or myocyte death with subsequent replacement by fibrotic tissue. Numerous signaling pathways are implicated in stress-induced growth of the heart, several of which are further implicated in cell death.[2] However, mechanisms governing the transition from compensated hypertrophy to heart failure are incompletely characterized.

It has been known for 30 years that lysosomal pathways are activated in a variety of models of heart disease.[3–7] Indeed, a number of groups report increases in lysosomal activity in tissue samples from diseased and failing human hearts.[8–14] More recent studies reveal an important role for autophagy in the cardiomyocyte response to numerous types of stress, and compelling evidence has emerged that this autophagic response participates in the pathogenesis of disease. For example, pressure overload, chronic ischemia, ischemia-reperfusion and diphtheria toxin-induced injury each provokes an increase in autophagic activity in cardiomyocytes.[15,16] Our group demonstrated recently that in pressure-overload heart failure, a common form of clinical disease, induction of autophagic activity is both robust and maladaptive.[17] Work is underway now to identify molecular mechanisms governing autophagic activation in cardiac remodeling and to determine whether the autophagic response promotes disease progression or antagonizes it.

Protein Quality Control and Proteotoxic Disease

Strict regulation of proteolysis is critical in long-lived postmitotic cells such as cardiac myocytes, where the ability to replace cells is limited, yet intracellular proteins and organelles turn over continuously. Failure of this system leads to aggregation of misfolded proteins, which are toxic to the cell. In fact, proteinopathy, a disease characterized by toxic aggregations of misfolded proteins, is a growing family of human disorders, which includes Alzheimer disease, Parkinsonism, amyotrophic lateral sclerosis, and both poly-glutamine and polyalanine expansion disorders.[18] Consistent with proteotoxicity being a mechanism contributing to heart disease, abnormal protein aggregation and accumulation of ubiquitinated proteins in the cytosol are sometimes detected in human hearts with idiopathic or ischemic cardiomyopathies.[12,19,20]

Insoluble protein aggregates are processed by pathways that are just now being deciphered (Fig. 1). First, misfolded proteins can be degraded by proteasomes throughout the cytoplasm. However, as proteins begin to aggregate, they are delivered to the MTOC (microtubule organizing center) by dynein-dependent retrograde transport along microtubules. When the degradative capacity of the proteasome is exceeded, protein aggregates accumulate in perinuclear inclusions called aggresomes,[21] organized structures surrounded by vimentin filaments that recruit chaperones, ubiquitin, proteasomes and mitochondria. Relatively little is known regarding whether intra-cellular inclusions are toxic themselves, or whether they represent a compensatory mechanism that sequesters harmful, soluble proteins within the cytoplasm. Whereas toxicity is sometimes disease-specific—related to loss of function of the mutated or misfolded protein—there is general agreement that early, still-soluble aggregates are potentially harmful.[22] Indeed, evidence in neurons suggests that it is the soluble pre-amyloid aggregates that are the most toxic,[23] perhaps through the exposure of buried moieties such as main chain amino and carboxyl groups that could serve as hydrogen bond donors or acceptors in abnormal interactions with other proteins. Also, in many instances, mutations responsible for proteinopathies confer a toxic gain of function to the relevant protein.

Autophagy serves both to recycle cellular components and to eliminate damaged proteins or organelles that might otherwise be toxic or trigger apoptotic death. For example, targeted inhibition of *Atg7*, a gene required for autophagic activity, leads to accumulation of ubiquitin-positive aggregates.[24] Further, in the absence of basal levels of autophagic activity in the brain[25,26] and the heart,[27] abnormal aggregates of intracellular proteins develop. In some

settings, however, autophagic activity is associated with the pathogenesis of disease, and unrestrained autophagic activity can cause cell death.[28]

In many instances of proteinopathy, autophagy is activated as a clearance mechanism. For example, autophagy is activated in proteinopathic neuronal diseases, including Huntington's disease, amyotrophic lateral sclerosis, Parkinsonism and Alzheimer disease.[29] The prevailing notion is that autophagic pathways serve a beneficial function by facilitating removal of aggregates too large for efficient proteasome-mediated clearance.[30] In fact, in several neurodegenerative diseases, a strong association exists between induction of autophagy and the presence of protein aggregates.[31,32] Further, pharmacologic or genetic induction of autophagy is sufficient to reduce polyglutamine-induced cytotoxicity in animal models of Huntington's disease.[33] That we and others do not detect membrane-bound inclusions, and the inclusions we detect are much larger than mammalian autophagosomes,[34,35] suggests that autophagy serves to clear monomeric and oligomeric precursors of aggregates, rather than the large inclusions themselves. Taken together, these data are consistent with the notion that intracellular protein aggregates are capable of stimulating autophagic activity which serves, in turn, to facilitate clearance of the aggregates.

Proteotoxicity in Load-induced Heart Disease

Our group has focused recently on heart disease stemming from pressure overload, i.e., settings where the ventricle must work against, and generate, abnormally high levels of pressure. Common examples include hypertension, prior myocardial infarction (such that the myocardium which remains viable and functioning must perform the work of the tissue that has died), or stenotic aortic valvular disease. The public health significance of these diseases is highlighted by the fact that one-third of U.S. adults have hypertension.[36]

We set out to determine the molecular events within the pressure-stressed cardiomyocyte that trigger autophagy. First, it is clear that numerous processes can trigger autophagy in a variety of settings.[37–40] Among these, we established a link between protein aggregation and induction of cardiomyocyte autophagy,[34] finding that accumulation and aggregation of ubiquitinated protein is a powerful inducer of autophagy, capable of activating autophagy to levels comparable to pharmacologic induction. We also described the accumulation in vivo of ubiquitinated proteins in a spatial and temporal pattern consistent with our prior report of pressure overload-induced autophagy.[17] In other words, the regions with maximal autophagic activity contained the highest density of ubiquitinated protein aggregates. We further characterized the organization of damaged proteins into vimentin associated, peri-nuclear, aggresome-like structures. We found that total proteasome activity is increased in heart failure, suggesting increased flux through proteasomal degradation pathways and consistent with similar findings in a model of desmin-related cardiomyopathy.[41] Thus, proteasomal and autophagic activities increase in parallel, and the accumulation of ubiquitinated aggregates is not due to diminished proteasome-mediated degradation but rather stems from de novo protein synthesis.

Our findings are the first to describe aggresome formation in a common cardiovascular disorder, that is, load-induced heart disease, placing pressure-overload heart disease in the category of proteinopathies. Further, they are consistent with a model where autophagic activity is a general response to protein aggregation in the heart and point to a potential role for autophagy in cardiomyopathies of diverse etiology.

In another study,[35] we tested whether autophagy plays a role in a different form of proteotoxic heart disease, namely desmin-related myopathies (DRCM) where mutations in genes encoding desmin or the chaperone protein alpha-B-crystallin (CryAB) lead to accumulation of protein aggregates, profound heart failure, and eventually death.[42–44] In that study, we also observed

robust activation of autophagic clearance pathways. In the context of this disease, however, we find that autophagy is a beneficial, adaptive response which serves to antagonize disease progression.[35]

How do Protein Aggregates Trigger Autophagy?

In many instances, autophagy and the ubiquitin-proteasome system are activated in parallel as clearance mechanisms to eliminate aggregating (and aggregated) proteins. For example, atrophy of mammalian skeletal muscle depends on an increase in abundance of ubiquitin ligases, ubiquitination of myosins and other sarcomeric proteins, and then degradation via the proteasome,[45] whereas mitochondria and other organelles are engulfed in autophagic vacuoles. Many degenerative muscle diseases are associated with an increase in protein ubiquitination, protein aggregates and autophagic vesicles. If protein ubiquitination outpaces proteasome capacity, aggregates of ubiquitinated proteins may accumulate. Consistent with this, accumulation of ubiquitin aggregates is used as a marker for autophagocytosis in neurons and insect flight muscle.[46] Thus, activation of autophagy at early stages of the disease may be a protective mechanism to scavenge and eliminate misfolded, polyubiquitinated protein aggregates that have overwhelmed the degradative capacity of the proteasomal system.

Another way in which protein aggregates may elicit an autophagic response is through interaction with mitochondria. Some types of protein aggregates stain positive for Congo red, indicative of an amyloid protein configuration. This is true of protein aggregates found in a number of neurological diseases associated with increased autophagic activity[22] and in the DRCM CryAB mutant heart.[47] Interestingly, amyloid proteins are capable of triggering mitochondrial permeability transition (MPT) by inserting into mitochondrial membranes.[48–50] MPT can trigger either apoptosis or selective autophagic degradation of the affected mitochondria through a process termed mitophagy.[51] Many other cellular stresses are capable of inducing MPT, including reactive oxygen species (ROS) and Ca^{2+} overload, processes frequently associated with cardiac stress. As a consequence of MPT, mitochondria depolarize, uncouple, swell and release cytochrome *c* as well as other pro-apoptotic proteins. Furthermore, uncoupled mitochondria are not only unable to generate ATP, they become a futile sink of ATPase activity. Thus, mitochondria that have undergone MPT must be repaired or removed to prevent a catastrophic loss of ATP, and consequent necrotic death, or triggering of apoptotic death. Mitophagy carries out this critical protective function. Ultimately, however, loss of too much mitochondrial content may be a key component of autophagic cell death.

Although protein aggregates accumulate in the myocardium in response to either hemodynamic stress or genetic mutation of critical proteins, experimental evidence indicates that autophagy is maladaptive in one context and beneficial in the other. Important questions for the future include whether there are inherent differences in the types of protein aggregates that form and/or in the associated autophagic response. What other factors stimulate autophagic activity in the heart? Is the pathophysiological outcome determined by severity of the autophagic response or the nature of the autophagy substrate?

Perspective

There is urgent need to identify mechanisms governing disease-related remodeling of the heart —and consequent systolic dysfunction, clinical heart failure, and arrhythmic sudden death— to improve treatment and prevention. It is apparent that cardiac autophagy is induced by diverse forms of cardiovascular stress, and the net effect of this activity, adaptive versus maladaptive, appears to be context dependent. A fundamental function of autophagocytosis is the removal of damaged protein aggregates,[30] a concept we recently extended to pressure-stressed myocardium[34] and to a genetic model of chaperone malfunction.[35] Further, our data point to a progression of protein damage, aggregation and coalescence into aggresomes as a previously

unrecognized mechanism of heart disease. As new advances emerge in deciphering molecular regulation of autophagy, it may soon be possible to enhance or inhibit autophagic activity selectively to have a meaningful impact upon heart disease.

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References

1. Hill JA, Olson EN. Cardiac plasticity. New Engl J Med 2008;358:1370–80. [PubMed: 18367740]
2. Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. Nat Rev Mol Cell Biol 2006;7:589–600. [PubMed: 16936699]
3. Sybers HD, Ingwall J, DeLuca M. Autophagy in cardiac myocytes. Recent Adv Stud Cardiac Struct Metab 1976;12:453–63. [PubMed: 1032000]
4. Decker RS, Wildenthal K. Lysosomal alterations in hypoxic and reoxygenated hearts 1. Ultrastructural and cytochemical changes. American Journal of Pathology 1980;98:425. [PubMed: 7355988]
5. Decker RS, Decker ML, Herring GH, Morton PC, Wildenthal K. Lysosomal vacuolar apparatus of cardiac myocytes in heart of starved and refed rabbits. J Mol Cell Cardiol 1980;12:1175–89. [PubMed: 7441766]
6. Dammrich J, Pfeifer U. Cardiac hypertrophy in rats after supravalvular aortic constriction II. Inhibition of cellular autophagy in hypertrophying cardiomyocytes. Virchows Arch B Cell Pathol Incl Mol Pathol 1983;43:287–307. [PubMed: 6137901]
7. Pfeifer U, Fohr J, Wilhelm W, Dammrich J. Short-term inhibition of cardiac cellular autophagy by isoproterenol. J Mol Cell Cardiol 1987;19:1179–84. [PubMed: 3443985]
8. Yamamoto S, Sawada K, Shimomura H, Kawamura K, James TN. On the nature of cell death during remodeling of hypertrophied human myocardium. Journal of Molecular and Cellular Cardiology 2000;32:161–75. [PubMed: 10652200]
9. Knaapen MWM, Davies MJ, De Bie M, Haven AJ, Martinet W, Kockx MM. Apoptotic versus autophagic cell death in heart failure. Cardiovascular Research 2001;51:304–12. [PubMed: 11470470]
10. Shimomura H, Terasaki F, Hayashi T, Kitaura Y, Isomura T, Suma H. Autophagic degeneration as a possible mechanism of myocardial cell death in dilated cardiomyopathy. Jpn Circ J 2001;65:965–8. [PubMed: 11716248]
11. Lockshin RA, Zakeri Z. Caspase-independent cell deaths. Current Opinion in Cell Biology 2002;14:727–33. [PubMed: 12473346]
12. Kostin S, Pool L, Elsasser A, Hein S, Drexler HC, Arnon E, Hayakawa Y, Zimmermann R, Bauer E, Klovekorn WP, Schaper J. Myocytes die by multiple mechanisms in failing human hearts. Circ Res 2003;92:715–24. [PubMed: 12649263]
13. Hein S, Arnon E, Kostin S, Schonburg M, Elsasser A, Polyakova V, Bauer EP, Klovekorn WP, Schaper J. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. Circulation 2003;107:984–91. [PubMed: 12600911]
14. Elsasser A, Vogt AM, Nef H, Kostin S, Mollmann H, Skwara W, Bode C, Hamm C, Schaper J. Human hibernating myocardium is jeopardized by apoptotic and autophagic cell death. J Am Coll Cardiol 2004;43:2191–9. [PubMed: 15193679]
15. Rothermel BA, Hill JA. Myocyte autophagy in heart disease: friend or foe? Autophagy 2007;3:632–4. [PubMed: 17786025]
16. Martinet W, Knaapen MW, Kockx MM, De Meyer GR. Autophagy in cardiovascular disease. Trends Mol Med 2007;13:482–91. [PubMed: 18029229]
17. Zhu H, Tannous P, Johnstone JL, Kong Y, Shelton JM, Richardson JA, Le V, Levine B, Rothermel BA, Hill JA. Cardiac autophagy is a maladaptive response to hemodynamic stress. J Clin Invest 2007;117:1782–93. [PubMed: 17607355]

18. Taylor JP, Hardy J, Fischbeck KH. Toxic proteins in neurodegenerative disease. Science 2002;296:1991–5. [PubMed: 12065827]
19. Heling A, Zimmermann R, Kostin S, Maeno Y, Hein S, Devaux B, Bauer E, Klovekorn WP, Schlepper M, Schaper W, Schaper J. Increased expression of cytoskeletal, linkage and extracellular proteins in failing human myocardium. Circ Res 2000;86:846–53. [PubMed: 10785506]
20. Weekes J, Morrison K, Mullen A, Wait R, Barton P, Dunn MJ. Hyperubiquitination of proteins in dilated cardiomyopathy. Proteomics 2003;3:208–16. [PubMed: 12601813]
21. Johnston JA, Ward CL, Kopito RR. Aggresomes: a cellular response to misfolded proteins. J Cell Biol 1998;143:1883–98. [PubMed: 9864362]
22. Rubinsztein DC. The roles of intracellular protein-degradation pathways in neurodegeneration. Nature 2006;443:780–6. [PubMed: 17051204]
23. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 2004;431:805–10. [PubMed: 15483602]
24. Komatsu M, Waguri S, Ueno T, Iwata J, Murata S, Tanida I, Ezaki J, Mizushima N, Ohsumi Y, Uchiyama Y, Kominami E, Tanaka K, Chiba T. Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice. J Cell Biol 2005;169:425–34. [PubMed: 15866887]
25. Komatsu M, Waguri S, Chiba T, Murata S, Iwata J, Tanida I, Ueno T, Koike M, Uchiyama Y, Kominami E, Tanaka K. Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature 2006;441:880–4. [PubMed: 16625205]
26. Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, Mizushima N. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature 2006;441:885–9. [PubMed: 16625204]
27. Nakai A, Yamaguchi O, Takeda T, Higuchi Y, Hikoso S, Taniike M, Omiya S, Mizote I, Matsumura Y, Asahi M, Nishida K, Hori M, Mizushima N, Otsu K. The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress. Nat Med 2007;13:619–24. [PubMed: 17450150]
28. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell 2008;132:27–42. [PubMed: 18191218]
29. Ross CA, Poirier MA. Opinion: What is the role of protein aggregation in neurodegeneration? Nat Rev Mol Cell Biol 2005;6:891–8. [PubMed: 16167052]
30. Kopito RR. Aggresomes, inclusion bodies and protein aggregation. Trends Cell Biol 2000;10:524–30. [PubMed: 11121744]
31. Ravikumar B, Duden R, Rubinsztein DC. Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy. Hum Mol Genet 2002;11:1107–17. [PubMed: 11978769]
32. Fortun J, Dunn WA Jr, Joy S, Li J, Notterpek L. Emerging role for autophagy in the removal of aggresomes in Schwann cells. J Neurosci 2003;23:10672–80. [PubMed: 14627652]
33. Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, Rubinsztein DC. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nat Genet 2004;36:585–95. [PubMed: 15146184]
34. Tannous P, Zhu H, Nemchenko A, Berry JM, Johnstone JL, Shelton JM, Miller FJ Jr, Rothermel BA, Hill JA. Intracellular protein aggregation is a proximal trigger of cardiomyocyte autophagy. Circulation 2008;117:3070–8. [PubMed: 18541737]
35. Tannous P, Zhu H, Johnstone JL, Shelton JM, Rajasekaran NS, Benjamin IJ, Nguyen L, Gerard RD, Levine B, Rothermel BA, Hill JA. Autophagy is an adaptive response in desmin-related cardiomyopathy. Proc Natl Acad Sci USA 2008;105:9745–50. [PubMed: 18621691]
36. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:25–146.

37. Levine B, Klionsky DJ. Development by self-digestion: molecular mechanisms and biological functions of autophagy. Dev Cell 2004;6:463–77. [PubMed: 15068787]

38. Klionsky DJ. Autophagy: from phenomenology to molecular understanding in less than a decade. Nat Rev Mol Cell Biol 2007;8:931–7. [PubMed: 17712358]

39. Mizushima N. Autophagy: process and function. Genes Dev 2007;21:2861–73. [PubMed: 18006683]

40. Kundu M, Thompson CB. Autophagy: basic principles and relevance to disease. Annu Rev Pathol 2008;3:427–55. [PubMed: 18039129]

41. Chen Q, Liu JB, Horak KM, Zheng H, Kumarapeli AR, Li J, Li F, Gerdes AM, Wawrousek EF, Wang X. Intrasarcoplasmic amyloidosis impairs proteolytic function of proteasomes in cardiomyocytes by compromising substrate uptake. Circ Res 2005;97:1018–26. [PubMed: 16210548]

42. Vicart P, Caron A, Guicheney P, Li Z, Prévost MC, Faure A, Chateau D, Chapon F, Tomé F, Dupret JM, Paulin D, Fardeau M. A missense mutation in the αB-crystallin chaperone gene causes a desmin-related myopathy. Nat Genet 1998;20:92–5. [PubMed: 9731540]

43. Wang X, Osinska H, Klevitsky R, Gerdes AM, Nieman M, Lorenz J, Hewett T, Robbins J. Expression of R120G-αB-crystallin causes aberrant desmin and αB-crystallin aggregation and cardiomyopathy in mice. Circ Res 2001;89:84–91. [PubMed: 11440982]

44. Rajasekaran NS, Connell P, Christians ES, Yan LJ, Taylor RP, Orosz A, Zhang XQ, Stevenson TJ, Peshock RM, Leopold JA, Barry WH, Loscalzo J, Odelberg SJ, Benjamin IJ. Human αB-crystallin mutation causes oxido-reductive stress and protein aggregation cardiomyopathy in mice. Cell 2007;130:427–39. [PubMed: 17693254]

45. Attaix D, Ventadour S, Codran A, Bechet D, Taillandier D, Combaret L. The ubiquitin-proteasome system and skeletal muscle wasting. Essays Biochem 2005;41:173–86. [PubMed: 16250905]

46. Davis WL, Jacoby BH, Goodman DBP. Immunolocalization of ubiquitin in degenerating insect flight muscle. Histochemical Journal 1994;26:298–305. [PubMed: 8040003]

47. Sanbe A, Osinska H, Saffitz JE, Glabe CG, Kayed R, Maloyan A, Robbins J. Desmin-related cardiomyopathy in transgenic mice: a cardiac amyloidosis. Proc Natl Acad Sci USA 2004;101:10132–6. [PubMed: 15220483]

48. Moreira PI, Santos MS, Moreno A, Oliveira C. Amyloid β-peptide promotes permeability transition pore in brain mitochondria. Biosci Rep 2001;21:789–800. [PubMed: 12166828]

49. Kayed R, Sokolov Y, Edmonds B, McIntire TM, Milton SC, Hall JE, Glabe CG. Permeabilization of lipid bilayers is a common conformation-dependent activity of soluble amyloid oligomers in protein misfolding diseases. J Biol Chem 2004;279:46363–6. [PubMed: 15385542]

50. Thundimadathil J, Roeske RW, Jiang HY, Guo L. Aggregation and porin-like channel activity of a β sheet peptide. Biochemistry 2005;44:10259–70. [PubMed: 16042403]

51. Lemasters JJ. Modulation of mitochondrial membrane permeability in pathogenesis, autophagy and control of metabolism. J Gastroenterol Hepatol 2007;22:31–7.

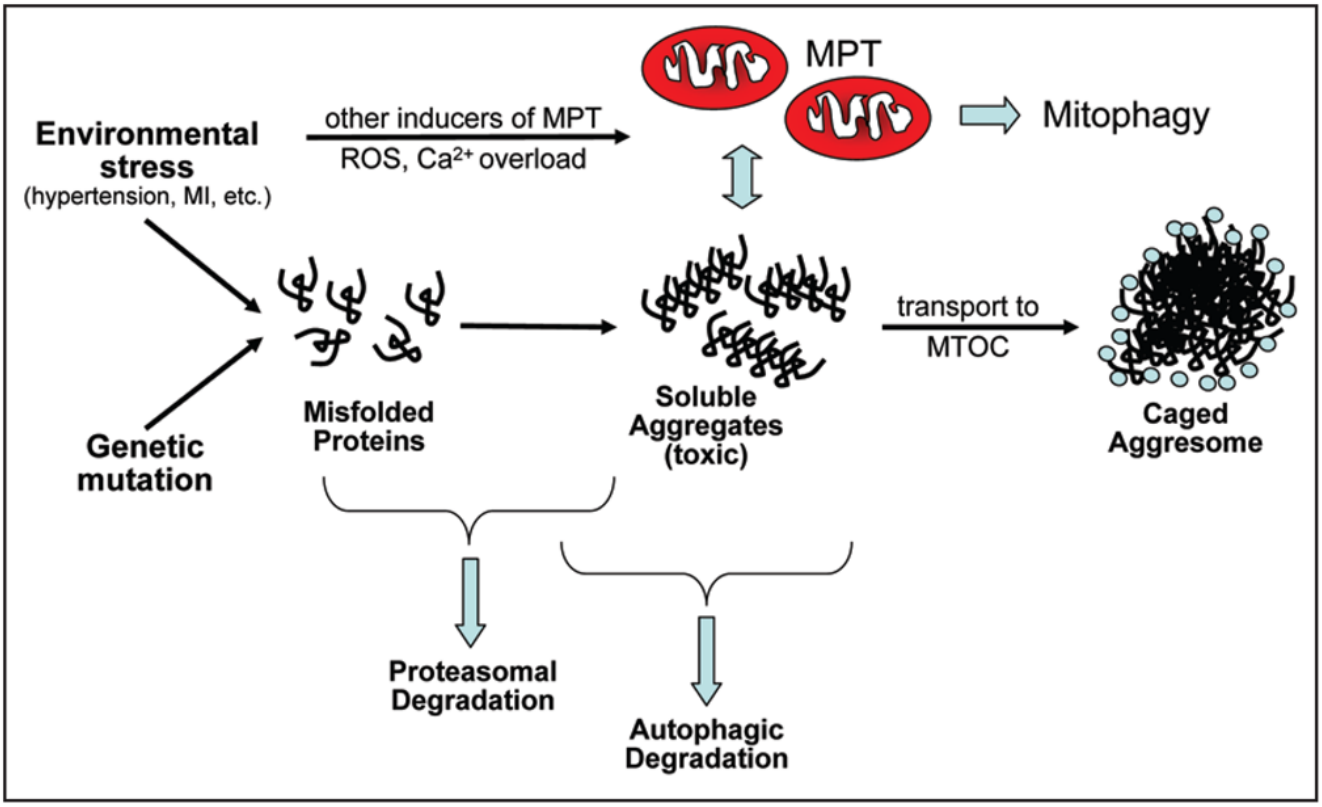

Figure 1.

Working model of the cellular response to proteotoxicity in cardiomyocytes. Misfolded proteins can arise as a consequence of either environmental cardiac stress or inherited genetic mutation. Accumulated proteins aggregate into soluble complexes that are then transported along microtubules toward the MTOC to form insoluble, caged aggresomes. Proteasomal and autophagic pathways are activated in parallel, targeting different but overlapping sets of substrates. Soluble aggregates are thought to be the toxic species and may induce a specialized form of autophagy called mitophagy by promoting MPT. MPT can also occur in response to aggregate-independent signals occurring in stressed myocardium. The pathophysiological consequences of cardiac autophagy likely depend upon both the rate of flux through these pathways and the cellular components being degraded.