Life, death, the unfolded protein response and apoptosis

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See article by Nickson et al. [1] (pages 48–56) in this issue.

The unfolded protein response (UPR) occurs in cells in response to accumulation of unfolded proteins in the endoplasmic reticulum (ER). When unfolded protein accumulates secondary to a mild stress, universal protein synthesis is inhibited, but then resumes upon recovery. In contrast, a more severe or persistent stress would lead to apoptosis. UPR has not been extensively studied in the heart, though it has been described recently in association with some disease states such as hypertrophy and ischemia. In the current issue, Nickson et al. report the role of p53-upregulated modulator of apoptosis (PUMA) in the apoptotic response to UPR in neonatal rat cardiac myocytes [1].

Nickson et al. found that UPR induced by either tunicamycin, which blocks glycosylation, or by thapsigargin, which reduces ER calcium, upregulated expression of PUMA beginning at 8 h from R N A A with a increase in PUMA protein observed at 12 h, and returned to normal by 48 h in isolated rat neonatal cardiomyocytes [1]. Induction of the UPR resulted in apoptosis, which was manifest by 24 h and maximal by 48 h, with 40 to 70% of cells being apoptotic. Using an adenoviral shRNA, the authors blocked PUMA induction and greatly inhibited apoptosis. In a second approach, isolated mouse neonatal cardiomyocytes were prepared from wild-type, PUMA +/−, and PUMA −/− mice. Thapsigargin treatment induced apoptosis in the wild-type and PUMA heterozygotes, while the PUMA knockout mice were resistant to apoptosis, as measured by caspase-3 cleavage. Thus, PUMA has an important role in UPR-associated apoptosis in cardiac myocytes.

1. UPR

There have been a number of excellent, recent, in-depth reviews on UPR [2–4]. The accumulation of unfolded proteins in the ER triggers UPR. Under normal conditions, GRP78 (also known as BiP), which is a heat-shock protein resident in the ER, binds and blocks three sensor proteins present in the ER membrane (Fig. 1). When unfolded protein accumulates in the ER lumen, GRP78 shifts from blocking the sensor proteins to binding the unfolded proteins, triggering UPR. The three sensor proteins PERK, IRE1α and ATF6, once activated, lead to inhibition of translation and increased transcription of chaperones, stress response genes, and redox-related genes. Despite phosphorylation of eIF2 after activation of PERK, certain mRNA, particularly coding for chaperones, can still be translated. Initially, the UPR response triggers a pause in new protein synthesis. This can allow time for recovery with synthesis of more chaperones for folding of proteins in the ER. If UPR persists, then a second phase is entered, triggering apoptosis. The impact of the UPR is evident in the Akita mouse, a relatively new model of diabetes. The Akita mouse has a mutation converting one of the cysteine–cysteine double bonds in insulin to tyrosine. As a result, proinsulin cannot be processed to its final form and accumulates in the ER, resulting in a sustained UPR [5,6]. The sustained UPR leads to apoptosis and loss of the β cells of the Islets, resulting in type I diabetes.

A number of inherited diseases have been linked to abnormalities in the response to ER stress [2]. Several of these cause diabetes, but other diseases associated with ER stress include Parkinson’s, familial Alzheimer’s, and amyotrophic lateral sclerosis. One would expect that ER stress would be a factor in cardiomyopathy, although few studies have addressed this issue. Mutation of KDEL, a retrieval receptor for luminal chaperones (such as GRP78), caused a dilated cardiomyopathy [7]. Aortic banding has been found to increase expression of
GRP78, and this was blocked by angiotensin II inhibitors [8]. Ischemia/reperfusion in the mouse heart was shown to upregulate GRP78 and GRP94, both of which are ER chaperones [9]. As shown in Fig. 1, ATF6, once activated, increases expression of GRP78 and GRP94. In a model with tamoxifen induction of the active form of ATF6, GRP78 and GRP94 had markedly increased expression, and there was less necrosis and apoptosis after ischemia/reperfusion. Thus, in a limited number of studies, UPR and ER stress have been found to have important roles in cardiomyopathy and ischemic injury.

2. PUMA and apoptosis

PUMA is a BH3-only, pro-apoptotic protein, and there have been several excellent reviews on PUMA and BH3 proteins recently [10,11]. When activated, BH3 proteins bind Bcl-2-like proteins and block their anti-apoptotic function. PUMA binds all the pro-survival proteins, Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and A1 [11]. As Nickson et al. demonstrate, PUMA has an important role in UPR-related apoptosis in the neonatal cardiac myocyte [1]. Blocking expression of PUMA greatly reduced apoptosis after induction of the UPR. Similarly, knockout of PUMA also inhibited apoptosis after induction of the UPR. Although Nickson et al.’s results would suggest that PUMA is the lynchpin for UPR-related apoptosis in the cardiac myocyte, further work will be needed to evaluate the role of PUMA vs. other pro-apoptotic factors in cell death after induction of the UPR.

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References