VOLUME-8, ISSUE-12, DECEMBER-2019 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Biochemistry

ROLE OF UNFOLDED PROTEIN RESPONSE IN CARDIAC DISEASES.

Smita Sharma*	MD,DTCD,clinical Biochemist,regional Lab.,nejran.[KSA] *Corresponding Author
Rami Abdullah Ali Al Dagrer	Master In Biotechnology,director Blood Banks And Laboratories,nejran Zone.[KSA]
Sk Mathur	DM(Endo), Md(Paediatrics), Consultant Endocrinologist, Max.hospital, Chandigarh.[india]
Ramesh Maheshwari	Md.(Medicine),General Physician, Punjab Civil Medical Services, bhatinda [india]
Simmi Kharab	MD(Biochemistry), Sr.Prof.&Head, PGIMS, Rohtak.[INDIA]

ABSTRACT Cardiovascular disease is the leading cause of death worldwide. Multiple forms of the cardiovascular disease involve acute or chronic disturbance in cardiac myocytes, which may lead to potent activation of the unfolded protein response (UPR), a cellular adaptive reaction to accommodate protein-folding stress. Ample evidence has firmly established that the UPR is strongly induced in heart disease. Recently, the mechanism of action and multiple pharmacological means to favorably modulate the UPR are emerging to curb the initiation and progression of cardiovascular disease.In this review we tried to focus the unfolded protein response in cardiovascular disease. Modulating the UPR may be clinically beneficial. For example, in heart failure, UPR activation contributes to arrhythmic risk and inhibiting the UPR may decrease that risk. Targeting the UPR seems to be a potentially fruitful approach in novel therapeutics for cardiac disease.

KEYWORDS : Cardiovascular Disease ,unfolded Protein Response,arrythmias.

INTRODUCTION:

The unfolded protein response (UPR) is a cellular stress response related to the endoplasmic reticulum (ER) stress. The UPR is activated in response to an accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum. In this scenario, the UPR has three aims: initially to restore normal function of the cell by halting protein translation, degrading misfolded proteins, and activating the signalling pathways that lead to increasing the production of molecular chaperones involved in protein folding.

MOLECULAR MECHANISM:

The molecular chaperone BiP/Grp78maintains specific transmembrane receptor proteins involved in initiating of the downstream signalling of the UPR in an inactive state by binding to their luminal domains. An overwhelming load of misfolded proteins or simply the over-expression of proteins [1] requires more of the available BiP/Grp78 to bind to the exposed hydrophobic regions of these proteins, and consequently BiP/Grp78 dissociates from these receptor sites to meet this requirement. Dissociation from the intracellular receptor domains allows them to become active. PERK dimerizes with BiP in resting cells and oligomerizes in ER-stressed cells. An alternative model has been proposed, whereby unfolded proteins interact directly with the ER-lumenal domain of Ire1, causing oligomerization and transautophosphorylation.[2]

THE INITIAL PHASES OF UPR ACTIVATION HAVE TWO KEY ROLES:

Translation Attenuation and Cell Cycle Arrest by the PERK Receptor This occurs within minutes to hours of UPR activation to prevent further translational loading of the ER. PERK (protein kinase RNA-like endoplasmic reticulum kinase) activates itself by oligomerization and autophosphorylation of the free luminal domain. The activated cytosolic domain causes translational attenuation by directly phosphorylating the α subunit of the regulating initiator of the mRNA translation machinery, eIF2. This also produces translational attenuation of the protein machinery involved in running the cell cycle, producing cell cycle arrest in the G1 phase[3]. PERK deficiency may have a significant impact on physiological states associated with ER stress.

Increased Production of Proteins Involved in the Functions of the UPR UPR activation also results in upregulation of proteins involved in chaperoning malfolding proteins, protein folding and ERAD, including further production of Grp78. Ultimately this increases the cell's molecular mechanisms by which it can deal with the misfolded protein load. These receptor proteins have been identified as:

Inositol-requiring kinase 1[4], whose free luminal domain activates itself by homodimerisation and transautopho sphorylation[5]. The activated domain is able to activate the transcription factor XBP1(Xbox binding protein) mRNA (the mammalian equivalent of the yeast Hac1 mRNA) by cleavage and removal of a 26bp intron. The activated transcription factor upregulates UPR 'stress genes' by directly binding to stress element promoters in the nucleus[6].

ATF6 (activating transcription factor 6) is a basic leucine zipper transcription factor[7].Upon Grp78 dissociation, the entire 90kDa protein translocates to the Golgi, where it is cleaved by proteases to form an active 50kDa transcription factor[8] that translocates to the nucleus. It binds to stress element promoters upstream of genes that are upregulated in the UPR [9].

UNFOLDED PROTEIN RESPONSE IN CARDIOVASCULAR DISEASE

Abnormal intracellular calcium (Ca^{2+}) handling can trigger endoplasmic reticulum (ER) stress, leading to activation of the unfolded protein response (UPR) in an attempt to prevent cell death. Mechanical unloading with a left ventricular assist device (LVAD) relieves pressure-volume overload and promotes reverse remodeling of the failing myocardium. Estibaliz Castillero et al hypothesized that mechanical unloading would alter the UPR in patients with advanced

heart failure (HF). UPR was analyzed in paired myocardial tissue from 10 patients with dilated cardiomyopathy obtained during LVAD implantation and explantation. Samples from healthy hearts served as controls. Markers of UPR [binding immunoglobulin protein (BiP), phosphorylated (P-) eukaryotic initiation factor (eIF2), and X-box binding protein (XBP1) were significantly increased in HF, whereas LVAD support significantly decreased BiP, P-eIF2 , and XBP1s levels. Apoptosis as reflected by C/EBP homologous protein and DNA damage were also significantly reduced after LVAD support. Improvement in left ventricular dimensions positively correlated with P-eIF2 /eIF2 and apoptosis level recovery[10]. Sen et al. [11]have previously suggested an attenuation of the UPR by mechanical unloading in HF patients. These authors reported a decrease in the ER chaperones Grp72, Grp94, and BiP in HF patients after LVAD support. LVAD-induced reverse remodeling is accompanied by improvement in -adrenergic signal transduction, lower natriuretic peptide levels, increased cell viability, and reduced inflammation . It is likely that these effects are partially mediated not only by an improvement in Ca^{2+} cycling but also improvement in UPR.

The ER is recognized as a vitally important organelle that determines cell survival or death. UPR plays critical roles in the pathophysiology of ischemic heart disease. The three signaling branches may elicit distinct but overlapping effects in cardiac response to ischemia.

Cardiac injury results in UPR activation, which induces ion channel downregulations. These downregulations can explain some of the arrhythmic risk. downregulation of multiple cardiac ion channels corresponds to the APD prolongation and dV/dtmax reduction [١٢]. Inhibition of either the PERK or IRE1 arm led to a shortened APD and recovered dV/dtmax. This suggests that PERK- and IRE1-mediated channel downregulations are specific for a certain set of channels, and that some cross talk exists between the PERK and IRE1 arms of UPR. with 4μ8C [١٢], suggesting that the UPR results in changes in post-translational modifications of Nav1.5 or possibly changes in associated channel subunits. It is noteworthy that inhibition of IRE1 under physiological condition downregulates Cav1.2, hERG and KvLQT1 and prolongs the APD, indicating that certain IRE1 activity may be necessary to maintain these channels under physiological conditions. Inhibition of either PERK or IRE1 shows partial reversal of electrical remodeling, suggesting that the ATF6α arm may play a role in electrical remodeling or that there are overlapping effects of the UPR arms. Blocking UPR activation can raise ion channel levels and may represent a new and potentially fruitful antiarrhythmic paradigm.

CONCLUSION:

Unfolded Protein response plays a vital role in Cardiovascular Disease. It can be used as therapeutic target in future to treat life threatning conditions especially arrhythmias.

CONFLICT OF INTEREST:

There is no conflict of interest.

REFERENCES:

1. Hammond, C; Braakman, I; Helenius, A ."Role of N-linked oligosaccharide recognition, glucose trimming, and calnexin in glycoprotein folding and quality control". Proceedings of the National Academy of Sciences of the United States of America.1994; 91 (3): 913–7.
2. Ron, D.; Harding, H. P.; Zhang, Y."Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase". Nature.1995. 397 (6716): 271–4.
3. .Lee, A. H.; Iwakoshi, N. N.; Anderson, K. C.; Glimcher, L. H. "Proteasome inhibitors disrupt the unfolded protein response in myeloma cells". Proceedings of the National Academy of Sciences.2003; 100 (17): 9946–51.
4. Lee, AS Trends Biochem Sci .1987;12: 20-23.
5. .Machamer, CE., Doms, RW., Bole, DG,. Helenius, A., Rose, JK. J Biol Chem 1995;265 (12) 6879-6883
6. McCullough, K., Martindale, J., Klotz, L., Aw, T., Holbrook. Mol Cell Biol 2001;21 : 1249-1259.
7. Molinari, M., Galli, C., Piccaluga, V., Pieren, M., Paganetti, P.) J Cell Biol.2002; 158 (2) 247-257.
8. Mori, K., Ogawa, O., Kawahara, T., Yanagi, H., Yura, T. (2000) Proc Natl Acad Sci USA 97 4660-4665.
9. Urano, F; Wang, X; Bertolotti, A; Zhang, Y; Chung, P; Harding, H. P.; Ron, D . "Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1". Science.2000; 287 (5453): 664–6.
10. Estibaliz Castillero, Hirokazu Akashi, Klara Pendrak, Halit Yerebakan, Marc Najjar, Catherine Wang. Attenuation of the unfolded protein response and endoplasmic reticulum stress after mechanical unloading in dilated cardiomyopathy Am J Physiol Heart Circ Physiol.2015; 309: H459–H470, 2015.
11. Sen S, Kundu BK, Wu HC, Hashmi SS, Guthrie P, Locke LW, Roy RJ, Matherne GP, Berr SS, Terwelp M, Scott B, Carranza S, Frazier OH, Glover DK, Dillmann WH, Gambello MJ, Entman ML, Taegtmeyer H. Glucose regulation of load-induced mTOR signaling and ER stress in mammalian heart. J Am Heart Assoc 2013;2: e004796.
12. Liu M, Shi G, Zhou A, et al. Activation of the unfolded protein response downregulates cardiac ion channels in human induced pluripotent stem cell-derived cardiomyocytes. J Mol Cell Cardiol. 2018;117:62–71.