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Krishna Sundar Twayana, Palaniyandi Ravanan

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Eukaryotic cell survival mechanisms: Disease relevance and therapeutic intervention

Krishna Sundar Twayana and Palaniyandi Ravanan

Apoptosis and Cell Survival Research Laboratory, Department of Biosciences, School of Biosciences and Technology, VIT University, Vellore, Tamil Nadu, India-632014.

*For Correspondence: Dr. P. Ravanan, Associate Professor, Department of Biosciences, School of Biosciences and Technology, VIT University, Vellore, Tamil Nadu, India - 632014.
Email: ravanan.p@vit.ac.in; Ph: 0416-2202715; Fax: 91-416-2243092

Abstract

Cell responds to stress by activating various modes of stress responses which aim for minimal damage to cells and speedy recovery from the insults. However, unresolved stresses exceeding the tolerance limit lead to cell death (apoptosis, autophagy etc.) that helps to get rid of damaged cells and protect cell integrity. Furthermore, aberrant stress responses are the hallmarks of several pathophysiologies (neurodegeneration, metabolic diseases, cancer etc.). The catastrophic remodulation of stress responses is observed in cancer cells in favor of their uncontrolled growth. Whereas pro-survival stress responses redirected to death signaling provokes excessive cell death in neurodegeneration. Clear understanding of such mechanistic link to disease progression is required in order to modulate these processes for new therapeutic targets. The current review explains this with respect to novel drug discoveries and other breakthroughs in therapeutics.

Keywords: Cellular stress responses, cell survival, cancer, therapeutics.

Abbreviations:

ATM: Ataxia telangiectasia mutated; **ATR:** ATM-Rad3-related; **AMPK:** AMP-activated protein kinase; **AD:** Alzheimer's disease; **ARE:** Antioxidant response element**; ATF6:** Activating transcription factor 6; **BiP:** Binding immunoglobulin protein; **BRAC1:** Breast cancer 1; **CHOP:** CΆEBP homology protein; **CDC1:** conventional dendritic cells**; Chk:** checkpoint kinase; **CpT1C:** carnitine palmitoyltransferase 1C; **DDR:** DNA damage response; **ERAD:** ER-associated degradation**; ERSE:** ER stress response element; **ERK1/2:** extracellular regulated kinases; **GADD34:** Growth arrest and DNA damage inducible protein; **GPX:** glutathione peroxidase; **GRP:** glucose-regulated protein; **GSH:** glutathione; **GSSG:** glutathione (GSH) to oxidized glutathione**; GSTs:** glutathione S-transferases; **Grx:** glutaredoxin; **HD:** Huntington's diseases; **HSE:** heat shock elements; **HSPs:** Heat shock proteins; **HIF:** Hypoxia-inducible factor; **HSF:** heat shock factor**; IRE1:** inositol requirement 1; **IAP:** Inhibitor of apoptotic protein; **ISR:** Integrated stress response; **JNK:** Jun N-terminal kinase; **KIRA:** Kinase Inhibitors RNase Attenuators; **MOMP:** mitochondrial outer membrane permeabilization; **mTOR**: mammalian target of rapamycin**; mTORC1:** mammalian target of rapamycin complex 1**; MST1:** Mammalian sterile 20-like kinase 1; **NOX:** NAD(P)H oxidase; **Nrf2:** nuclear factor erythroid 2–related factor 2; **NER:** nucleotide excision repair; **NSAID:** non-steroidal anti-inflammatory drug; **PARP:** Poly (ADP-ribose) polymerase**; PBA:** 4-phenyl butyric acid; **PCD:** programmed cell death**; PD:** Parkinson's diseases; **PDI:** Protein disulfide isomerase; **PDK1:** pyruvate dehydrogenase kinase 1; **PERK:** protein kinase RNA (PKR)-like ER kinase; **PHD:** prolyl hydroxylase domain; **PI3K:** Phosphoinositide 3-kinase; **PRRS:** pattern recognition receptors; **Prxs:** Peroxiredoxins; **ROS:** reactive oxygen species; **RNS:** reactive nitrogen species; **Sirt1:** NAD-dependent deacetylase sirtuin-1**; SOD:** superoxide dismutase; **SREBP:** sterol response element binding protein; **STAT3:** Signal transducer and activator of transcription 3; **TILs:** tumor infiltrating lymphocytes; **TRAF2:** TNF-receptor-associated factor 2; **Trx:** thioredoxin; **TUDCA:** Tauroursodeoxycholic acid; **UPR:** unfolded protein response; **VEGF:** Vascular endothelial growth factor; **XBP1:** x-box binding protein 1

1. Introduction

Cellular stresses are extracellular milieus that are least supportive for cell growth or even challenge with their fitness. Cells always face stress stimuli that can be environmental or intracellular. Therefore, cells are left with no option than to execute adaptive responses for maximal survival. This redirects cells to become more adaptive. Stresses are bearable up to a point within which, arrays of intracellular signaling pathways are activated to shield cellular integrity. The fact that cell survival relies on timely elicitation of these adaptive responses demand the stress response proteins to be phylogenetically conserved throughout all three super kingdoms- archaea, eubacteria, and eukaryotes (Hecker and Völker, 2001, Kültz, 2003, Macario and de Macario, 1999, Pearce and Humphrey, 2001). Cells go through plenty of cellular threats including ER (Endoplasmic reticulum) stress, oxidative stress, inflammatory stress, and