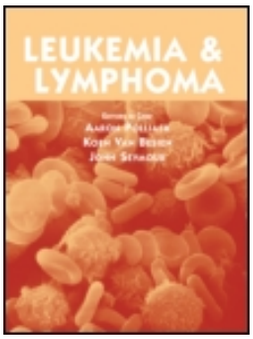

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Kumudha Balakrishnan & Varsha Gandhi

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COMMENTARY

Uncoupling endoplasmic reticulum stress and autophagy: a potential implication for chronic lymphocytic leukemia therapy

Kumudha Balakrishnan[1] & Varsha Gandhi[1,2]

[1]*Department of Experimental Therapeutics and* [2]*Department of Leukemia, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA*

Defective apoptosis is a fundamental hallmark feature of chronic lymphocytic leukemia (CLL) biology. Therefore, significant effort in cure of this disease is toward sensitizing malignant lymphocytes to programmed cell death. In parallel to mitochondrial oxidative stress, endoplasmic reticulum (ER) stress also triggers an essential pathway for B-CLL cell apoptosis, suggesting that genetic or pharmacologic manipulation of ER signaling could represent an important therapeutic strategy [1,2]. ER stress activated unfolded protein response (UPR) leads to up-regulation of downstream ER chaperone molecules such as PERK, eIF2α, glucose regulatory protein GRP78 and pro-apoptotic CHOP and direct activation of initiator caspase 4 [3]. Once activated, caspase 4 in turn activates caspase 9 or 3, thereby leading to mitochondrial outer membrane permeabilization (MOMP)-independent cell death. Several anti-cancer agents including homoharringtonine, sorafenib, obatoclax and flavopiridol are identified to induce ER stress mediated, caspase-dependent apoptosis, as a caspase inhibitor in turn can reverse this process [4,5].

The regulatory role of the Bcl-2 family proteins in ER stress mediated signaling pathways has been well documented. Combining an ER stress inducing agent with a mitochondrial targeting agent demonstrated a synergistic effect, suggesting a link between these two pathways [6]. Agents such as trichosanthin (TCS) and cardiotoxin III are shown to activate both mitochondrial and ER signaling pathways of apoptosis. While loss of the ATM gene was correlated with increased ER stress, activation of the MEK/ERK signaling pathway linked with high levels of oncogenes such as Mcl-1, Bcl-2 or Tcl-1 was inversely correlated with ER stress induced apoptosis. Inhibiting Mcl-1 with siRNA sensitized tumor cells to apoptosis initiated by ER stress inducers thapsigargin or tunicamysin [7,8].

In the past decade, extensive studies have established the connection between ER stress and autophagy in several tumor models (Figure 1). While autophagy is activated by all classic stimuli of this process, only unfolded protein ER stress-mediated autophagy protects the cells from cell death. The connection between ER stress and autophagy was first established using the tyrosine kinase inhibitor imatinib, which was demonstrated to exhibit a cytoprotective effect by inducing autophagy and forming autophagosomes in chronic myeloid leukemia (CML) cells [9]. This mechanism was indeed in association with the ER stress response, but not in reflection of cABL/Bcl-2 activities. Consistently, the combination of imatinib with autophagy inhibitors enhanced imatinib induced apoptosis [10]. Mechanistically, the association between ER stress and autophagy was mediated through phosphorylation of eIFα, which impacts protein translation and mediates LC3 conversion and autophagosome formation, shifting the equilibrium toward a pro-survival mechanism [11]. Importantly, abrogating autophagy restored cells vulnerable to ER stress, suggesting that autophagy plays an important role in cell survival after ER stress [12].

Mahoney *et al*. in this issue of ***Leukemia and Lymphoma*** demonstrate that nelfinavir, an ER stress inducing agent, exhibits modest apoptosis as a single agent in CLL [13]. Detailed studies revealed that treatment with this agent also induced signature proteins of autophagic response, leading to pro-survival mechanisms [13]. Nelfinavir causes two types of cell death programs, caspase dependent and caspase independent apoptosis characterized by induction of ER stress and autophagy. Autophagy was regarded as a pro-survival mechanism because an inhibitor of autophagy combined with nelfinavir increased nelfinavir-induced cell death in lung cancer cells [14]. This proof-of-principle is now established in a CLL model system, proposing a new paradigm of treating CLL. These results engender several unanswered questions. While authors report up-regulation of IRE1, whether ATF6 and PERK mediated signal transduction axes [15] become activated in CLL cells after nelfinavir treatment is unknown. What could be the effect of nelfinavir on mRNA translation, which appears to be a primary mode of action of ER stress inducing agents [16]? As unmitigated ER stress can eventually lead to cell death [15], does extended treatment with nelfinavir result in apoptosis? What could be the biological effect of nelfinavir in normal lymphocytes? Finally,

Correspondence: Kumudha Balakrishnan, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. Tel: 713-563-6975. Fax: 713-794-4316. E-mail: kbalakr@mdanderson.org

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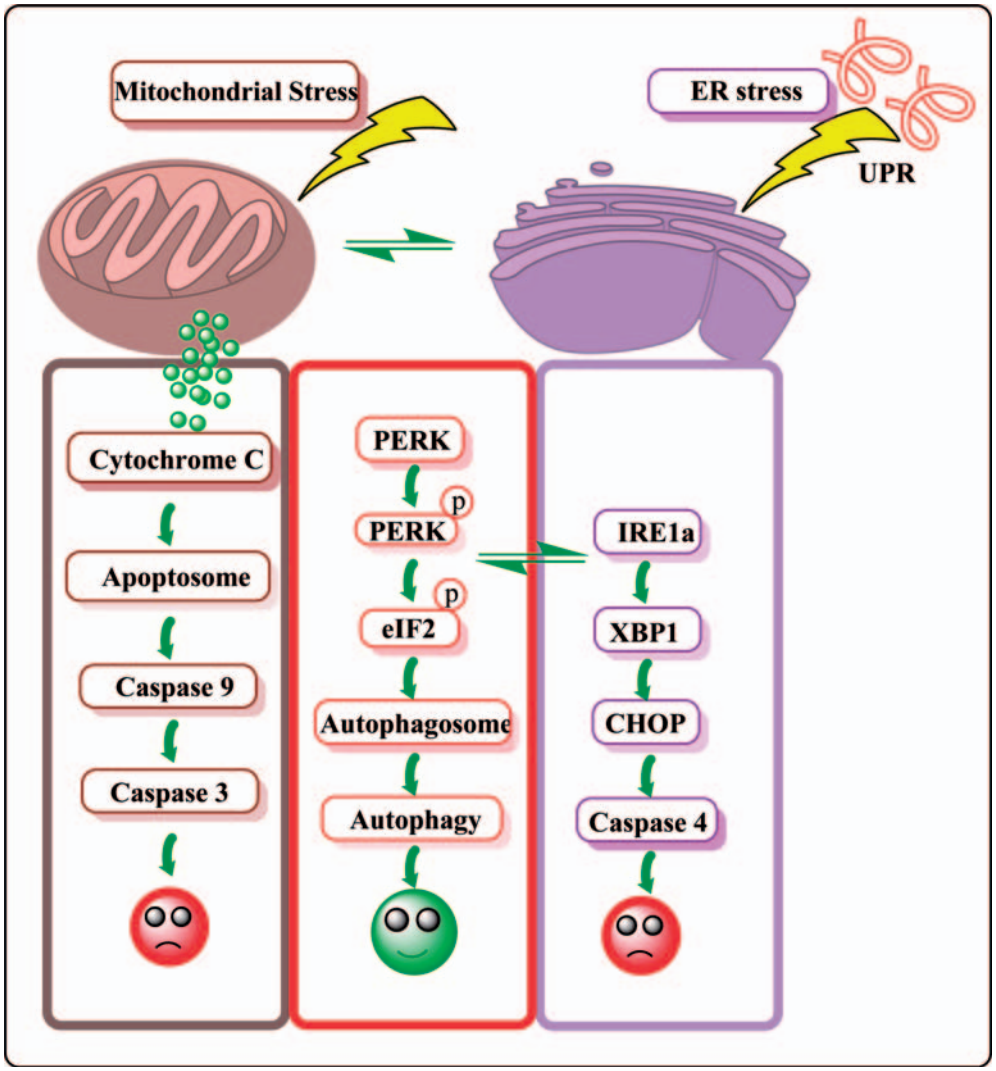

Figure 1. Crosstalk between multiple pathways including mitochondrial stress, ER stress and autophagy. UPR, unfolded protein response; PERK, PKR-like ER-localized eIF2α kinase; EIF2α, translation initiation factor; CHOP, C/EBP-homologous protein.

the novel B cell receptor (BCR) targeting kinase inhibitors that are currently in clinical trial for CLL including GS-1101 and ibrutinib induce modest apoptosis *in vitro*. Do these agents induce ER stress and/or autophagy? Is lymphocytosis observed following treatment an indication of the mechanism of survival? Screening these compounds for ER stress response or autophagic response might provide additional information on the mechanism of action of these agents and combination strategies.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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