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Review

Endoplasmic reticulum-mediated unfolded protein response and mitochondrial apoptosis in cancer

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ABSTRACT

Abrogation of endoplasmic reticulum (ER) protein folding triggered by exogenous or endogenous factors, stimulates a cellular stress response, termed ER stress. ER stress re-establishes ER homeostasis through integrated signaling termed the ER-unfolded protein response (UPR^{ER}). In the presence of severe toxic or prolonged ER stress, the pro-survival function of UPR^{ER} is transformed into a lethal signal transmitted to and executed through mitochondria. Mitochondria are key for both apoptotic and autophagic cell death. Thus ER is vital in sensing and coordinating stress pathways to maintain overall physiological homeostasis. However, this function is deregulated in cancer, resulting in resistance to apoptosis induction in response to various stressors including therapeutic agents. Here we review the connections between ER stress and mitochondrial apoptosis, describing potential cancer therapeutic targets.

Contents

1. Introduction

Coordination of external or internal cellular stress into overall stress signaling is an essential cellular process vital for cell growth and survival during organism development. The endoplasmic reticulum (ER) is a central eukaryotic cellular organelle that provides crucial biosynthetic, stress-sensing, and signaling functions [1,2]. In addition to its role in folding and posttranslational modifications of proteins that are destined for the secretory pathway, the ER also maintains an efficient oxidizing and Ca^{2+}-rich folding environment within cells [3–5]. ER-resident chaperones, such as calnexin, calreticulin, the glucose-regulated protein GRP78 (HSPA5, also called BiP), and protein disulfide isomerases, are involved in protein folding, signal transduction, and maintenance of Ca^{2+} buffering [6–10]. Pathophysiological conditions, including hypoxia, ER Ca^{2+} depletion, oxidative injury, hypoglycemia, and viral infections, affect ER homeostasis and hinder protein folding processes [11–15]. These activities ultimately result in an imbalance between protein folding load/capacity and the physiological condition is known as "ER stress." ER stress initiates a stress response via a well-coordinated and

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integrated signal transduction pathway, called the unfolded protein response (UPR) [6,11,16–19], which primarily re-establishes ER homeostasis by harmonizing various processes of ER-UPR (UPR^{ER}) to promote cell survival [20]. In the presence of severe and irreparable ER stress, a switch in UPR^{ER} from a pro-survival mode towards a pro-death response occurs through mitochondrial engagement, leading to the activation of the intrinsic apoptosis pathway [17,21–26]. Autophagy, another mode of inducing cell death, can also be activated in response to such unresolved stress, maintaining cellular integrity under ER stress [27–30].

Mitochondria play pivotal role in the cellular processes of bioenergetics and apoptosis [31,32]. In the intrinsic apoptosis pathway, a signaling platform containing oligomers of the BCL2 family proteins BAX or BAK assembles on the mitochondrion to induce mitochondrial outer membrane permeabilization (MOMP), leading to release of apoptogenic factors, including cytochrome c and Smac/DIABLO, ultimately triggering apoptosis [33,34]. The assembly of this platform is influenced by the dynamic behavior of the mitochondria and *vice versa*, ultimately regulating initiation of the cell death process. Such dynamic mitochondrial behavior is dependent on mitochondrial division (i.e., fission) and fusion processes that determine cellular characteristics including morphology and cellular distribution [35,36]. In turn, these changes modulate overall cellular physiology by impacting cellular bioenergetics as well as the apoptosis potential in response to stress [37].

Mitochondrial division and fusion events have been linked with the ultimate cellular stress response, which is cell death [38]. Furthermore, the ER actively participates in mitochondrial division (fission), suggesting a new model that links ER stress with cell death induction involving mitochondrial dynamics and apoptosis [39]. Extrinsic or intrinsic stress signals are normally processed via the ER system and result in induction of cell survival. In the case of unresolved stress signals, cross talk with the mitochondrial system results in differential processing and induction of cell death [22,40]. Such a relationship between the ER and mitochondria in response to various stressors could be exploited for potential development of anticancer therapies that would link the stress processed in the ER with mitochondrial apoptosis. Here, we describe the different mechanisms employed by the ER system to process and resolve various stress signals and to engage the mitochondrial system for cell death induction in the case of unresolved cellular stress (Fig. 1).

2. The role of ER stress and UPR^{ER} in prosurvival signaling

The ER is an essential cellular organelle involved in several processes, including protein homeostasis, stress response, survival signaling, and Ca^{2+} homeostasis [28]. The ER is responsible for protein folding and import as part of the cellular secretory machinery pathway, and this organelle functions to maintain tightly regulated oxidizing conditions and a Ca^{2+}-rich environment [6,22,40,41]. These functions of ER have been attributed to ER-resident chaperones, such as calnexin, calreticulin, BiP/GRP78, and protein disulfide isomerases, and Ca^{2+} buffering in the ER. Pathophysiological conditions, such as oxidative insult, hypoxia, Ca^{2+} depletion, hypoglycemia, ATP depletion, and viral infections affect ER homeostasis and interfere with protein folding. This triggers an imbalance between protein folding load and capacity, generating ER stress [6,22,40]. In response to such stress conditions, the ER induces the UPR^{ER} signaling pathway [16,20]. The UPR^{ER} initially restores ER homeostasis by relieving stress conditions. However, when the stress conditions are too severe and cannot be reversed, the UPR^{ER} activates a cell death pathway, usually via intrinsic apoptosis, which involves the mitochondria [16,22]. Thus, under toxic and unresolved stress conditions, UPR^{ER} alters the cell fate from a pro-survival pathway to a pro-death mechanism, eventually inducing cell death [17,22,40].

The UPR^{ER} is primarily mediated by three main signaling cascades, which are activated by three unique ER stress sensors: pancreatic ER kinase-like ER kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) [42]. These ER transmembrane proteins are negatively regulated and maintained in an inactive state via binding of their luminal domains to the inhibitory chaperone BiP/GRP78 [2]. Under conditions of ER stress, BiP/GRP78 inhibition is titrated downward by the accumulation of unfolded or misfolded proteins, activating ER sensors. The Ser/Thr kinase PERK phosphorylates eukaryotic initiation factor 2 alpha (EIF2α) and nuclear factor E2-related factor 2 (NRF2) under stress conditions [42]. Phosphorylation of EIF2α inhibits global translation while preferentially promoting expression of the UPR transcription factor ATF4 [43,44]. ATF4 regulates many genes involved in ER homeostasis, including BiP/GRP78 and GRP94, the oxidative stress response, apoptosis and amino acid biosynthesis and transport [45–49]. NRF2, a cytoprotective transcription factor, is pivotal to the antioxidant response and cell survival under oxidative stress conditions. PERK-mediated phosphorylation of NRF2 leads to its dissociation from its cytosolic repressor kelch-like Ech-associated protein 1 (KEAP1). This dissociation frees NRF2 to facilitate nuclear translocation, which ultimately induces the expression of genes involved in the antioxidant stress response [50–52].

As discussed earlier, activation of UPR^{ER} is primarily an anti-apoptotic adaptive response against toxic insults like ROS, whereas sustained activation of UPR^{ER} signaling causes cell death. Therefore, induction of UPR^{ER} is an attractive strategy to target cancer cells. Many drugs have shown promising results in inducing UPR^{ER} and some of these drugs are under clinical trials [11,53–55]. Although, these UPR^{ER} inducing drugs are not as successful as expected (Reviewed in [56] and [11]), the activation of NRF2 by PERK has been considered as one of the main reasons for the pro-survival effect of UPR^{ER}. The activation of NRF2 induces antioxidant defense system as well as upregulates the expression of BCL-2 and Bcl-xL by binding to the ARE (antioxidant response element) leading to the prevention of apoptosis [57–60]. BCL-2 and Bcl-xL are anti-apoptotic proteins and prevent the oligomerization of pro-apoptotic proteins BAX and BAK, thus blocking the release of cytochrome c from mitochondria [61–63]. Bcl-xL also interacts with apoptotic protease activating factor 1 (Apaf-1) in the cytosol and inhibits the Apaf-1 dependent activation of caspase-9 [64]. Furthermore, prolonged UPR^{ER} induces apoptosis in p53-dependent manner via p53-up-regulated modulator of apoptosis (PUMA) and NOXA, pro-apoptotic members of Bcl-2 family proteins [65]. Thus, induction of UPR^{ER} results in the activation of the PERK-EIF2α-ATF4 and PERK-NRF2 signaling cascades, which promotes survival of ER-stressed cells by restoring ER quality control and enhancing oxidative stress adaptation along with overexpression of BCL-2 and Bcl-xL (Fig. 1). These studies clearly suggest that inhibition of NRF2 along with UPR^{ER} induction is required for anti-cancer strategies.

Stimulation of IRE1, another ER-stress sensor, provides both protein kinase and endoribonuclease activity, although IRE1 itself is the only known direct substrate of this protein kinase activity. Auto phosphorylation of IRE1 is required for its endoribonuclease activity and splicing of XBP1u (u for unspliced) mRNA to yield mature XBP1s (s for spliced) mRNA, which encodes XBP1s, a potent transcription factor that induces expression of genes involved in ER quality control, ER/Golgi biogenesis, and ER-associated protein degradation (ERAD) components in addition to expression of genes involved in redox homeostasis and oxidative stress response, ultimately impacting cell fate decisions [66–68]. Finally, BiP/GRP78 dissociation activates ATF6 and induces its translocation to the Golgi apparatus. In the Golgi apparatus, proteases cleave and process ATF6 to produce an active transcription factor that regulates genes encoding ER chaperones and ERAD components and also those that play essential roles in lipid biogenesis and ER expansion [69,70].

3. ER stress-mediated UPR^{ER} in pro-death signaling

Under tolerable stress conditions UPR^{ER} signaling induces pro-survival pathways that lead to resistance and cell survival. While, in the presence of stress conditions that are severe, highly toxic, and irreversible, the same UPR^{ER} pathway induces pro-death mechanisms [22].