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The unfolded protein response as a target for anticancer therapeutics

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ABSTRACT

The endoplasmic reticulum (ER) is an essential organelle in eukaryotic cells, responsible for protein synthesis, folding, sorting, and transportation. ER stress is initiated when the unfolded or misfolded protein load exceeds the capacity of the ER to properly fold protein. Tumor microenvironmental conditions, such as nutrient deprivation, hypoxia, and oxidative stress perturb protein folding and trigger chronic ER stress. Cancer cells can tolerate mild ER stress, however, persistent and severe ER stress kills cancer cells by inducing their autophagy, apoptosis, necroptosis, or immunogenic cell death. Based on this rationale, many drugs have been developed for triggering irremediable ER stress in cancer cells by targeting various processes in the secretory pathway. This review discusses the mechanisms of protein targeting to the ER, the key signaling cassettes that are involved in the ER stress response, and their correlation with cancer formation and progression. Importantly, this review discusses current experimental and FDA approved anti-cancer drugs that induce ER stress, and emerging targets within the secretory pathway for the development of new anticancer drugs.

1. Introduction to the ER, ER stress initiation, and its relationship to cancer development

The Endoplasmic Reticulum (ER), including the smooth ER (sER) and rough ER (rER), is an essential organelle in eukaryotic cells, responsible for protein synthesis, folding, sorting, and transportation. Approximately one-third of cellular proteins traffic through the rER for processing before arriving at their proper intracellular or extracellular locations (Wang and Kaufman, 2016). Secretory proteins are synthesized by the membrane-bound ribosomes found on the rER and then translocated into the lumen of the ER. The ER is optimized for protein folding and quality control. The ER lumen provides a unique oxidizing environment which supports the formation of disulfide bonds during protein folding, and it contains a specialized set of chaperones and folding enzymes (Chen et al., 2010). Only properly folded proteins exit the ER via coat protein complex II (COPII)–dependent vesicular transport. Unfolded and misfolded proteins, on the other hand, are under the surveillance of ER chaperones, such as GRP78/BiP and Calnexin/Calreticulin, which are responsible for proofreading newly synthesized proteins. Misfolded proteins are trafficked to the cytosol for ubiquitination and degradation by the proteasome. When the unfolded or misfolded protein load exceeds the capacity of the ER to fold protein, the cells are under a state of ER stress. ER stress in turn induces a coordinated adaptive program termed the Unfolded Protein Response (UPR).

It is well documented that both ER stress and UPR activation are involved in the development of various types of cancer (Wang and Kaufman, 2016; Clarke et al., 2014). UPR activation can be tumor-supporting and promote cancer cell survival by: 1. increasing the protein folding capacity of the ER by stimulating the synthesis of ER chaperones and 2. promoting the ER-Associated Degradation (ERAD) pathways for alleviating ER stress and maintaining ER homeostasis. However, UPR activation can also be tumor-suppressive, especially when ER stress in cancer cells is intense and persistent. Under such conditions, the UPR cannot resolve the protein-folding defect, but induces cancer cell death. The complicated roles of ER stress and UPR pathways in cancer development provide significant potential for the development of new anti-cancer strategies. This review discusses the key proteins that are involved in the ER stress and UPR activation pathways and their correlation with cancer formation and progression. Importantly, the current anti-cancer drugs that target the ER stress and UPR pathways, and approaches for investigating novel anticancer strategies, are summarized and analyzed here, and important directions for future research are outlined.

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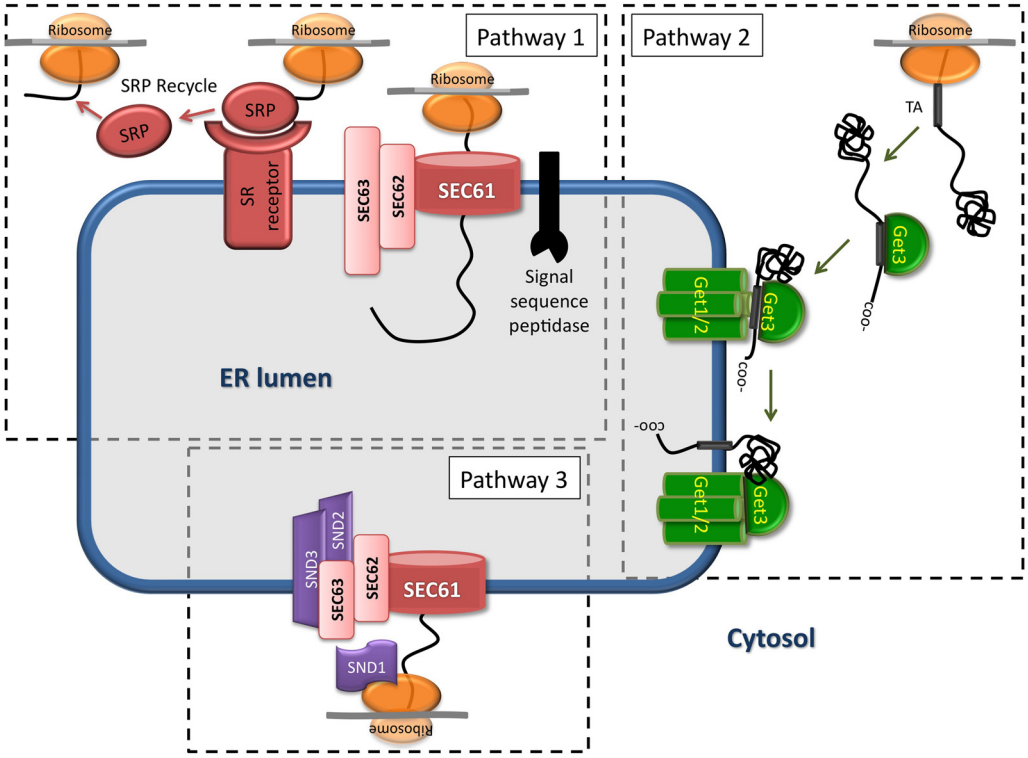

Fig. 1. The pathways that target proteins to the ER. Pathway 1: signal recognition particle (SRP) pathways, which include the co-translational translocation pathway and post-translational translocation pathway. Pathway 2: tail-anchored proteins (GET) pathway. Pathway 3: SRP-independent pathway.

2. Proteostasis in the ER

2.1. The signal recognition particle (SRP), tail-anchored proteins (GET), and SRP-independent pathways that target proteins to the ER

There are three known pathways that guide protein entry into the ER. These include the co-translational translocation and post-translational translocation pathways (Fig. 1). Most of the secreted or membrane-bound proteins use the co-translational translocation pathway (Fig. 1, pathway 1), which is mediated by the signal recognition particle (SRP). The process begins with SRP binding to the signal sequence that is located at the N-terminus of the nascent polypeptide as it is still being synthesized by the ribosome. The SRP then interacts with a membrane-localized SRP receptor (SR) and delivers the ribosome-nascent polypeptide complex (RNC) to the ER membrane. With the arrival of the SRP at the SR, the RNC releases the nascent polypeptide to the translocational channel, termed the translocon, on the ER membrane. Once the nascent polypeptide is inserted into the translocon, the signal sequence is cleaved by the signal peptidase. The interaction between SRP and SR is coordinated by two homologous GTPases, one in the SRP and one in the SR (Shan and Walter, 2005).

Some nascent polypeptide chains that are not recognized by the SRP, or the ones that are fully synthesized in the cytosol, enter into the ER via the post-translational translocation pathway, which is also called the SRP-independent pathway. In this pathway, the heptameric post-translational translocon complex (post-translocon) plays an important role. The post-translocon consists of a protein-conducting channel and a Sec62/63 tetramer (Harada et al., 2011). The protein-conduction channel is a heterotrimeric Sec61 complex, comprised of Sec61α, Sec61β, and Sec61γ. Sec61α is the major component, which is highly conserved and has ten transmembrane (TM) domains. The β subunits may contribute to recruitment of the SRP receptor to the vicinity of the channel by providing a transient docking site. The γ subunit is important for regulating the oligomerization of the translocon complex and its stability (Cheng, 2010). The Sec62/63 complex is located adjacent to the Sec61 complex and assembles into the post-translocon via the sixth cytosolic loop of Sec61. It regulates the import of SRP-independent protein substrates into the post-translocon. Sec62 has recently been identified as an important component in the maintenance and recovery of ER homeostasis, as it functions as a receptor for the autophagy protein LC3-II (Fumagalli et al., 2016). The interaction of LC3-II and Sec62 promotes the clearance of select ER constituents by autolysosomes. Importantly, Sec62-regulated ER delivery to autolysosomes is selective for ER stress-induced proteins, such as BiP/GRP78, during recovery from ER stress, but not for ERAD factors. The overexpression of Sec62 is correlated with increased ER stress tolerance and reduced sensitivity to ER stress-induced cell death (Fumagalli et al., 2016).

The Tail-anchored proteins (GET) pathway (Fig. 1, pathway 2) also regulates the post-translational translocation of proteins to the ER, but, as its name indicates, it is designed specifically for Tail-Anchored (TA) proteins. TA proteins belong to a special class of membrane proteins that are anchored in intracellular membranes by a single transmembrane domain (TMD) that is close to the C terminus. A study showed that the TMD Recognition Complex of 40 kDa (TRC40) recognizes TMDs of TA proteins and targets them to the secretory pathway (Stefanovic and Hegde, 2007). However, the TMDs of proteins can also be recognized by SRP, but there is no competition between TRC40 and SRP. SRP, which is positioned near the ribosomal exit tunnel, is more likely to interact with the TMDs of nascent chain substrates when they first emerge from the ribosome, whereas the interaction between TRC40 and its substrates occurs only after the complete release of the substrates from the ribosome into the cytosol. The binding between TRC and the TMD-containing substrate is fairly stable until TRC releases the substrate at the ER membrane by interacting with a putative receptor there (Stefanovic and Hegde, 2007). In addition to the TRC40-dependent pathway, another study (Schuldiner et al., 2008) showed that the yeast homolog of TRC40 (GET3) also contributes to targeting of TA proteins to the secretory pathway. The study revealed that the GET1/GET2 receptor on the ER membrane recruits GET3-TA protein