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A Possible Crosstalk Between GRP78 and mTOR: New Therapeutic Target in Disease Management

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Abstract

The Endoplasmic Reticulum (ER) is the fundamental organelle which plays an imperative role in numerous cellular activities including protein synthesis, folding, and post-translational modifications. ER stress is caused by multiple pathological and physiological conditions like the accumulation of misfolded proteins. ER stress plays a dual role by either promoting cell survival or triggering cell death which is dependent on the imbalance between ER protein folding load and capacity. ER stress due to the buildup of misfolded proteins in ER lumen causes the Unfolded Protein Response (UPR) that recruit the expression of various chaperones and proteins, like Glucose-Regulated Protein 78 (GRP78), calnexin and calreticulin. GRP78 is an ER chaperone which plays a vital role in protein folding and misfolding. Protein homeostasis in the cells is also maintained by another protein namely mTOR (mammalian target of rapamycin), a serine/threonine kinase. For the cells to function correctly, a balance is to be maintained between protein synthesis, maturation, and degradation. mTOR plays a role in protein synthesis while the regulation of protein folding and repair/or degradation of misfolded proteins is maintained by the ER, and, more specifically the ER chaperones. Any dysregulation in either one or both of these pathways will lead to different diseases including cancer. In this review, we discuss a possible connection between ER chaperone GRP78 and mTOR and also highlight the significance of their functional interaction in different diseases.

Keywords: Endoplasmic Reticulum; mTOR; UPR; Crosstalk

Abbreviations: ER: Endoplasmic Reticulum; UPR: Unfolded Protein Response; GRP78: Glucose-Regulated Protein 78; ERAD: ER-Associated Degradation;

Introduction

The ER is an intracellular organelle present adjacent to the nucleus found in the eukaryotic cells. ER is a tube-like structure that forms a series of flattened sacs inside the cytoplasm of the cells. ER plays a crucial role in normal cellular functioning, by processing of posttranslational modification and folding of secretory and membrane proteins. The ability of ER to properly fold nascent proteins depends on chaperone proteins [1]. Chaperones play an important role in the proper folding of proteins, and any dysfunction in these chaperones may lead to protein folding disorders in the human body. Maintaining protein homeostasis within the cell is vital for the cells to function and survive. However, under conditions of cellular stress, proteostatic mechanisms must be activated to recycle, refold, or initiate degradation of misfolded or unfolded proteins [2]. Thus, in this mini-review, we will discuss the importance of chaperones, specifically the 78 kD glucose-regulated protein GRP78 (also known as BiP and HSP5a), and its possible relation with mTOR. mTOR has a significant role in the maintenance of protein homeostasis.

Protein homeostasis can be called as a fragile balance between protein synthesis, correcting misfolded proteins and degradation of damaged proteins [3]. Molecular chaperones are responsible for overseeing the process of protein folding, refolding of misfolded proteins and degradation of damaged proteins. Any change in the function of these chaperones can lead to disturbance in protein homeostasis which may further cause several diseases including neurological disorders and cancer [4]. mTOR kinase and ER stress pathway also trigger UPR which controls many cellular processes like translation, apoptosis, autophagy, metabolism, and inflammation [5].

Discussion

GRP78 is a major ER chaperone of HSP-70 family that plays a pivotal role in normal ER functioning and its increased expression also works as an indicator of ER stress. GRP78 is commonly localized inside the ER lumen however it has been reported that GRP78 can be detected in the mitochondria, cytosol, nucleus, or even the cell surface, depending on specific cell type and conditions [6,7]. Therefore, different locations prime GRP78 to activate different molecular signaling events [7]. GRP78 also helps in many cellular processes, like translocation of the newly synthesized polypeptides across the ER membrane, help in protein folding and assembly of proteins, regulating calcium homeostasis, targeting misfolded/unfolded proteins for ER-Associated Degradation (ERAD) pathway as well as serving as an ER stress sensor [8, 9]. Moreover, GRP78 is known as a master regulator of ER stress because of its antiapoptotic properties and its ability to control the UPR signaling [9]. UPR is usually activated after ER stress in the cells and regulates many cellular processes [10].

The UPR is a well-conserved pathway from yeast to mammalian cells. Misfolded proteins and their accumulation generate protein aggregates and depletion in ATP levels which in turn leads to ER stress and UPR activation [11]. To manage ER stress, UPR increases the ER folding capacity through transcriptional upregulation of ER folding, lipid biosynthesis, and ERAD (Endoplasmic-reticulum-associated protein degradation) along with a decrease in folding load through selective degradation of mRNA and translational repression. GRP78 manages the UPR by regulating three ER transmembrane proteins: transcription factor 6 (ATF-6), inositol-requiring enzyme 1 (IRE1), and protein kinase R-like endoplasmic reticulum kinase (PERK) [12]. GRP78 also has a role in autophagic protein quality control wherein it participates in the destruction of misfolded proteins in the cytosol [11].

Apart from the regulation of autophagy, GRP78 may also control activated phosphatidylinositol 3-kinase (PI3K)/AKT pro-survival pathways [13]. Activation of the PI3K/AKT pathway eventually leads to the upregulation of mTOR (Figure 1).

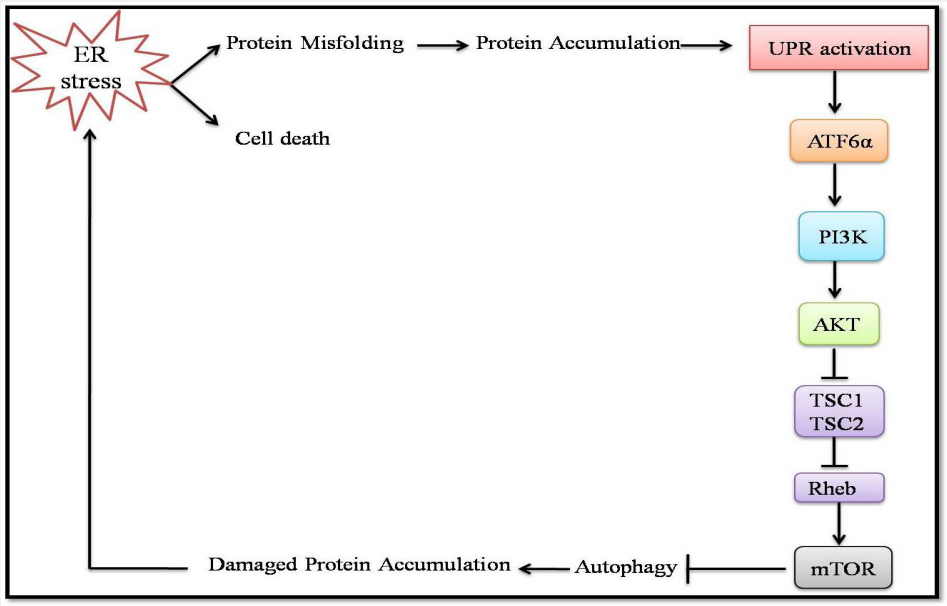

Figure 1: Schematic representation of possible crosstalk between ER stress and mTOR.

Although both of these signaling pathways, i.e., UPR (via GRP78) and mTOR have attracted extensive attention, the crosstalk between the two pathways has emerged recently. mTOR complex 1 (mTORC1) functions both upstream and downstream of ER stress signals, which can either upregulate or downregulate the anabolic output of mTORC1. Upon prolonged ER stress, mTORC1 aids in apoptosis by suppressing the Akt through feedback inhibition. Similarly, constant ER stress inhibits activation of Akt by mTOR complex 2 (mTORC2) [5]. Functioning of ER stress upstream of mTORC1 can add different molecular players in controlling this crosstalk. Inhibiting UPR leads to the activation of PI3k-Akt-mTORC1 [14, 15] signaling pathway via ATF6α through a still unknown mechanism [16]. As mTORC1 and UPR are interdependent, there are several common targets for these two. UPR and mTORC1 work synergistically and regulates angiogenesis [17], insulin resistance [18], hepatic lipid synthesis [19], and NF-κB signaling [20,21]. Alternatively, the antagonistic effect of these two signals when they work together is observed in apoptosis, autophagy, translation and ribosome biogenesis [22-25].

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Although not much is known about the relation between ER stress and mTORC2, it was observed that ER stress when induced pharmacologically for long hours, led to GSK3β catalyzed phosphorylation of rictor, a major component of mTORC2, which also suppresses activation of Akt [26]. Till now there is no substantial evidence which suggests whether mTORC2 plays any role either in activation or downregulation of Akt. Although one study demonstrates that a portion of mTORC2 is present on the ER membrane, thus making it a possibility that mTORC2 may phosphorylate Akt on ER membrane [27]. Thus, we would like to hypothesize mTOR's association with specific membranes may control the mTOR complexes, as demonstrated by mTORC1, which couples the sensing of amino acids in the lysosomal lumen with its activation on the surface of lysosomes [28].

Interdependence of UPR and mTORC1 have been observed in some pathologies, one such example being Tuberous sclerosis (TSC) [29]. TSC, a multisystem disorder is caused by activation of ER stress pathways and mTORC1 [30,15]. An epileptic seizure is the most common symptom of TSC which is usually caused by cerebral cortical tubers but now is also thought to be associated with mTORC1-dependent ER and oxidative stress through the ATF4-CHOP pathway [15]. Another disease characterized by an interaction between mTORC1 and ER stress is diabetic nephropathy [31]. As mTOR is important in maintaining the overall cell viability, it is suggested that low doses of rapamycin along with phenylbutyric acid (PBA), an ER-stress-alleviating 'chemical chaperone', for inhibition of ER stress, can be used to treat nephropathies [31]. However, the combination of mTOR inhibitors and PBA requires preclinical studies for the treatment of TSC or diabetic nephropathy. TSC cells are usually sensitive to ER-stress-induced cell death. Thus, activation of ER stress along with the activation of PI3K-Akt–mTORC1 pathway could kill tumors selectively. For this, Mcl-1, a member of the Bcl-2 family, may provide a link between ER stress- mTORC1 based therapy. Further the inhibition of 4E-BP, downstream effectors of mTOR, controlled translation of Mcl-1 plays a key role in the treatment of mTORC1-hyperactive cancers [22]. Therefore, understanding of the mTOR and GRP78 axis may help in opening of new avenues in the treatment of different diseases.

Conclusion

Even though some of the interplays between ER stress and mTOR has been uncovered, several recent studies have reported new links between the two. Thus, this field of combined effect of mTOR and ER stress is significantly intriguing and needs lot of scientific progress for its understanding.

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