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MECHANISTIC INTERPLAY BETWEEN ER STRESS AND AUTOPHAGY: INTEGRATIVE CONTROL OF PROTEOSTASIS AND CELLULAR HOMEOSTASIS

Arjita Ghosh*

Assistant Professor, School of Biotechnology, Sathyabama Institute of Science and Technology, Sriperumbadur Campus, Tamil Nadu, India
*Corresponding Author
Address - School of Biotechnology, Sathyabama Institute of Science and Technology, Sriperumbadur Campus, Vadamangalam, Sriperumbudur,Tamil Nadu 602108
E-mail - arjita.ghosh.bte.spd@sathyabama.ac.in
Orcid ID: 0000-0001-5583-1037

Abstract:
The endoplasmic reticulum (ER) is crucial for protein folding, post-translational modifications, calcium storage, and lipid production. Disruptions in these functions cause an accumulation of unfolded or misfolded proteins, leading to ER stress and triggering the unfolded protein response (UPR). The UPR aims to restore balance by modulating translational attenuation, increasing the transcription of chaperones, and activating degradation pathways. However, if the stress is intense or prolonged, these adaptive responses shift towards apoptosis. Of the three UPR pathways, the PERK–eIF2α–ATF4–CHOP and IRE1–XBP1 pathways are key in connecting ER stress to autophagy, while ATF6 helps maintain proteostasis by controlling the transcription of ER quality components. Autophagy functions as a critical compensatory mechanism during ER stress, facilitating the clearance of aggregated proteins and damaged organelles to re-establish the cellular balance. Crosstalk between the UPR and autophagic machinery occurs through multiple signalling nodes, including the AMPK–mTOR axis, ubiquitin–proteasome system, and calcium-mediated signalling pathways. The disruption of these interactions contributes to several pathological states, including cancer, neurodegenerative disorders, and metabolic diseases. This review integrates current insights into the molecular interplay between ER stress and autophagy, emphasizing their coordination through ER-associated degradation (ERAD), lipophagy, and metabolic signalling. Understanding these interconnected pathways offers potential therapeutic opportunities to modulate proteostasis and improve cellular resilience under stressful conditions.

Key Words: ER Stress, Autophagy, UPR, Apoptosis.

1.INTRODUCTION:

Endoplasmic Reticulum is an essential cellular organelle where proper folding of proteins and post-translational modification of proteins takes place. The appropriate folding of protein in the Endoplasmic reticulum is assisted by many components of ER chaperons, after which they are transported to Golgi apparatus and then further to the vesicles [1]. But in case there are unfolded or partially folded proteins in the ER, they are detected and transported by the help of components called as “Endoplasmic Reticulum Associated Degradation” also known as ERAD, which take the unfolded proteins and transport them to cytosol where the proteins are degraded by proteasomes. But if the amount of unfolded proteins becomes unmanageable by ER, a reaction called as “ER stress” takes place. The ER stress starts a Unfolded Protein Response (UPR), which is a set of complex signal transduction pathways used to retain back the homeostasis of the organelle [2] .The Unfolded protein response in ER can be differentiated into three distinct types. They are IREα, PERK, and ATF6 pathways. For the activation of these pathways an ER chaperon called BiP/GRP78 which is attached to these complexes during homeostatic conditions, dissociates in response to ER stress and activates them. UPR basically activates these signal transduction pathways to decrease the protein load in ER and increasing the protein folding and degradation process so as to restore the balance in ER. But if UPR fails to restore homeostasis then it leads to apoptosis which causes cell death. If the amount of unfolded proteins increases they tend to aggregate together because they expose the hydrophobic amino acid residues that should be inside the proteins. If the aggregation amount is high it may lead to toxicity which can cause apoptotic cell death. Too much of this aggregation may also lead to many conformational diseases like Alzheimer’s, Parkinson’s, various Ophthalmology disorders, Inflammations, Cancer, etc [1].

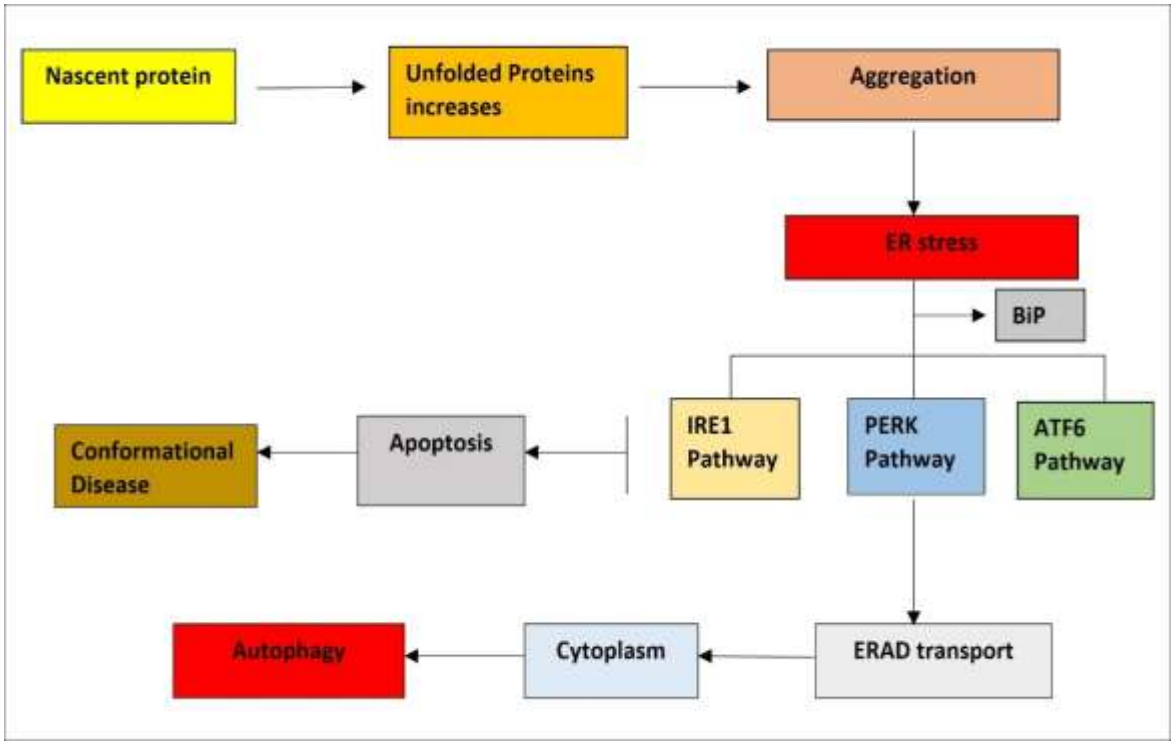

Fig1- The overview of the ER stress mechanism in relation to autophagy

The ER stress can trigger two proteosomal pathways: one is ERAD mediated ubiquitin-proteasome pathway, and another is Autophagy where lysosome mediated protein degradation happens [3]. It was observed that during ER stress, the ER expanded in size considerably by UPR signalling pathways. It was also observed that during the proliferation of ER autophagosme like structures are formed, which are densely and selectively packed with membrane stacks derived from the expanded ER. The UPR signalling pathways also activates a lot of autophagic genes that leads to autophagy specific ER stress. This process is essential for cell survival and homeostasis. Many metabolic diseases are caused by impairment of the autophagy process, but it is also seen that by supressing autophagy may also help in Cancer treatment. It has been observed that both up regulation and down regulation of Autophagy may be beneficial for the medical community [4].

Despite extensive research on ER stress and autophagy as individual processes, the precise mechanisms that interconnect these two adaptive systems remain incompletely understood. Although the three canonical UPR sensors—PERK, IRE1, and ATF6—are known to influence autophagy, their specific roles and downstream targets vary across cell types, stress intensities, and disease contexts. This variability has made it difficult to establish a unified model explaining how ER stress determines the shift between adaptive and pro-death autophagy [5].

Another unresolved issue involves the contribution of metabolic and calcium signalling to this crosstalk. Pathways governed by AMPK and mTOR act as critical regulators of both UPR activation and autophagic flux; yet the extent to which energy-sensing and calcium-mediated feedback loops integrate with ER stress signalling is still unclear. Similarly, selective forms of autophagy, such as ER-phagy, mitophagy, and lipophagy, have recently emerged as key modulators of proteostasis, but their direct regulation by UPR sensors has not been fully delineated [6].

Furthermore, the role of the UPR–autophagy axis in disease remains context dependent. While autophagy activation downstream of UPR signalling promotes survival in tumor cells and contributes to therapy resistance, it is largely cytoprotective in neurodegenerative and metabolic disorders by facilitating the clearance of protein aggregates [6]. Understanding this duality requires more integrative analyses across model systems and stress conditions [7].

Finally, despite promising pharmacological agents targeting the UPR or autophagy individually—such as PERK inhibitors, ISRIB, and mTOR modulators—their combined or sequential therapeutic impact remains insufficiently explored in vivo. The lack of precise knowledge regarding dose dependency, specificity, and long-term cellular outcomes presents a major translational barrier [5,7].

Therefore, this review aims to synthesize current mechanistic and therapeutic insights to provide a cohesive understanding of how ER stress–induced UPR signaling coordinates with autophagy in determining cell fate. It further highlights the emerging regulatory nodes that may serve as potential therapeutic targets in cancer, neurodegeneration, and metabolic diseases.

2.UPR SIGNALLING PATHWAYS:

The Unfolded Protein Response during ER stress triggers signalling pathways important for mediating the ER stress and bringing back the cell to homeostasis [2]. There are three major signalling pathways. First is the IRE1 pathway, which has two genes named IRE1α and IRE1β, during ER stress the chaperon BiP is inhibited by the IRE1 and this activates it, causing dimerization and phosphorylation of IRE1α which in turn activates it [5,8]. This triggers XBP-1(X-box binding protein-1) to unconventionally splice the mRNA at 26 nucleotide intron and convert it to mature mRNA which encodes bZIP family transcription factor sXBP1[9,10]. XBP-1 ORFs codes for the DNA binding domain and the activation domain in the nascent mRNA state. Proteins translated from this mRNA cannot activate transcription, but the mature mRNA (pXBP1(S) will be able to transcribe components of ERAD such as EDEM, Derlin-2, Derlin-3 etc[11]. In response to increase in stress levels of ER the dimerized and phosphorylated IREα works together with modulators and adaptors present in the cystolic end to trigger signalling events. Additionally IRE1α also activates Apoptotic signalling kinase-1(ASK-1) which leads to the activation of Jun-N-terminal kinase (JNK), p38, and MAPK, which triggers apoptosis. It also activates the CHOP transcription factor which makes changes in the gene expression and makes it more viable toward apoptosis. It is also seen that IRE1α is shown to activate ERKs (Extra cellular signal regulated kinase) and NFκB pathways (Nuclear factor κB). It has also been observed that in epithelial cells of gastrointestinal tract IREβ is specifically expressed where they cleave the rRNA so as to slow its translation in response to ER stress [12].

In the ATF6 pathway, the BiP is released from its domain in response to ER stress. ATF6 is transcriptional factor which translocates to Golgi apparatus upon activation. There it is cleaved by two kinds of proteasomes S1P (Site 1 Protease), and S2P (Site 2 Protease). The S1P cleaves ATF6 in its luminal domain, whereas S2P cleaves it at N-terminal cytosolic domain. This causes the release of ATF6 transcriptional factor from cytosol and translocates to nucleus where they homodimerize or hetrodimerize other regulators of gene expression related to UPR. Various target genes such as BiP, Grp9 and CHOP gets activated in response to ATF6 binding to CRE (ATF/cAMP response element) and ERSE-1(ER response stress elements-1) [13]. The ATF6 like IRE1 has two sets of genes ATF6α and ATF6β they are shown to have similar functions and expressions. Some new bZIP type transcriptional factors were also observed that have shared the same structural and proteolytic pattern as ATF6. These include OASIS, CERB-H, Luman, Tis 40 which also takes part in UPR transduction. CERB-H is a liver specific transcription factor that regulates ER stress response genes with ERSE in there promoter [14]. In response to ER stress CERB-H is cleaved thus activating the APR (Acute phase response genes) which forms a correlates to inflammatory factors in ER stress. OASIS in astrocytes triggers the transcription of BiP in response to ER stress. Tis 40 also activates the transcription of EDEM during ER stress. These all factors helps in the regulation of UPR [2,3].

The PERK pathway like the previous IRE1 and ATF6 pathways activates when BiP is released from its domain in response to ER stress. PERK is a type I transmembrane protein located in the ER[15] .Its majorly known for translational attenuation of mRNA during stress. The activated PERK phosphorylates eukaryotic translation initiation factor 2(eif2α) which leads to attenuation of mRNA translation. By the phosphorylation of eif2α there is also inhibition of initiation phase of polypeptide chain synthesis, as it stops the recycling of eif2α to its active GDP bound form which is essential for synthesis. Thus it reduces the amount of protein produced by the ER and arrests cell cycle. By phosphorylation of eif2α, it up regulates ATF4 (Activating transcription factor 4), it is a part of cAMP response element binding (CREB) family. ATF4 triggers factors like GADD34, CHOP, and ATF3 [16]. Phosphorylation of PERK may also lead to dissociation of NRF2-Keap1 complex, which increases expression of genes containing ARE (Antioxidant response factor), this makes integration of antioxidant genes such as heme oxygenase-1 (HO-1),which prevents oxidative stress in the ER[16,17]. It has also been observed that in polyQ72 (poly glutamine 72 repeats) ER stress-mediated cell death, the phosphorylation of eif2α leads to conversion of LC3 (Light chain3), leading to autophagy [18,19].

While the molecular mechanisms of the three UPR branches—PERK, IRE1, and ATF6—are fairly well understood, several important questions remain unanswered. Recent research indicates that these signaling pathways do not operate in isolation but instead show significant interaction and feedback regulation. However, the exact molecular hierarchy that controls their activation and coordination during prolonged ER stress is still not well defined. Additionally, most current data come from static endpoint analyses, leaving the temporal dynamics of UPR signaling largely unexplored [20,21]. The absence of quantitative, time-resolved studies makes it challenging to ascertain how the intensity and duration of stress selectively trigger adaptive and apoptotic responses. Moreover, although the downstream connections between UPR signaling and autophagy have been identified, the specific contribution of each UPR branch to autophagy induction in various physiological and pathological settings remains unclear. Addressing these gaps is crucial for understanding how UPR signalling integrates with other stress-adaptive pathways to maintain cellular homeostasis.

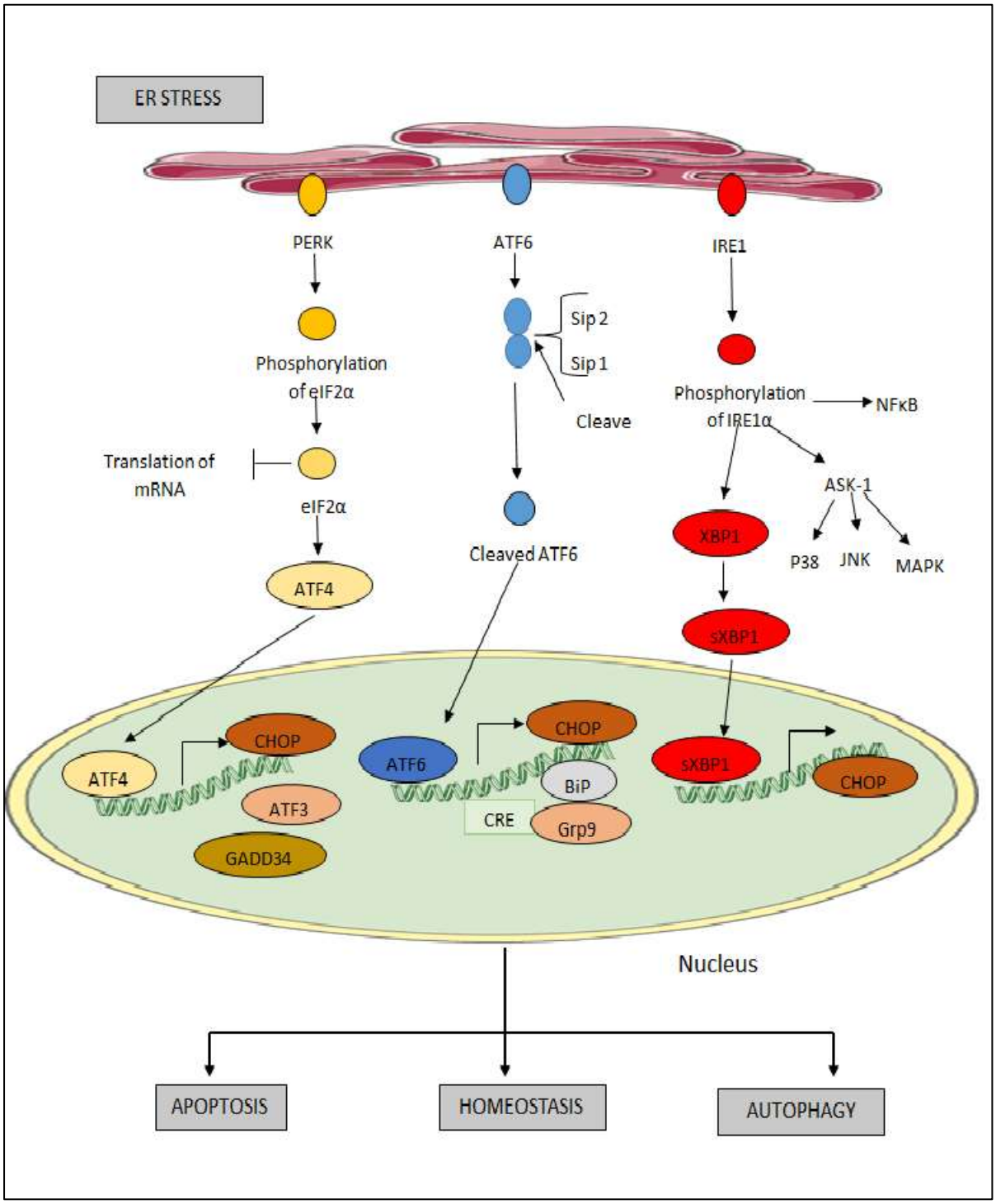

Fig 2- The overview of the UPR system. The ER stress causes the UPR system consisting of PERK, ATF6, IRE1 to activate to regain back cellular homeostasis. Failure to attain which leads either apoptosis or cytoprotective autophagy. The PERK phosphorylates eIF2αwhich in turn triggers CHOP, ATF3, GADD34. The ATF6 upon activation gets cleaved and triggers CHOP, Bip, Grp9. The IRE1 upon activation phosphorylates to IRE1α which in turn triggers XBP-1 which in turn transcripts CHOP. IRE1α also triggers NFκB, p38, JNK pathways, which can lead to apoptosis.

3.MECHANISM OF AUTOPHAGY:

Autophagy is the name given to all the pathways in the cell, where cytosolic materials are transported to the lysosome for degradation. In mammalian cells, three different types of autophagy have been observed: macroautophagy, microautophagy and chaperone mediated autophagy. In macroautophagy substrates are sequestered in a double membrane structure called phagophore. The phagophore containing all the cytosolic

substrate is called as “autophagosome” [22]. This autophagosome is a double membrane cytosolic vesicle. This autophagosome then fuses with the lysosome thus becoming autolysosome where the substrate is degraded permanently. In microautophagy the lysosome itself engulfs the substrates of cell and degrades it. In the third type of autophagy substrates are translocated to the lysosome with the help of chaperones like HSC70 (Heat shock cognate 70), and cochaperones which specifically targets proteins that contain KFERQ like pentapeptide [22,23]. The lysosomal associated membrane protein type -2A (LAMP-2A) plays an important role in this process. An isoform of LAMP-2A called LAMP 2 acts as a receptor on lysosome [23,24] . It has been observed that LAMP-2A levels increases in lysosome by decrease in degradation levels. The substrates are delivered to lysosome through multimeric translocational complex. Macroautophagy is the most well-known of all these processes and hence when autophagy is referred most think of macroautophagy. The autophagosomes can be induced in response to starvation and various other kinds of stresses. It has been observed that autophagosome formation takes place in the proximity of Endoplasmic reticulum. Autophagy is a complex process. Once it is activated it follows cargo selection, packaging, expansion of phagophore membrane, formation and maturation of autophagosome, fusion of autophagosome with lysosome, and finally degradation. Multiple molecular factors help in this process. First is the formation of Phagophore membrane where many Atg proteins are seen to work together. It has been observed that Atg 8 protein is first among the Atg protein characterized to mark phagophore and autophagosomes. It is seen that Atg 8 is transiently present in Phagophore assembly site (PAS) [23,25]. Various Atg proteins assemble in this PAS site and help in the formation of phagophore in a systematic manner. It is marked by Atg 11 assembly at the site when autophagy is triggered. Once autophagy is initiated then the site transitions to autophagy specific PAS structure and Atg 11 is replaced by Atg17-Atg31-Atg 29 complex along with Atg1 and Atg13 [26]. This makes Atg9 move in between PAS and peripheral site playing important role in in autophagy formation. It localizes PAS at the same time as Atg 1kinase complex. Then the Class III phosphatidylinositol 3kinase complex (PtdIns3k) along with Atg12-Atg5-Atg16 complex is brought to the PAS site and there they act as E3 ligase for the formation of Atg8-PE which is one of the last proteins brought in PAS for phagophore formation. The initiation phase of autophagy is controlled by ULK1/2 complex, which contains ULK1, Atg 13, Atg101- a novel autophagic factor, and RB1CC1/FIP200 (a functional ortholog of yeast Atg17). It is seen that this ULK1/2 complex remains inhibited by mTOR (mechanistic target of rapamycin (ser/thr kinase) components in a stress less time and inhibits autophagy itself [27,28]. However, in response to acute stress mTOR components attenuate and ULK1/2 complex can activate leading to the formation of phagophore. PtdIns3k also greatly helps in phagophore formation. The PtdIns3k complex is composed of BECN1/BECLIN1, PIK3C3/VPS34, PIK3R4/p150, Atg14, and UVRAG. It has been observed that BECN1 is inhibited by anti-apoptotic BECLIN2 which binds to it and inhibits the formation of PtdIns3K complex and thus stops phagophore formation. The Beclin-2 is phosphorylised by JNK-1 to activate the Beclin-1 and free it. For the closure and expansion of phagophore several ubiquitin like protein (UBL) are needed [23,26]. They take part in 2 conjugation reaction. The Atg12-Atg5-Atg16L complex is a product of the first conjugation process [29]. It stimulates, recruits and converts of proteolytically processed cytosolic MAP1LC/LC3 (microtubule-associated associated prot-1 light chain 3), LC3-I to the lapidated form LC3-II. Then the pre-LC3 is cleaved by conjugation with membrane-bound phosphotidyltheothanolamine. This causes the Atg7 and Atg3 enzyme to incorporate it into phagophore. Atg4 enzyme can also de-conjugate the LC3-II recycling it to the outer surface of autophagosome, whereas the inner autophagosomal membrane bound L3C-II monitors the autophagosomes and their ability of autolysosome for reaching degradation. Hence LC3-II also acts as marker for autophagy detection [30,31]. The autophagosome then accesses to the lysosome in the perinuclear region of the cells. For transferring the autophagosome to lysosome majorly cytoskeletal microtubules and motor protein dynein plays a great role. Similarly small GTPase like RAB7A/RAB7 with FYCO1 along with LAMP1/2 helps in autophagosomal transport to lysosome and accelerate the fusion of both [28,32]. The fusion machinery also gets help from ATG9 for transportation of vesicle fusion protein, SNAREs and helps in phagophore and autophagosome formation. Then C vacuolar protein sorting HOPS complex activates RAB7A and regulates autophagosomes fusion with lysosomes. Finally the autophagosomal substrate is degraded in lysosome with the help of hydrolytic acids like CTSB, CTSD, and CTSL [31,33].

While the fundamental molecular components of autophagy have been thoroughly studied, several mechanistic details remain unclear. The exact sequence of events that control the initiation and formation of the phagophore, especially the spatial regulation of the ULK1–ATG13–FIP200 complex and its interaction with membrane sources like the ER, mitochondria, and Golgi, is not yet completely understood [22,34]. The molecular factors that dictate the shift from non-selective to selective autophagy, along with the impact of post-translational modifications—such as phosphorylation, ubiquitination, and acetylation—on essential ATG proteins, need further investigation. Additionally, the way in which the autophagic machinery dynamically interacts with other stress-responsive pathways, including the UPR, mTOR, and AMPK signaling networks, is still not fully comprehended. Understanding these unresolved mechanisms is crucial for grasping how autophagy maintains proteostasis and influences cell fate under different physiological and pathological conditions [19].

Table 1: Autophagy Stages and Key Regulators

Autophagy Stage	Key Components	Function
Initiation	ULK1/2 complex (ULK1, Atg13, Atg101, FIP200), mTOR	Senses stress, initiates phagophore formation
Nucleation	PtdIns3K complex (BECN1, VPS34, p150, Atg14, UVRAG)	Generates membrane for phagophore
Expansion	Atg12–Atg5–Atg16L complex, LC3-I to LC3-II conversion	Expands phagophore, marks autophagosome
Cargo Selection	HSC70, LAMP-2A, KFERQ motif	Targets specific proteins for degradation (chaperone-mediated autophagy)
Fusion	RAB7A, FYCO1, LAMP1/2, SNAREs, HOPS complex	Autophagosome fuses with lysosome
Degradation	CTSB, CTSD, CTSL	Lysosomal enzymes degrade cargo

4. UPR SIGNALLING PATHWAYS RELATION WITH AUTOPHAGY:

The three UPR signalling pathways have been found to induce autophagy in response to ER stress. It was observed that tumour cells activate autophagy to combat against the toxicity caused by ER stress. The UPR signalling pathway IRE1 is known to phosphorylate MAPK8 which is a stress regulated protein kinase. So, it plays an important role in stress induced autophagy. It was seen that MAPK8 phosphorylation can activate autophagy mechanism[35]. This MAPK8 also activates BECIN1 autophagic gene by phosphorylating it from BCL2 which keeps on bound to it and is anti-autophagic [36]. Endoribonuclease IRE1 activities have also reported to cause autophagy. MAPK8 activity has been reported to regulate both apoptosis and autophagy. In autophagy induced by MAPK8 it is found that BH3 domain containing proteins like Beclin1 and BAX are its important key regulators [36] . Under these situations when Beclin1 dissociates with BCL2, though BCL2's interactions with BAX remains unchanged. C-Jun-NH2 kinase (JNK) is activated by binding of IRE1α with TRAF2 (TNF receptor associated factor-2), a process that requires ASK-1 a signal regulating kinase. As ASK-1 is strongly associated with ER stress and autophagy, it is implied that activation of IRE1α is accompanied by ASK-1 activation. The JNK also plays a role in phosphorylating BCL2 from BECIN1 and helps in there dissociation and usher in the formation of autophagosomes. By this we can imply JNK plays a dominant role in autophagy[37].

It is seen that antiestrogens can cause both apoptosis and autophagy. It was observed that resistant cells that are desensitized to antiestrogen through BCL2 inhibition die of autophagy induced cell death rather than apoptosis. A major component of apoptotic cell death DRF5 (Death receptor-5) is regulated through CHOP.CHOP also regulates the expression of BCL-2 [38]. CHOP is activated by UPR signalling pathways PERK and ATF6. CHOP's interaction with ATF4 also transcriptionally upregulates p62, NBR1, and Atg7 genes respectively. Plus, CHOP transcription activation alone activates Atg10, Atg5, GABARA, etc. These are all important for autophagosome induction. Under ER stress conditions a branch of UPR called EIF2AK3 (Eukaryotic translation initiation factor 2- alpha kinase 3) helps in regulation of LC3-II and other Atg genes which is important for autophagosome[39].

There is an observation showing that polyQ expression activates the EIF2AK3 factor and phosphorylates its downstream factor eIF2α. The phosphorylation of EIF2S1 a downstream regulator of EIF2AK3, was shown to influence Atg12 mRNA greatly. This causes the upregulation of the Atg12 gene, which induces autophagy. Under hypoxia it was noted that EIF2AK3-dependent ATF4 and CHOP induction causes upregulation of ATG5 and LC3 genes [40]. EIF2AK3-mediated activation of ATF4 is also shown to upregulate various other genes like MAP1LC3B, BECIN1, Atg12, Atg3, Atg16L1. Furthermore, in breast cancer cells it was found that by inhibiting proteasome, ATF4 dependent LC3 can be stimulated. This links between ER stress and autophagy in PERK independent manner. Also EIF2AK3's downstream regulators lead to autophagy. It was also noted that PERK-EIFS2 (Eukaryotic translation initiation factor subunit 2) ATF4 pathway mediated autophagy has both cytotoxic and cytoprotective mechanism [41]. However, cytoprotective activity is more prominent under ER stress. The XBP1 downstream transcription factor of IRE1, when spliced can bind with BCIN1 and promote autophagy by upregulating BECIN1 transcription factor. Although it is also observed that XBP1 can also cause BCL-2 overexpression, in an attempt to protect the cell from destruction. Therefore XBP1's splicing and regulation of BCL2 expression is noted to be very important in the downstream activity that integrate UPR to autophagy. In Huntington disease mouse model it was observed that XBP1 deficiency caused resistance towards the disease. XBP1 enhances neural survival and increases the animal's chances of survival. This mechanism is said to be related to upregulation of autophagy. It was also observed that FOXO1 factor, a major key in ageing and autophagy pathways in neurons, is negatively regulated by XBP-1 post-transcriptional levels in β cells of the

pancreas. By this, we can indicate a relation between XBP1 and its regulation of autophagy [42,43]. ATF6 pathway also induces autophagy through HSPA5 upregulation which sequentially downregulates AKT1/AKT, which ushers autophagy. CEBPB a transcription factor associated with ATF6 expresses DSPK1 (Death associated protein kinase-1) which induces IFNG1-dependent autophagy. This subsequently leads to dissociation between BECIN1 and BCL2 and initiates autophagy. However, ATF6 is also known to decrease DSPK1 expression which leads to inhibition of apoptosis [40].

Although substantial advancements have been made in understanding the molecular connections between the unfolded protein response and autophagy, several critical questions remain unanswered. The exact sequence and timing of activation for the PERK, IRE1, and ATF6 pathways during endoplasmic reticulum stress are not well-defined, complicating predictions about which signaling pathway primarily influences autophagy under certain conditions [43]. Additionally, the common mediators linking these pathways—such as CHOP, JNK, and Beclin1—constitute a complex regulatory network that is not fully mapped. This complexity is further exacerbated by contradictory findings regarding the effects of UPR-induced autophagy in various disease models, where the same pathway may either support cell survival or lead to cell death. Lastly, the lack of comprehensive systems-level and computational analyses hinders our ability to quantitatively model this interaction. Bridging these knowledge gaps is crucial for pinpointing the regulatory checkpoints that decide whether UPR-mediated autophagy serves as a protective or harmful mechanism in response to cellular stress [41].

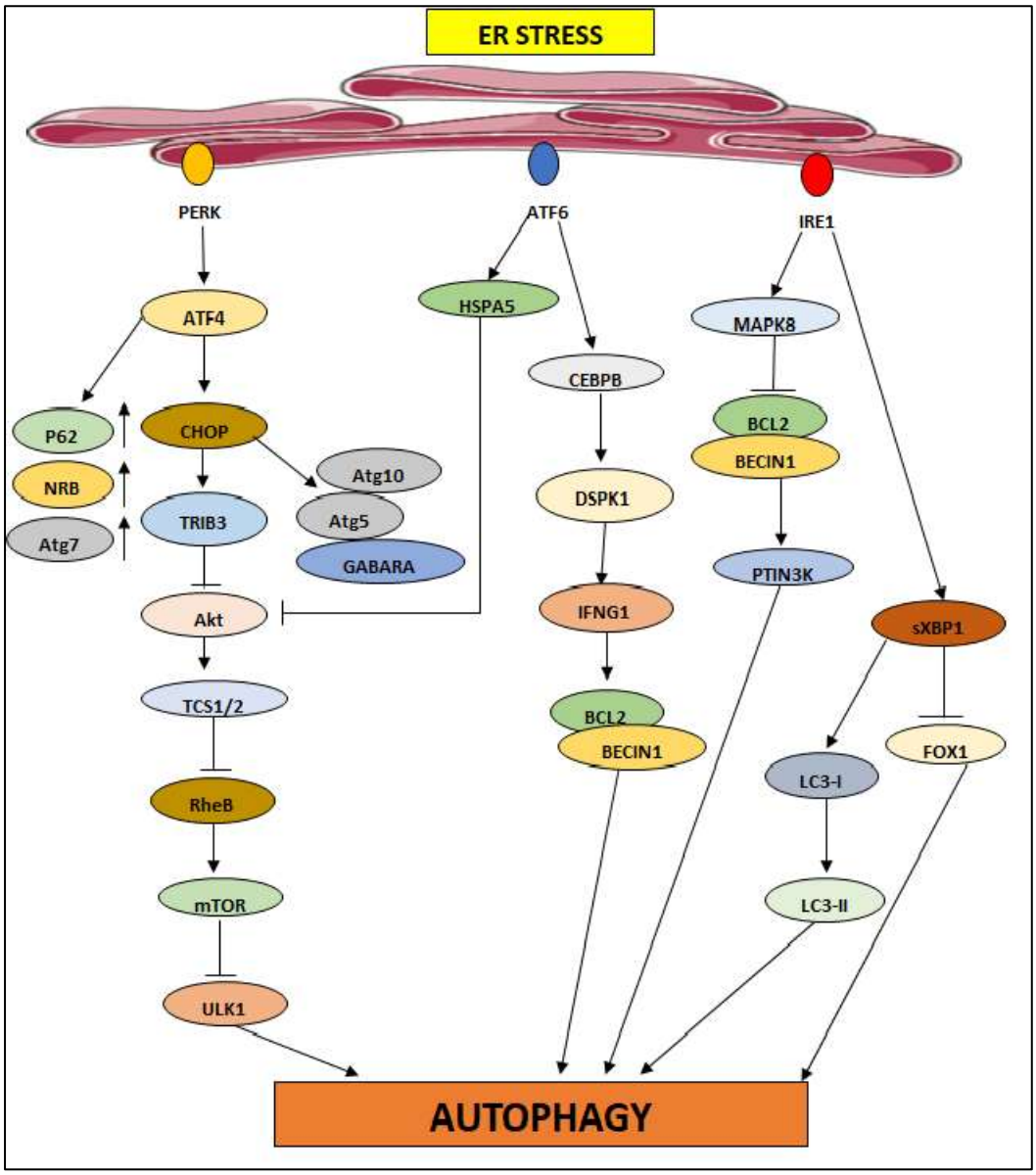

Fig 3- The molecular mechanism how UPR is connected with autophagy. PERK gives rise to ATF4 which in turn triggers CHOP. This causes inhibition of mTOR/Akt pathway leading to autophagy. The ATF6 pathway triggers HSPA5 which in turn inhibits mTOR/Akt pathway; It also triggers CEBP which ultimately leads to dissociation

of BCL2 and BECIN1 leading towards autophagy. The IRE1 pathway phosphorylates MAPK8 which leads to BECIN1 and BCL2 dissociation.Also it triggers Xbp-1 which in turn inhibits FOX-1, and converts LC3-I to LC3-II which helps in the formation of autophagosome.

Table 2: UPR Pathways and Their Role in Autophagy

UPR Pathway	Key Activators	Autophagy Mediators	Mechanism of Action	Outcome
PERK	BiP dissociation, PERK phosphorylation	ATF4, CHOP, GADD34, LC3, ATG genes	PERK phosphorylates eIF2α, leading to ATF4 and CHOP activation, which upregulate autophagy-related genes	Autophagy may be cytoprotective or cytotoxic depending on stress intensity
IRE1	BiP dissociation, IRE1α dimerization and phosphorylation	XBP1, JNK, MAPK8, Beclin1, TRAF2, ASK-1	IRE1 splices XBP1 mRNA to produce sXBP1; JNK phosphorylates BCL2, releasing Beclin1 and promoting autophagosome formation	Regulates balance between apoptosis and autophagy
ATF6	BiP dissociation, proteolytic cleavage by S1P/S2P	CHOP, HSPA5, CEBPB, DSPK1	Cleaved ATF6 enters nucleus and activates autophagy-related genes such as DSPK1 and HSPA5	Induces autophagy via mTOR/Akt inhibition and Beclin1–BCL2 dissociation

5. AUTOPHAGY CONTROLLED THROUGH ERAD:

Unfolded or misfolded proteins are sensed by the ERAD (ER associated degradation) system which transports it to the cytoplasm for the lysosome to degrade it. In many diseases we see ERAD induced autophagy. The ERAD has two mechanisms – ERAD I (ubiquitin proteasome dependent) and ERAD II (autophagy lysosome dependent) [1,8]. Initially autophagy comes into play when the unfolded proteins are too much for ubiquitin based ERAD system to handle. It has been observed that ER stress may be one of the factors behind ALS (amyptrophic lateral sclerosis). The UPR signalling transcription factor XBP-1 is effected in this case. It was seen that XBP-1 increases the SOD-1 levels in the cells during ALS. By increase in SOD1 it triggers autophagy to reduce the SOD1 aggregates in shXBP-1 cells [10]. One of the targeted genes of XBP-1 is EDEM1 a major component of ERAD system. It was observed that knocking out EDM1 in shXBP-1 cells decreased its binding to XBP-1 and hence XBP-1 deficiency may occur. Due to this there may be increase in unfolded proteins in ER due to ERAD inactivity, this may lead to upregulation of autophagy through XBP-1 deficiency[36,44]. The ubiquitin based ERAD system requires HSP40DNAJB12 and cytosolic HSP70 for sensing the misfolded proteins. It is observed that multitude of mutant proteins fails to get translocated by ERAD and hence aggregate leading to autophagy. For example, studies on ER Quality control (ERQC) show that mutants of α1-antitrypsin (α-1AT) are prone to aggregation by avoiding being translocated by ERAD and hence leading the cell toward autophagy[22,45]. The ER chaperon HSP 70 helps in the selection of misfolded protein aggregates for autophagy. It also helps in the initiation of autophagy by co-operating through Vps34/Beclin-1 to select proteins for autophagic degradation. The ERQC autophagy was seen to have a selective degradation process where it could degrade a partially folded mutant through either the autophagy or ERAD system. For example, the gonadotropin releasing hormone receptor (GnRHR), a mutant form of a G coupled receptor (GPCR), its proper folding requires many on and off pathways to be triggered, and it is easily misfolded. The E90K-GnRHR is partially folded, detergent soluble degradation intermediates are unable to be transported by ERAD and hence ERQC autophagy through its selective degradation, degrades it [46,47].

NF-E2 related factor1 (Nrf1) and NF-E2 related factor2 (Nrf2) are transcription factors activated during ER stress in response to UPR signalling. It was observed that they are components of the crosstalk between autophagy and ERAD. Nrf2 is known to increase levels of ERAD once ER stress is triggered. Also, through the P62-IKK-NFκB pathway, which initiates through ER stress, Nrf2 is shown to initiate autophagosomes. But evidence has been found that Nrf2 also contain autophagy inhibitor pathways. Nrf1 also initiates the formation of proteasome subunits of ERAD during ER stress [48]. In diseases caused by serpins, which are characterized by accumulation of polymer mutant protein on the ER include α-1AT deficiency and also FENIB [49]. It was observed that both ERAD and autophagy work together in the degradation of Serpin polymers. However, serpin polymers have shown resistance towards ERAD in in vivo studies. This is because for ERAD to function the serpin polymer needs to dissociate to serpin monomer so as to deliver it to cytosol, however such dissociation of serpin polymer in animal disease models have yet not been observed [43]. In this case autophagy seems like the better of the two options to degrade the serpin polymers. It was observed in neuronal PC-12 cells that ERAD provided selective and specific degradation of mutant neuroserpin, not autophagy. It was noted that in protein degradation, of both

specific ERAD and nonspecific autophagy degradation take place. Eventually it is the cell type and the degree, duration, and the severity of the stress that determines which degradation pathway it chooses [50].
Despite the growing recognition of the mechanistic framework of ER-associated degradation and its interaction with autophagy, numerous questions remain unresolved. The specific molecular mechanism that dictates whether misfolded proteins are channeled towards proteasomal degradation through ERAD or lysosomal degradation via autophagy is still not well understood. Additionally, several components of ERAD, such as p97/VCP, EDEM1, and Derlin-1, are known to be involved in both processes, yet their dual regulatory functions are not fully defined. Another unanswered question is the extent to which ERAD and autophagy work redundantly or in synergy to maintain proteostasis during prolonged stress [36,43]. Moreover, most research on the crosstalk between ERAD and autophagy has been conducted in vitro, leaving their significance in in vivo or disease-specific scenarios largely speculative. Addressing these gaps is essential for understanding how cells coordinate proteasomal and lysosomal degradation pathways to maintain endoplasmic reticulum homeostasis.

6. LINKING AUTOPHAGY AND ER STRESS THROUGH UBIQUITIN-PROTEASOME SYSTEM:

The ubiquitin proteasome system (UPS) is a protein degradation system that degrades misfolded, partially folded proteins. The degradation process occurs when misfolded proteins are marked by ubiquitin, making it easier for the 26S proteasome complex to specifically identify and degrade them. It's a highly selective process [51]. UPS also helps to take out nascent partially folded protein formed in ER, and maintain ER homeostasis. UPS is thought to be a major part of the ERAD system. Both autophagy and UPS are capable of degrading dysfunctional proteins, whereas autophagy is able to degrade long-lived bulk substrates, UPS is only able to degrade short lived protein substrates. However UPS is more selective and it can direct towards a more selective autophagy. By ubiquitination one can link between autophagy and UPS. It was observed that when autophagic genes Atg5 or Atg7 were knocked out there was an increase in the levels of ubiquitinated proteins [52]. By this we can infer that autophagy might degrade proteins that are specifically ubiquitinated. Another observation noticed in this was that when autophagy becomes defective UPS takes up on protein degradation. It was also seen that a defective UPS increases autophagy in cells exponentially. In Drosophilia it was noted that by inhibiting proteasome system, UPR brought forth autophagy. It was seen that autophagy protected the genetic materials from cell death caused due to proteasome inhibition [52,53].

It was noted that both autophagy and UPS can regulate ER stress. ER stress can be brought about by accumulation of misfolded proteins due to proteasome inhibition and also defective function of ERAD. This may bring autophagy to action so as to alleviate the ER stress from the cells, and also to supress the cell death brought about due to proteasome inhibition. It is seen that p62 plays an important role in linking autophagy to UPS, by inducing autophagic degradation to ubiquitinated proteins. p62 is essential for autophagosome formation for degrading polyubiqutinated proteins in response to stress. The FoxO3 is seen to control key transcription factors of both autophagy and UPS [54]. Like in cardiac cells they activate E3 ubiquitin ligase such as atrogin-1 or MuRF-1. In skeletal muscle cells, FoxO3 induces autophagy by directly binding to promoters of LC3b, Gabrap1, atg121, Bnip3, and controlling transcription of other autophagy related genes. Thus by controlling key elements of both the systems it can create crosstalk between autophagy and UPS. The factor HDAC6 (Histone Deacetylase 6) is seen to be controlling both aggresome and autophagosome formation [55]. It is one of the major factors which help in transport of autophagosomes and lysosome to MTOC, where aggresomes are present. An aggresome is a large inclusion body which packs the toxic and active oligomers from the misfolded proteins so as to detoxify them. HDAC6 helps in autophagosome transportation, and initiates autophagic degrading of aggresomes. In fly models it was observed in cases of UPS defect HDAC6 implemented autophagy in response to stress. p62 and HDAC6 is seen to work together in the formation of phagaphore and providing signals by interacting with K63 linked polyubiquitin chain to promote autophagic degradation. TRIM13 also known as Rfp2, Leu5 of the TRIM family of RING proteins is shown to play an important part in ER stress by mediating through the ERAD system via UPS. TRIM13 gets polyubiquitinated and interacts with p62 and through this helps in the binding of UBA (ubiquitin associated domain) to the ubiquitinated protein. Then it decides the degradation pathway for the protein either through autophagy or UPS [53,55,56].
While the link between the ubiquitin–proteasome system, ER stress, and autophagy has attracted considerable interest, many questions remain unanswered. The cellular mechanism that detects proteasomal overload and triggers compensatory autophagy is not yet fully understood, nor is the involvement of UPR sensors in this transition. Additionally, certain E3 ubiquitin ligases and deubiquitinases, including HRD1, CHIP, and Parkin, seem to operate at the junction of both degradation pathways, but their substrate specificity and dual regulatory roles are not completely characterized [51,53]. The compensatory dynamics between UPS and autophagy also differ among cell types and stress levels, resulting in conflicting outcomes in various experimental settings. Furthermore, the importance of different ubiquitin chain linkages in steering substrates toward either proteasomal or lysosomal degradation remains to be fully clarified. Filling these mechanistic gaps is crucial for comprehending how ubiquitin signaling manages proteostasis through both the UPS and autophagy under conditions of ER stress.

7. P62 INVOLVED IN AUTOPHAGY AND ER STRESS:

The p62 protein also known as sequestosome 1 (SQSTM1) is a ubiquitin-binding protein that aggregates in case of diseases involving misfolding of protein, like the neurodegenerative diseases. This proteins polymerizes through N-terminal PBI domain and can interact with ubiquitinated proteins through its C-terminal UBA domain. Also p62 binds to the LC3 and GABARAP family proteins through certain specific sequence motifs [54]. The protein is degraded through autophagy. p62 can be seen as a link between how ubiqitinated proteins are degraded by lysosome through autophagy. It was noted that the levels of p62 increased when autophagy was inhibited, but when autophagy was activated p62 levels decreased. So p62 is like a marker for autophagy [57].

In Huntington's disease, the aggregation of poly Q expanded mutant Huntington protein (mtHTT) is common. Autophagy is one of the best protein degradation pathways through which these aggregates are removed. However, recently it was found that ectodermal neural cortex-1 (ENC1) which is a novel binding factor to p62 was seen to inhibit autophagy under ER stress. ENC1 can bind directly to p62 through BTB and C terminal Kelch (BACK) domain, and there interaction is increased by ER stress. ER stress is known to increase ENC1 expression through IRE-1, TRAF2 and JNK pathway. The expression of ENC1 is known to increase mHTT aggregates. The ENC1 also associates with the mHTT aggregates through the c-terminal Kelch domain and interferes with p62's ability to recognise ubiquitinated mHTT. Thus, decreasing autophagy's degradation pathways under ER stress causing increased neurotoxicity [58].

It was observed in autophagy deficient tumour cells, that the misfolded protein levels increased causing severe ER stress. In these cells there was a marked increase of p62 and ER chaperons. It was seen in these cases that increase in p62 levels may be the reason for ROS expression which results in severe oxidative stress [57,59], which may in turn lead to DNA damage and tumorogenesis. But in brain tissues during autophagic inhibition the Keap-1-Nrf2-ARE pathway (oxidative response elements) protects the cells from ROS and severe oxidative stress. It was seen that p62/ZIP can increase Nrf2 activity by interacting with Keap1, through Keap1 interacting region (KIR), which in turn causes autophagic degradation of Keap1. p62/ZIP also binds directly to the promoter region of ARE thus creating a positive feedback loop between Nrf2 and p62. So we can conclude that in autophagy inhibited brain tissue; p62 helps not only to alleviate oxidative stress, but also decreases ER stress through Keap1-Nrf2-ARE signalling pathway [60].

Patulin (PAT) is a mycotoxin produced by moulds like Aspergillus spp. and Penicillium spp. This PAT causes skin toxicology and severe skin carcinogenicity. This carcinogenicity is the result of PAT causing autophagy inhibition. This autophagy inhibition is marked by accumulation of p62. It was observed that in these situations p62 causes a pro survival signalling, which increases the chances of cell's survival, but this also causes an imbalance in cell death and cell growth levels [61,62]. This pro survival signals may create a cytoprotective ER stress. This ER stress is brought about by IRE1/2 which inhibits the phosphorylation of BAD. By accumulation p62 it was observed there was an increase in the ROS levels in the cell. It was observed that PAT inhibition of autophagy led to induction of ER stress. However when p62 was inhibited by RNAi the PAT induced ER stress was dissolved. By this we can assume that p62 plays a major role in autophagy inhibited induced ER stress [63]. Although p62/SQSTM1 is well-known as a versatile adaptor that connects autophagy, the ubiquitin–proteasome system, and ER stress responses, many aspects of its regulation are still not fully understood. The transcriptional regulation of p62 during ER stress involves both ATF4 and Nrf2, but the specific contributions and timing of these pathways have yet to be clearly defined [57,59]. Furthermore, p62 plays a dual role in determining cell fate—helping cells adapt to proteotoxic stress under mild conditions, while encouraging apoptosis or inflammation during prolonged stress. The mechanisms that control this functional shift remain unclear. Additionally, the way p62 interacts with UPR components and directs substrates between proteasomal and autophagic degradation pathways has not been clearly outlined. Finally, structural and quantitative studies are needed to comprehend how post-translational modifications influence p62's scaffolding roles. Addressing these gaps is crucial for establishing p62 as a precise therapeutic target in diseases marked by ER stress and disrupted proteostasis [57].

8. UPR SIGNALLING INHIBITS MTOR/AKT-1/PI3K PATHWAYS TO INDUCE AUTOPHAGY:

mTOR (mammalian target of rapamycin) complex is an important molecular pathway regarding apoptosis, autophagy, and ER stress. mTOR complex 1 (mTORC1) is found in both upstream and downstream of ER signalling and regulates it accordingly. This factor may antagonize the anabolic output of mTORC1 [64]. It was noticed in prolonged ER stress condition, mTORC1 inhibits AKT pathway through negative feedback and hence supressing survival kinase and ushering in apoptotic signalling. Prolonged ER stress also contributes to AKT inhibition through mTOR complex2 (mTORC2) [65]. AKT is a ser/thr kinase positive regulator of mTOR. Regulation of mTOR-AKT pathway leads to autophagy initiation [66]. It is a well-established fact that downregulation of mTOR/AKT/PI3K (phosphatidylinositol 3 kinase) upregulates autophagy. The family of cell

surface growth factor- receptor tyrosine kinase (RTK) such as PDGFR, IGFIR, and EGFR have intrinsic tyrosine activity. They regulate various pathway such ass RAS/RAF1/2/ERK, JAK/STAT, PI3K/AKT, etc. AKT fluctuations may lead to various types of cancer. Hence AKT is flanked in both sides by phosphate and tensin analog (PTEN). PTEN inhibits AKT by increasing the catalysis of phosphatidylinositol (3, 4, 5)-triphosphate (PIP3) to phosphatidylinositol (4, 5) biphosphate (PIP2). It also catalyses tuberous sclerosis complex 1 /2 (TCS1/ 2) heterodimers that inhibits mTOR. Hence when AKT is activated it inhibits TCS1/2 and activates mTOR. However, when AKT is downregulated in a negative feedback mTOR too gets inhibited. Studies have shown that TCS1/2 regulation of AKT/mTOR signalling is in response to energy availibility. AMP activated protein kinase a regulator of energy metabolism also functions as ser/thr kinase and also directly phosphorylates TCS2. Though cells deprived of TCS1/2 can't be phosphorylated by AMPK in response to energy depletion and hence mTOR will not be inhibited [67–70].

It was observed in myeloma cells that treating them with PI3K inhibitor (PI-103) an increase in LC3 genes. There was also downregulation of PSMD14, a gene responsible for the maturation of 20s proteasome; along with this, many other proteasome genes were downregulated. It also upregulates many autophagosome-related genes like ULK-1 (Unc-51 like kinase-1). ULK-1 is also seen to be upregulated in response to mTOR inhibition. ER stress is known to inhibit AKT/mTOR pathways and consequently bring in autophagy. The UPR pathway ATF6 inhibits AKT-1 phosphorylation by HSPA5 expression in placental choriocarcinoma. It was observed that ATF6 pathway activates and inhibits mTOR/AKT/PI3 pathways upon ER stress through HSPA5 [40]. During ER stress downstream activation of ATF4 takes place by the phosphorylation of eIF2α. ATF4 activation also leads to Redd1 expression. It was noticed that ATF4 and CCSST/enhancer binding proteinβ (C/EBP-β) negatively regulates mTOR through Redd1 expression. The Redd1 –A hypoxia induced gene in response to ER stress regulates the TCS1/2 extensively. It is seen that prolonged hypoxia during ER stress activates PERK and upregulates transcription factor ATF4. The Redd1 regulation is done extensively by PERK-ATF4-eIF2α factors, they monitor Redd1's induction and inhibition of mTORC1 as observed in In vivo models. Insulin like growth factor is also known to inhibit mTOR. In response to these growth factors class I PI3K and PI3K protein depended kinase becomes activated which in turn proliferates AKT. They also activate Ras which initiates cascade of Raf-1, which stimulates MEK1/2 and ERK1/2. As both AKT and ERK1/2 can phosphorylate TCS1/2 they can regulate mTOR expression. During oxidative stress induced autophagy, the exogenous hydrogen peroxide can phosphorylate eiF2α and hence activate PERK, it also directly oxidises the protease Atg4 which accelerates the activation of mature proteolytic LC3. These factors contribute in the inhibition of mTOR pathway. The MAPK/IRE1 factors present in the downstream of UPR also is known to regulate mTORC1 through monitoring TCS1/2 activities and also inhibiting AKT signals [71,72].

ER stress is also known to upregulate transcription cofactor p8 and pseudo tribbles homolog3 (TRB3) which inhibits the mTOR/AKT pathway, and induces autophagy [22]. Δ9-tetrahydrocannabinol a major compound of marijuana can help TRIB3 to inhibit mTOR and cause autophagy in human glioblastoma multiforme model [73]. In HeLa cells ER stress caused by DL-homocystine, DTT, or tunicamycin is shown to inhibit mTOR through transcription of ATF4 and C/EBP-β. In mouse models it is shown that ER stress causes serine phosphorylation of JNK thus inhibiting mTOR/AKT pathways [68,74]. AKT and MAPK are two survival signalling pathway that rapidly activate in response to the downstream effector of PI3K in acute ER stress. During mild ER stress, in response to the UPR the cells may activate MAPK/AKT cascade for their survival. However, evidence show that prolonged ER stress causes diminishing of mTOR/AKT/PI3K leading to autophagy and apoptosis. Also evidence were found that sometimes due to ER stress mTOR gets hyper activated and causes serine phosphorylation of IRS1 through JNK pathway. This phosphorylation of IRS1 causes inhibition of AKT pathway [67,68].
Although extensive evidence supports the suppression of mTOR signaling during ER stress, the mechanistic details of how UPR sensors regulate this pathway remain incompletely understood. Activation of PERK and eIF2α phosphorylation can reduce global protein synthesis and energy demand, thereby indirectly inhibiting mTOR activity; however, the specific mediators connecting UPR signaling to mTORC1 repression—such as REDD1, TSC2, or AMPK—are variably implicated across different systems. Similarly, the modulation of the PI3K/AKT axis by UPR signaling is highly context-dependent: transient stress can activate AKT to promote cell survival, whereas prolonged ER stress suppresses AKT via CHOP-mediated transcriptional changes [68,69]. The precise temporal hierarchy among PERK, AMPK, and mTOR activation remains poorly defined, as does the feedback regulation between these pathways. Moreover, few integrative models have quantitatively analyzed these dynamic interactions. Addressing these gaps will be vital to understanding how UPR-mediated inhibition of the PI3K/AKT/mTOR axis determines the threshold between adaptive autophagy and apoptotic cell death.

9. UPR SIGNALLING INDUCES AUTOPHAGY THROUGH HYPOXIA:

Deprivation of oxygen can lead to a state called as hypoxia. During hypoxic stare cell metabolism gets severely affected. Hypoxia also activates hypoxia inducing factors (Hif). Recent studies have shown that Hif can regulate

mTOR pathways. The Hif is a hetrodimeric transcription factor made up of α and β subunits, which is controlled by the oxygen tension in the cells [75]. It is observed in TCS2 deficient cells there is an increase in levels of Hif than in comparison to wild type cells. Increase in Hif levels increases mTOR activity, as mTOR regulates the stability of Hif in the cells [76]. It has been observed recently that mTOR functions are being regulated by hypoxia. During severe oxygen depletion major functions such as mRNA translation comes to a halt. mRNA translation is critically regulated by the assembly of m^7-GTP cap binding to EIF4E/eiF4A/eiF4G (eiF4F) of the 40s ribosome subunit binding to eIF2/GTP/met-tRNA tertiary complex. These complexes are all regulated by phosphorylation of eIF4E binding protein (4-EBP) and eIF2α.It is also seen hypoxia (15% oxygen) can stop mRNA translation by hypophosphorylation of 4EBP-1,$p70^{s6k}$ and rpS6 [77]. The ER stress pathway, specifically PERK, is known to phosphorylate eIF2α. It is observed that severe hypoxia may lead to the induction of ER stress in many cells. mTORC1 is seen to phosphorylate this 4EBP thus causing them unable to bind to eIF4E and promoting cap-depended translation of mTOR activity. This may cause aggregation of misfolded proteins and may lead to tumerogenesis and threaten the cell homeostasis and may lead to apoptosis and autophagy [78].

In hypoxic condition it leads to accumulation of the protein aggregation, which causes activation of the PERK pathway. The PERK then phosphorylates eIF2α which in turn activates ATF4. ATF4 expression is due to selective translation during hypoxia mediated by the downstream ORFs in 5'UTR factor. It is observed that severe hypoxia regulates PERK and ATF4. Initiation of autophagy is depended on lot of pre-autophagosomal complexes like LC3B/MAP1LC3B. It was observed that LC3B is transcriptionally upregulated in response to hypoxic ATF4 in HeLa cells [79]. The autophagic gene Atg5 and LC3B are transcriptional targets of ATF4 and CHOP. ATF4 protects the HeLa cells from apoptosis by upregulating LC3B transcriptional factor in response to ATF4 binding to AMP in the binding site of LC3B promoter and thus protecting the cells from hypoxic cell death. It was also observed that during chronic hypoxia both ATF4 and LC3B kept increasing lysosymal mass, and the quantity of autophagosomes. PERK activates autophagy during hypoxia to relive the ER of excessive toxic protein aggregate. In SHS5Y cells it was observed that Lysosomal associated membrane protein 3 (LAMP3) induced by PERK/ATF4 arm in response to hypoxia regulates conversion of LC3-I to LC3-II and hence increases autophagic flux. Hence, it proves that LAMP3 is important for the initiation of autophagy [80,81].

Hypoxia is seen to downregulate many apoptotic genes through translational changes like BID (BH3 interacting domain death agonist), BAD (BCL-2 agonist of cell death) and BAX. During hypoxia autophagy can be even induced by RNA interference of knockdown of essential autophagy related protein such as Beclin-1 or Atg5 [82]. In response to hypoxic ER stress there is transcription and expression of Redd1 factor. This Redd1 factor inhibits mTOR through downregulation of TCS1/2. The Redd1 is seen to effect TCS1/2's GAP activity for inhibiting them. Also mTOR inhibitors, AMPK and LKB1 play important part in mTOR inhibition in response to acute hypoxia and Redd1 expression. Under hypoxic conditions TCS2 deficient cells fails to downregulate S6K activity and this causes accumulation of high amount of Hif. In cell lines like HeLa, MEF, and HEK293 hypoxic TCS2 downregulation is important for the inhibition of mTOR [83].
Although extensive evidence indicates that UPR signaling contributes to hypoxia-induced autophagy, several mechanistic aspects remain unclear. The precise coordination between the UPR and HIF-1α pathways has not been fully defined, with conflicting reports suggesting both cooperative and antagonistic interactions. While PERK activation may stabilize HIF-1α by inhibiting prolyl hydroxylases, IRE1-mediated RIDD activity has been proposed to degrade HIF-1α transcripts under severe stress [82,83]. Similarly, the extent to which PERK–eIF2α–ATF4–CHOP signaling directly induces autophagy-related genes versus indirectly through metabolic adaptation remains uncertain. The dependence of BNIP3/NIX-mediated mitophagy on UPR signaling also appears to be cell type– and context-specific. Furthermore, most current data are derived from in vitro hypoxia models, with limited validation in in vivo or tumor microenvironmental settings. Addressing these gaps is crucial for understanding how ER stress and hypoxia cooperatively regulate autophagy and cell fate decisions in physiological and pathological conditions [75,78,79,83].

10. LINKING AUTOPHAGY AND ER STRESS THROUGH AMPK:

AMPK or 5'AMP-activated protein kinase or 5'adenosine monophosphate activated protein kinase is an enzyme which can detect energy levels in the cell and maintain energy homeostasis. When the cell energy becomes low it increases the uptake of glucose and fatty acids, and oxidation rates to reach homeostasis. The ser/thr kinase is a heterodimer composed of subunits of AMPK, a catalytic subunit AMPKα, and two regulatory subunits AMPKβ, AMPKγ [84]. These subunits are activated through upstream kinase LKB1 when there is a decline in the levels of ATP and AMP levels increase as in the case of ER stress due to acute hypoxia. This activated AMPK directly phosphorylates the tumour suppressor TCS2, which in turn causes inhibition of Rheb, which directly binds and initiates the activation of mTORC1 kinase [85,86]. It was observed that AMPK also regulates mTORC signalling by phosphorylating serine residues Ser722 and Ser792, by this AMPK induces 14-3-3 binding to those raptors, this causes inhibition of mTORC1 in response to energy stress [86,87]. It was observed that AMPK may control

autophagy through ULK-1. AMPK binds to the PS domain of ULK-1, which causes phosphorylation of its raptors, which inhibits mTORC1 actions and initiates autophagy. AMPK can also directly phosphorylate TCS2 thus inhibiting mTORC1 signals. FIP200 an ULK-1 binding protein also interacts with TCS1/2 complex through TCS1. It was noticed in mammalian cells that ULK1 interacts with mAtg13 through FIP200 to form a stable complex under normal nutritious conditions [88,89]. However if there is an impairment in the nutrition levels caused due to stress, the AMPK may phosphorylate the raptors and recruit 14-3-3 to them causing mTORC1 to dissociate from ULK-1-mAtg13-FIP200 complex. This dissociation of ULK-1 from mTORC1 is crucial for initiation of autophagy. It is possible to speculate that under cell duress AMPK through phosphorylation can create conformational changes between ULK-1 and mTORC1, causing the dissociation. There is evidence to suggest that AMPK can also directly phosphorylate ULK-1 leading to autophagy [90].

In liver injury, Ischemic repurfusion injury (IRI) leads to graft injury. In steatotic liver cells the chances of ER stress and autophagy both are high in presence of IRI. Here it was noted that by combining melatonin and trimetazidine to additives in IGL-1 solution, ER stress and autophagy was modulated through AMPK. In liver cell injury the autophagy plays a protective role, it decreases the liver injury and mitochondrial damage. Activation of autophagy leads to reduction in cell death and ER stress inhibition. It was noted that when liver cells were treated with IGL-1 solution supplemented with metatonin and trimetazidine, GRP78, CHOP proteins as well as PERK protein's levels reduced significantly. Also when AMPK inhibitor Ara was applied to the solution of IGL-1, reduction to ER stress was nullified. It is speculated that AMPK decreases mitochondrial damage and ROS production in the IGL-1 complex solution, which decrease the ER stress levels in the cells. The autophagy related genes however increased in level in the presence of AMPK in IGL-1 complex solution. There was an increase in LC3B conversion and also Atg7 protein levels, however there is decline in autophagy related ubiquitin binding protein SQSTM1/p62 [91,92] .

Similarly in gastric cancer cells it was seen that chicoric acid (CA) can induce autophagy and ER stress through AMPK. AMPK and p70S6 kinase (p70S6k) helps to promote CA in both in vitro and in vivo expression. The CA was shown to increase LC3II level which helps in autophagy induction. It also promotes ER stress through increasing PERK, ATF4 and ATF6 expression [85]. However it was also observed that by inhibiting AMPK negates the upregulation of not only LC3II , but also of PERK,ATF6 and ATF4, demoting ER stress and autophagy , hence we can say that AMPK can regulate autophagy and ER stress [93] .
Despite strong evidence that AMPK serves as a critical mediator linking ER stress to autophagy, several aspects of this relationship remain unresolved. The bidirectional nature of the ER stress–AMPK connection is not fully established, as AMPK can be both activated by and act upstream of UPR signaling depending on the cellular context. Furthermore, the extent to which individual UPR branches, such as PERK–eIF2α or IRE1–JNK, differentially regulate AMPK activity is still unclear [84,85]. This ambiguity is compounded by the dual role of AMPK-induced autophagy, which can support cell survival during transient stress yet promote apoptosis under prolonged energy depletion. Moreover, the lack of integrated metabolic and ER stress models limits our understanding of how AMPK dynamically coordinates energy homeostasis and proteostasis. Future studies employing quantitative and systems-level approaches will be essential to delineate the precise mechanistic hierarchy of AMPK activation in ER stress–induced autophagy.

11. CALCIUM CONTROLS ER STRESS AND AUTOPHAGY:
ER is known to have an abundance of calcium and is known as a calcium reservoir in the cell. This calcium is important for proper folding of the proteins and maintaining ER homeostasis. In fact calcium ion is very important for many ER chaperons including Bip [19,94]. In ER the release of stored calcium ions is mediated through two membrane receptor channels called RYR (rayandine receptor) and IP3R (inositol 1, 4, 5 triphosphate receptor) [95]. It was observed that autophagy induction can occur through calcium channel's activity of IP3-R-Beclin1-Beclin2 pathway. Inhibition of IP3 leads to autophagy, and IP3-R is its important secondary messenger. During ER stress UPR activation of IP3-R may lead to macroautophagy through an mTOR dependent pathway. The IP3-R can both inhibit and induce autophagy depending on the cellular environment. IP3-R mediated calcium is a key factor in starvation mediated autophagy [18,22]. During starvation of cell the IP3-R calcium signalling increases from the ER calcium reservoir, which elevates there levels in the cell. The mTORC1 dependent autophagy is quite sensitive to these calcium ion stimulations. It is also observed that starvation induced autophagy occurs in upstream of Atg12-Atg5 complex, which can sense Ca^{2+} ions importance in mTORC1 dependent pathway [96].

Disbalance of calcium mobility or balance in cell may lead to many calcium regulating pathways which may lead to autophagy. For example in breast cells the calcium ion (Ca^{2+}) mobilizing factors (thaspigargin, ionomycin, Vitamin D) can activate calcium/calmodulin dependent protein kinase 2β (CAMKKβ) which causes AMPK to inhibit mTORC1 actions leading to autophagy [97].

Another work shows that ER content is regulated by T lymphocytes and this regulator is depended on autophagy. T lymphocytes which have autophagy deficiency are also seen to have defect in there calcium influx when it is TCR stimulated. This causes an unusual increase in ER which leads to increase in level of calcium, which causes defect in calcium ion stores. This in turn disrupts CRAC channel function which majorly functions in calcium mobilization [98]. This increase in calcium stores in ER and its inability to deplete its stores can be inhibited by treatment with thaspigaegin. This may suggest that autophagy may have some amount of control over calcium mobility in cell, especially in ER, and suggests that these two factor may influence each other [99].

DAPK-1 is a tumour suppressor and it was found that it can control autophagy caused by calcium influx during autophagy [100]. DAPK-1 is known to disrupt Beclin1 and BCL2L1 interaction by phosphorylating Beclin1 on Thr119 which causes autophagy. Hypoxia can also cause severe calcium influx and activate CAMK1 (calcium/calmodulin dependent protein kinase1) and CAMK4 (calcium/calmodulin dependent protein kinase4) which in turn stimulates the formation of autophagosomes [100,101]. Members of PKC family, (protein kinase C) like PKCθ needs ER stress induced autophagy to activate. It was seen that Ca^{2+} is an essential component required during PKCθ activation during ER stress. It is also observed that BAPT-AM and calcium chelating agent could inhibit PKCθ activation via blocking autophagy. PKCθ also acts as an ER stress sensor in skeletal muscles [102]. It is observed that PKCθ activation alone can cause autophagy without ER stress, however ER stress strengthens the autophagy formation. BAPT-AM mediated Ca^{2+} chelation is shown to hamper lysosomal function which consequently leads to inhibit autophagosomal degradation. This suggests that if there is some problem with cytosolic calcium influx it might cause disruption in lysosomal activities causing autophagy to take place [98,103].

12. AUTOPHAGY AND LIPOPHAGY AND LIPID MOVEMENTS:

Cells store fat as lipid droplets (LD), these are basically lipid esters surrounded by monolayer of phospholipids which protects the structure from hydrophilic cytosol [104,105]. LDs are generally found in adipose tissues, but they originate from ER where they play important role in lipid mobilization and metabolism [106]. The mobilisation of lipids inside LDs is facilitated by lipolysis. It has been recently found that autophagy may play a role in LD breakdown. The LDs have been reported to have lipases in there lysosomal lumen along with other hydrolases such as proteases, glycases, nucleases. The lysosomal lipases, also known as “acid lipases” because of their optimal acidic pKa, is basically used for lipid degradation via endocytosis or is thought to be present in organelles that are being digested through autophagic process[22,107]. It was observed in cultured hepatocyte cells in which Atg5 was knocked out in response to acute oleic acid challenge that there was an increase in the number of LDs, and also there enlargement in the absence of autophagy due to Atg5 knockdown [28,108]. Generally in hepatocytes in response to acute challenges increase in lipolysis takes place which prevents enlargement of the LDs. Similar case was observed in in vivo studies of knockout liver cells of Atg7 gene [108]. Here autophagy impairment leads to severe case of fatty liver, compared to that of control animals. This establishes that lack of autophagy may lead to enlargement of LD compartment. However biochemical tests suggest that lipid accumulation is not linked with enlargement of LDs but it may be linked with reduction of lipolysis. Hence we can also conclude that autophagy can be used as a control factor in the case of fatty liver, lipid accumulations. Besides it has been observed that stimuli such as starvation also engage lipolytic contribution to autophagic system [106,109].

Lipophagy has been found in other cells too, like immune cells and neuronal cells. It may suggest that in order to use cellular fat stores autophagic turnover lipids may be a common mechanism used by various cells. The neurons within mediobasal hypothalamus (MBH) forms a part of focal neuronal network [106,110]. It gets most of its hormonal and nutritional information from two major sources, PI3K and mTOR; they help to maintain control over food and energy balance. The hypothalamic fatty acid metabolism also helps to maintain appetite. It also has been observed that free fatty acid (FFA) and oxidation provide energy for firing of orexigenic agouti related peptide (AgRP) neurons [68,111]. It is possible that autophagy activated by starvation in most cells causes lipids to mobilize in hypothalamus causing generation of FFA which in turn initiates food intake mechanism, and hence the cells get nutrition. Recent studies in mice knocked out Atg7 in AgRP neurons in hypothalamus showed that nutritional depletion leads to autophagy which in turn generates higher levels of AgRP[105,112]. Activation of autophagy in hypothalmus in response to acute lipid stimulus is also related to increase in AMPK and ULK1 kinases, which can suggest that they are also related to sensing FFA mechanism that controls autophagy in response to nutrient fluxing [113].

In a study made in indomethacin induced LD accumulation in erythrocytes, it was found that the accumulation of LDs may be due to de novo lipogenesis and increased cytosolic fatty acid formation [110,114]. Major evidence also suggest that LD accumulation may be due to ER stress [115]. The time dependent study showed that lipophagy was activated in erythrocytes. This was marked by high level expression of autophagy proteins such as LC3-II and LAMP-2. This shows there is a clear connection between LC3-II and LD. The increase in lipophagy

marks with the decrease of LDs in erythrocytes, hence we can conclude that lipophagy is a cytoprotective mechanism to eliminate LDs in erythrocytes. This was proved when levels of LD increased when autophagy was inhibited which also led to lipophagy viability. However due to indomethacin treatment there is a decrease in LAMP-2 protein after a certain time point, this creates problems for autophagosomal compartments to fuse with lysosomal compartment. LAMP-2's decrease can be attributed to the accumulation of LDs in treated erythrocyte cells which causes elevated lipoappoptosis. This In vitro study also clearly indicates indomethacin induced lipophagy and apoptosis in erythrocytes are very much ER stress mediated, this was confirmed by blocking ER stress with 4-PBA and suppression of mTOR. It is strongly hinted that ER stress accumulates the LDs as a form of cytoprotective activity, but prolonging this action leads to apoptosis [116].

Autophagy plays a role in pancreatic β cells. At diabetic conditions chronic exposure to high fat concentration due to high fat diet may lead to change in lipid composition of the autophagosome and lysosome's membranes which can cause hindrance to their fusing capabilities. Hence it can be said that FFA can cause problem to autophagy in β cells [117,118]. It is also seen that FFA induced lipid accumulation in β cells also inhibit autophagy as autophagy can degrade lipids and decrease triglyceride levels. Inhibiting autophagy increases triglycerides in various cells like adipocytes, hepatocytes, etc. Recent studies have shown that kaempeferol protects pancreatic β cells from PA induced apoptosis by activating autophagy. It was found in this study that kaempeferol can delete unwanted stored lipid droplets from β cells through AMPK/mTOR mediated lipophagy [106,110,119]. PLIN-2 a lipid droplet that increases triglyceride levels, coats the proteins of pancreatic β cell, and during lipid deposition PLIN-2's levels increase however when treated with kaempeferol there levels get decreased drastically[120]. When autophagy inhibitors like wortamin and chloroquinone were introduced to kaempferol treated cells, the keampferol's decreased LD levels increased along with the triglyceride levels, and PLIN-2 levels. This establishes the importance of autophagy in the manipulation of LD levels. It is well known that ER stress is one of the main reasons for obesity and diabetes related pathologies. Oxidative ER stress and accumulation of ubiquitinated proteins can lead to exposure of saturated FFA in pancreatic β cells leading to apoptosis. The CHOP present in downstream of ER stress is a key factor in cell death signalling which gets opposed by PA and high glucose treated β cells. Studies have shown in murine models of type 2 diabetes, where CHOP deletion restores stimuli in β cell mass. It is shown that activated autophagy reduces ER stress and in turn decreases apoptosis in β cells. Hence it is proven that kaempferol treatment causes CHOP expression to decrease along with that of ER stress that leads autophagy expression to increase [121].

13. CONCLUSION:

The endoplasmic reticulum (ER) and autophagy are central to maintaining cellular proteostasis and metabolic equilibrium. Under physiological conditions, the unfolded protein response (UPR) orchestrates adaptive signaling through the PERK, IRE1, and ATF6 branches to restore ER homeostasis. When stress persists, these pathways converge with autophagic machinery to remove misfolded proteins, defective organelles, and lipid aggregates. Crosstalk among UPR signaling, autophagy, ER-associated degradation (ERAD), and the ubiquitin–proteasome system (UPS) defines a finely balanced network that determines whether a cell survives or undergoes programmed death. Dysregulation of this axis contributes to diverse pathological conditions including cancer, neurodegeneration, metabolic disorders, and inflammation.

Despite significant advances, several critical questions remain unresolved. The temporal hierarchy and coordination among UPR branches in controlling autophagy are still unclear. The molecular switches that determine whether UPR-induced autophagy acts as a protective or pro-death mechanism remain undefined. The integration of metabolic sensors such as AMPK and mTOR into ER stress signaling networks is incompletely understood, as is the link between selective autophagy types (ER-phagy, mitophagy, lipophagy) and UPR sensors. Furthermore, the inter-organelle communication between ER, mitochondria, and lipid droplets, which governs energy flux and membrane biogenesis, requires deeper exploration. While numerous chemical chaperones and pathway inhibitors have shown promise in modulating these stress responses, their specificity, timing, and safety remain major translational barriers.

Future research should emphasize quantitative, systems-level, and multi-omics approaches to dissect these dynamic signaling events. Integrating structural, biochemical, and in vivo studies will be essential for mapping precise regulatory nodes within the ER stress–autophagy–lipid metabolism triad. Such mechanistic insight will pave the way for developing targeted interventions capable of restoring proteostasis without compromising essential stress-adaptive functions. Ultimately, decoding the interplay between ER stress and autophagy holds great promise for next-generation therapeutics across metabolic, neurodegenerative, and oncological diseases.

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