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New-targeted therapy for leukemia based on Endoplasmic Reticulum Stress

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ABSTRACT

The unfolded protein response (UPR) is an evolutionarily conserved adaptive pathway, which is activated by the stress of the endoplasmic reticulum (ER). ER stress often occurs due to the high protein demand in cells and protein folding errors in several diseases, such as different cancers and autoimmune diseases. UPR is mediated by three primary arms called inositol-requiring enzyme-1α (IRE1α), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6α (ATF6α). Given that homeostasis in protein synthesis is frequently deregulated in cancers, UPR plays a critical role in controlling survival and cell death. In addition,, resistance to apoptosis is mediated by the pro-survival mechanism of ER stress in cancer cells. Recent evidence highlighted the deregulation of UPR signaling in hematopoietic stem cells (HSCs) and leukemic cells, so that targeting UPR-driven pro-survival pathways may present new therapeutic benefits in leukemia. In this review article, we aim to provide an updated knowledge on the role of UPR as a novel therapeutic target in leukemia. We first define the different types of leukemia and their challenges with current treatments, and then explore the contribution of UPR to leukemia pathogenesis and treatment. Finally, UPR targeting strategies in pre-clinical and clinical trials of patients with leukemia will be presented.

Keywords: Endoplasmic reticulum stress (ER), Leukemia, Targeted therapy, Unfolded protein response (UPR)

Headlines

INTRODUCTION:

1-Leukemia

As an abnormal growth of white blood cells (WBC), leukemia is common in both children and adults. Clinically and pathologically, leukemia is classified into four major groups: acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML) [1]. This grouping is based on the type of blood cells and includes both lymphoid and myeloid classes. In the lymphoid group, the malignancy alteration observes in the marrow cells which transfer to lymphocytes. In the myeloid leukemia, malignancy occurs in erythrocytes, other types of white blood cells, and platelets [2,3]. The classification also indicates that the leukemia is acute or chronic in each category. In acute leukemia, abnormal blood cells or blasts which are not well differentiated are immature and can circulate in all blood systems as nonfunctional cells. Acute leukemia progresses very quickly and must be treated promptly. In chronic leukemia, not all blasts are immature, but some may remain mature and act normally. Thus, the progression of chronic leukemia is usually slower than acute leukemia [4,5]. Although studying leukemia has enhanced in recent years, it is still the main problem in the recurrence of the disease in most patients. Nowadays, the treatment of leukemia and lymphoma has evolved significantly and usually consists of medicines with specific targets, which are called "targeted therapies."

In targeted cancer therapies, agents or factors are mainly used to block the pathways which lead to tumor growth. Thus they induce cancer cell apoptosis directly or indirectly stimulate the immune system to recognize and kill the cancer cells. For example, the agents that prevent cell growth such as inhibitors of tyrosine kinase, histone deacetylase (HDAC), proteasomes, and/or hypermethylation are used as targeted therapy [6]. A new targeted therapy that has been getting significant attention and has been developing dramatically is the use of endoplasmic reticulum the ER stress pathway against cancers and other diseases such as inflammatory disorders [7]. ER is an intracellular organelle responsible for producing, processing, and transporting lipids and proteins in eukaryotic cells. The unfolded or misfolded proteins produced in this organelle will undergo protein degradation to keep cell homeostasis; however, under severe circumstances such as hypoxia or oxidative stress, the concentration of these misfolded proteins would cause autophagy or apoptosis. However, the first decision in cells is the survival of the cells [8]. In this review, we bring up the current knowledge of the ER stress effect in acute and chronic leukemia, and the mechanisms associated with cancer drug resistance. We also emphasize the therapeutic approaches for the use of the UPR as a novel target pathway to improve the outcome of leukemia patients.

1-1Unfolded Protein Response (UPR)

ER as the intracellular organelle of the secretory path extended from the cell membrane or external nuclear membrane (ENM) [9,10]. The function of protein folding and the quality control is arranged by chaperones and foldases proteins of ER [11]. The molecular chaperones in the ER can recognize the appropriate proteins for folding as well as detection and mark inappropriately folded proteins to ruin them. Following induction stress (such as loading too many proteins), an intracellular signaling network called the unfolded protein response

(UPR) activates to recruit ER function [12]. The UPR helps cells restore homeostasis via different pathways such as reducing protein fusion and increasing the rate of protein loading to fold them or clear unfolded/misfolded proteins by activating chaperones/heat shock proteins (HSPs) [13]. To establish homeostasis in the cell, UPR helps survival and cell death in various situations. This procedure is performed by the crosstalk between plasma membrane, ER, cytosol, mitochondria, and nucleus through induction or inhibition of apoptosis and or autophagy [14,15]. ER has three sensors that are activated during stressful situations, including inositol-requiring kinase/endoribonuclease 1 (IRE1), protein kinase activated by double-stranded RNA (PKR)-like ER kinase (PERK), and activating transcription factor 6 (ATF6).

Under normal situations or resting the three arms of ER, IRE-1α, PERK, and ATF6α, are inactive through binding to the ER chaperone 78-kDa glucose-regulated proteins (GRP78). Under different stress stimuli, GRP78 dissociates from the three sensors and binds to the proteins with a higher affinity. So IRE-1α and PERK can oligomerize and autotransphosphoryle to set the homeostasis [16]. The primary purpose of ER is to check the folding of the proteins and let them reach the final destination only if they are folded correctly. During the stressed situation in the cell, such as high demand for protein fusion, failure in the autophagy pathway, alteration in calcium and pH, low level of nutrients (e.g., hypoglycemia), high level of reactive oxygen species (ROS), inflammation, hypoxia, and cancers, ER stress is activated [17]. Under acute situations, UPR acts as a pro-survival mechanism to provide nutrients and oxygen poverty for the high demand of the cells [18,19]. The accumulation of misfolded/unfolded proteins could be also active another pathway of UPR to remove and degrade them called endoplasmic reticulum-associated protein degradation (ERAD) [20,21].

2- UPR Signaling

2-1 IRE-1α—XBP1/RIDD

IRE1 has two isoforms of α and β. The arm of IRE-1α is the most conserved sensor of the ER which is activated by autophosphorylation and oligomerization during accumulation of misfolded or unfolded proteins [22]. IRE-1α has two main domains of endoribonuclease (RNase) and kinase Upon activation, IRE-1α with its RNase domain splices the X-box binding protein 1 (XBP1) mRNA by removing 26-nucleotide of the intron. The spliced form of XBP1 (XBP1s) acts as a transcription factor. XBP1s could transfer into the nucleus and control the expression of the genes associated with protein folding, secretion, ERAD system, or lipid metabolism [13]. The RNase domain of IRE-1α is also responsible for RNA degradation in a pathway known as regulated IRE-1α-dependent decay (RIDD) [23]. The role of RIDD is to reduce a load of proteins to ER to help the homeostasis maintenance during cell differentiation and inflammation. In severe ER stress, the RIDD pathway may induce apoptosis to degrade the ER-resident proteins and de-repress Caspase 2 [24].

2-2 PERK-eIF2α

PERK is a kind of transmembrane kinase and, while activating by homodimerization and trans-autophosphorylation, can phosphorylate eukaryotic initiation factor-2α (eIF2α) at Ser51. This procedure prevents forming the 80s ribosome translation initiation complex, so the protein translation is attenuated globally [25]. still, some transcription factors such as ATF4 are activated and control some genes, such as the ones involved in ER stress responses, protein folding, autophagy, apoptosis and survival [26].

Indeed, ATF4 function is the different duration of stress ; in the initiation of stress, pro-survival pathways are activated, whereas when the stress is prolonged, the proapoptotic signal is turned on through C homologous protein (CHOP) [27].

In addition, one of the other PERK pathway responsibilities is to control the antioxidant pathway through nuclear factor erythroid-derived (NRF2) phosphorylation [28].

2-3 ATF6α

ATF6 is identified with the basic leucine zipper (bZIP) transcription factor and has two known isoforms of α and β. Following ER stress initiation, ATF6α transfers from the ER to the Golgi. Two Golgi peptidases, the site-1 (S1P, also named membrane-bound transcription factor peptidase, site 1 MBTPS1) and site-2 protease (S2P),

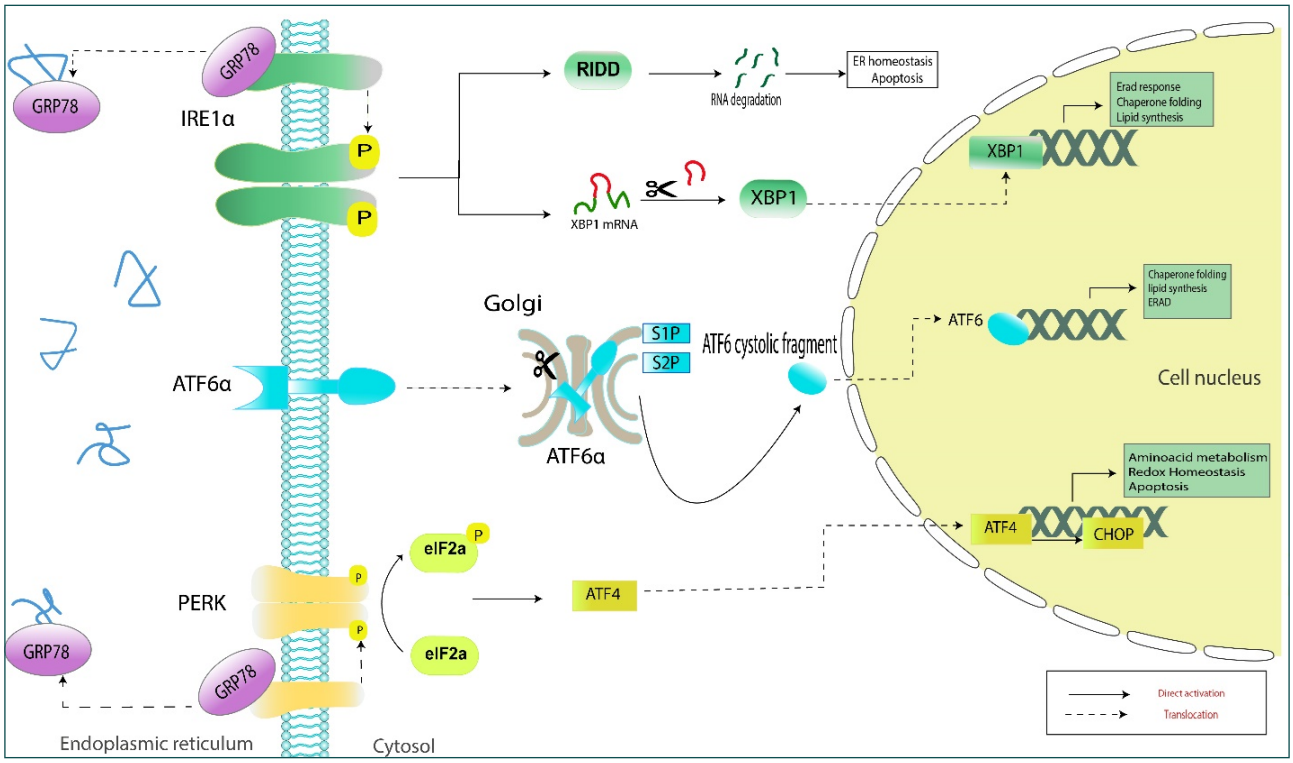

Figure.1. Unfolded Protein Response (UPR) signaling cascade during protein accumulation. Physiological or pathological stress induce three resident ER sensors; IRE1α, PERK, and ATF6. IRE1α activates and then splices the XBP1 mRNA. Spliced form of XBP1s move to the nucleus as a transcription factor to induce genes associated in lipogenesis and protein degradation system (ERAD). PERK arm inhibits the general protein translation by phosphorylation of eIF2α which enables ATF4 activation. ATF4 then translocates to the nucleus and control the genes which are needed for ER homeostasis. ATF6 is activated through the S1P and S2P of Golgi by removing the luminal domain and then transferring to the nucleus to activate the genes associated with ER stress responses.

sliced ATF6α. Following its cleavage, the ATF6α cytosolic domain translocates to the nucleus and binds to the genes associated with ER stress response genes, including protein folding and quality control of protein folding and up-regulation of ER-associated deprivation (ERAD) system. The ERAD system is activation followed by the accumulation of unfolded proteins to remove unfolded/misfolded proteins from the ER [29]. Figure 1 illustrates the UPR signaling. In this figure, three sensors of UPR and their signaling pathway shows in brief.

3- UPR involvement in cancers

One of the signaling pathways that have a vital role in cancer progression is the ER stress pathway that was first reported in 1988 [30] and is now believed by most scientists. The main mediators of the UPR, such as IRE1α, unspliced and spliced form of XBP1, PERK and ATF6 were up-regulated in various cancers and autoimmune diseases such as rheumatoid arthritis (RA) [31,32]. In most research experiments including, both in vitro and in vivo studies, GRP78 was introduced as the first factor in UPR to be activated in cancers and autoimmune diseases [32]. [33]. The activation of the UPR in cancers lets the tumor cells struggle with difficult situations, including hypoxia, oxidative stress, and low nutrient accessibility, to survive themselves [34]. Moreover, UPR activation in cancer cells leads to disturbance of antitumor immune response and chemotherapy resistance. In this situation, proinflammatory cytokines such as cytokines IL-6, IL-23p19, and TNF are secreted more than usual [35]. The researchers are studying UPR activity in tumor cells or targeted therapy based on ER stress signaling [36].

The role of ER stress pathway in cancer is different in various situations. For example, in the early stage of hypoxia and stress, UPR supports tumor survival, while during chronic stress, this adaptive pathway culminates

in apoptosis cascade [37]. Furthermore, the crosstalk between UPR and autophagy in different malignancies is observed because the tumor cells need to re-use their organelles to keep their proliferation [38].

4- Role of UPR in leukemia

4-1 ER Stress Activation in HSCs

Hematopoietic stem cells (HSCs) as immature cells can make all types of hematopoietic cells [39]. HSCs are sensitive to protein accumulation and need regulated protein quality control(PQC). In a steady state, HSC has lower protein synthesis than their progeny, and in the deregulation of protein synthesis, the survival and self-renewal capacities are changed [40].

During regulation of HSC, up-regulation of PERK occurred. By activation of PERK, the downstream pathway, peIF2α-ATF4/CHOP mediator activates to promote apoptosis. So the damaged cells are destroyed [41]. The IRE1α-XBP1 arm also switches on with its cytoprotective function. The ERAD pathway can maintain the proteins homeostasis in HSCs [42]. In the case of hypoxia in bone marrow, increased ER stress activity leads to clearance of damaged HSC in the early phase of hematopoiesis [43].

4-2 The role of the UPR in AML

AML originates from myeloid stem cells but is not fully differentiated and is recognized with immature white blood cells (myeloblasts) or abnormal red blood cells/platelets named leukemia cells or blasts. The reason for the undifferentiated AML is due to several factors such as mutation in transcription factor CCAAT/enhancer-binding protein alpha (C/EBPα) [44] and internal tandem duplications in the FMS like tyrosine kinase 3 gene (FLT3-ITD) [45]. AML subtypes are based chiefly on the maturation status at the time of diagnosis and the similarity of the cells with normal cells. Acute promyelocytic leukemia (APL) and promyelocytic leukemia (PML) are the two crucial AML subtypes. APL is a kind of AML that accounts for about 15% of AML cases that are created when translocation (15;17) is happened (namely PML-RARα) [46]. In PML-RARα+ AML patients, retinoic acid receptor alpha (RARα) is attached to the promyelocytic leukemia (PML) on chromosome 15 [47]. The PML-RARα new molecule acts as a transcriptional repressor and blocks myeloid differentiation. Wild-type of RARα creates heterodimers with the nuclear receptor co-repressor 1 (N-CoR) family which belongs to co-repressors mediating transcription and releases the co-repressors such as all trans-retinoic acid (ATRA) in response to cognate agonists. The N-CoR protein is an essential molecule for transcriptional repression by the tumor suppressor of Max dimerization protein 1 [48]. If too much PML-RARα binds to NCoR, abnormal proteins conformation and insolubility of the N-CoR protein will form and induce ER stress in an ERAD system [49].

The role of UPR in AML is also defined in some studies. However, there is no significant correlation between UPR activity and genetic models [50]. For instance, the researchers showed the activation form of GRP78, IRE-1α/XBP1s and Calreticulin in 17.4 % of AML patients [51]. Besides, the expression of XBP1s and GRP78 in 16 out of 92 patients showed that the ER protein quality control, lectin and calreticulin, were increased in leukemia patients, too [52]. Calreticulin could bind the C/EBPα and block it, so it negatively affects the myeloid differentiation. The overexpression of calreticulin in U937 AML cells suppressed the translation of C/EBPα [53]. Disulfide isomerase protein (PDI), a thiol-disulfide oxidoreductase that resides in the ER lumen and interacts with calreticulin, can equally bind to the C/EBPα mRNA and form a complex to regulate the translation of C/EBPα [54].

4-3 UPR Involvement in ALL

ALL is a kind of leukemia that originating from the B-cell (B-ALL) and or the T-cell lineage (T-ALL). In B-ALL, the immature hematopoietic stem cells(HSCs) in the bone marrow, and blood circulation accumulates. The reason for ALL is due to several factors; one is for the creation of philadelphia chromosome(Ph). This chromosome is formed in chromosome 22 from a reciprocal translocation between two genes, ABL-1 from chromosome 9 and BCR from chromosome 22 and formed BCR-ABL gene on chromosome 22 [55]. The other reasons are a duo to other genetic alteration such as activating point mutations, rearrangements in the mixed-lineage leukemia

gene (MLLr) [56] and deviation in main genes of B-cell development, such as paired box 5 (PAX5) and Ikaros family zinc finger protein 1(IKZF1) [57]. Mutations in the RAS/RAF pathway have also been identified in ~20–30 % of B-ALL patients correlated with poor prognosis [58,59]. During terminal differentiation of B-lymphocytes into plasma cells, the XBP1, IRE1α, and GRP78 are up-regulated in plasma cells and are essential for the terminal differentiation of B-lymphocytes into plasma cells [60]. A great number of experiments demonstrated that UPR mediators are primarily involved in the pathology and the outcome of ALL. GRP78, IRE1α and XBP1, were highly expressed in B-ALL patients [61]. XBP1s and GRP78 were also higher expressed in the Ph+ leukemia cell lines [62,63]. Therefore, the IRE1α suppression is one strategy in leukemia treatment. For example, the IRE1α RNase activity was inhibited by STF-083010, and apoptosis in B-ALL xenografts was occurred [5].

The increased level of UPR is also observed in T-ALL cells. c-Myc regulates the UPR response in T-ALL cells through increased the ubiquitin fusion degradation 1 (UFD1) gene transcription. UFD1 is a component of the ERAD complex to eliminate of misfolded/unfolded proteins from the ER. By inhibiting the UFD1 gene in T-ALL cells, UPR is induced and promotes apoptosis via PERK-ATF4-CHOP signaling. These findings suggested c-Myc/UFD1 signaling as a novel targeted therapy in T-ALL [64].

4-4 The role of UPR in B-CLL

B-chronic lymphocytic leukemia (B-CLL) is caused by the accumulation of malignant B CD5+ cells and is resistant to chemotherapy and apoptosis. Overexpression of BiP/GRP78 in B-CLL cells leads to survival of the cells and inhibition of GRP78 induced apoptosis through CHOP/GADD153 up-regulation [65].

4-5 The role of UPR in CML

Chronic myeloid leukemia (CML) as a common hematologic malignancy is occurred in 90% of patients due to the creation of the Philadelphia chromosome (Ph) which is performed by the translocation between the long arms of chromosome 9 (BCR gene) and 22 (ABL gene) results in a shortened chromosome 22 (BCR/ABL gene). This fusion protein shows the increased activity of tyrosine kinase [66]. So tyrosine kinase inhibitor (TKI) agents is one of approach in treatment of CML [2,3]. The BCR-ABL in CML cells up-regulates the expression of Xbp1 and Grp78, resulting in chemotherapy-resistant [67].

The PERK-eIF2α arm is also upregulated in both CML cell line CD34+ cells from CML patients and is associated in cancer progression and chemotherapy resistance. Imatinib (tyrosine kinase inhibitor) induces apoptosis and downregulates the PERK-eIF2α phosphorylation arm. Indeed, inactivation of PERK phosphorylation could affect the imatinib efficacy. Thus, the PERK-eIF2α phosphorylation branch may be crucial in therapeutically targeting CML disease [68].

5-UPR targeting in leukemia

Given the role of ER stress in numerous cancers, two strategy approaches are introduced for leukemia therapeutic target, first by inhibition of UPR cytoprotective role and second by its activation of the cytotoxic function. Targeting each of these items is vital in a different situation. In recent years, pharmacological agents for UPR targeting different cancers and leukemia is largely under investigation to be used in pre-clinical and clinical trials [69]. Several pharmacological drugs have recently been discovered to have anti-tumor activity by targeting UPR components. The creation of effective and selective chemicals that target UPR components has not only provided information on UPR regulation in cancer cells. Still, it has also taken the field closer to treatment possibilities. Recent discoveries have made UPR a viable target for developing novel anticancer treatments. These techniques might pave the way for individualized therapy in the future, giving hope to millions of people living with cancer.

For example, GRP78 was up-regulated in B-ALL and targeting it by epigallocatechin gallate(EGCG) compound could sensitize the cells to the anti-leukemia drug [61]. Other experiment targeting of IRE1α RNAse domain by STF-083010 reduced the proliferation rate of cells in pre-B ALL cells [61]. One of the reasons for resistance to

Table 1. UPR targeting in pre-clinical and clinical trial of patients with leukemia

Number	Compound	Mechanism	Type of leukemia	Stage of clinical trial	Reference
1	epigallocatechin gallate (EGCG),	GRP78 inhibitor	In B-ALL	Pre-clinical	[76]
2	MKC-3946	IRE1 inhibitor	AML	Pre-clinical	[72]
3	GSK2606414	PERK inhibitor	APL	Pre-clinical	[77]
4	Eeyarestatin I (EerI)	ERAD	multiple myeloma ALL, CLL	Pre-clinical	[78]
5	Pep42	GRP78	ALL	Pre-clinical	[76]
6	BMTP-78	GRP78	AML	Pre-clinical	[79]
7	Bortezomib	proteasome	AML	Phase I–III clinical trials	NCT01861314, NCT04173585, NCT01371981
8	Bortezomib	Proteasome Inhibitor	ALL	Phase III clinical trials	NCT02112916
9	STF-083010	IRE1	Multiple myeloma	Pre-clinical	[80]
10	Retinoic acid and arsenic trioxide	PERK	APL, AML	Pre-clinical	[81]

imatinib in CML is the activation of ATF6α, mediated by the protein disulfide isomerase 5 (PDIA5). It has been shown that using PDIA5 inhibitor causes the sensitivity of the cells to treatment with imatinib [70].

In CLL, the inhabitation of IRE1α, by B109 pharmaceutical drug, prevents cancer progression in a murine model [71]. Inhibition of IRE1α arm in AML by 2-hydroxy-1-naphthaldehyde (HNA), a pharmacological agent promotes apoptosis [72]. The Ph chromosome in AML patients cause the resistance to imatinib, and the inhibition of the IRE1α and ATF6α pathways increased the treatment response to this drug [73]. Another strategy in leukemia is inducing a cytotoxic response by increasing the unfolded protein load. For example, in ALL treatment, using agents that effects on proteasome, the degradation of misfolded proteins are impaired and apoptosis is observed [74]. The targeting of ERAD pathway in ALL also induces apoptosis [75]. Therefore, it seems important to further investigate UPR targeting by different pharmacological agents with combination therapy with chemotherapy.

5-1 UPR targeting in pre-clinical and clinical trial of patients with leukemia

Targeting UPR from the initiation of ER stress pathway has been studied in several experiments. For example, using epigallocatechin gallate (EGCG), a green tea extract, GRP78 was suppressed through its ATPase activity in B-ALL cells results in apoptosis [76]. The preclinical studies mainly focused on IRE1 inhibitors, PERK inhibitors and other ER stress pathways like ERAD inhibitors (table 1). The only clinical trial study performed in AML and ALL patients is Bortezomib as a proteasome inhibi-

tor. These approaches persuade the cells to apoptosis or other cell death, such as autophagy.

Concluding remarks

Next-generation of cancer treatment is finding new targeted-therapy. ER stress and UPR pathway is a known signaling pathway in cancers and leukemia, which is recently most attracted by scientists. Although targeting the mediators in UPR pathway has great potential in leukemia, further studies are needed to select which mediators are suitable in different leukemia before initiating clinical trials.

Abbreviation

1- Activating transcription factor 6α (ATF6α)
2- Acute lymphoblastic leukemia (ALL)
3- Acute myeloid leukemia (AML)
4- Acute promyelocytic leukemia (APL)
5- Basic leucine zipper (bZIP)
6- B-cell acute lymphocytic leukemia (B-ALL)
7- C homologous protein (CHOP)
8- Chronic lymphoblastic leukemia (CLL)
9- Chronic myeloid leukemia (CML)
10- Chronic stress (CHR)
11- Endoplasmic reticulum stress (ER)
12- Endoplasmic reticulum-associated protein degradation (ERAD)
13- Endoribonuclease (RNase)
14- Epigallocatechin gallate (EGCG)
15- External nuclear membrane (ENM)
16- Eukaryotic initiation factor-2α (eIF2α)
17- Glucose-regulated proteins 78-kDa (GRP78)
18- Heat shock proteins (HSPs)
19- Hematopoietic stem cells (HSCs)
20- Histone deacetylase (HDAC)
21- Inositol-requiring enzyme-1α (IRE1α)
22- Philadelphia chromosome (Ph)Protein kinase RNA-like endoplasmic reticulum kinase (PERK)
23- Protein disulfide isomerase 5 (PDIA5)
24- Protein quality control (PQC)
25- Reactive oxygen species (ROS)
26- Rheumatoid arthritis (RA)
27- T-cell acute lymphocytic leukemia (T-ALL)
28- Unfolded protein response (UPR)
29- White blood cells (WBC)
30- X-box binding protein 1 (XBP1)
31- XBP1 spliced form (XBP1s)

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