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Review article

GRP78: A cell's response to stress

Ibrahim M. Ibrahim, Doaa H. Abdelmalek, Abdo A. Elfiky*

Biophysics Department, Faculty of Science, Cairo University, Giza, Egypt

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ABSTRACT

Background: Glucose-Regulated Protein 78 (GRP78) is a chaperone heat shock protein that has been intensely studied in the last two decades. GRP78 is the master of the unfolded protein response (UBR) in the Endoplasmic Reticulum (ER) in normal cells. GRP78 force the unfolded proteins to refold or degrade using cellular degradation mechanisms.

Scope: Under stress, the overexpression of GRP78 on the cell membrane mediates the vast amount of disordered proteins. Unfortunately, this makes it a tool for pathogens (bacterial, fungal and viral) to enter the cell and to start different pathways leading to pathogenesis. Additionally, GRP78 is overexpressed on the membranes of various cancer cells and increase the aggressiveness of the disease.

Major conclusions: The current review summarizes structure, function, and different mechanisms GRP78 mediate in response to normal or stress conditions.

General significance: GRP78 targeting and possible inhibition mechanisms are also covered in the present review aiming to prevent the virulence of pathogens and cancer.

1. Introduction

Glucose-Regulated Protein 78 (GRP78) or immunoglobulin heavy chain binding protein (BiP) is a member of the Heat Shock Protein 70 (HSP70) family. It is found in all eukaryotes on the membrane of Endoplasmic Reticulum (ER) [1]. The 654 amino acid protein, GRP78, corrects the folding and assembly and prevents the transport of proteins or protein subunits that are folded incorrectly [2–4]. GRP78 expression is increased in cases of ER stressors like when the cell is abridged from sugar, treated with reagents that inhibit the process of protein glycosylation or disturb the intercellular calcium storage [5]. It is a water-soluble protein, and only small patches are reported to be hydrophobic. These hydrophobic patches are essential for its function as it recognizes the unfolded proteins that are directed either to the degradation or refolding mechanisms [6]. GRP78 structure is divided into two domains, ATP binding domain (ABD) (or nucleotide binding domain NBD), at the amino terminal and substrate binding domain (SBD) at the carboxyl-terminal [7]. Fig. 1 shows the x-ray apo form of GRP78 solved structure (PDB ID 6EOC) at 1.67 Å resolution and ABD domain with bound ATP molecule (PDB ID 5F1X) at 1.90 Å resolution.

GRP78 shares 60% homology with the HSP70 family, with the conservation of ABD and SBD domains. ABD domain shows the most considerable sequence conservation over the HSP70 family [1,7,8]. Although GRP78 is an HSP70 family A member and shares the properties of abnormal protein binding under conditions of stress, it differs in protein expression regulation. GRP78, but HSP70, is sensitive to the protein synthesis inhibitor cycloheximide [9,10], which is a protein synthesis inhibitor in eukaryotic cells [11]. The most potent induction reasons for GRP78 expression, like calcium ionophore A23187 and β-mercaptoethanol, doesn't affect the expression level of HSP70 proteins [12–14]. Treating cells with such inducers increases the GRP78 gene expression up to 10–25 folds in 5 h [12,15].

GRP78 expression appears to be in a direct correlation with the activity of the ER. This means that intermediate molecules must exist and travel between both membranes of the ER and the nucleus to reach the GRP78 gene and communicate the signal. The way between the two membranes is not tricky as the ER membrane is associated with the prenuclear membrane. GRP78 is regulated over the transcriptional level [8].

2. GRP78 gene

In human, the gene responsible for GRP78 encoding is on chromosome number 9 with a length of 4532 nucleotides [1,2]. Fluorescence *in situ* hybridization with a 24,000 bases genome phage clone that contains the whole coding region of GRP78 gene is used to prove the positive signals of hybridization at the distal end of the long arm of chromosome 9, at band 9q34 [2]. In human there are two genes

* Corresponding author.
E-mail address: abdo@sci.cu.edu.eg (A.A. Elfiky).

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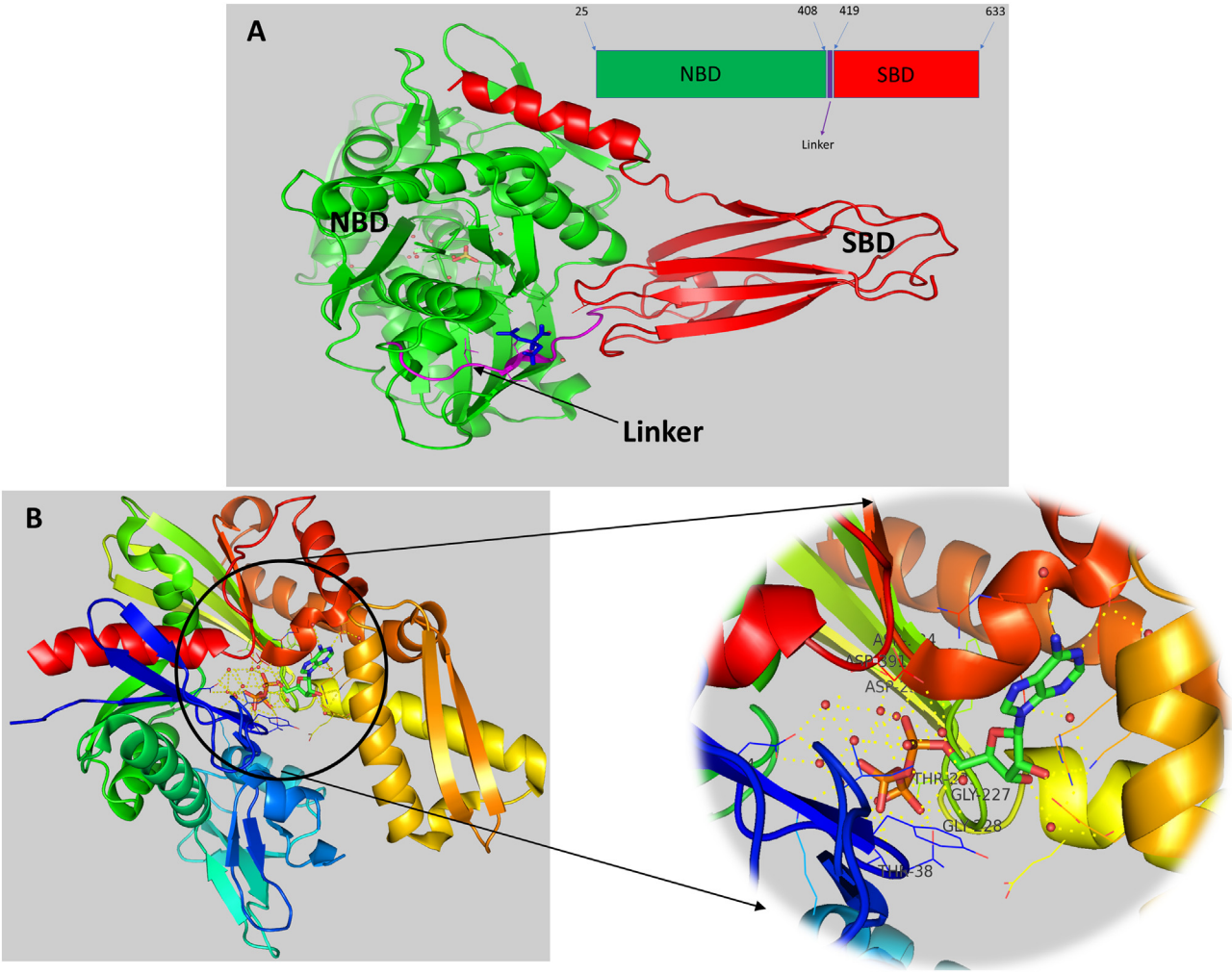

Fig. 1. A) shows the x-ray apo form of GRP78 solved structure (PDB ID 6EOC) at 1.67 Å resolution. The protein is represented by cartoon colored green (NBD), red (SBD) and purple (linker). GRP78 sequence is represented also with the same color as the protein domains. B) ATP binding domain with pound ATP molecule (PDB ID 5F1X) at 1.90 Å resolution represented as the rainbow-colored cartoon. The binding site with ATP is enlarged to show the amino acids involved in the interaction. PyMOL software is used to represent the entire figure [127]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

encoding GRP78, one is a functional gene, and the other is a pseudogene (processed gene) [1,2,6]. The functional gene contains eight exons [6,8]. Pseudogene doesn't contribute to gene transcription, and it is in a genomic A-T rich region. The functional gene promoter has two parts, proximal and distal domains. The distal domain is responsible for enhancing the basal level of expression, and the proximal domain is responsible for responding to various stimuli that arouses the cell. The two domains are highly conserved in human and rat [6]. GRP78 promoter of the functional gene contains a TATA box and five CCAAT sequences. From the 5′ end, the TATA box is located 25 nucleotides upstream, and the CCAAT sequences are within 250 nucleotides upstream from RNA initiation site. At the 3′ end of the gene, a polyadenylation sequence AATAAA is found. In the functional human GRP78 gene, there are short domains in the hydrophobic region that are highly conserved with HSP70 from five species, human, Drosophila, Xenopus, yeast and *E. coli* with homology that is over 80%. These domains are divided into regions from A to H. These regions cover almost all the hydrophobic patches in GRP78 protein. The A region consists of 11 amino acids near the amino terminus. Other six domains B to F are divided into two groups, B, C, D and E, F, G and are around the center of the protein. Retaining GRP78 in the ER is the responsibility of the last four amino acids (Lys, Asp, Glu, Leu). This motif is highly conserved between human, rat and hamster genome. The most divergent sequences are found at highly hydrophilic domains at the carboxyl third of the protein [6,16,17].

A deletion of 12 nucleotides near the amino-terminal and insertion of four nucleotides within exon number 5 was found in pseudogene compared to the functional gene. GRP78 pseudogene is surrounded by GAAAATTAAACAA sequence. upstream from the pseudogene, 100 nucleotides are 66% A-T rich while this ratio is 75% for the 200 downstream nucleotides [6].

In human, the 5′ flanking region is 1650 nucleotides. When this region is reduced to 358 nucleotides, no changes are observed in the basal or induced activity. On the other hand, the reduction of this region to 170 nucleotides results in two folds decline in both basal and induced activity [6,8]. Analysis of the human GRP78 gene reveals that GRP78 promotor contains a region that is sensitive to stress. This region is within the 170 nucleotides upstream from the transcription initiation site [6].

3. Functions of GRP78 in normal *versus* stressed cells

3.1. Function in normal cells

GRP78 function is to work as a molecular chaperone. It binds to misfolded proteins and unassembled complexes and initiates ER-

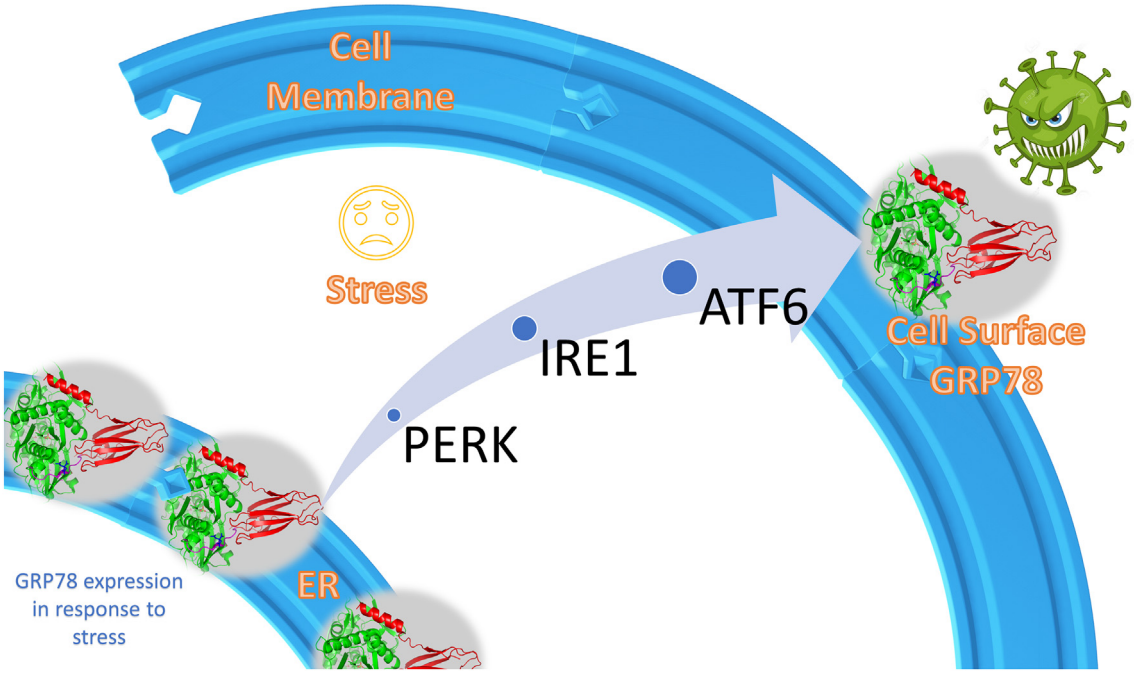

Fig. 2. Illustration showing the cell in response to a stress condition. Accumulated unfolded proteins make activation of PERK, IRE1, and ATF6 which induce overexpression of GRP78 and other chaperone proteins. GRP78 may be cell surface expressed making the stressed cell susceptible to pathogens (viral or fungal). Besides, if the cell is cancerous, CS GRP78 will induce resistance to chemotherapy.

associated degradation (ERAD) responsible for UPR regulation [18–20]. It binds to unfolded peptides with the SBD and gets the energy to prevent aggregation by the mean of ATP hydrolysis in the (NBD) [21]. In the standard conditions of balance in the cell (homeostasis) GRP78 is bounded in an inactive form to Activating transcription factor 6 (ATF6), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and Inositol-requiring enzyme 1 (IRE1) which are UPR transmembrane stress sensors. When the cell is exposed to unfolded proteins that are accumulated in the ER, this stress can be revealed when GRP78 is released from the UPR sensors. The active form of UPR then decreases the translation of protein and enhance the correct folding [19] (see Fig. 2).

PERK, when activated, phosphorylates the alpha (α) subunit of eukaryotic translation initiation factor (eIF2α). The phosphorylated eIF2α then can inhibit the initiation of translation and inhibit protein synthesis reducing the influx of nascent proteins into the lumen of the ER [20,22]. The activated form of ATF6 translocates to the Golgi apparatus where it is cleaved. After that, the cleaved ATF6 moves to the nucleus and works as an active transcription factor and upregulate the transcription of proteins that increase the folding capacity of the ER like GRP78. The IRE1 active form has an endoribonuclease activity. It breaks a 24-base segment of mRNA intron and encodes X-box binding protein 1 (XBP1). XBP1 target genes which are responsible for protein folding and ERAD [2]. At this point, if the homeostasis of the ER could not be restored, the unfolded protein response can induce apoptosis [19].

3.1.1. GRP78; other functions to do

In its basal level of expression, GRP78 plays a role in the development of the embryo. It was found that homozygous mice, with GRP78 gene, knocked down, witnessed fatality at day 3.5 of embryogenesis with a massive apoptotic inner cell mass death [20]. In human, when GRP78 is knocked down, the expression of Glucose-regulated protein 94 (GRP94), CCAAT-enhancer-binding protein homologous protein (CHOP), c-Jun N-terminal kinase (JNK), and X-box binding protein 1 (XBP1) are spontaneously increased. As GRP78 is suppressed down, the UPR sensors are activated. GRP94 expression is improved, but this increment does not compensate for the GRP78 absence. This result shows that GRP78 has an anti-apoptotic role and it is essential for cell viability. GRP78 binds to caspase 7 and caspase 12 which are the main cytosolic implementers for apoptosis, despite there is no binding to caspase 3 [23].

There is a relation between aging and ER stress. Aging causes a decrease in protein expression and a decrease in the activity of several ER chaperones such as GRP78. This decline in the expression increases the tendency to ER stress. This unmitigated ER stress leads to age-related diseases [19].

GRP78 has a non-chaperon function as it is the primary binding protein of Ca^{+2} in the ER and maintain its balance in the lumen. There is no specified domain for Ca^{+2} binding, but it binds to the anionic amino acid residues. One hundred eleven anionic residues, from which 19 only paired, are found in GRP78 leaving many residues to be favorable for Ca^{+2} binding. This binding capacity still less than other ER proteins [24].

3.2. Cell surface GRP78 expression in response to stress

GRP78 can also be found on the cell surface. The last four amino acids in the GRP78 protein (the motif KDEL) which are responsible for ER retention, is present in the cell surface GRP78 (CS GRP78). Thus, the cleavage of this motif sequence is not required in surface expression. When GRP78 is overexpressed, a fraction of it can escape the motif retention and translocate to the cell surface [20,25]. As when the GRP78 is overexpressed, the KDEL motif receptors are fully saturated, and then GRP78 can escape the retention. Another thing is KDEL receptor can be downregulated under some circumstances. There is a theory saying that it could be another protein that helps GRP78 to escape retention by masking KDEL sequence, but it has yet to be determined [25].

When GRP78 moves to the surface of the cell, it can interact with plenty of ligands or other proteins on the cell surface and works as a multifunctional receptor. CS-GRP78 plays an essential role as in cellular signaling, proliferation, migration, invasion, apoptosis, inflammation, and immunity. According to the ligand or the peptide that bind to CS-GRP78, it will be activated in a defined signaling pathway that affects

the cell in different ways. When GRP78 is on the cell surface, autoantibodies are secreted. Antibodies for the N-terminal of the protein induces cell proliferation while antibodies bind to the C-terminal causes the induction of cell apoptosis [26]. Ligand α2 macroglobulin (α2M), a plasma proteinase inhibitor, affects promoting cell proliferation and viability. CS-GRP78 has a high affinity to α2M. When Isthmin, 60 kDa protein, binds to CS-GRP78, it works as a proapoptotic ligand by induction of mitochondrial dysfunction [27]. Par-4, which is prostate apoptosis response 4, can interact with CS-GRP78 and induce apoptosis through ER stress and the activation of the FADD/caspase-8/caspase-3 pathway. Another way of cell apoptosis induction is by plasminogen Kringle 5 which requires CS-GRP78 to induce apoptosis of dermal microvessel endothelial cells [26].

As we remarked before hypoxia, glucose starvation or tumors cause ER stress. Hypoxia induces CS-GRP78 levels to be increased over fourfold. Besides, levels of cell surface GRP78 is correlated to several pathological conditions like many cancers, arthrosclerosis, and rheumatoid arthritis. The presence of GRP78 on the cell surface caused the immune system to generate an autoimmune response and circulating autoantibodies to CS-GRP78 expressed cells [24].

4. GRP78 and fungal infection

Mucorales, which are thermotolerant fungi, can be found in decaying organic material [28]. These fungi can cause Mucormycosis disease which is considered as the third common invasive fungal infection in patients who undergo organ transplantations or having hematologic malignant tumors [29]. Although there are treatment options for mucormycosis, this disease is characterized by high mortality rates often higher than 40% and in some cases can reach 100% [30,31]. Some of the risk factors that mediate the infection are hematologic malignancy, organ transplantation, and uncontrolled diabetes mellitus [31]. All Mucorales can cause blood vessel thrombosis leading to tissue necrosis. Therefore, the interaction of Mucorales with the endothelial cells of blood vessels is responsible for their pathogenesis [31]. One of the most common fungi belonging to Mucorales order is *Rhizopus oryzae* (*R. oryzae*) which is responsible for 70% of reported Mucormycosis cases [31,32]. GRP78 is found to be the receptor mediating the binding of *R. oryzae* during cell invasion [33]. The ligands on the surface of the *R. oryzae* that bind to GRP78 are spore coat protein homolog (CotH) cell surface proteins [32]. There are 3 of these surface proteins named (CotH1, CotH2, and CotH3) surface proteins. The expression of CotH2 and CotH3 is increased 4- and 16- fold, respectively, when *R. oryzae* germlings were incubated on endothelial cells [32]. CotH2 and, to a greater extent, CotH3 surface proteins bind to GRP78 and are responsible for adherence and invasion (endocytosis) of *R. oryzae*. Both CotH2 and CotH3 proteins bind to the same alpha-helical bundle domain of GRP78, *in silico* [32].

5. GRP78 and viral infection

GRP78 has an essential role in the development of some viruses' envelope proteins such as sindbis virus, hepatitis C virus, vesicular stomatitis virus, and influenza A virus [34–37]. For some viruses to enter a cell, they need first to attach to a specific cell surface molecule, then uses another molecule that mediates their internalization [38]. This complex multi-step process is essential for the viruses to survive the hostile environment of the host immunity [39].

5.1. Ebola virus

One of the deadliest re-emerging viruses is filoviruses Ebola virus (EBOV). Human infection by EBOV causes hemorrhagic fever with case fatality rates in some outbreaks that reached 90% [40]. The epidemic of EBOV requires the utilization of host factors in the different stages of the viral life cycle [41]. Epigallocatechin gallate (EGCG) can inhibit the ability of GRP78 to bind ATP by binding to the ATP-binding site [42]. Using this compound, Shurtleff et al. found that EGCG can inhibit the EBOV infection, demonstrating that the ATPase activity of GRP78 is required for the infection [43]. Besides, they found that using GRP78 siRNA caused a decrease of viral transcript production [43]. Also, the infection by EBOV results in an increase of HSPA5 expression due to the accumulation of EBOV glycoproteins 1 and 2 (GP1 and GP2) in the endoplasmic reticulum causing a stress response [44]. Although GRP78 is involved in the entry of some viruses [38], knockdown of GRP78 did not affect the entry of EBOV [43]. GRP78 has a role in the budding of VP40 protein [43]. This interaction was suggested earlier by Yamayoshi et al. [45].

5.2. Zika virus

One of the emerging infectious viruses is Zika virus (ZIKV). ZIKV is a flavivirus related to microcephaly, a neurodegenerative disorder, and Guillain-Barré syndrome which is an autoimmune disorder [46,47]. Two possible routes of transmission are through Aedes mosquitos, as they are the major species of mosquitos responsible for the transmission of the virus, or through sexual intercourse, though it is not significant [48,49]. The genome of ZIKV is nearly 11 kb long with a single open reading frame (ORF) flanked by noncoding regions at the two ends [50]. The end products of ORF are capsid, the precursor of membrane, envelope, and seven non-structural proteins [51]. The envelope protein is responsible for cellular attachment, entry, and fusion [52]. One of the receptors responsible for the endocytosis of the virus is GRP78 [53,54].

5.3. Dengue virus

Another mosquito-borne virus belonging to the flavivirus genus is Dengue virus (DENV) [55,56]. Its genome is positive-stranded RNA, which encodes, after the processing of the polyprotein produced from the RNA, three structural and seven non-structural proteins. It has four serotypes (DENV1-4) [57]. This virus can cause a wide range of diseases such as; dengue fever (benign self –limited febrile illness), dengue hemorrhagic fever, or dengue shock syndrome [55]. GRP78 is identified as a receptor for dengue virus serotype 2 in hepatoma cells (HepG2) [58]. **Jindadamrongwech et al. found that using an antibody against N-terminal of GRP78** inhibited binding and infection while using antibodies against the C-terminal of GRP78 increase the infection and, to a less noticeable degree, the binding of the virus to the receptor. This increase is related to the concentration of antibodies [58]. This may be due to the conformational changes produced from the C-terminal antibody binding to GRP78, enhancing the binding ability of the virus to the protein [58].

5.4. Japanese Encephalitis Virus

Japanese Encephalitis Virus (JEV) is a member of the Flaviviridae family. Other mosquito-borne, and medically important pathogens viruses belonging to this family are DENV and West Nile virus [59]. JEV is a neurotropic virus which causes encephalitis in humans and has a mortality rate ranging from 25% to 30% [59]. For the JEV to enter a cell, it needs first to attach to the cell membrane through the help of specific receptors such as heparan sulfate proteoglycans (HSPGs) and glycosaminoglycans (GAGs) [60,61]. Nain et al. identified GRP78 as a receptor for JEV envelope domain III (ED3) [62]. They checked the interaction between GRP78 and JEV ED3 by using firefly luciferase gene which showed a substantial activity, confirming this interaction [62]. Using N-terminal GRP78 antibody, the interaction is revealed to be between the N-terminal GRP78 and JEV ED3 as the binding between GRP78 and JEV ED3 reduced by nearly 38% [62]. Besides, they confirmed the role of GRP78 in the internalization of JEV by using GRP78 siRNA, then measuring the JEV RNA 2 h post infection, at this time the level of RNA is an indication of the viral entry only. This test shows a

significant reduction in JEV RNA in cells by nearly 60% [62]. GRP78 also has a role in the replication of JEV [62]. This role is demonstrated by using Subtilase cytotoxin which can break GRP78 into its C-and N-terminals leading to its deactivation [63]. A 90% reduction in the viral RNA in all cells was reported, indicating the significant role of GRP78 JEV replication [62].

5.5. Middle-East Respiratory Syndrome coronavirus

Coronaviruses are enveloped single-stranded positive-sense RNA viruses that can infect a wide range of species including humans [64]. They are classified into alpha-, beta-, gamma-, and delta coronaviruses [64]. One of the viruses belonging to betacoronaviruses is Middle East Respiratory Syndrome Coronavirus (MERS-CoV) which causes severe lower respiratory tract infection with a high mortality rate reaching 35% [64,65]. The MERS-CoV spike protein utilizes dipeptidyl peptidase 4 (DPP4) as its functional receptor for host cell entry [66]. In addition to its functional receptor, MERS-CoV can recognize other molecules to facilitate their attachment and entry, for example, carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), and tetraspanin CD9 are identified as a factor promoting the virus entry in permissive cells [67,68]. Recently GRP78 was recognized as an attachment factor for MERS-CoV spike protein that enhances the virus entry in the presence of DPP4 [65]. In addition to GRP78 role in the entrance of the virus, it has a role in the replication of MERS-CoV [65]. CS GRP78 is upregulated after the entry of MERS-CoV, which helps in the attachment of the virus [65]. Although knockdown of GRP78 led to a decrease in the replication of the virus, this decrease is lesser compared to the reduction in the replication of the virus when DPP4 is reduced [65].

5.6. Coxsackievirus A9

Coxsackievirus A9 (CAV9) is a non-enveloped RNA virus that can cause flaccid paralysis, and chronic dilated cardiomyopathy [69]. Besides, it is involved in autoimmune episodes that result in insulin-dependent diabetes mellitus [70,71]. Integrin alpha-v beta 3(αvβ3) is a receptor that can be used by CAV9 [72–74], but its utilization is not sufficient for its infection [72]. GRP78 was identified by Triantafilou et al. to be utilized by CAV9 for infection [38]. GRP78 delivers viral peptides to MHC-I [75], and it is found that GRP78 is associated with MHC-I molecules on the cell membrane [38]. After CAV9 binds to GRP78, it causes an increase in the clustering of GRP78 and MHC-1 molecules [38]. Triantafilou et al. used anti-MHC-I antibodies (W6/32, MCA1115) to determine whether MHC-I helps in internalization of the CAV9 virus [38]. Although there is no change in binding, they found that the internalization is inhibited by 85% using these antibodies [38]. They suggested a model in which CAV9 attach to the cell by binding to GRP78 and Integrin αvβ3, then uses MHC-I which is associated with GRP78 for entry so it can use the cell machinery [38].

5.7. Borna Disease virus

One of the viruses that belong to Bornaviridae is Borna Disease Virus (BDV) [76]. BDV is non-segmented, negative-strand RNA virus with high neurotropic and non-cytopathic infection [76]. This virus infects many animals and causes central nervous system diseases which are associated with behavioral disturbances [77]. Virus entry is mediated by endocytosis after the viral envelope glycoprotein (G) attach to the cell receptor [78,79]. The N terminal in G protein is responsible for the attachment to the cell receptor [78]. One of these receptors is GRP78 as demonstrated by Honda et al. [80]. They used GRP78 antibody and found that binding of the G protein to GRP78 reduced to 40%. The GRP78 domain that binds to G protein is the ATP-binding domain [80].

6. GRP78 and cancer

GRP78 has a crucial role in proliferation, invasion, and metastasis of many cancer cells such as renal cell [81], endometrial [82], gastric [83], and prostate cancer [84].

6.1. Breast cancer

The most common cancer in females worldwide is breast cancer [85]. The treatment of advanced breast cancer patients starts with gemcitabine [86]. Gemcitabine is a pro-drug cytotoxic chemotherapeutic agent similar to cytarabine. Its anticancer effects are manifested by its phosphorylated active metabolites (gemcitabine di- and triphosphate) [87]. These metabolites are combined with DNA to stop replication and cell growth leading to apoptosis [87]. The major problem that affects therapy is drug resistance [88]. GRP78 was demonstrated to promote drug resistance in breast cancer against doxorubicin [89]. Usually, apoptosis has two pathways (extrinsic or intrinsic) [90]. Extrinsic pathway requires that death receptors on the cell surface be activated. On the other hand, the intrinsic pathway involves a series of events that are processed in the mitochondria [90]. Caspase 9 is triggered by the intrinsic pathway [91] and is found to be responsible for gemcitabine resistance and GRP78-regulated chemosensitivity [88]. Xie et al. show that overexpression of GRP78 reduced the sensitivity of gemcitabine so it may have a critical role in the resistance of breast cancer cells. This reduction in sensitivity is caused by apoptosis inhibition [88]. The same group shows that caspase 9 and its phosphorylated form p37 were excessively down-regulated in GRP78-overexpressed breast cancer cells and was markedly increased in GRP78-downregulated breast cancer cells [88]. The levels of anti-apoptosis protein Bcl-2 is found to be high in GRP78-overexpressing breast cancer cells, on the other hand, the levels of pro-apoptosis proteins, Bax and Bim are low, and *vice versa* [88]. AKT can affect mitochondrial apoptosis by either targeting the pro-apoptotic protein Bad or by inhibition of pro-apoptotic signals produced by transcription factors such as FoxO [88]. AKT is found to be markedly increased in gemcitabine resistance breast cancer and is related to the expression of GRP78, so an increase in GRP78 leads to AKT increase. If AKT expression is reduced in GRP78-overexpressing breast cancer cells, their sensitivity to gemcitabine increases and apoptosis also increases [88]. These results are in agreement with other types of cancers such as colon cancer [92], and prostate cancer [93].

6.2. Ovarian carcinoma

The fourth common cause of death in women is ovarian carcinoma which represents the most lethal type of gynecological malignancies [94]. Epithelial ovarian carcinoma has only 30% 5-year survival rate because of the difficulty of early detection due to unclear symptoms [95]. GRP78 overexpression in cancer cells and human tumors resulted in cancer malignancy and increased survival of cancer cells due to treatment resistance [96,97]. The accumulation of polypeptides in endoplasmic reticulum due to the elevated metabolism of ovarian cancer cells leads to the overexpression of GRP78 [98]. Although the use of taxane and platinum-based chemotherapy in the treatment of ovary cancer results initially in high response rates, many of the patients suffer a relapse and develop resistance [99]. Paclitaxel can lead to apoptosis by preventing microtubule formation leading to a mitotic block of the cell [100] and partly to endoplasmic reticulum unfolded protein response [101]. Zhang et al. [97] demonstrated that treatment of three groups of HO-8910 cells with paclitaxel after transfection with GRP78 siRNA for one group, nonspecific siRNA for the second group, or untreated HO-8910 cells led to a different decrease in survival rates of the three groups to paclitaxel. The survival rates of the GRP78 siRNA treated group is significantly lower than the other two groups which indicate the higher sensitivity of the treated group to paclitaxel

treatment after the inhibition of GRP78 protein [97]. In addition to the protective role of GRP78 to paclitaxel, the apoptosis ratio in the siRNA GRP78 treated group reaches 56.92 ± 0.46% after 72 h of transfection, which corresponds to a previous study by Martin et al. [102]. The increase in apoptosis may be due to the prevention of the interaction between GRP78 and apoptosis pathway compounds such as caspase-7 [103]. Chen and Xu [104] studied the effect of cisplatin, which is a platinum-based chemotherapy reagent [105], on ovarian cancer cells. In their study, they showed that GRP78 overexpression in ovarian chronic cisplatin-treated cells leads to chemoresistance, which reduces the effectiveness of the treatment [98].

6.3. Pancreatic cancer

One of the most aggressive types of malignant tumors is pancreatic ductal adenocarcinoma (PDAC) [106]. The only cure for PDAC is surgery; however, the 5-year survival rate of patients after removal of the pancreatic cancer is approximately 20–25% [81,107]. Because of this, the identification of specific new factors that can increase the survivability of patients is critical [81]. Zheyu et al. [108] found a strong relationship between the expression of GRP78 and tumor stage indicating a potential role of GRP78 in PDAC progression. They show that low overall survival of patients was strongly related to the overexpression of GRP78 on tumor cells [108]. Overexpression of GRP78 affects proliferation, cell cycle, invasion, and migration of PDAC cells. Such that overexpression increases proliferation, invasion, and migration, and increases the percentage of cells in S phase of the cell cycle [108].

The underlying mechanism of invasion of pancreatic cancer cell was demonstrated by Yuan et al. [109]. He showed that the overexpression of GRP78 caused an elevation of matrix metalloproteinase-2 and 9(MMP-2 and MMP-9) secretion and activity [109]. Although MMPs are degrading proteases, they have a vital role in invasion and metastasis [109]. Dynamics of actin filaments, especially cytoskeletal F-actin stress fibers, is increased in response to knockdown to GRP78 [109]. Ras homolog gene family, member A (RhoA) and Rac have an essential role in cytoskeleton dynamics and act as a downstream of focal adhesion kinase (FAK) [110], which have a crucial role in cancer invasion [109,111]. The activity of Rac and RhoA are related to the levels of GRP78. Overexpression of GRP78 increases the activity of Rac but decreases RhoA activity [109]. FAK activity is regulated by the expression of GRP78 such that, overexpression of GRP78 increase the phosphorylation of FAK Y397 [109]. The c-Jun N-terminal kinase (JNK), has a critical role in the invasion of many epithelial cancers. Its activity is related to the expression of GRP78 in a direct way [109].

6.4. Colon cancer

Colorectal cancer is the third cancer type according to incidence but is considered to be the second for its mortality [112]. This cancer can be treated by surgical intervention if it is still in the primary site; however, metastasis is the main factor leading to death from colorectal cancer patients [113]. The expression of GRP78 was found to be high in colon cancer cells [114], and its downregulation led to an increase of epirubicin-induced apoptosis, which is due to an increase in the nuclear factor erythroid 2–related factor 2 (Nrf-2) expression [115]. Moreover, silencing of GRP78 resulted in a suppression of colon cancer growth by the downregulation of Vascular endothelial growth factor/Vascular endothelial growth factor Receptor 2 (VEGF/VEGFR2) pathway [115]. High surface expression of GRP78 in colon cancer shows a reduction in tumor proliferation and growth [116], though, an increase in the invasiveness is observed with high surface GRP78 expression [117]. The downregulation of GRP78 increased colon cancer metastasis, due to a rise in NRF-2 and Heme oxygenase -1 (HO1) level and change in the epithelial-to-mesenchymal transition (EMT) biomarker expression [113]. NRF-2 has a function in cell migration ability [118]. The migration ability of colon cancer is increased after the downregulation of GRP78 [113]. The raised migration is caused by an increase in vimentin and decrease in E-cadherin [113]. Vimentin is an intermediate filament protein [119], one of the EMT markers, and considered to be important in EMT induction [120]. E-cadherin is essential in cell polarity and organization of epithelium and can be regarded as a significant epithelial marker [121]. Its level decreased in some cases such as tumor metastasis, and progression from adenoma to carcinoma [122].

7. GRP78 targeting; a grant from an ordeal

Usually treatment of cancer is done by chemotherapy; however, it is limited by its severe side effects. Therefore, it is inevitable to develop new methods for cancer treatment [123,124]. One of these new methods utilizes peptidic ligands as they can specifically target the tumor cells and deliver drugs [125]. One of these peptides is Pep42 which is a cyclic 13-mer CTVALPGGYVRVC [126]. The internalization of this peptide is studied after it was mutated at position 12 (valine to lysine) (Mut42) for fluorescein isothiocyanate coupling (FITC), and it is found that this mutation doesn't affect Pep42 internalization negatively [126]. Pep42 can enter the cell through a receptor-mediated pathway, this receptor was identified to be GRP78, and it is found on the surface of human melanoma cells (Me6652/4) [126]. After internalization, Mut42 was found to be colocalized with the ER but not lysosomes. After using different concentrations of monoclonal antibodies against GRP78, the uptake of Mut42 is reduced according to the level of the antibodies. Moreover, overexpression of GRP78 increases the entry of Mut42 which indicates the specificity of Pep42 to GRP78. Mut42 is used with Taxol on human Melanoma cells, and 92.1% of the cells are found to be in the late stages of apoptosis [126].

The cyclic shape of this peptide is vital for internalization as reported by Kim et al. [126]. Besides, the peptide is mainly hydrophobic supporting the selectivity of the peptide to bind to GRP78, which has the affinity to attach to the hydrophobic clusters of unfolded proteins under stress conditions. These are two crucial points for consideration when studying the interaction between CS GRP78 and pathogenic proteins (envelope and spore coat proteins). Also, targeting such binding site on the CS GRP78 with cyclic peptides may be the future preventive routine for patients living with diabetes or cancers.

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