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# GRP78: A Multifunctional Receptor on the Cell Surface

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## Abstract

The 78 kDa glucose-regulated protein (GRP78) is an endoplasmic reticulum chaperone, whose function is generally thought to be restricted to controlling the structural maturation of nascent glycoproteins. However, GRP78 also is expressed on the cell surface where it functions as a receptor for a wide variety of ligands, behaving as an autoantigen for several classes of autoantibodies. GRP78 is a signaling receptor for activated $\alpha_2$-macroglobulin, plasminogen kringle 5, and microplasminogen, and it plays a critical role in viral entry of coxsackie B, and dengue fever viruses. GRP78 is also implicated in the regulation of tissue factor procoagulant activity and functions as a receptor for angiogenic peptides via a mechanism independent of the VEGF receptor. Cell surface GRP78 is found associated with such diverse proteins as the voltage-dependent anion channel (VDAC), the major histocompatibility complex class I (MHC-I), the teratocarcinoma-derived growth factor I (Cripto), and the DnaJ-like protein MTJ-1. These associations suggest a unique GRP78 cell surface topography, which appears to be compartmentalized to respond differently to agonists that bind to its N- or C-terminal domains. Here, we discuss the significance of these associations, and the possible mechanisms involved in the transportation of GRP78 from the cytosol to the cell surface. *Antioxid. Redox Signal.* 11, 2299–2306.

## Introduction

GRP78, a well-characterized endoplasmic reticulum (ER) chaperone that belongs to the heat-shock protein (HSP) family, is present in all cells and plays an important role in maintaining cellular homeostasis (18, 23). The primary functions of GRP78 are related to its capacity to bind to hydrophobic patches on nascent polypeptides in the ER and its role as one of the initial components of the signaling cascade that produces the unfolded protein response (UPR) (27, 30). Although best known as an ER luminal protein, GRP78 is also found on the cell plasma membrane where it functions as a cell surface signaling receptor for activated $\alpha_2$-macroglobulin ($\alpha_2$M*) (34, 35, 68).

Cell-surface GRP78 is a major autoantigen in prostate (33), ovarian (9), and gastric cancer patients (46), and participates in several physiologic processes that include inhibition of tissue factor (TF) procoagulant activity (1, 61), and angiogenesis on endothelial cells (17). It is also found associated with the major histocompatibility complex class I (MHC-1) and is a receptor for coxsackie A9 virus (59, 60) and dengue virus serotype 2 (20) on the cell surface. It is a receptor for plasminogen kringle 5 (K5) and microplasminogen (14) and is found associated to cell surface voltage-dependent anion channel (VDAC) (14).

Autoantibodies against GRP78 isolated from cancer patient sera show different affinities and functions. For example, an anti-GRP78 IgG from the serum of prostate cancer patients, which binds to an N-terminal region of GRP78, enhances cell survival and proliferation (13). However, a mouse monoclonal IgG against the amino acid sequence KDEL, in the C-terminal region of GRP78, inhibits cellular proliferation and induces apoptosis (44). Conversely, a human monoclonal GRP78 antibody against a region in the last C-terminal 20 amino acid residues does not affect cell proliferation or induces apoptosis (19). In contrast, a serum monoclonal anti-GRP78 IgM antibody isolated from gastric cancer patients recognizes an O-linked carbohydrate moiety in GRP78 and induces apoptosis in tumor cells (46).

In cancer cells, adaptation to chronic stress in the tumor microenvironment includes enhanced expression of GRP78 on the cell surface, which helps the tumor to evade immune surveillance while increasing its resistance to apoptosis and tolerance to a wide variety of therapies (26, 27). As discussed above, cell surface GRP78 acts as a receptor or target for a large number of agonists and antibodies. Different physiological responses may occur depending on whether GRP78 is engaged at the N- or C-terminus. In order to perform such diverse functions, the topography of GRP78 on the cell surface must be conditioned to respond to these agonists via specific

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pathways controlling the expression of GRP78. In this review, we describe some of the possible mechanisms involved.

## The Stress Response and GRP78 Function on the Cell Surface

GRP78 induction plays a critical role in maintaining cell viability against several kinds of stress, including ER $Ca^{2+}$ depletion and accumulation of unglycosylated proteins. ER stress can be chemically induced by agents that inhibit the glycosylation of newly synthesized proteins or by agents that induce ER $Ca^{2+}$ depletion (41, 57, 58). One study using prostate cancer cell lines demonstrated that both the calcium ionophore ionomycin (IM) and the glycosylation inhibitor tunicamycin (TM) induce GRP78 expression (41). However, induction of GRP78 and apoptosis was only observed in response to IM which produces ER $Ca^{2+}$ depletion, but not in response to inhibition of protein glycosylation, suggesting the presence of at least two different pathways mediating the GPR78 stress response.

Thapsigargin (TG), an inhibitor of the ubiquitous sarcoendoplasmic reticulum $Ca^{2+}$-ATPases, also induces the expression of GRP78 (5). Inhibition of the reticulum $Ca^{2+}$-ATPases leads to the depletion of intraluminal $Ca^{2+}$ and a concurrent increase of cytosolic free calcium $Ca^{2+}$ ($[Ca^{2+}]_c$) (57, 58), which plays a critical role in the TG-induced ER stress mechanism (67). Although IM and TG function via different mechanisms, they both induce depletion of $Ca^{2+}$ from ER stores.

The unfolded protein response (UPR) is initiated by a sensitization of the proteins accumulated in the ER lumen to the transmembrane protein kinase/endoribonuclease Ire1($\alpha$), the activating transcription factor 6 (ATF6), and the endoplasmic reticulum resident kinase (PERK) (21, 22). Ire1 generates spliced mRNA of the X-box binding protein (XBP1) using its RNase activity, and then the XBP1 protein upregulates the expression of GRP78 (21, 22). ATF6 is cleaved by site 1 protease (S1P) and site 2 protease (S2P) to generate a p50ATF6 fragment that has transcriptional activity. Upon cleavage, the p50ATF6 fragment upregulates the expression of GRP78 through an ER stress response element (ERSE) found in the promoter region of the GRP78 gene (21, 22). PERK has a kinase domain which phosphorylates the translational factor eIF2$\alpha$, thereby suppressing most of the *de novo* protein synthesis during ER stress but stimulating the translation of certain mRNAs, including ATF4 (21, 22). All of these processes are necessary to attentuate the accumulation of unfolded proteins during ER stress, especially Ire1 and ATF6 that are critical in the prevention of ER stress-induced apoptosis via upregulation of GRP78 expression (66).

The role of GRP78 in the prevention of apoptosis was indirectly confirmed in a study using nicotine as an antagonistic agent of the ER stress induced by TM and TG (50). As explained above, induction of GRP78 and apoptosis is only observed in response to ER $Ca^{2+}$ depletion, but not in response to inhibition of protein glycosylation. Since nicotine inhibits expression of GRP78 in TM-treated cells, but not in TG-treated cells, the activation of pro-apoptotic caspase-12 was inhibited by nicotine only in TM-treated cells, but not in TG-treated cells (50). The protective effect of nicotine is mediated by a calcium influx activation of the PI 3-kinase/Akt-mediated pathway (50). Nicotine also suppressed the TM-induced, but not TG-induced, splicing of XBP1 mRNA or production of cleaved ATF6 in PC12 cells (50), suggesting that nicotine halts TM-induced ER stress-mediated apoptosis via mechanisms closely related to the activation of the IRE1-XBP1 and ATF6 pathways, and this protective effect does not occur in TG-treated cells. Nicotine suppresses a common and weak step upstream of both the Ire1-XBP1 and ATF6 pathways which are required for the expression for GRP78 in TM-treated PC12 cells via mechanisms not yet determined (50), but does not affect it in TG-treated PC12 cells (50). This common step may be closely related to the accumulation of unfolded proteins in the ER during ER stress (50). The contribution of caspase-12 to the progression of ER stress induced apoptosis is only marginal in these cells (50). That explains why nicotine completely downregulates the activation of caspase-12 in PC12 cells, while weakly suppressing the TM-induced expression of GRP78 (50).

All these studies help to clarify why GPR78 on the cell surface responds to a2M* in ways that resemble those observed in cells undergoing ER stress (34, 37). First, binding of a2M* to GRP78 initiates a signaling cascade which results in an increase of $[Ca^{2+}]_c$ and IRE1$\alpha$, ATF6, and PERK expression (39). Also, eIF2$\alpha$ phosphorylation occurs which would inhibit protein synthesis as observed in the UPR (39). ATF4 is also upregulated, leading to GADD34 upregulation which later restores protein synthesis through inhibition of eIF2$\alpha$ (39). In contrast to what is observed in the UPR, $\alpha_2$M*-induced upregulation of IRE1$\alpha$, the apoptosis signal-regulating kinase 1 (ASK1), and the TNF receptor associated factor 2 (TRAF2) does not promote an increase in the c-Jun N-terminal kinase (JNK) or caspase-12 activation which lead to apoptosis (39). The induction of Akt, which phosphorylates and inactivates ASK1 and NF-$\kappa$B, upregulates the growth arrest and DNA-damage inducible factor beta (GADD45$\beta$) and inhibits JNK, thereby blocking the pro-apoptotic signaling expected from activation of UPR proteins (39). In the ER, GRP78 and its partners IRE1$\alpha$, ATF6, and PERK span the ER membrane to facilitate signal transduction, but they are known to affect phosphatidylinositol-3-kinase (PI 3-kinase) or downstream Akt phosphorylation and NF-$\kappa$B induction. However, cell surface GRP78 forms a complex with the ER membrane DnaJ-like protein MTJ-1 and the G-protein-alpha-11 (G$\alpha$q11) which facilitates through PI 3-kinase/Akt pathways as well as NF-$\kappa$B-dependent mechanisms (38, 40, 63). The result is that plasma membrane GRP78 signaling resembles the signals sent by GRP78 from the ER with the addition of an increase in IP3, Akt phosphorylation, NF-$\kappa$B, and a rise in cytosolic $Ca^{2+}$. The signal transduction cascade components induced by binding of $\alpha_2$M* to GRP78 is summarized in Fig. 1. The net result is an increase in DNA synthesis, protein synthesis, and cellular proliferation.

## Topography of Cell Surface GRP78 Is Critical for its Activity as a Multireceptor

Although several reports identified GRP78 on the cell surface (12, 62), the first evidence that GRP78 exhibits the properties of a transmembrane protein was reported by Reddy *et al.* in 2003 (47). A map showing GRP78 transmembrane domains in CHO cell microsomes predicts a pattern suggesting that both N- and C-terminal regions are localized outside of the membrane (48). This topography was later confirmed by studies on human liver HepG2 cells and hepatocellular carcinoma tissue (8, 20). This model reveals that

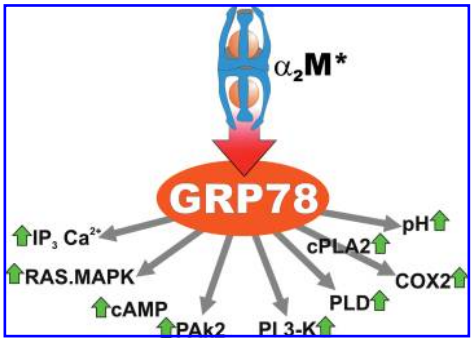


**FIG. 1. Signal transduction cascade components induced by binding of $\alpha_2$M* to cell-surface GRP78 that result in an increase in DNA synthesis, protein synthesis, and cellular proliferation.** (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

GRP78 contains four hydrophobic domains (I through IV) that may form transmembrane helices (Fig. 2). In this figure we also show the GRP78 regions possibly involved in interactions with several of its ligands and autoantibodies.

Although both the ATP and the peptide binding domains appear to be localized on the extracellular domain of the plasma membrane, there is evidence suggesting that GRP78 functions as a receptor independently from its chaperone activity. For instance, GRP78 on the cell surface inhibits tissue factor procoagulant (TF) activity (61) via physical interaction between the TF extracellular domain and a region localized in the C-terminus of GRP78, distant from either its ATP or peptide binding domain (1).

Also, plasminogen K5 binds to a segment in the N-terminal region of GRP78 and microplasminogen binds to a segment in the C-terminal region of GRP78 (14). A region in microplasminogen including plasminogen amino acid residues $Ser^{759}$–$Phe^{778}$ was identified as the binding segment to GRP78 (14). This segment is homologous to amino acid sequence $Gly^{100}$–$Phe^{119}$ of dengue virus serotype 2 viral protein coat (32). Therefore, a segment in the C-terminal region of GRP78 is the receptor for microplasminogen and dengue virus serotype 2. The peptide CTVALPGGYVRVC, homologous to the plasminogen sequence $Ser^{759}$–$Phe^{778}$ binds to GRP78 on the cell surface and is rapidly internalized via clathrin-mediated endocytosis (24). When conjugated to taxol, this peptide was extremely effective in promoting apoptosis of a human melanoma cell line, thereby demonstrating that the C-terminal region of GRP78 can be used as a target for delivery of peptide–drug conjugates in cancer (29).

Cell surface GRP78 is also an angiogenic receptor on endothelial cells (17). Roy, a 12 amino acid synthetic peptide selected from a phage display library (16), induced *in vitro* angiogenic activity under hypoxic conditions by increasing endothelial cell proliferation, migration, and tube formation (17). This peptide did not induce VEGF receptor gene expression, suggesting a possible VEGF-independent mechanism (16). The angiogenic peptide binds to an N-terminal region of GRP78 (17), thereby suggesting that GRP78-mediated angiogenesis is independent from functions performed by the C-terminal region. Since plasminogen K5 is a potent anti-angiogenic protein (11), and it binds to a site in the N-terminus of GRP78 (14), it is possible that K5 interferes with the binding of proteins normally engaged in angiogenic functions of GRP78.

GRP78 also associates with MHC-I on the cell surface (59). Since GRP78 controls the folding of MHC-I (43), its association involves a site in the peptide binding domain, towards the C-terminus of GRP78. The complex between these two proteins serves as a receptor for coxsackie virus A9, which interacts only with GRP78, followed by internalization via MHC-I-associated endocytosis (60).

GRP78 at the cell surface forms a complex with the teratocarcinoma-derived growth factor I (Cripto) with important functions in vertebrate embryogenesis and the progression of human tumors, since it modulates the signaling of transforming growth factor $\beta$ (TGF-$\beta$) superfamily members by forming complexes with some of these ligands and their respective signaling receptors (54). Formation of the GRP78/Cripto complex does not depend on GRP78 ER chaperone function (54), although it is known that a cysteine-rich CFC domain in Cripto is involved in the interaction (54). As discussed above, GRP78 also functions as a cell surface signaling receptor for $\alpha_2$M* (35, 36, 55, 68).

## Autoimmunity to GRP78

Autoantibodies to GRP78 have been identified in serum from rheumatoid arthritis (2), prostate cancer (32), ovarian (9), and gastric cancer patients (46). The frequently opposite responses of GRP78 to autoantibodies against the N-terminus from prostate cancer (13), the amino acid sequence KDEL on the C-terminus (44), or an IgM from gastric cancer patients, which recognizes an O-linked carbohydrate moiety in GRP78 (46), suggests that the topography of GRP78 on the cell surface is an important factor that modulates its autoimmune response. GRP78 itself does not contain the sequence required for N-linked glycosylation (42). However, using the O-GLYCBASE database provided by SWISS PROT databank (www.expasy.org). we obtained a consensus sequence for the possible

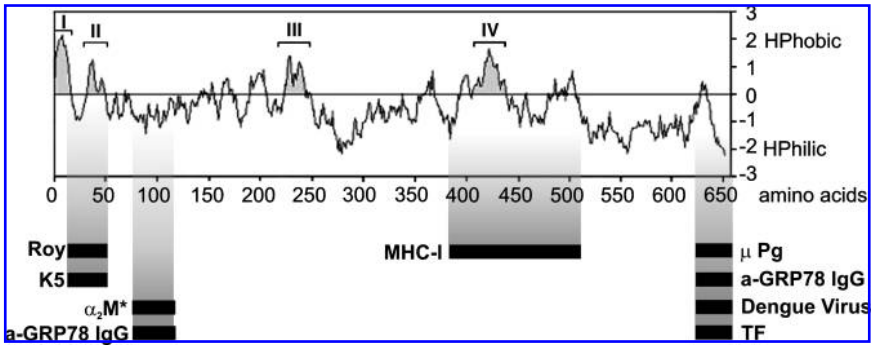


**FIG. 2. Hydropathicity transmembrane model of GRP78 using the Kyte–Doolitle method.** Four putative hydrophobic domains (I–IV) are identified. Represented below are the ligands and antibodies thus far identified, showing the GRP78 amino acid patches involved in these interactions.

O-glycosylation of GRP78. This was the amino acid residue $Thr^{643}$ which is preceded by three proline residues, an amino acid commonly found in sequences close to O-glycosylated serine or threonine residues (65). The amino acid $Thr^{643}$ is localized only 12 amino acid residues upstream from GRP78 C-terminus. Therefore, it is possible to get O-glycosylated GRP78 on the cell surface, but its expression is possibly caused by aberrant glycosylation which is common in cancer cells (15).

We raised a sheep anti-GRP78 polyclonal antibody and purified two IgG populations. The first IgG was similar to the antibody isolated from the serum of prostate cancer patients (13) which recognizes an epitope in the N-terminal region of GRP78, and the second one recognized an epitope in the C-terminal region of GRP78 (13). Both antibodies were tested for their capacity to induce a $Ca^{2+}$ signaling cascade in human prostate 1-LN cells. The antibody against the N-terminal region induced a rise in cytosolic $Ca^{2+}$ which increased for 200 s reaching a peak which gradually decreased thereafter (Fig. 3A), whereas the antibody against the C-terminal region induced a rise in cytosolic $Ca^{2+}$ which increased for 200 s reaching a constant plateau which did not change for up to 300 s (Fig. 3B). To generate different signals, both GRP78 N- or C-terminal regions must be part of separate signaling compartments, readily available to the different autoantibodies. A section of a human prostatic intraepithelial neoplasma (PIN) high grade was stained with the anti-GRP78 IgGs against the N-terminal (Fig. 4A) or the C-terminal regions (Fig. 4B). Both sections demonstrate diffuse staining with the antibodies, thereby confirming the availability of both GRP78 region on the cell surface.

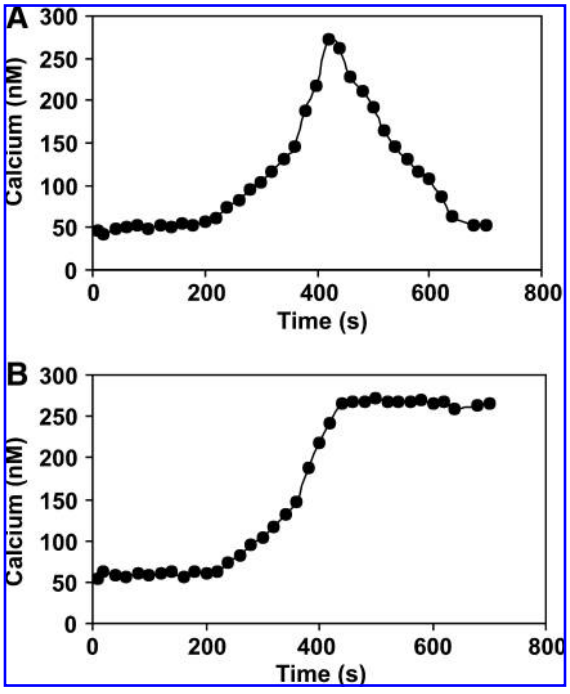


**FIG. 3. (A) Changes in intracellular $Ca^{2+}$ of human prostate cancer 1-LN cells exposed to a sheep anti-GRP78 IgG specific for an epitope in the N-terminal region of GRP78.** (**B**) Changes in intracellular $Ca^{2+}$ of human prostate cancer 1-LN cells exposed to a sheep anti-GRP78 IgG specific for an epitope in the C-terminal region of GRP78.

An explanation for the development of autoimmunity to GRP78 in humans can be obtained from animal models. There is evidence suggesting that spreading of humoral autoimmunity from Ro ribonucleoproteins to GRP78 occurs in mice immunized with Ro52 and Ro60 (25). These studies demonstrated the association of GRP78 to a carboxy-terminal region of Ro52 in apoptotic cell membrane blebs. This study was repeated immunizing mice with GRP78 or Ro52 and demonstrated reciprocity in the intermolecular spreading of B cell immunity between Ro52 and GRP78 (45). Humans suffering from two systemic rheumatic diseases, systemic lupus erythematosus and Sjögren's syndrome, show elevated levels of anti-Ro60 autoantibodies (6), but a correlation between these antibodies and autoimmunity to GRP78 remains to be determined.

However, a correlation between the regression of tumors and immunity against heat shock proteins is known (56).

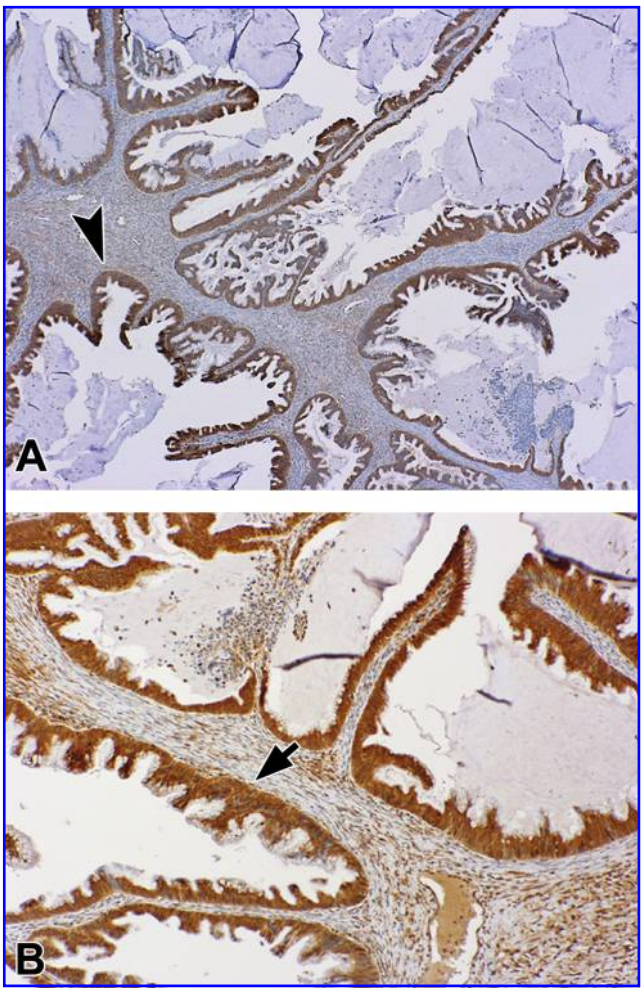


**FIG. 4. Prostatic intraepithelial neoplasm (PIN) high grade.** (**A**) Immunostaining of a PIN tissue section with a sheep anti-GRP78 IgG specific for an epitope on its N-terminal region showing diffuse expression of GRP78 (*arrow*). (**B**) Immunostaining of a PIN section with a sheep anti-GRP78 specific for an epitope on its C-terminal region showing a diffuse reactivity (*arrow*), as observed above. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

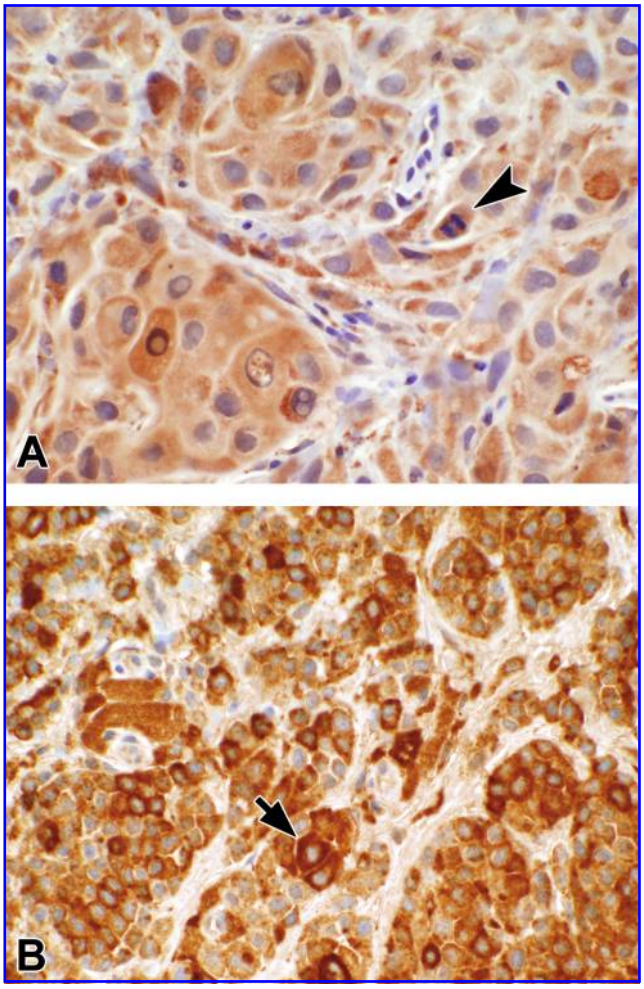


**FIG. 5. Immunohistological analyses of sections of invasive nests of malignant human melanoma.** (**A**) Staining with a sheep anti-GRP78 IgG specific for an epitope in the N-terminal region of GRP78 showing diffuse surface staining with some cells demonstrating a more pronounced perinuclear rim of immunoreactivity. There is a mitotic figure off center to the right (*arrow*). (**B**) Immunostaining of invasive nests of malignant melanoma with a rabbit anti-MTJ1 IGG specific for an epitope in the MTJ1 region comprising amino acids V110AIYEVLKDDERRQRYDDIL129 showing high expression of MTJ-1. There is a coarse, diffuse cytoplasmic staining (*arrow*). The nuclei are negative. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

These studies demonstrate that autoimmunity against tumor-derived heat shock proteins protect the host from fatal tumor loads. However, in prostate cancer patients an enhanced immune response against GRP78 increases tumor growth and metastases, and diminishes overall patient survival (33).

To understand this paradox, it will be necessary to understand how expression of GRP78 may assist the tumor cells to evade immune surveillance. One mechanism may involve the association of GRP78 with MHC-I on the cell surface (60). Expression of GRP78 on the surface is not dependent on MHC-I, because in its absence GRP78 expression is upregulated (60). In the absence of functional MHC-I, GRP78 is still expressed on the cell surface in increased amounts, possibly acting as an alternative antigen-presenting structure, compensating for the loss of MHC-I molecules (60).

MHC-I downregulation is a widespread mechanism used by tumor cells to evade immune surveillance (4, 29, 31, 52, 53). Alterations in the expression of GRP78 may have important implications for MHC-I assembly, peptide loading, and presentation on the tumor cell surface and may be involved in the failure of the immune system to control tumor progression. The downregulation of MHC-I expression in cells overexpressing GRP78 not only protects the tumor cell from immune surveillance, but is also related to its capacity to initiate the signal transduction cascade discussed above. Association of GPR78 with MTJ-1 appears to be critical for this function, and a possible explanation for the appearance of such a protein complex on the cell surface can be inferred from studies using TG (22). The depletion of $Ca^{2+}$ stores in normal cells by TG abolishes the retention of the KDEL-containing GRP78, and results in the appearance of the protein in the surface or the cell culture medium before inducing its synthesis (64). GRP78 is normally associated with the DnaJ protein P58 (IPK) in the ER (49). TG-treated cells showed the GRP78 was transported from the Golgi to p58-containing pre-Golgi intermediate compartment (IC), but was not transported further to the ER. Similarly, p58 that normally cycles between the ER, IC, and cis-Golgi, was largely depleted from the cell periphery and arrested in large-sized IC elements and numerous vesicles in the Golgi region, demonstrating that TG selectively blocks p53 recycling from the IC back to the ER (64). Therefore, the depletion of ER-$Ca^{2+}$ induced by stress signaling facilitates dissociation of GRP78 from p58. At this point GRP78 possibly forms a complex with MTJ-1 (38), a different member of the DnaJ-like protein

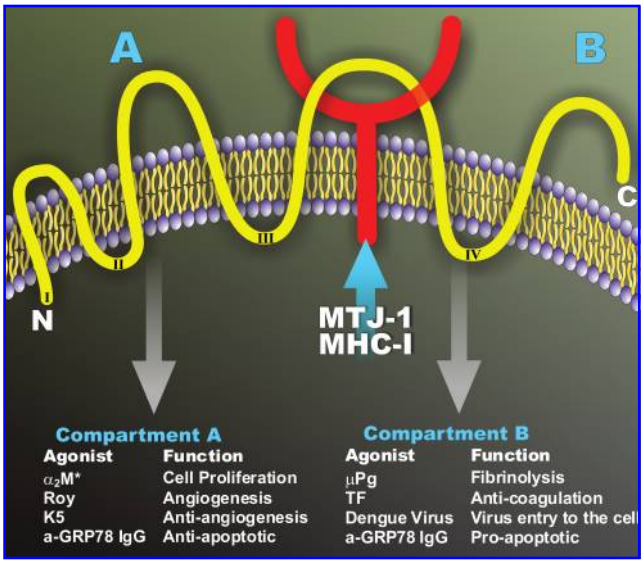


**FIG. 6. Model of GRP78 inserted in the cell surface membrane, with its four hydrophobic domains and its two compartments (A) and (B), displaying their known agonists and functions.** The function of these compartments would be determined by the co-chaperones MTJ-1 or MHC-I. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

family, which binds to a site upstream from its KDEL, C-terminus (7). This association presumably facilitates localization of GRP78 at the cell surface in conjunction with Gαq11 and facilitates signaling through PI 3-kinase, Akt, and NF-κB (38, 40, 63). Tissue sections from invasive nests of a human malignant melanoma were stained with an antibody against the N-terminal region of GRP78 (Fig. 5A) and an antibody against the MTJ-1 region comprising amino acids $V^{110}$ AIYEVLKDDERRQRYDDIL129 (Fig. 5B), showing that the GRP78 and MTJ-1 are not only present in highly metastatic human prostate 1-LN cells (67), but they also appear in malignant melanoma.

As discussed above, the topography of cell surface GRP78 adapted to function as a signaling receptor also seems to affect its immunogenicity. This is the case in prostate cancer patients who show high titers of an IgG that binds to the N-terminal region of GRP78 (13). This antibody recognizes a tertiary structure motif containing the amino acid sequence CNVKSDKC (33). This arrangement is contained within the linear GRP78 primary amino acid sequence $L^{98}$IGRTWND PSVQQDIKFL$^{115}$ (13). This antibody induces proliferation of several human prostate, breast, and melanoma cancer cell lines, protecting these cells from apoptosis via mechanism mimicking the function of $\alpha_2$M* (13). In addition to increasing its antigenic properties, cell surface GRP78 topography also appears to condition its physiological responses, as suggested by the different cytosolic $Ca^{2+}$ wave patterns induced by antibodies against its N- or C-terminal regions.

In summary, expression of GRP78 on the cell surface is adapted for critical functions related to UPR in the normal cell. However, alterations in the pathway of trafficking towards the cell surface, as those observed in tumor cells, may induce changes in its structural topography, thus converting GRP78 into a receptor with additional functions not observed in the ER-linked chaperone. Changes in the surface topography of normal cells occur during their transformation to malignant cells (3), as a result of alterations in the expression of membrane proteins (48). Examples of these changes are the reappearance in the expression of membrane fetal proteins (51) and alterations in the tertiary structure of cell-surface antigens induced by aberrant glycosylation (15). These changes have been also correlated with tumor progression, metastasis, and low patient survival rates (10), as is observed with GRP78 cell-surface expression in prostate cancer (33). It is clear from the evidence described above that the responses of GRP78 on the cell surface are channeled via two compartments, as demonstrated by the ability of the N- or C-terminal anti-GRP78 antibodies to induce different calcium signaling waves. In a hypothetical model (Fig. 6), we show GRP78 inserted in the cell surface membrane, with its four hydrophobic domains and its two compartments (A and B), displaying some of their agonists and their functions. The function of these compartments would be determined by the co-chaperones MTJ-1 or MHC-I, which bind to areas equidistant from either the N- or C-terminal regions of GRP78. When GRP78 is co-expressed with MHC-I, the C-terminal region of GRP78 may be recognized as an autoantigen by the immune surveillance, being the target of autoantibodies which ultimately induce apoptosis. When GRP78 is co-expressed with MTJ-1, the molecule evades the immune surveillance and becomes a multifunctional receptor whose functions include protection from apoptosis, stimulation of cell proliferation, control of coagulation, and regulation of angiogenesis. The association between GRP78 and MTJ-1 would make also possible the internalization of dengue virus via a binding site specific for microplasminogen (14) in the C-terminal or the GRP78 receptor. Since GRP78 acts primarily as a protective molecule, the evidence suggests that the cell surface GRP78-MTJ-1 complex may play a major role in all these functions.

## References


1. Bhattacharjee G, Ahamed J, Pedersen B, El–Sheikh A, Mackman N, Ruf W, Liu C, and Edgington TS. Regulation of tissue factor–mediated initiation of the coagulation cascade by cell surface grp78. *Arterioscler Thromb Vasc Biol* 25: 1737–1743, 2005.
2. Bodman–Smith MD, Corrigal VM, Berglin E, Cornell HR, Tzioufas AG, Mavragani CP, Chan C, Rantapää–Dahlqvist S, and Panayi G. Antibody response to the human stress protein BiP in rheumatoid arthritis. *Rheumatology* 43: 1283–1287, 2004.
3. Boon T, Old LJ. Cancer tumor antigens. *Curr Opin Immunol* 9: 681–683, 1997.
4. Chang CC, Campoli M, and Ferrone S. HLA class I antigen expression in malignant cells: Why does it not always correlate with CTL-mediated lysis? *Curr Opin Immunol* 16: 644–650, 2004.
5. Chen LY, Chiang AS, Hung JJ, Hung HI, and Lai YK. Thapsigargin-induced GRP78 expression is mediated by the increase of cytosolic free calcium in 9L rat brain tumor cells. *J Cell Biochem* 78: 404–416, 2000.
6. Chen X and Wolin SL. The Ro60 kDa autoantigen: Insights into cellular function and role in autoimmunity. *J Mol Med* 82: 232–239, 2004.
7. Chevalier M, Rhee H, Elguindi EC, and Blond S. Interaction of murine BiP/GRP78 with the DnaJ homologue MTJ1. *J Biol Chem* 275: 19620–19627, 2000.
8. Chignard N, Shang S, Wang H, Marrero J, Brechot C, Hanash S, and Beretta L. Cleavage of endoplasmic reticulum proteins in hepatocellular carcinoma: Detection of generated fragments in patient sera. *Gastroenterology* 130: 2010–2022, 2006.
9. Chinni SR, Falchetto R, Gercel-Taylor C, Chabanowitz J, Hunt DF, and Taylor DD. Humoral immune responses to cathepsin D and glucose-regulated protein 78 in ovarian cancer patients. *Clin Cancer Res* 3: 1557–1564, 1997.
10. Cianfrocca M and Goldstein LJ. Prognostic and predictive factors in early stage breast cancer. *Oncologist* 9: 606–616, 2004.
11. Davidson DJ, Haskell C, Majest S, Kherzai A, Egan DA, Walter KA, Schneider A, Gubbins EF, Solomon L, Chen Z, Lesniewski R, and Henkin J. Kringle 5 of human plasminogen induces apoptosis of endothelial and tumor cells through surface-expressed glucose-regulated protein 78. *Cancer Res* 65: 4663–4672, 2005.
12. Delpino A and Castelli M. The 78 kDa glucose-regulated protein (GRP78/BIP) is expressed on the cell membrane, is released into cell culture medium and is also present in human peripheral circulation. *Biosci Rep* 22: 407–420, 2002.
13. Gonzalez–Gronow M, Cuchacovich M, Llanos C, Urzua C, Gawdi G, and Pizzo SV. Prostate cancer cell proliferation in vitro is modulated by antibodies against glucose-regulated protein 78 isolated from patient serum. *Cancer Res* 66, 11424–11431, 2006.
14. Gonzalez–Gronow M, Kaczowka SJ, Payne S, Wang F, Gawdi G, and Pizzo SV. Plasminogen structural domains exhibit different functions when associated with cell surface

GRP78 or the voltage-dependent anion channel. *J Biol Chem* 282: 32811–32820, 2007.
15. Hakomori S. Tumor-associated carbohydrate antigens defining tumor malignancy: basis for development of anticancer vaccines. *Adv Exp Med Biol* 491: 369–402, 2001.
16. Hardy B, Raiter A, Weiss C, Kaplan B, Tenebaum A, and Battler A. Angiogenesis induced by novel peptides selected from a phage display library by screening human vacuolar endothelial cells under different physiological conditions. *Peptides* 3: 691–701, 2000.
17. Hardy B, Battler A, Weiss C, Kudasi O, and Raiter A. Therapeutic angiogenesis of mouse hind limb ischemia by novel peptide activating GRP78 receptor on endothelial cells. *Biochem Pharmacol* 75: 891–899, 2008.
18. Henderson LM. The ER chaperone BiP is a master regulator of ER function. *Mt Sinai J Med* 71: 289–297, 2004.
19. Jakobsen CG, Rasmussen N, Laenkholm AV, Ditzel HJ. Phage display-derived human monoclonal antibodies isolated by binding to the surface of the live primary breast cancer cells recognize GRP78. *Cancer Res* 67:9507–9517, 2007.
20. Jindadamrongwech S, Thepparit C, and Smith DR. Identifications of GRP78 (BiP) as a liver cell expressed receptor element for dengue virus serotype 2. *Arch Virol* 149: 915–927, 2004.
21. Kaufman RJ. Stress signaling from the lumen of the endoplasmic reticulum: Coordination of gene transcriptional and translational controls. *Genes Dev* 13: 1211–1233, 1999.
22. Kaufman RJ. Orchestrating the unfolded protein response in health and disease. *J Clin Invest* 110: 1389–1398, 2002.
23. Kiang JG and Tsokos GC. Heat shock protein 70kDa: molecular biology, biochemistry, and physiology. *Pharmacol Ther* 80: 183–201, 1998.
24. Kim Y, Lillo AM, Steiniger SC, Liu Y, Ballatore C, Anichini A, Mortarini R, Kaufmann GF, Zhou B, Felding-Habermann B, and Janda KD. Targeting heat shock proteins on cancer cells: Selection, characterization, and cell-penetrating properties of a peptidic GRP78 ligand. *Biochemistry* 45: 9434–9444, 2006.
25. Kinoshita G, Purcell AW, Keech CL, Farris AD, McCluskey J, and Gordon TP. Molecular chaperones are targets of autoimmunity in Ro(SS-A) immune mice. *Clin Exp Immunol* 115: 268–274, 1999.
26. Lee AS. Mammalian stress response: Induction of the glucose-regulated protein family. *Curr Opin Cell Biol* 4: 267–273, 1992.
27. Lee AS. The glucose-regulated proteins: Stress induction and clinical applications. *Trends Biochem Sci* 26: 504–510, 2001.
28. Lee AS. GRP78 induction in cancer: T andprognostic implications. *Cancer Res* 67: 3496–3499, 2007.
29. Liu Y, Steiniger SC, Kim Y, Kaufmann GF, Felding–Habermann B, and Janda KD. Mechanistic studies of a peptide GRP78 ligand for cancer cell-specific drug delivery. *Mol Pharm* 4: 435–447, 2007.
30. Ma Y and Henderson LM. The role of the unfolded protein response in tumor development: Friend or foe? *Nat Rev Cancer* 4: 966–977, 2004.
31. Marincola FM, Jafee EM, Hicklin DJ, and Ferrone S. Escape of human solid tumors from T-cell recognition: Molecular mechanisms and functional significance. *Adv Immunol* 74: 181–273, 2000.
32. Markoff LJ, Innis BL, Houghten R, and Henchal LS. Development of cross-reactive antibodies to plasminogen during the immune response to dengue virus infection. *J Infect Dis* 164: 294–307, 1991.
33. Mintz PJ, Kim J, Do KA, Wang X, Zinner RG, Cristofanilli M, Arap MA, Hong WK, Troncoso P, Logothetis CJ, Pasqualini R, and Arap W. Fingerprinting the circulating repertoire of antibodies from cancer patients. *Nat Biotechnol* 21: 57–63, 2003.
34. Misra UK, Chu CT, Gawdi G, and Pizzo SV. Evidence for a second a2-macroglobulin receptor. *J Biol Chem* 269: 12541–12547, 1994.
35. Misra UK, Gonzalez–Gronow M, Gawdi G, Hart JP, Johnson CE, and Pizzo SV. The role of GRP78 in alpha-2-macroglobulin induced signal transduction. Evidence from RNA interference that the low density lipoprotein receptor-related protein is associated with but not necessary for GRP78-mediatedsignal transduction. *J Biol Chem* 277: 42082–42087, 2002.
36. Misra UK, Gonzalez–Gronow M, Gawdi G, Wang F, and Pizzo SV. A novel receptor function for the heat shock protein GRP78: Silencing of GRP78 gene expression attenuates alpha-2M*-induced signaling. *Cell Signal* 16: 929–938, 2004.
37. Misra UK and Pizzo SV. Potentiation of signal transduction mitogenesis and cellular proliferation upon binding of receptor-recognized forms of a2-macroglobulin to 1-LN prostate cancer cells. *Cell* 16: 487–496, 2004.
38. Misra UK, Gonzalez–Gronow M, Gawdi G, and Pizzo SV. The role of MTJ-1 in cell surface translocation of GRP78, a receptor for a2-macroglobulin-dependent signaling. *J Immunol* 174; 2092–2097, 2005.
39. Misra UK, Deedwania R, and Pizzo SV. Activation and crosstalk between Akt, NF-kappB, and unfolded protein response signaling in 1-LN prostate cancer cells consequent to ligation of cell-surface GPR78. *J Biol Chem* 281: 13694–13707, 2006.
40. Misra UK and Pizzo SV. Heterotrimeric Galpha11 co-immunoprecipitates with surface-anchored GRP78 from plasma membranes of alpha-2M*-stimulated macrophages. *J Cell Biochem* 104: 96–104, 2008.
41. Miyake H, Hara I, Arakawa S, and Kamidono S. Stress protein GRP78 prevents apoptosis induced by calcium ionophore, ionomycin, but not by glycosylation inhibitor, tunicamycin, in human prostate cancer cells. *J Cell Biochem* 77: 396–408, 2000.
42. Munro S and Pelham HRB. An Hsp70-like protein in the ER: Identity with the 78 kd glucose-regulated protein and immunoglobulin heavy chain binding protein. *Cell* 46: 291–300, 1986.
43. Paulsson KM, Wang P, Anderson PO, Chen S, Petterson RF, and Li S. Distinct differences in association of MHC Class I with endoplasmic reticulum proteins in wild-type, and beta-2-microglobulin- and TAP-deficient reticulum proteins in wild-type, and beta-2-microglobulin- and TAP-deficient cell lines. *Int Immunol* 13: 1063–1073, 2001.
44. Pizzo SV and Misra UK. Attentuation of mitogenesis and cellular proliferation in 1-LN prostate cancer cells treated with antibodies against GRP78, a surface binding protein of $\alpha_2$M*. *FASEB J* 19: A253, 2005.
45. Purcell AW, Todd A, Kinoshita G, Lynch TA, Keech CL, Gething MJ, and Gordon TP. Association of stress proteins with autoantigens: A possible mechanism for triggering autoimmunity. *Clin Exp Immunol* 132: 193–200, 2003.
46. Rauschert N, Brändlein S, Holzinger E, Hensel F, Muller–Hermelink HK, and Vollmers HP. A new tumor-specific variant of GRP78 as target for antibody-based therapy. *Lab Invest* 88: 375–386, 2008.
47. Reddy R, Mao C, Baumeister P, Austin R, Kaufman RJ, and Lee AS. Endoplasmic reticulum chaperone protein GRP78

protects cells from apoptosis induced by topoisomerase inhibitors. *J Biol Chem* 278: 20915–20924, 2003.
48. Rosenberg SA. Progress in human tumor immunology and immunotherapy. *Nature* 411: 380–384, 2001.
49. Rutkowski DT, Kang SW, Goodman AG, Garrison JL, Taunton J, Katze MG, Kaufman RJ, and Hedge RS. The role of p58IPK in protecting the stressed endoplasmic reticulum. *Mol Biol Cell* 18: 3681–3691, 2007.
50. Sasaya H, Utsumi T, Shimoke K, Nakayama H, Matsumura Y, Fukunaga K, and Ikeuchi T. Nicotine suppresses tunicamycin-induced, but not thapsigargin-induced expression of GRP78 during ER stress-mediated apoptosis in PC12 cells. *J Biochem* 144: 251–257, 2008.
51. Scanlan MJ, Gure AO, Jungbluth AA, Old J, and Chen YT. Cancer/testis antigens: an expanding family of targets for cancer immunotherapy. *Immunol Rev* 188: 22–32, 2002.
52. Seliger B, Maeurer MJ, and Ferrone S. Antigen-processing machinery breakdown and tumor growth. *Immunol Today* 21: 455–464, 2000.
53. Seliger B, Atkins D, Bock M, Ritz U, Ferrone S, Huber C, and Storkel S. Characterization of human lymphocyte antigen class I antigen-processing machinery defects in renal cell carcinoma lesions with special emphasis on transporter-associated with antigen-processing down-regulation. *Clin Cancer Res* 9: 1721–1727, 2003.
54. Shani G, Fischer WH, Justice NJ, Kelber JA, Vale W and Gray PC. GRP78 and Cripto form a complex at the cell surface and collaborate to inhibit transforming growth factor $\beta$ signaling and enhance cell growth. *Mol Cell Biol* 28: 666–677, 2008.
55. Shen X, Zhangh K, and Kaufman RJ. The unfolded protein response: stress signaling pathway of the endoplasmic reticulum. *J Chem Neuoroanat* 28: 79–92, 2004.
56. Tamura Y, Peng P, Liu K, Daou M, and Srivastava PK. Immunotherapy of tumors with autologous tumor-derived heat shock protein preparations. *Science* 278; 117–120, 1997.
57. Thastrup O, Dawson AP, Scharff O, Foder B, Cullen PJ, Drobak BK, Bjerrum RJ, Christensen SB, and Hanley MR. Thapsigargin, a novel molecular probe for studying intracellular calcium release and storage. *Agents Actions* 43: 187–193, 1994.
58. Treman M, Caspersen C, and Christensen SB. A tool coming of age: Thapsigargin as an inhibitor of sarcoplasmic reticulum $Ca^{2+}$-ATPases. *Trends Pharmacol Sci* 19: 131–135, 1998.
59. Triantafilou M, Fradelizi D, and Triantafilou K. Major histocompatibility class one molecule associates with glucose related protein (GRP)78 on the cell surface. *Hum Immunol* 62: 764–770, 2001.
60. Triantafilou K, Fradelizi D, Wilson K, and Triantafilou K. GRP78, a co-receptor for Coxsackie virus A9, interacts with major histocompatibility complex class I molecules which mediate virus internalization. *J Virol* 76: 633–643, 2002.
61. Watson LM, Chan AK, Berry LR, Li J, Sood SK, Dickhout JG, Werstuck GH, Gajzar L, Klamut HJ, and Austin RC. Overexpression of the 78-kDa glucose-regulated protein/immunoglobulin-binding protein (GRP78/BiP) inhibits tissue factor procoagulant activity. *J Biol Chem* 278: 17438–17447, 2003.
62. Xiao G, Chung TF, Pyun HY, Fine RE, and Johnson RJ. KDEL proteins are found on the surface of NG108-15 cells. *Brain Res Mol Brain Res* 72: 121–128, 1999.
63. Xie P, Browning DD, Hay N, Mackman N, and Ye RD. Activation of NF-kappa B by bradykinin through a Galpha(q)- and Gbeta gamma-dependent pathway that involves phosphoinositide 3-kianse and Akt. *J Biol Chem* 275: 24907–24914, 2000.
64. Ying M, Sannerud R, Flatmark T, and Saraste J. Cololocalization of $Ca^{2+}$-ATPase and GRP94 with p58 and the effects of thapsigargin on protein recycling suggests the participation of the pre-Golgi intermediate compartment in intracellular $Ca^{2+}$ storage. *Eur J Cell Biol* 81: 469–483, 2002.
65. Young JD, Tsuchiya D, Sandlin DE, and Holroyde MJ. Enzymatic O-glycosylation of synthetic peptides from sequences in basic protein myelin protein. *Biochemistry* 18: 4444–4448, 1979.
66. Yoshida H, Haze K, Yanagi H, Yura T, and Mori K. Identification of the cis-acting endoplasmic reticulum stress response element responsible for the transcriptional induction of mammalian glucose-regulated proteins. Involvement of basic leucine zipper transcription factors. *J Biol Chem* 273: 33741–33749, 1998.
67. Yoshida I, Monji A, Tashiro K, Nakamura K, Inoue R, and Kanba S. Depletion of intracellular $Ca^{2+}$ store itself may be a major factor in thapsigargin-induced ER stress and apoptosis in PC12 cells. *Neurochem Int* 48: 696–702, 2006.
68. Zhang K, and Kaufman RJ. The unfolded protein response: A stress signaling pathway critical for health and disease. *Neurology* 66: S102–S109, 2006.

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**Abbreviations Used**

$\alpha_2$M* = the activated form of $\alpha_2$-macroglobulin that binds to cellular receptors
$[Ca^{2+}]_c$ = cytosolic free calcium
ER = endoplasmic reticulum
GRP78 = the glucose-regulated protein of 78 kDa
HSP = heat-shock proteins
IM = ionomycin
MHC-I = the major histocompatbility complex class I
MTJ-1 = the ER DnaJ-like protein 1
p58 = the Golgi DnaJ-like protein p58
TG = thapsigargin
TM = tunicamycin
VDAC = the voltage-dependent anion channel

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1. Chao Li, Aki Harada, Youngman Oh. 2012. IGFBP-3 sensitizes antiestrogen-resistant breast cancer cells through interaction with GRP78. *Cancer Letters* **325**:2, 200-206. [CrossRef]
2. Britta Hardy, Annat Raiter, Maxim Yakimov, Alexander Vilkin, Yaron Niv. 2012. Colon cancer cells expressing cell surface GRP78 as a marker for reduced tumorigenicity. *Cellular Oncology* **35**:5, 345-354. [CrossRef]
3. Kenichi Miharada, Göran Karlsson, Matilda Rehn, Emma Rörby, Kavitha Siva, Jörg Cammenga, Stefan Karlsson. 2012. Hematopoietic stem cells are regulated by Cripto, as an intermediary of HIF-1# in the hypoxic bone marrow niche. *Annals of the New York Academy of Sciences* **1266**:1, 55-62. [CrossRef]
4. S Grkovic, V C O'Reilly, S Han, M Hong, R C Baxter, S M Firth. 2012. IGFBP-3 binds GRP78, stimulates autophagy and promotes the survival of breast cancer cells exposed to adverse microenvironments. *Oncogene* . [CrossRef]
5. Ravshan Z. Sabirov, Petr G. Merzlyak. 2012. Plasmalemmal VDAC controversies and maxi-anion channel puzzle. *Biochimica et Biophysica Acta (BBA) - Biomembranes* **1818**:6, 1570-1580. [CrossRef]
6. P. Ribaux, P. Petignat, V. Finci, F. Pelluard Nehmé, D. Carles, O. Irion, M. Epiney, M. Cohen. 2012. Overexpression of GRP78 in complete hydatidiform moles. *Gynecologic Oncology* **125**:3, 580-584. [CrossRef]
7. Francisco R.M. Laurindo, Luciana A. Pescatore, Denise de Castro Fernandes. 2012. Protein disulfide isomerase in redox cell signaling and homeostasis. *Free Radical Biology and Medicine* **52**:9, 1954-1969. [CrossRef]
8. Hui-Ming Chen, Pi-Hsueh Wang, Swey-Shen Chen, Chih-Chun Wen, Yun-Hsiang Chen, Wen-Chin Yang, Ning-Sun Yang. 2012. Shikonin induces immunogenic cell death in tumor cells and enhances dendritic cell-based cancer vaccine. *Cancer Immunology, Immunotherapy* . [CrossRef]
9. B Luo, A S Lee. 2012. The critical roles of endoplasmic reticulum chaperones and unfolded protein response in tumorigenesis and anticancer therapies. *Oncogene* . [CrossRef]
10. Gustaaf G. de Ridder, Rupa Ray, Salvatore V. Pizzo. 2012. A murine monoclonal antibody directed against the carboxyl-terminal domain of GRP78 suppresses melanoma growth in mice. *Melanoma Research* 1. [CrossRef]
11. Yi-Bing Ouyang, Rona G. Giffard. 2012. ER-Mitochondria Crosstalk during Cerebral Ischemia: Molecular Chaperones and ER-Mitochondrial Calcium Transfer. *International Journal of Cell Biology* **2012**, 1-8. [CrossRef]
12. Peter C. Gray, Wylie Vale. 2012. Cripto/GRP78 modulation of the TGF-# pathway in development and oncogenesis. *FEBS Letters* . [CrossRef]
13. Hongdan Li, Huijuan Song, Junsheng Luo, Jia Liang, Song Zhao, Rongjian Su. 2012. Knockdown of glucose-regulated protein 78 decreases the invasion, metalloproteinase expression and ECM degradation in hepatocellular carcinoma cells. *Journal of Experimental & Clinical Cancer Research* **31**:1, 39. [CrossRef]
14. Liu Yang , Mingquan Su , Yueyun Ma , Xiaoke Hao . 2011. Novel Immunohistochemical Monoclonal Antibody Against Human Glucose-Regulated Protein 78. *Hybridoma* **30**:6, 559-562. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
15. Esmaeil Sadroddiny, Arthur Moir, Birgit Helm. 2011. A Proteomics Approach to Study the Molecular Consequence of IgE-Mediated Cell Signaling in RBL-2H3.1 Cells and 2-D Reference Map Preparation for RBL-2H3.1 Cell Line. *Cell Biology International* . [CrossRef]
16. Nitza Goldenberg-Cohen, Annat Raiter, Vera Gaydar, Olga Dratviman-Storobinsky, Tamar Goldstein, Abraham Weizman, Britta Hardy. 2011. Peptide-binding GRP78 protects neurons from hypoxia-induced apoptosis. *Apoptosis* . [CrossRef]
17. Kenichi Miharada, Göran Karlsson, Matilda Rehn, Emma Rörby, Kavitha Siva, Jörg Cammenga, Stefan Karlsson. 2011. Cripto Regulates Hematopoietic Stem Cells as a Hypoxic-Niche-Related Factor through Cell Surface Receptor GRP78. *Cell Stem Cell* **9**:4, 330-344. [CrossRef]
18. S. Wey, B. Luo, C.-C. Tseng, M. Ni, H. Zhou, Y. Fu, D. Bhojwani, W. L. Carroll, A. S. Lee. 2011. Inducible knockout of GRP78/BiP in the hematopoietic system suppresses Pten-null leukemogenesis and AKT oncogenic signaling. *Blood* . [CrossRef]
19. Florence Quesada Calvo, Marianne Fillet, Jenny Renaut, Ce#line Crahay, Maud Gueders, Jonathan Hacha, Genevie#ve Paulissen, Jean-Michel Foidart, Agnes Noel, Natacha Rocks, Pierre Leprince, Didier Cataldo. 2011. Potential Therapeutic Target Discovery by 2D-DIGE Proteomic Analysis in Mouse Models of Asthma. *Journal of Proteome Research* 110803151518014. [CrossRef]
20. Ying Fang, Jingui Mu, Yushui Ma, Duan Ma, Da Fu, Xizhong Shen. 2011. The interaction between ubiquitin C-terminal hydrolase 37 and glucose-regulated protein 78 in hepatocellular carcinoma. *Molecular and Cellular Biochemistry* . [CrossRef]

21. Wen-Chin Weng, Wang-Tso Lee, Wen-Ming Hsu, Bei-En Chang, Hsinyu Lee. 2011. Role of Glucose-regulated Protein 78 in Embryonic Development and Neurological Disorders. *Journal of the Formosan Medical Association* **110**:7, 428-437. [CrossRef]
22. Xiuzhen Fan, Jianling Wang, Kizhake V. Soman, G.A.S. Ansari, M. Firoze Khan. 2011. Aniline-induced nitrosative stress in rat spleen: Proteomic identification of nitrated proteins. *Toxicology and Applied Pharmacology* . [CrossRef]
23. T. Winder, P. Bohanes, W. Zhang, D. Yang, D. G. Power, Y. Ning, A. Gerger, P. M. Wilson, L. H. Tang, M. Shah, A. S. Lee, H.- J. Lenz. 2011. GRP78 promoter polymorphism rs391957 as potential predictor for clinical outcome in gastric and colorectal cancer patients. *Annals of Oncology* . [CrossRef]
24. Min Ni, Yi Zhang, Amy S. Lee. 2011. Beyond the endoplasmic reticulum: atypical GRP78 in cell viability, signalling and therapeutic targeting. *Biochemical Journal* **434**:2, 181-188. [CrossRef]
25. Gustaaf de Ridder, Rupa Ray, Uma K. Misra, Salvatore V. PizzoModulation of the Unfolded Protein Response by GRP78 in Prostate Cancer **489**, 245-257. [CrossRef]
26. Britta Hardy, Annat Raiter. 2010. Peptide-binding heat shock protein GRP78 protects cardiomyocytes from hypoxia-induced apoptosis. *Journal of Molecular Medicine* **88**:11, 1157-1167. [CrossRef]
27. Xian-kun Tong, Hong Qiu, Xin Zhang, Li-ping Shi, Gui-feng Wang, Fei-hong Ji, Hui-yong Ding, Wei Tang, Kan Ding, Jian-ping Zuo. 2010. WSS45, a sulfated #-D-glucan, strongly interferes with Dengue 2 virus infection in vitro. *Acta Pharmacologica Sinica* **31**:5, 585-592. [CrossRef]
28. Richard C. Austin . 2009. The Unfolded Protein Response in Health and Disease. *Antioxidants & Redox Signaling* **11**:9, 2279-2287. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]