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GRP78: A Multifaceted Role in Cancer Progression and Infectious Disease Transmission

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Abstract

The 78-kDa glucose-regulated protein GRP78, also known as HSPA5 or BiP, is a heat shock protein 70 family member that promotes functions of the endoplasmic reticulum, such as protein folding and assembly, prevention of aggregation of misfolded proteins, translocation of secreted proteins, and initiation of the unfolded protein response. GRP78 may also be a cancer marker. When small extracellular vesicles containing GRP78 are released from cancer cells, recipient cells exhibit enhanced malignant progression and angiogenesis. Further, GRP78 has a critical role in infectious diseases. For example, GRP78 is thought to be involved in the entry mechanism of SARS-CoV-2, the causative agent of COVID-19, into host cells through the angiotensin-converting enzyme 2. Thus, GRP78 has multifaceted roles. The development of GRP78 inhibitors is now being investigated in the cancer field. Whether these inhibitors will also be effective against infectious diseases, however, remains unclear. Here, we review the functions of GRP78 in cancer and infectious diseases, thereby highlighting the need for further research and development.

Keywords: ACE2, COVID-19, ER stress, Heat shock protein, Isoliquiritigenin, SARS-CoV-2, Spike protein

Introduction

Exposure of cells to glucose starvation significantly increases the synthesis of several proteins called glucose-regulated proteins (GRPs) [1]. GRP78, a 78-kDA GRP that is also known as HSPA5 or BiP, is a member of the heat shock protein 70 family that is involved in protein folding and assembly in the endoplasmic reticulum (ER) [2]. Substrate dissociation and binding by GRP78 promotes diverse functions in the ER, including folding and assembly of nascent proteins, prevention of aggregation of misfolded proteins, translocation of secreted proteins, and initiation of the unfolded protein response [3].

GRP78 has attracted attention in the field of cancer research [4]. Cancer cells communicate through the exchange of small extracellular vesicles (sEVs), which have an approximately 100-nm diameter and are also known as exosomes [5]. sEVs are exchanged in the tumor microenvironment and promote the malignant progression of cancer [6]. In cancer, rapid cell proliferation creates an environment that induces ER stress, such as hypoxia and nutrient starvation [7]. This ER stress response leads to the expression of GRP78. In normal cells, GRP78 is only present in the ER, where it functions as an ER molecular chaperone and ER stress sensor [8]. Cancer cells overexpress GRP78, and, in addition to the ER, it has been observed in the cell membrane, cytoplasm, mitochondria, nucleus, and cell secretions [9]. GRP78 is involved in tumor cell proliferation, resistance to apoptosis, evasion of immune responses, invasion, metastasis, and angiogenesis [7,10]. Overexpression of GRP78 in solid gastric tumors has been reported [11].

GRP78 also plays an important role in infectious diseases, particularly viral infections such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19 [12]. In COVID-19, the spike protein on the viral envelope

binds to angiotensin-converting enzyme receptor 2 (ACE2) on host cells [13]. While ACE2 is expressed in most organs, it is highly prevalent in the pulmonary airway epithelium, where it functions systemically to lower blood pressure. The spike protein is activated by serine protease 2 transmembrane protein on host cells, which facilitates the internalization of viral particles [13]. Viral RNA is then released into the host cytoplasm, from where it travels to host ribosomes to generate new viral particles and infect other cells. A recent study investigating the relationship between GRP78 and COVID-19 through biochemical experiments and genetic analysis using the SARS-CoV-2 spike protein revealed that both cell-surface and secreted GRP78 induced by cell stress bind to the SARS-CoV-2 spike protein and enhance the accumulation of SARS-CoV-2 in cells expressing ACE2 [14].

In this article, we outline the roles of GRP78 in the cancer environment and infection processes.

GRP78 in Cancer

In normal cells, GRP78 localizes to the ER through an ER signal peptide. In cancer cells, however, GRP78 is significantly upregulated and translocate to the mitochondria, nucleus, cytoplasm, and cell surface [15], which may be due to the lack of ER signal peptides in cancer cells. A significantly higher GRP78 expression is reported in most malignant cancers [16]. GRP78 is secreted into the extracellular fluid and contributes to the progression of cancers such as colorectal cancer, lung cancer, gastric cancer, breast cancer, and advanced thymic cancer [17,18]. Previous studies demonstrated that intracellular GRP78 levels are also high in metastatic non-small cell lung cancer cells, contributing to lymph node metastasis and human metastatic lesions [19]. Furthermore, GRP78 expression is significantly upregulated in thyroid cancer, brain low-grade glioma, cholangiocarcinoma, colon adenocarcinoma, esophageal carcinoma, lymphoid tumor diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, rectal adenocarcinoma, prostate adenocarcinoma, gastric adenocarcinoma, thymoma, uterine body endometrial carcinoma, skin cutaneous melanoma, and uterine sarcoma cancers [20-22].

GRP78 secreted onto the cancer cell surface functions as a multifunctional receptor for cell proliferation, survival, chemoresistance, and metastasis [8]. Secreted GRP78 binds to transforming growth factor β1 receptor, epidermal growth factor receptor, or GRP78 present on the cell surface. GRP78 plays important roles both on the surface and in the cytoplasm of cancer cells and may affect the tumor microenvironment [23,24]. Thus, while sEV membrane GRP78 may directly interact with these receptors, sEV luminal GRP78 and membrane-bound GRP78 proteins may have distinct roles in tumorigenesis [25].

GRP78 promotes the tumor microenvironment, leading to angiogenesis **(Figure 1)**. Accurately measuring the GRP78 concentration in sEVs, however, has been challenging. Successful measurement of the GRP78 concentration in sEVs using an ultrasensitive ELISA, however, was recently reported

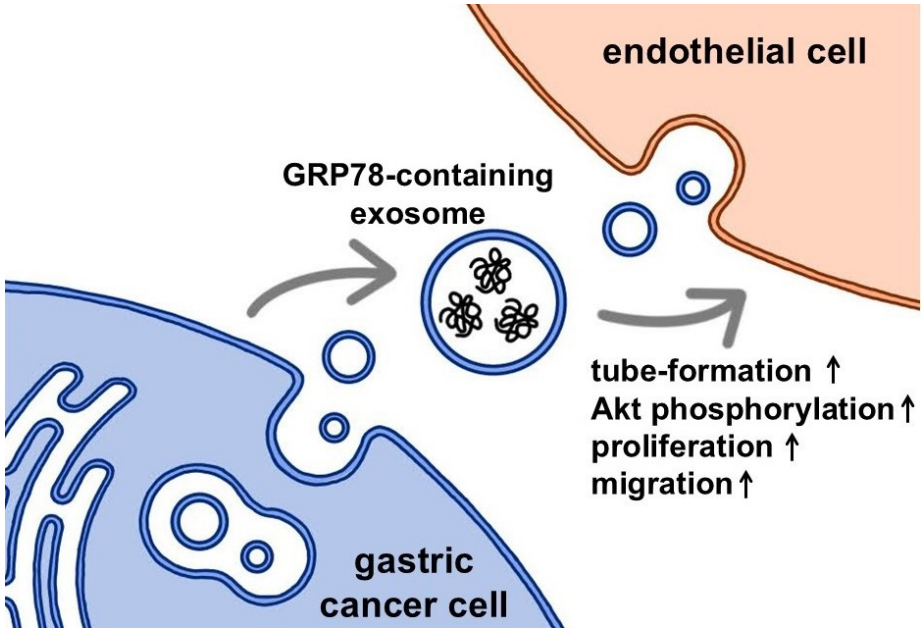

Figure 1. GRP78 in cancer progression. Gastric cancer cells release sEVs (i.e., exosomes) containing GRP78, and endothelial cells that receive them undergo angiogenesis, phosphorylation of AKT, increased proliferation, and increased migration ability [26].

[25]. This method enabled the quantification of the GRP78 concentration in exosomes collected from gastric cancer AGS cells with GRP78 overexpression (OE), GRP78 knockdown (KD), or mock GRP78 (mock). After incubation of these three types of sEVs with vascular endothelial cells, their effects on angiogenesis in vascular endothelial cells were examined. Tube formation assays showed that GRP78-OE exosomes promoted angiogenesis compared with GRP78-KD or GRP78-mock exosomes. To clarify the mechanism of this effect, we investigated the Ser473 phosphorylation state ratio of AKT, which is involved in the angiogenesis process, and found that the application of GRP78-OE exosomes to endothelial cells increased AKT phosphorylation. An MTT assay showed that GRP78-OE exosome treatment increased the proliferation rate of endothelial cells, and a wound healing assay showed that this treatment increased the migration ability of endothelial cells. Together, these findings demonstrated that sEVs containing GRP78 promote the tumor microenvironment and induce angiogenesis [26].

GRP78 in COVID-19

As mentioned above, GRP78 also facilitates SARS-CoV-2 infection by supporting spike protein binding to ACE2 on host cells [13,27]. High expression of GRP78 in malignant tumors may promote the invasion of SARS-CoV-2 [28]. The spike protein, activated by serine protease 2 transmembrane protein on host cells, facilitates viral particle internalization [29], enabling the release of viral RNA into the host cytoplasm for replication and infection of other cells.

In addition, GRP78 appears to be involved in an infection mechanism of COVID-19, in which older age, obesity, and diabetes are risk factors [30,31]. Shin and colleagues examined the relationship between GRP78 and COVID-19 using the spike protein of SARS-CoV-2 and found that both cell-surface and secreted GRP78 induced by cell stress bind to the spike protein of SARS-CoV-2 and enhance the accumulation in cells expressing ACE2 **(Figure 2)** [30,31]. In addition, GRP78 is highly expressed in adipose tissue and is induced in a high insulin environment, which is often seen in aging, obesity, and diabetes. Old age, obesity, and diabetes are known risk factors for increased COVID-19 severity, but the underlying mechanism has not been fully elucidated.

Inhibitors of GRP78

Various approaches targeting GRP78 have been designed to discover and develop potential cancer treatments, including antibodies, peptides, and small molecule inhibitors [32]. Whether these treatments could also be effective therapeutic agents against infectious diseases, especially COVID-19, remains unclear.

Lee *et al.* demonstrated the role of GRP78 in gastric cancer stemness and evaluated GRP78-mediated inhibition of the stemness, regulation of the tumor microenvironment, and promotion of chemotherapy sensitivity by isoliquiritigenin, a bioactive flavonoid found in licorice [33]. Isoliquiritigenin not only suppressed GRP78-mediated gastric cancer stem cell-like properties, expression of stemness-related proteins, and

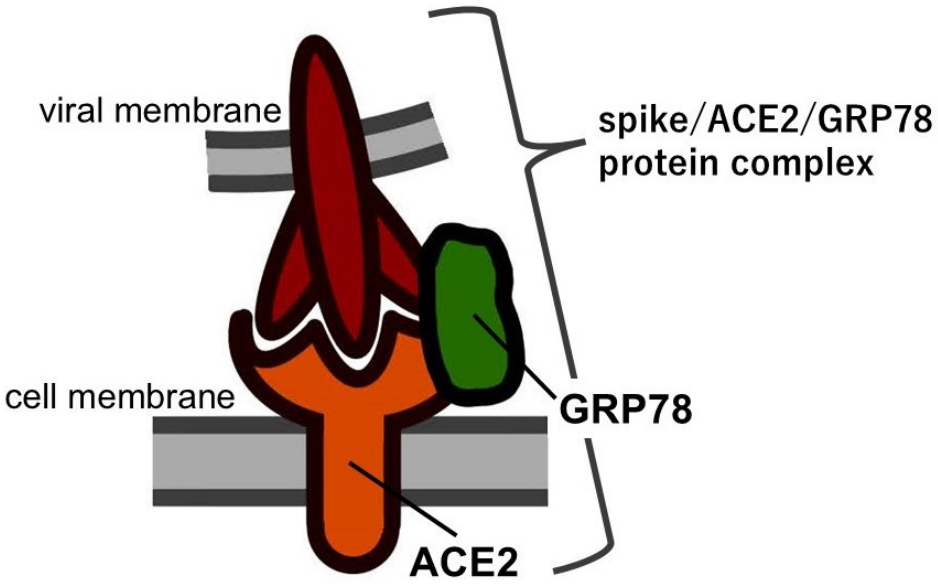

Figure 2. GRP78 in infectious diseases. In COVID-19 infection, GRP78 assists the SARS-CoV-2 spike protein in binding to ACE2 on cells [31].

activation of cancer-associated fibroblasts, but also inhibited gastric tumor growth in xenograft animal studies. This study demonstrated that isoliquiritigenin is a promising candidate for clinical use in combination with chemotherapy.

Discussion

The present article discusses the important roles of GRP78 in cancer progression and COVID-19 infection, and highlights its potential as a therapeutic target. Suppressing GRP78 function might be effective in attenuating the malignant progression of cancer as well as the severity of COVID-19. The bioactive flavonoid isoliquiritigenin inhibits GRP78-mediated gastric cancer stem cell-like characteristics, stemness-related protein expression, and cancer-associated fibroblast activation as well as gastric tumor growth in xenograft animal studies [33].

Given the involvement of GRP78 in many other diseases beyond those discussed here [28], further studies of GRP78 and its mechanisms and functions could unlock new therapeutic strategies, with GRP78 inhibitors offering promising treatment for a wide range of diseases.

Author Contributions

Conceptualization: E.I.; Writing - Original Draft: A.S.; Writing - Review & Editing: E.I.; Funding acquisition: E.I.

Conflicts of Interest

A.S. and E.I. have received honoraria from BioPhenoMA Inc.

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