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Review

Glucose regulated protein 78: A critical link between tumor microenvironment and cancer hallmarks

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ABSTRACT

Glucose regulated protein 78 (GRP78) has long been recognized as a molecular chaperone in the endoplasmic reticulum (ER) and can be induced by the ER stress response. Besides its location in the ER, GRP78 has been found to be present in cell plasma membrane, cytoplasm, mitochondria, nucleus as well as cellular secretions. GRP78 is implicated in tumor cell proliferation, apoptosis resistance, immune escape, metastasis and angiogenesis, and its elevated expression usually correlates with a variety of tumor microenvironmental stresses, including hypoxia, glucose deprivation, lactic acidosis and inflammatory response. GRP78 protein acts as a centrally located sensor of stress, which feels and adapts to the alteration in the tumor microenvironment. This article reviews the potential contributions of GRP78 to the acquisition of cancer hallmarks based on intervening in stress responses caused by tumor niche alterations. The paper also introduces several potential GRP78 relevant targeted therapies.

Contents

1. Introduction

Glucose regulated protein 78 (GRP78), also known as the immunoglobulin heavy chain binding protein (BiP), belongs to the heat shock protein 70 (HSP70) family. GRP78 has a signal peptide sequence which targets it to the endoplasmic reticulum (ER) as a molecular chaperone, involved in proper protein folding and assembly, proteasome degradation of misfolded protein, ER Ca^{2+} binding, and controlling the activation of transmembrane ER stress sensors [1]. GRP78 function is obligatory for early embryonic development. However, in adult animals, deregulation of GRP78 has a causal relationship with neurological disorders as well as tumor progression [2]. Besides being elevated in virally, chemically and radiation transformed cells [3], GRP78 is usually highly induced in poorly perfused solid tumors through ER stress pathway by the microenvironment factors, such as glucose deprivation, hypoxia and acidosis [4].

Solid tumors can be recognized as organs composed of cancerous cells (including cancer stem cells) and non-cancerous cells. The non-cancerous cells include cancer-associated fibroblasts, myofibroblasts, endothelial cells, pericytes, mesenchymal stem cells and immune

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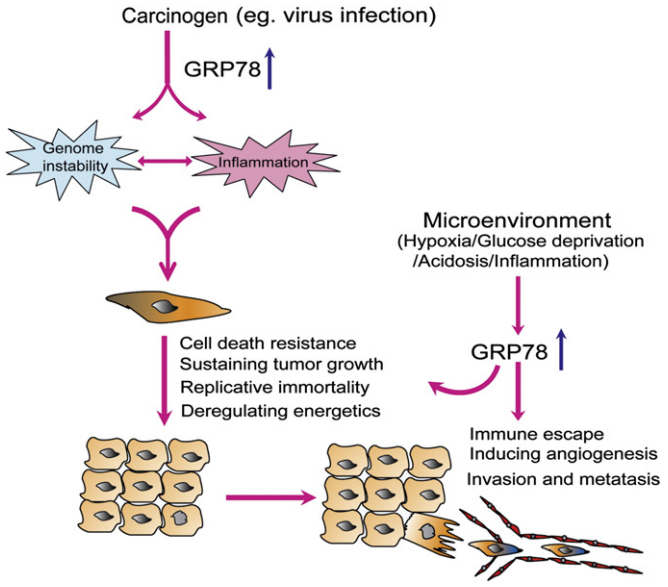

Fig. 1. GRP78 contributes to the acquisition of cancer hallmarks by tumor cells. The development of human cancer is a multistep process, during which tumor cells acquire series of cancer hallmarks. Upon carcinogen stimulus, such as virus infection and chemical carcinogens, the induced GRP78 may promote genome instability and mutation as well as cancer-related inflammation, which may initiate or promote the cell malignant transformation. The proliferation of transformed cells usually excesses the normal blood supply, resulting in the microenvironmental stress, which in turn induces the expression of GRP78 and drives the malignant transformation to acquire additional cancer hallmarks.

inflammatory cells [5–8]. These non-cancerous cells provide important support for cancer cell growth, angiogenesis and metastasis [7,9–11]. Solid tumors often grow faster than their blood supply, and this creates the specific growth conditions characterized by hypoxia, glucose deprivation and lactic acidosis [12]. The cancer-associated stromal cells, immune inflammatory cells and growth conditions of low blood supply together constitute the "tumor microenvironment". The interactions between cancerous cells and tumor microenvironment during the courses of multistep tumorigenesis play a critical role in modulation of tumor growth, metabolism and metastasis to distant sites [7,11,13]. And during this process, cancer cells acquire a series of features which have been summarized as "the ten hallmarks of cancer" and described as follows: (1) genome instability and mutation, (2) tumor-promoting inflammation, (3) sustaining proliferative signaling, (4) evading growth suppressors, (5) resisting cell death, (6) enabling replicative immortality, (7) inducing angiogenesis, (8) activating invasion and metastasis, (9) reprogramming energy metabolism, and (10) evading immune destruction [14].

Though best known as an ER retention chaperone, GRP78 is also found to be present in the cell plasma membrane, cytoplasm, mitochondria, nucleus as well as cellular secretions of tumor cells [15]. The cellular translocation mechanism of GRP78 is less known, but the tumor microenvironment-induced high GRP78 expression may be a prerequisite for its various locations. Importantly, several lines of evidence indicate that GRP78 at different cellular locations contributes to the acquisition of tumor hallmarks during the process of multistep tumorigenesis. Thus the induction of GRP78 by the tumor microenvironment in solid tumor is a crucial link between tumor microenvironment and cancer cell hallmarks (Fig. 1).

2. Roles of GRP78 in genomic instability and gene mutation

Cancer can be viewed as a disease of underlying genetic instability. Most human tumors display some forms of genomic instability, including DNA sequence alterations, chromosomal rearrangements, aneuploidy or gene amplifications. These alterations have the potential to affect the function of cell growth-related genes, such as proto-oncogenes and tumor suppressor genes, which are associated with the malignant transformation of cells. DNA mutations leading to activation of proto-oncogenes or inactivation of tumor suppressor genes can potentially lead to the unregulated growth seen in cancer.

GRP78 may promote the genome instability and mutations through inhibition of p53 activity or facilitation of virus infection. p53 protein is the central protein in maintenance of genomic integrity and regarded as "guardian of the genome". GRP78 is a member of HSP70 protein family. Stabilization, cytoplasmic sequestration and inactivation of p53 due to interaction of p53 with other members of HSP70 family have been described in cancer cells [16,17]. The interaction between GRP78 and p53 was subsequently identified in nasopharyngeal carcinoma (NPC) cells, and the interaction was suggested to increase the stabilization of p53 protein and result in p53 accumulation in NPC cells [18]. In addition, potent interactions between p53 and GRP78 also occur in nonmalignant trophoblasts. The interaction of GRP78 with the N-terminus of p53 can form the protein complex which leads to inactivation and stabilization of p53, and knockdown of GRP78 expression decreases the formation of high molecular weight p53 complexes and p53 monomer [19]. Interestingly, the interaction between GRP78 and p53 is likely to occur on the membranes of trophoblasts. If this interaction pattern also occurs in cancer cells, we can suspect that upregulation of p53 activity by antibodies directed against C-terminus of GRP78 may be caused by interfering with GRP78 and p53 interaction on cell membranes of prostate cancer cells [20]. A variety of bortezomib-resistant solid tumor cells are able to secrete high amounts of GRP78, which induces prosurvival signals of extracellular signal-related kinase and inhibits p53-mediated expression of proapoptotic Bok and Noxa proteins in endothelial cells. However, the detailed signaling mechanisms linking secreted GRP78 to p53 inhibition remain unclear [21]. It can be deduced that upon the microenvironmental stress, such as hypoxia, glucose deprivation and inflammation, the intracellular induced- or extracellular secreted-GRP78 is able to inhibit the function of p53 protein, facilitating genome instability and the related mutations (Fig. 2).

Virus infection can lead to genome instability and induce potentially harmful mutations that may initiate many cancers [22]. After the viral infection, the virus genome can be inserted into the

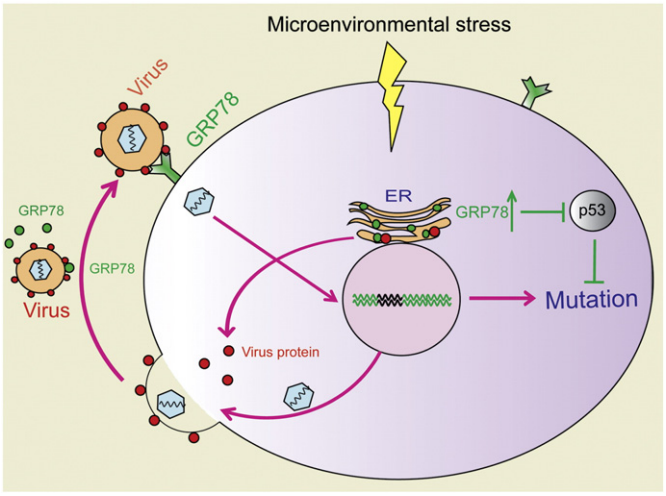

Fig. 2. Induction pathways of genome mutation by GRP78. Cell-surface GRP78 functions as a receptor for viral entry into host cells. After viral infection, the virus genome may be inserted into the host genome, resulting in host genome mutation. Cytosolic GRP78 also aids cytoplasmic virion assembly and egress. In addition, virus infection or microenvironmental stress can elevate the expression of cellular GRP78 through ER stress pathway. The elevated GRP78 can further inhibit p53 activity, which may compromise multiple cell-cycle checkpoints, including DNA damage and mitotic spindle checkpoints, and result in genomic instability.