GRP94 in Cancer

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Glucose-regulated protein 94 (GRP94) is an endoplasmic reticulum (ER)-resident member of the heat shock protein 90 (HSP90) family. In physiological conditions, it plays a vital role in regulating biological functions, including chaperoning cellular proteins in the ER lumen, maintaining calcium homeostasis, and modulating immune system function. Recently, several reports have shown the functional role and clinical relevance of GRP94 overexpression in the progression and metastasis of several cancers. Therefore, the current review highlights GRP94's physiological and pathophysiological roles in normal and cancer cells. Additionally, the unmet medical needs of small chemical inhibitors and the current development status of monoclonal antibodies specifically targeting GRP94 will be discussed to emphasize the importance of cell surface GRP94 as an emerging therapeutic target in monoclonal antibody therapy for cancer.

GRP94 cancer therapeutic target therapy monoclonal antibody

1. Clinical Relevance of GRP94 in Cancer

Many studies have demonstrated that under stress conditions, GRP94 assists in the folding of newly synthesized polypeptides and prevents the aggregation of unfolded or misfolded proteins in the ER lumen [1]. Tumors particularly exhibit a wide range of stress conditions, including hypoxia, redox homeostasis changes, altered cell metabolism, acidosis, and increased cell proliferation and protein synthesis, all of which can trigger ER stress [2][3][4].

Reports have shown that GRP94 mRNA is upregulated in several types of cancer tissues, including liver cancer, breast cancer, esophageal cancer, and glioma tissues [5][6][7][8]. Furthermore, several immunohistochemical studies have revealed that GRP94 protein is highly overexpressed in various cancers, including breast, lung, colorectal, oral, esophageal, and gastric, suggesting a strong relationship with cancers [7][9][10][11][12][13]. Several among the mentioned cancers have shown an inverse correlation between GRP94 overexpression and patient survival. For instance, Liu et al. reported that patients with breast cancer tissues expressing high GRP94 had a statistically significantly shorter survival time than those with a low GRP94 expression [6]. Moreover, multiple studies have suggested that GRP94 may be a potential poor prognostic factor in various types of cancers, including lung, gastric, colorectal, and esophageal cancers [10][14][15][16]. In summary, available evidence suggests that GRP94 is closely associated with cancer progression and metastasis.

2. Role of GRP94 in Cancer Progression and Metastasis

During the multistep development of human tumors, cancer hallmarks include uncontrolled cell proliferation, tumor angiogenesis, invasion, and metastasis [17][18]. Accumulating evidence has revealed that GRP94 is strongly associated with increased cancer proliferation. Several in vitro experiments have demonstrated that GRP94 knockdown in cancer cells promoted growth reduction. For instance, Duan et al. reported that GRP94 knockdown in lung cancer cells inhibits its proliferation and promotes cell apoptosis by increasing caspase-7 and C/EBP homologous protein levels [10]. Moreover, Huang et al. reported that GRP94 knockdown in two different esophageal cancer cell lines using short hairpin RNA (shRNA) promoted more than 50% growth inhibition [16]. Similarly, multiple in vitro studies demonstrated that GRP94 knockdown facilitated growth inhibition in various cancer cell lines, such as gastric cancer, breast cancer, and colorectal cancer cells [9][19][20]. Another study using an in vivo xenograft mouse model showed that subcutaneous injection of GRP94-deficient hepatocellular carcinoma (HCC) cells resulted in significant tumor growth reduction [19].

Tumor angiogenesis is a vital process wherein new blood vessels are formed to properly establish a supportive microenvironment rich in oxygen and nutrients, necessary for optimal growth. Zhang et al. reported considerable growth suppression after orthotopically injecting a GRP94-knockdown melanoma cell line into mice. Further mechanistic studies demonstrated that GRP94 depletion reduced VEGF-A expression, inhibiting tumor-associated angiogenesis [20].

Subsequently, an increasing number of reports have shown a strong relationship between GRP94 and cancer invasion and metastasis. Accordingly, Calderon et al. observed a significant decrease in invasion following GRP94 knockdown in MDA-MB-231, a highly aggressive human breast cancer cell line [21]. Wei et al. also reported that GRP94 knockdown in GRP94 shRNA-treated HCCs inhibited their invasive characteristics, including wound healing, migration, and invasion. Further analysis revealed the inhibition of the chaperonin-containing TCP1 subunit 8/c-Jun/epithelial–mesenchymal transition (CCT8/c-Jun/EMT) cascade in GRP94 shRNA-treated HCCs attenuated its invasive characteristic [22]. Moreover, the influence of GRP94 on cancer cell invasion may be explained by the fact that its client proteins include cell adhesion components, such as integrins. Recently, Hong et al. demonstrated a cell-permeable peptide that competitively inhibited the interaction between GRP94 and integrins, blocking cell invasion in leukemia [23]. Furthermore, Wang et al. reported that GRP94 expression was significantly higher in poorly differentiated colon cancers with metastasis than in well-differentiated cancers without metastasis [24]. Additionally, a statistical analysis study by Pamplona et al. demonstrated significant associations between brain metastasis progression and high GRP94 expression [25].

3. Role of GRP94 in Tumor Resistance

Tumor resistance to conventional therapies has remained a major challenge for successful cancer treatment [26]. Thus, discovering factors predicting cancer resistance is crucial for screening and improving adjuvant therapies for patients with cancer and preventing unnecessary treatment side effects. Multiple studies have suggested that GRP94 participates in tumor radio- and chemoresistance. Accordingly, Lin et al. observed that GRP94 was overexpressed in radioresistant head and neck cancer cells, and using siRNA against GRP94 restored radiosensitivity in the same cancer cell lines [27]. Moreover, Kubota et al. found that cervical cancer cells with

increased GRP94 expression were more resistant to X-ray, while Wang et al. reported that incubation of malignant cells with chemotherapeutic agents, such as 5-fluorouracil, cisplatin, and paclitaxel, upregulated GRP94 expression [28][29]. Additionally, Zhang et al. reported that GRP94 was associated with decreased sensitivity to doxorubicin in ovarian carcinoma cell lines. Similarly, Calderon et al. reported that siRNA-induced knockdown of GRP94 expression in human breast cancer cells helped increase their sensitivity to doxorubicin [21].

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