Roles of glucose transporter-1 and the phosphatidylinositol 3-kinase/protein kinase B pathway in cancer radioresistance (Review)

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Abstract. The mechanisms underlying cancer radioresistance remain unclear. Several studies have found that increased glucose transporter-1 (GLUT-1) expression is associated with radioresistance. Recently, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway was reported to be involved in the control of GLUT-1 trafficking and activity. Activation of the PI3K/Akt pathway may itself be associated with cancer radioresistance. Thus, increasing attention has been devoted to the effects of modifying the expression of GLUT-1 and the PI3K/Akt pathway on the increase in the radiosensitivity of cancer cells. This review discusses the importance of the association between elevated expression of GLUT-1 and activation of the PI3K/Akt pathway in the development of radioresistance in cancer.

Contents

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1. Introduction

Glucose is one of the primary energy sources required to maintain the normal functioning of cells. The glucose transporters (GLUTs) mediate glucose transport (1). Compared with their nonmalignant counterparts, the metabolic rate of glucose is higher in malignant cells. This phenomenon has been demonstrated using positron emission tomography (PET) scanning with the glucose analog tracer, ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) (2-4). Several mechanisms of ^{18}F-FDG uptake that may explain the accelerated glucose use in growing tumors and in transformed and malignant cells have been proposed, including passive diffusion, Na^+-dependent glucose transport, the activation of oncogenes, the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway and upregulation of facilitative GLUT (5-8). GLUT5 is considered to be the primary mechanism for increasing glucose influx into cells (5).

GLUTs are membrane proteins that facilitate the transport of glucose across cellular membranes. Thirteen members of the facilitative sugar transporter family are now recognized (GLUT-1 to -12 and HMIT; gene name, SLC2A) (9). The human genes encoding these proteins are named GLUT-l to -5 and GLUT-7 to -13; GLUT-6 and -14 are now known to be pseudogenes. Of the 14 isoforms, GLUT-1 appears to be the most ubiquitously distributed (10). A number of studies have shown increased GLUT-1 expression in various types of cancer (11-16), including in head and neck cancer (5,17-20). It has been reported that overexpression of GLUT-1 is associated with lymph node metastasis and a poor prognosis in head and neck cancers (17-20). Thus, GLUT-1 may be a potential therapeutic target in malignant tumors (14,16,21-24).

Radiotherapy is important in treating advanced cancers and in organ preservation strategies for cancers at an earlier stage (25). However, radioresistance of cancer cells affects treatment efficacy.

To date, a number of strategies have been introduced in an attempt to increase radiosensitivity, including hyperfractionation to overcome intrinsic radioresistance (26-28), concurrent chemoradiotherapy (29,30) and the use of certain radiosensitizers that enhance radiosensitivity by improving the hypoxic

status of tumors (31,32). Although these efforts have increased survival rates and regional control, certain issues have been reported and the effects are less than ideal, including the development of central radionecrosis as well as early or late toxicity. Thus, more efficacious treatments with fewer side effects are required in order to improve radiosensitivity.

Although a number of factors contributing to radioresistance are understood, such as hypoxia, re-population and DNA damage repair, other aspects remain unclear. A number of studies have found that increased GLUT-1 expression is significantly correlated with radioresistance (33-38). Thus, the suppression of GLUT-1 expression as a novel therapeutic target is a focus in research into increasing radiosensitvity of malignant tumors (33,34,39). However, abnormal expression of GLUT-1 in malignant tumors is not the only cause of radioresistance. Other genes, including epidermal growth factor receptor (EGFR) and NOTCH, may also be involved (40,41). Abnormal expression of GLUT-1 and its activity are regulated by a number of factors, including the activation of oncogenes (13,42), hypoxia via hypoxia-inducible factor (HIF)-1-dependent and independent mechanisms (42,43), and signaling pathways, such as mitogen-activated protein kinase (MAPK) (44), and the PI3K/Akt pathway (45-47). Recently, the PI3K/Akt pathway was reported to be involved in the control of GLUT-1 trafficking and activity (1,48,49). It was also suggested that the PI3K/Akt pathway may regulate GLUT-1 localization in T cells (1,47).

The PI3K/Akt pathway is often found to be overactive in a variety of tumor types and triggers a cascade of responses, from cell growth and proliferation to increased cell survival and motility, which drive tumor progression (40). Activation of the PI3K/Akt pathway may be associated with radioresistance of cancer (25,50-52). Thus, research has become increasingly focused on modifying the expression of GLUT-1 and the PI3K/Akt pathway in order to increase radiosensitivity.

Although GLUT-1 expression is a common feature in patients with cancer, the prognostic value of this parameter, along with the degree of FDG uptake, has not been evaluated with respect to PI3K/Akt. The selection of GLUT-1 and Akt as targets is logical considering their importance in cancer survival and resistance to radiation and chemotherapy.

This review discusses the role of an interaction between the elevated expression of GLUT-1 and activation of the PI3K/Akt pathway in cancer radioresistance. It is proposed that suppression of GLUT-1 expression and the PI3K/Akt pathway may be therapeutic targets for carcinomas (Fig. 1).

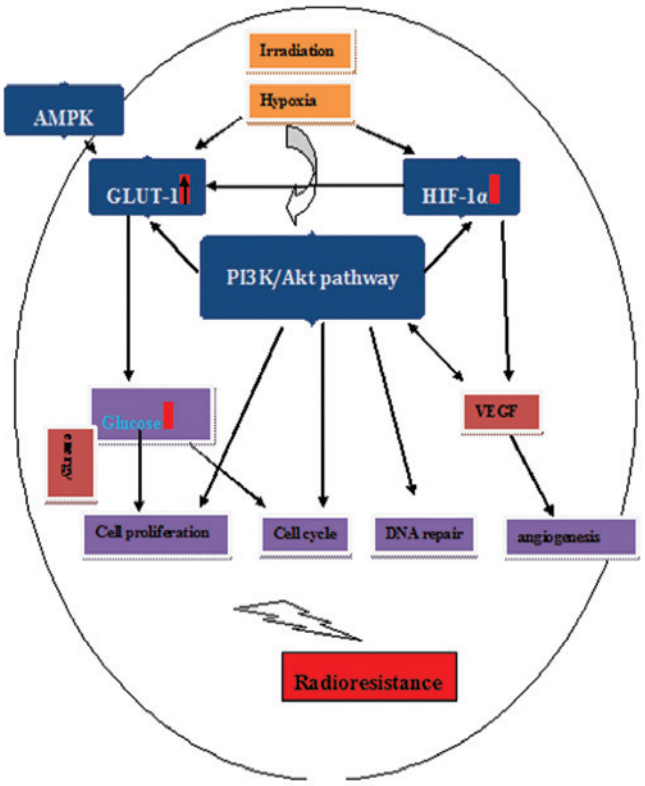

Figure 1. Role of GLUT-1 and PI3K/Akt in radioresistance. GLUT-1, glucose transporter 1; HIF-1α, hypoxia-inducible factor-1α; AMPK, AMP-activated protein kinase-α ; VEGF, vascular endothelial growth factor.

2. Overexpression of GLUT-1 and radioresistance

A number of studies have demonstrated that increased GLUT-1 expression is associated with the development of radioresistance in cancer. In the CPH 54A and CPH 54B lung cancer cell lines, CPH 54A tumors are more radiosensitive than CPH 54B tumors *in vivo* and *in vitro*. Pedersen *et al* (36) found that GLUT-1 mRNA and protein expression levels are higher in 54B than in 54A cells. They also detected greater FDG uptake in 54B tumors, using PET scans, and suggested that there appears to be a correlation between the level of GLUT-1 and FDG uptake. Brophy *et al* (53) investigated GLUT-1 expression in 69 pretreatment biopsy samples from patients with rectal cancer. The patients received preoperative chemoradiotherapy followed by surgical resection. GLUT-1 negative tumors had a 70% probability of a good response to chemoradiotherapy compared with a response rate of 31% for GLUT-1 positive tumors. Korkeila *et al* (37) compared the expression of GLUT-1 in 53 operative samples from patients who had undergone a surgical resection for rectal cancer and 78 preoperative biopsies of patients with rectal cancer who had been treated by preoperative radiotherapy. They found that negative or weak GLUT-1 expression was linked to pronounced tumor regression. There was a tendency towards improved disease-free survival following a long course of radiotherapy when GLUT-1 staining intensity in the operative sample was negative or weak (37). Another study found that preoperative radiotherapy markedly upregulated the expression of GLUT-1 (31). Saigusa *et al* (33) investigated whether GLUT-1 expression was associated with clinical outcome in 52 patients with rectal cancer following preoperative chemoradiotherapy. They found that elevated GLUT-1 gene expression was associated with a more advanced stage of the disease, lymph node metastasis and distant metastasis, and was an independent predictive factor for recurrence-free and overall survival. *In vitro*, DLD1 and LoVo colorectal cancer cell lines show high expression of GLUT-1 whereas the Caco-2 colorectal cancer cells have a lower level of expression of GLUT-1 (33). The relative gene expression levels of GLUT1 in DLD1 and LoVo cells were found to be 30- and 14-fold that of Caco-2, respectively. It was observed that DLD1 cells, which had the highest GLUT-1 gene expression levels, were more resistant to irradiation than Caco-2 and LoVo cells. However,

LoVo cells were more sensitive to radiation than Caco-2 cells. One possible explanation for this may be that radiosensitivity is dependent on Ki-67 expression, as LoVo cells exhibited the highest MKI67 gene expression of the seven cell lines examined. Following chemoradiotherapy, residual cancer growths may contain cells with different characteristics, depending on their location. GLUT-1 expression is predominantly found in the central portion of such residual cancer masses (33). Finally, it was observed that the growth of DLD1 and LoVo cells was inhibited by the glycolysis inhibitor 3-BrPA to a greater extent than that of Caco-2 cells. This suggested that the inhibition of glycolysis may be a potential novel strategy for the treatment of patients with colorectal cancer who express the KRAS mutation (33).

Few studies have investigated the association between GLUT-1 and radioresistance in cancer (19,35). A GLUT-1 labeling index (LI) was determined using immunohistochemistry in 40 biopsies from patients with oral squamous cell carcinoma (OSCC) prior to treatment (19). Clinical responders to radiation showed a significantly lower expression of GLUT-1 when compared with incomplete responders (P=0.009). A significant association (P=0.023) was observed between the GLUT-1 LI and the resistance of tumor cells. These results suggest that GLUT-1 expression could be considered to be a marker of radioresistance in OSCC, in which high GLUT-1 expression is associated with a poor radiation response and vice versa (19). Doki *et al* (35) found a high level of expression of GLUT-1 in squamous cell carcinoma of the esophagus following radiotherapy. In a previous study, it was shown that GLUT-1 overexpression *in vitro* is associated with increased cell proliferation and glucose uptake in Hep-2 laryngeal carcinoma cells. Conversely, the suppression of GLUT-1 expression by antisense oligodeoxynucleotides (AS-ODNs) may decrease glucose uptake and inhibit the proliferation of Hep-2 cells (54). Recently, it was shown that radioresistance in laryngeal carcinoma cells may be associated with increased expression of GLUT-1 mRNA and protein. GLUT-1 AS-ODNs may enhance the radiosensitivity of laryngeal carcinoma cells, primarily by inhibiting the expression of GLUT-1 *in vitro* and *in vivo* (55).

Possible mechanisms of GLUT-1-mediated radioresistance

Raised glucose metabolic rate. A higher glucose metabolic rate has been observed in malignant tumor cells compared with non-malignant cells, even during aerobic glycolysis. This phenomenon is referred to as the Warburg effect (56,57) and was demonstrated using PET scanning with the glucose analog tracer FDG (58). Transport of glucose across the plasma membrane is the initial rate-limiting step in glucose metabolism and it is mediated by facilitative glucose transporter proteins (59). GLUT-1 is important in glucose metabolism within malignant cells and may contribute to the observed increase in FDG uptake. In addition, GLUT-1 may be an intrinsic marker of hypoxia in malignant tumors (14,16,21-24). Elevated GLUT-1 expression may enable malignant tumors to increase their energy expenditure leading to proliferation and radioresistance of tumor cells.

Hypoxia. Hypoxic cells represent 10-50% of solid tumor cells. Hypoxia is known to promote chemoradioresistance in carcinomas (60,61). In addition, GLUT-1 is overexpressed in hypoxic states. HIF-1α, a transcription factor associated with the cellular response to hypoxia (62), upregulates the expression of several hypoxia response genes, including GLUT-1 (64). A correlation has been demonstrated between GLUT-1 and HIF-1α expression in laryngeal carcinoma (65). It is suggested that GLUT-1 expression is associated with cancer radioresistance as a result of upregulation by HIF-1α.

GLUT-1 expression increases cell metabolism. Evans *et al* (66) showed that GLUT-1 overexpression without a coordinated increase in HIF-1-regulated glycolytic enzymes increased glucose uptake but not the glycolytic rate (66). They found that increased GLUT-1 expression resulted in chemoresistance by increasing cell turnover. Thus, it is possible that a similar mechanism may be involved in GLUT-1-mediated radioresistance. However, this requires further investigation.

Involvement of cancer stem cells. $CD133^+$ cancer stem cells may be important in the development of cancer radioresistance (67,68). Ke *et al* (67) reported that GLUT-1 expression was higher in $CD133^+$ than $CD133^-$ cells in thyroid cancer following ^{131}I radiotherapy. Mai *et al* (69) showed that stem cells from proliferating hemangiomas may produce GLUT-1. In a previous study, our group found higher GLUT-1 mRNA and protein expression in $CD133^+$ Hep-2 laryngeal carcinoma cells than in $CD133^-$ cells (70). This also requires further investigation.

Mechanisms independent of hypoxia. A number of studies have shown that GLUT-1-mediated chemoradioresistance is independent of hypoxia. Mayer *et al* (44) found no correlation between the expression of GLUT-1 and oxygenation variables. Evans *et al* (66) showed that GLUT-1 overexpression was coordinated with increases in HIF-1-regulated glycolytic enzymes, which increased glucose uptake, but not the rate of glycolysis. GLUT-1 overexpression was correlated with higher levels of phosphodiesterase in xenografts, which was related to the metabolic turnover of phospholipids and involved in membrane lipid degradation, indicating a mechanism by which GLUT-1 may be involved in increased cell turnover (66). The regulation of GLUT-1 expression is dependent not only on HIF-1-induced transcription but also on the post-transcriptional steady-state of the GLUT-1 gene (71).

Changes in the cell cycle and apoptosis. The cell cycle may be involved in cancer radioresistance (72-74). G_2/M phase arrest occurs in a significant number of cancer cells following irradiation. A previous study found that the percentage of cells that were arrested in the G_2/M phase increased in a dose-dependent manner in response to radiation. This indicated that entry into mitosis had been delayed by the administration of radiation. G_2/M arrest in the 12-Gy group was maximal, whilst the expression of GLUT-1 mRNA and protein was higher than that in the control groups (55).

Involvement of signaling pathways. AMPK and PI3K/Akt signaling pathways may regulate the expression of GLUT-1.

3. Role of PI3K/Akt in radioresistance

Radiotherapy affects the expression of oncogenes and tumor suppressor genes. This alters internal and external signal transduction pathways of the cells, and affects the response of tumor cells to radiotherapy (24). Since 1995, the PI3K/Akt survival signal transduction pathways have been shown to be involved in regulating the expression of a variety of tumor biology

markers (25,53,75). PI3K is an important dimer enzyme that is involved in growth and proliferation, and growth factor signal transduction pathways have been found in recent years that may be activated primarily by a combination of growth factors and receptors (75,76). Akt is also termed PKB or Rac. PI3K is one of the important downstream serine-threonine regulation kinases. A variety of molecules may activate Akt, such as insulin, heat shock proteins and tumor necrosis factor-α. Activated Akt is central to the mediation of cell growth, survival and differentiation by the PI3K/Akt signal transduction pathways. The biological effects of the activation of this pathway include apoptosis, cell cycle regulation and promotion of invasion, metastasis and angiogenesis (75,76). The abnormal expression of certain proteins, as well as abnormal increases in kinase activity in the Akt cascade signal pathway have been identified in a number of human malignancies. The PI3K/Akt pathway is associated with the increased proliferation of tumor cells, and its activation is closely correlated with a poor prognosis and resistance to cancer radiotherapy.

Possible mechanisms of radiation resistance caused by PI3K/Akt include hypoxia, intrinsic radiation resistance, and external factors, such as tumor cell proliferation following radiation therapy (25,75).

PI3K/Akt and hypoxia in radiation resistance. The association between PI3K/Akt and the hypoxic microenvironment of tumors is of interest in research into radioresistance. Hypoxia often results in an increase in the glucose metabolic rate of malignant cells. The abnormal expression of GLUT-1 is known to be correlated with these factors. The supply and consumption of oxygen in the majority of solid tumors are not balanced, which results in tumor hypoxia. Cells that are progressing through the cell cycle become hypoxic so that their progression becomes delayed relative to well-oxygenated cells. Slower progression of hypoxic than normoxic cells through G_2 leads to a temporary accumulation of hypoxic G_2 cells in poorly differentiated mammary adenocarcinoma non-transgenic (NT) and anaplastic sarcoma F. Progression of hypoxic cells through the cell cycle in each tumor type is delayed as a result of the deprivation of oxygen and other nutrients (78). Koritzinsky *et al* (78) found that when cells that had arrested in G_1 during hypoxic conditions progressed through S-phase following re-oxygenation, the speed with which they progressed was similar to that of untreated cells. By contrast, the cells that had arrested in S-phase during hypoxia progressed more slowly through this S-phase following re-oxygenation. Groups of cells that maintain proliferative capacity under hypoxic conditions are a significant cause of treatment failure.

Hypoxia results in genomic instability and increased instability in the malignant phenotype by stimulating invasion and metastasis of tumors (79). Hypoxia induces and promotes the mutation of key regulatory genes (HIF-1, solute carrier family 2 and phosphatidylinositol-dependent kinase-1) (80), leading to increased resistance to therapy.

One of the key genes involved in the response to hypoxia is HIF. HIF regulates the expression of >60 genes involved in angiogenesis, anaerobic glycolysis and cell survival, and the coordinated expression of these genes results in cellular adaptation to acute and chronic hypoxia (81). Studies have shown that hypoxia of head and neck squamous cell carcinoma is associated with poor local control and overall survival (82,83). The PI3K/Akt signal pathway is important in promoting an adaptive response to low levels of oxygen in tumor cells.

Radiation increases HIF-1 activity, which has been hypothesized to be involved in regulating the tumor response to irradiation through a number of mechanisms (84). The PI3K/Akt pathway is involved in HIF-1α protein expression. Activation of PI3K/Akt/mammalian target of rapamycin (mTOR) leads to stimulation of *de novo* synthesis and transcriptional activation of HIF-1α (85,86). HIF-1α protects tumors from radiation damage directly and indirectly. Inhibition of the PI3K/Akt pathway by wortmannin and LY294002, and inhibition of HIF-1α by short interfering (si)RNA may therefore enhance the efficacy of radiotherapy.

PI3K/Akt, reoxygenation and neoangiogenesis in radiation resistance. Irradiation may lead to reoxygenation and neoangiogenesis of cancer cells following radiotherapy. The regulatory mechanism may occur via upregulation of VEGF. Inhibition of neoangiogenesis results in normalization of the vasculature and improved perfusion, leading to a reduction in tumor cell hypoxia (50). The PI3K/Akt pathway may induce the expression of VEGF via activation of HIF-1α (87). VEGF protects endothelial cells against radiation by activating the PI3K/Akt pathway, leading to enhanced expression of the antiapoptotic protein Bcl-2 (88). Antiangiogenic therapy may therefore enhance the cytotoxic effects of radiotherapy (89,90). Certain antiangiogenic drugs target the vasculature, directly or indirectly, by disrupting VEGF. These include inhibitors of the PI3K/Akt pathway. This may lead to increased blood flow and oxygenation, thereby potentially increasing radiosensitivity (91). A combination of low doses of a PI3K inhibitor (LY294002) and cisplatin significantly enhanced the therapeutic efficacy of radiation therapy by preferentially targeting tumor blood vessels (89). However, the hypothesis that an inhibitor of the PI3K/Akt pathway may also achieve prolonged vascular normalization, and thereby enhance radiosensitivity, requires further investigation (92).

PI3K/Akt and the cell cycle in radiation resistance. Radiation may activate p53-dependent or independent cell cycle G_1 and G_2 arrest (93). The PI3K/Akt pathway acts to overcome p53-independent cell cycle arrest via activation of cyclin D and inactivation of the cell cycle-dependent kinase inhibitor p27 (94). Activation of the Akt/PKB pathway is able to override the G_2/M phase cell cycle arrest that occurs as a result of irradiation-induced DNA damage (95). Phosphatase and tensin homolog (PTEN), a tumor-suppressor gene, antagonizes the PI3K/AKT signaling pathway that is involved in promoting escape from cell-cycle arrest. Park *et al* (94) found that PTEN may be essential in cancer cell radiosensitivity by using LY294002 or PTEN-specific siRNA to block PI3K/Akt signaling in non-small-cell lung cancer cells (NSCLC).

PI3K/Akt and DNA repair in radiation resistance. Irradiation may cause DNA damage, including single-strand breaks, double-strand breaks (DSBs), base excision and glucose damage. Enhanced DNA repair activity tends to be resistant to radiotherapy. DNA-dependent protein kinase catalytic subunit

(DNA-PKcs) and ataxia telangiectasia-mutated are two members of the PI3K family that repair DNA DSBs (97-99). Inhibition of PI3 kinases using a pharmacological approach may improve the response of cancer cells to radiotherapy. Nimotuzumab inhibits the radiation-induced activation of DNA-PKcs by blocking the PI3K/AKT pathway (99). Inhibition of the PI3K/Akt cell survival signaling pathway and DNA-PKcs may contribute to the wortmannin-induced radiosensitivity observed in NSCLC cells (100). Azad *et al* (101) found that BEZ235, a novel inhibitor of DNA-PK and PI3K/mTOR, abrogates radiation-induced DSB repair, resulting in cellular radiosensitization and growth delay in irradiated NSCLC xenografts.

PI3K/Akt, epidermal growth factor receptor (EGFR) and cell proliferation in radioresistance. Activated Akt promotes cell proliferation and inhibits apoptosis. Radiation-induced Akt activation may modulate the radioresistance of human cancer cells (102). Certain serum factors, including integrin-β1, and growth factor receptors, including EGFR, may also be involved (103,104). Minjgee *et al* (103) showed that there was increased basal Akt phosphorylation as well as augmented output from the PI3K/Akt pathway following EGF stimulation in cell lines with higher levels of ErbB1 and integrin-β1 expression. Akt phosphorylation may be related to adhesion and migration, which are regulated by integrin signaling. Inhibition of AKT, EGFR and integrin-β1 may thus improve radioresistance (104).

4. Association between GLUT-1 and PI3K/Akt

The abnormal expression of GLUT-1 is correlated with multiple signal transduction pathways, including the PI3K/Akt signaling pathway, which is known to be important in the regulation of GLUT-1 expression. Several studies have confirmed that the PI3K/Akt pathway and GLUT-1 expression affect glucose metabolism (1,47-49).

Hematopoietic cells and T lymphocytes depend on GLUT-1 as the primary source of intracellular glucose, while growth factors, such as interleukin (IL)-3, IL-7 or CD28 provide important signals for GLUT-1 synthesis and glucose uptake in these cells (47,105-107). Cell growth factors regulate GLUT-1 predominantly through PI3K and its downstream effector Akt. This leads to activation of mTOR and glycogen synthetase-3 (GSK-3), as well as other methods of controlling the activation, recirculation and internalization of GLUT-1.

In addition to the regulation of GLUT-1 expression at the cell surface, Akt also controls the activity of GLUT-1 via activation of mTOR (106). In hematopoietic cells and T cells that have been transfected with the GLUT-1 gene, an increase in glucose metabolism results in increased levels of phosphorylation of GSK-3α,β (108). It has been reported that Akt phosphorylates 21/9 serine of GSK-3 directly, thus inhibiting the activity of GSK-3 kinase (48). As a substrate of Akt, GSK-3 can also regulate the transmission of GLUT-1 by improving the recycling of integrin (109). Continuous activation of Akt expression increases the ability of lymphocytes to absorb and utilize glucose (48,107,110), improves the glycolysis of T lymphocytes (107) and may lead to the development of autoimmune disorders and lymphoma. Suppression of PI3K can prevent the activation of lymphocytes, increase glucose metabolism following stimulation by cytokines and reduce the ability of leukemic cells to absorb glucose (1,110-112).

PI3K pathways also affect insulin-induced glucose transport in fatty cells (113,114). Apigenin downregulates the expression of GLUT-1 mRNA and protein in CD18 and S2-013 pancreatic cancer cell lines, and inhibits the PI3K/Akt channel (49,115). It has been found that inhibition of the PI3K/Akt pathway may induce a decrease in GLUT-1 mRNA (112,116).

Research has shown that cell growth factors promote the transmission and activation of GLUT-1 in hematopoietic cells and T lymphocytes via the PI3K/Akt pathway (48,105-107), and that activated Akt is sufficient to maintain GLUT-1 and glucose uptake on the surface of cells in the absence of cytokines (107,117). A previous study found that expression of GLUT-1, p-Akt, and PI3K protein in adenoid cystic carcinoma (ACC) was higher than that in inflammatory lesions or benign tumors ($P<0.001$). The percentage of cells expressing these proteins for GLUT-1, PI3K and p-Akt protein in ACC were 38.1 (16/42), 38.1 (16/42) and 50.0% (21/42), respectively. Significant correlations between GLUT-1 and PI3K expression ($r=0.394$, $p=0.01$), between GLUT-1 and p-Akt expression ($r=0.528$, $P<0.001$), and between p-Akt and PI3K expression ($r=0.528$, $P<0.001$) were also observed. In this study, a multivariate analysis showed that p-Akt was a significant predictor of recurrence and that GLUT-1 expression was associated with T stage (according to the TNM classification) and distant metastasis of ACC (118). In a ceruminous adenoma of the external auditory canal, it was also shown by immunohistochemistry that tumor cells were positive for GLUT-1, HIF-1, PI3K and p-Akt (119). In U87MG glioblastoma cells, inhibition of the PI3K pathway by LY294002 may decrease the expression of GLUT-1 mRNA, VEGF mRNA, and HIF-1α mRNA (116).

mTOR is a downstream target of PI3K. Radhakrishnan *et al* (112) found that GLUT-1 was linked to the mTOR pathway and that GLUT-1 may be useful as a biomarker of mTOR status in head and neck cancers. mTOR inhibition may activate an AKT feedback loop in tumors sensitive to rapamycin treatment. In acute lymphoblastic leukemia, IL-17 upregulates the expression of GLUT-1 via PI3K activation (120,121). In endometrial carcinoma cells, GLUT-1, pAkt and pmTOR were found to be strongly expressed and the mTOR inhibitor, rapamycin, induced apoptotic cell death (122). However, in breast cancer cells, rapamycin and sorafenib downregulated GLUT-1 expression and glucose uptake to similar extents, whereas the dual PI3K/mTORC1-C2 inhibitor NVP-BEZ-235 did not have the same effect. This suggested that sorafenib-mediated activation of AMPK, rather than the PI3K/Akt pathway, initially stimulated glucose uptake by increasing GLUT-1 protein expression (123).

It is a novel idea to target GLUT-1 and AKT expression with the aim of improving the radiosensitivity of cancers. Other signaling pathways are involved in cancer radioresistance, not all of which regulate or interact with GLUT-1, and which may indeed be independent of the glucose/AKT pathway. The stress-activated protein kinase/c-Jun NH(2)-terminal kinase pathway has been found to be involved in the radioresistance of nasopharyngeal carcinoma (124). The RAF kinase/mitogen activated protein kinase/extracellular signal-regulated kinase (ERK) pathways are also important in the radiation resistance of squamous cell cancers, and kinase suppressor of RAS 1

AS-ODN may act a radiosensitizer for treating Ras-dependent human malignancies (125). It has been observed in clinical trials that inhibition of PI3K (126) and GLUT-1 (127) increase the expression of other oncogenes, such as that of pERK1/2 or pEGFR, and induce the persistent phosphorylation of ribosomal protein S6. ERK1/2 activates the p90 ribosomal S6 kinase (128), which subsequently phosphorylates S6 at Ser235/236, independently of PI3K/mTOR signaling, and increases tumor resistance to radiation therapy (129).

5. Conclusion

Activation of the PI3K/Akt pathway, and the transcription and expression of GLUT-1 (promoted by PI3K/Akt) are closely associated with glucose uptake, energy consumption, cell proliferation and the malignant transformation of tumor cells. GLUT-1 activation by PI3K/Akt is an important metabolic regulator of tumor cells. Overexpression of molecules in this pathway is associated with a poor prognosis and resistance to radiotherapy.

Radiation resistance of tumor cells, which develops during the course of radiotherapy, necessitates the development of novel therapies to combat this problem. The radiosensitivity of tumor cells is key to treatment efficacy and is associated with their inherent sensitivity prior to irradiation as well as adaptations developed to deal with injury following irradiation. Intrinsic radiosensitivity is determined genetically and by disorders involving tumor suppressor genes, while the response of cells to injury is induced by protein modifications and ultimately by relevant alterations in signal transduction pathways.

Preclinical data have shown that enhancing radiosensitivity by inhibiting PI3K/Akt is possible. LY294002 and wortmannin, which target the p110 catalytic subunit of PI3K, provide powerful preclinical tools with which to investigate the cellular consequences of inhibiting this pathway (94,100). RAD-001, a rapamycin analog, is a potent radiosensitizer that acts via mTOR-dependent enhancement of radiation-induced autophagy and the induction of apoptosis in vascular endothelial cells (130,131). In a phase III trial, CCI-779, another mTOR inhibitor, showed a significant improvement in progression-free survival (5.5 compared with 3.1 months) and in overall survival in patients with metastatic renal cell carcinoma (132). However, no data on enhancing radiosensitivity by combining inhibition of PI3K/Akt with that of GLUT-1 expression in carcinomas are available to date. A number of studies have shown that activation of the PI3K/Akt signaling pathway and abnormal expression of GLUT-1 are associated with tumor progression, a poor prognosis and the development of resistance to chemotherapy and radiotherapy. The ability of a malignancy to resist radiation-induced damage is associated with PI3K/Akt and the overexpression and activation of GLUT-1, which is one of the key regulators of radiotherapy sensitivity. Targeted therapy directed to the PI3K/Akt pathway and GLUT-1 may disrupt the development of radiation resistance and enhance radiosensitivity, thus increasing the survival rates of cancer. Targeting GLUT-1 with antisense oligonucleotides, and the PI3K/Akt pathway with wortmannin and LY294002, in an attempt to increase radiosensitivity in laryngeal carcinoma will be the next focus for our group. The prospect of targeted therapies aimed at these molecules currently holds promise for the treatment of a variety of types of cancer.

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