Emerging Role of High Glucose Levels in Cancer Progression and Therapy

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Extensive research has indicated that high glucose levels play an important role in cancer. A high glycaemic index, glycaemic load diet, high sugar intake, high blood glucose and diabetes mellitus all increase the risk of cancer. Various signals are involved in high glucose–induced tumorigenesis, cancer proliferation, apoptosis, invasion and multidrug resistance. Reactive oxygen species might be important targets in cancer progression that are induced by high glucose levels. Drugs such as metformin and resveratrol may inhibit high glucose–induced cancer. As the impact of high glucose levels on cancer progression and therapy is a novel finding, further research is required.

Key words: *cancer, high glucose, progression, therapy, tumorigenesis*
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Many studies have shown that high glucose (HG) is closely related to tumorigenesis and cancer progression. HG is linked to abnormal glucose metabolism[1,2]. The study of abnormal glucose metabolism is not only shedding light on carcinogenesis, but is also revealing new principles of the biochemistry of aberrant cancer cell proliferation, apoptosis and invasion, as well as multidrug resistance.

Foods that contain carbohydrates, which are digested, absorbed and metabolised quickly, are considered high glycaemic index (GI) foods (GI ≥ 70 on the glucose scale). The glycaemic load (GL) is the product of the GI and the total available carbohydrate content in a given amount of food (GL = GI × available carbohydrate/given amount of food)[3]. High GI and GL diets are associated with cancers of the upper aerodigestive tract and digestive system[1,2]. Table 1[4-37] lists specific risk factors and cancer types. High GI diets are associated with increased risk of oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, colorectal cancer, colon cancer, pancreatic cancer, renal cell carcinoma, prostate cancer and bladder cancer[5,6,16,18-20,30]. High GL diets increase the risk of oesophageal squamous cell carcinoma and mammary carcinomas, and gastric, colorectal, rectal, colon, pancreatic, endometrial, ovarian and bladder cancers[6,7,16,19,20,33,35,36]. Makarem et al[38] found that high sugar intake increases the risk of cancer by 60% to 95%, and high consumption of sugary beverages increases the risk by 23% to 200%. Dietary sugar is positively associated with hepatocellular car-

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Table 1 Clinical evidence of high glucose involved in tumorigenesis and progression[4-37].

Cancer type	Risk factors	Study
Thyroid cancer	High level of fasting plasma glucose, diabetes mellitus	Zhan et al[4]
Oesophageal carcinoma	Intake of sucrose, sweetened desserts/beverages, high GI diet, high GL diet, high level of fasting plasma glucose, diabetes mellitus	Zhan et al[4], Li et al[5], Eslamian et al[6]
Breast cancer	High GL diet, high fat/high sugar diet, high level of fasting plasma glucose, diabetes mellitus, high blood random glucose	Zhan et al[4], Thompson et al[7], Lambertz et al[8], Sieri et al[9], Raza et al[10], Contiero et al[11]
Lung cancer	High level of fasting plasma glucose, diabetes mellitus	Zhan et al[4], Luo et al[12]
Liver cancer	High sugar diet, high level of fasting plasma glucose, diabetes mellitus	Zhan et al[4], Fedirko et al[13], Healy et al[14]
Biliary tract cancers, gallbladder cancer	High consumption of sweetened beverages	Larsson et al[15]
Gastric cancer	High carbohydrate intake, high GL diet, high fasting plasma glucose	Ye et al[16], Ikeda and Kiyohara[17]
Colorectal cancer	High GI diet, high carbohydrate intake, high sugar, high level of fasting plasma glucose, diabetes mellitus	Sieri et al[18,19], Hu et al[20], Galeone et al[21], Cui et al[22], Vulcan et al[23], Jung et al[24], Shin et al[25]
Pancreatic cancer	High GI diet, high level of fasting plasma glucose, diabetes mellitus, high random plasma glucose	Zhan et al[4], Hu et al[20], Rossi et al[26], Nagai et al[27], Pang et al[28], Er et al[29]
Renal carcinoma	High GI diet	Zhu et al[30], Otunctemur et al[31]
Prostate cancer	High GI diet, high GL diet, high serum glucose	Hu et al[20], Arthur et al[32]
Bladder cancer	High GI diet, high GL diet, high consumption of refined carbohydrate foods, high level of fasting plasma glucose, diabetes mellitus	Zhan et al[4], Sieri et al[19], Augustin et al[33]
Cervical cancer	High level of fasting plasma glucose, diabetes mellitus, high nonfasting plasma glucose	Zhan et al[4], Lee et al[34]
Endometrial cancer	High GL diet	Nagle et al[35]
Ovarian cancer	High GL diet	Nagle et al[36]
Primary central nervous system lymphoma	High mean fasting plasma glucose (≥126 mg/dL)	Debata et al[37]
Leukemia	High level of fasting plasma glucose, diabetes mellitus	Zhan et al[4]
Lymphoma	High level of fasting plasma glucose, diabetes mellitus	Zhan et al[4]

cinoma[13]. Larsson et al[15] found that high consumption of sweetened beverages was associated with increased risk of biliary tract cancers, particularly gallbladder cancer. Galeone et al[21] determined that added sugars were associated with increased risk of colon cancer. A high sugar diet increased the risk of mammary cancer in developing mouse pups and incidence of liver tumours in mice[8,14]. High blood glucose increased the risk of leukaemia, lymphoma and lung, breast, thyroid, gastric, pancreatic, colorectal, colon, rectal, prostate, bladder and cervical cancers[4,9,17,22-25,32,34,37]. High blood glucose is associated with cancer stage, aggressiveness, mortality, recurrence and poor survival[10-12,27,32,34,37,39]. Diabetes mellitus (DM) increased the risk of developing oesophageal, thyroid, liver, pancreatic, colorectal, cervical and renal cancer and increased cancer aggressiveness[4,28,29,31].

HG and tumorigenesis

Table 2[40-104] and Fig 1 show the involvement of HG in tumorigenesis and the progression of different cancers through various molecules. HG induced O-GlcNAcylation, expression and transcriptional activity of Yes-associated protein (YAP) led to YAP-dependent tumorigenic phenotypes which contributed to liver tumorigenesis. YAP was found to promote glucose uptake, the synthesis of metabolites involved in the hexosamine biosynthesis pathway (HBP) and cellular O-GlcNAcylation, establishing a positive feedback loop[58]. Qiao et al[59] found that HG induced advanced glycosylation end product–specific receptor (AGER) activating HBP, leading to enhanced O-GlcNAcylation of target proteins, increasing the activity and stability of c-Jun via O-GlcNAcylation of this protein at Ser73 to promote

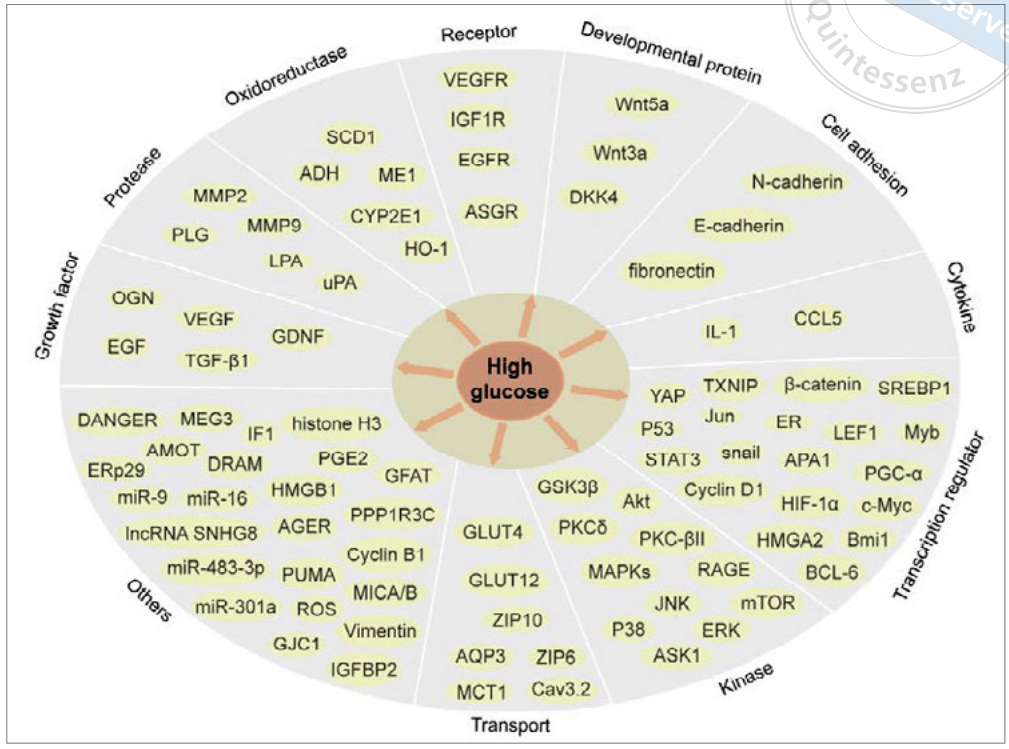

Fig 1 HG involved in tumorigenesis and progression through transcription regulators, kinase, growth factors, proteases, oxidoreductases, receptors, developmental protein, cytokines and other molecules.

tumorigenesis. The c-Jun enhanced AGER transcription thus established a positive feedback loop[59]. HG-induced thioredoxin-interacting protein (TXNIP) expression is involved in oxidative stress via p38 mitogen-activated protein kinases (MAPKs) and extracellular signal-regulated kinase (ERK) pathways, which promoted cancer development[78]. Ito et al found that HG led to cancer by increasing osteopontin (OPN) expression and oxidative stress, accelerating cell proliferation[79]. HG promoted the acquisition of mesenchymal and cancer stem cell (CSC) properties by activating transforming growth factor β1 (TGF-β) signalling and facilitated tumorigenesis[80]. Zhang et al[105] found that HG increased mutagenesis in lymphoblastoid cells via reactive oxygen species (ROS) and null or mutant p53. Overexpression of chemotactic cytokine ligand 5 (CCL5) accelerated diffuse large B cell lymphoma formation in HG[106]. HG maintained hepatic homeostasis by regulating the asialoglycoprotein receptor[107]. Langen et al[41] found that HG decreased the dose absorption ratio (DAR) of 2-18F-fluorodeoxyglucose (FDG) uptake in bronchial carcinoma.

HG and cancer cell proliferation

HG reduces Wnt antagonist Dickkopf 4 (DKK4) protein and promotes cancer cell proliferation by activating the wnt/β-catenin signal via wnt3a-ligand-mediated translocation of β-catenin into the nucleus[60,98]. HG increases ROS levels, which stimulates proliferation by inactivating the c-Jun-NH2-terminal kinase (JNK) pathway[81]. Rezende et al[92] found that HG increased cell proliferation by reducing AMPK activation and affecting oxidative stress. HG promotes cell proliferation by upregulating sterol regulatory element binding protein 1 (SREBP1); SREBP1 also mediates autophagy via negative feedback[82]. Han et al[83] found that HG promoted proliferation via the induction of epidermal growth factor (EGF) expression and transactivation of EGF receptor (EGFR). Zhang et al[42] found that HG stimulated proliferation via phosphoenolpyruvate (PEP)-induced poHis58-FAK signalling. HG stimulates proliferative capacity by elevating O-GlcNAcylation and the expression of zinc finger protein 410 (APA1) and gap junction protein gamma 1 (GJC1)[108]. Upregulation of glial cell line–derived neurotrophic factor (GDNF) and RET ligand–receptor interaction could play a role in the proliferation promoted by HG[84]. Gupta et al[109] found that HG induced proliferation via crosstalk between glycogen synthase kinase 3β (GSK-3β) activation, histone H3 phosphorylation and DNA methylation. Decreases in protein kinase C (PKC)-βII mRNA and protein levels could account for HG-stimulated proliferation[110]. Li et al[93] found that HG induced miR-301a expression, suppressed expression of p21 and smad4 and promoted G1/S

Table 2 Molecular mechanisms of HG involved in tumorigenesis and progression[40-104].

Cancer type	Molecular mechanisms	Study
Nasopharyngeal carcinoma	Snail protein	Zheng et al[40]
Bronchial carcinoma	Dose absorption ratio of FDG uptake	Langen et al[41]
Esophageal carcinoma	poHis58-FAK signalling	Zhang et al[42]
Breast cancer	EMT, ROS, proinflammatory and pro-oxidant environment characterised by the COX-2/PGE2 axis, Zn^{2+} transportation, NF-κB pathway; abrogate the effect of metformin, decrease cellular sensitivity to 4-MU	Zhu et al[43], Viedma-Rodríguez et al[44], Matsui et al[45], Flores-López et al[46], Kallens et al[47], Takatani-Nakase[48], Nasir Kansestani et al[49], Varghese et al[50], Wang et al[51], Pandey et al[52]
Gastric cancer	Multiplicative interaction; attenuate effect of 5-FU	Lin et al[53], Zhao et al[54]
Lung cancer	p53 pathway, RAGE-NOX-4 pathway, ERK/DAPK signal	Wang et al[55], Liao et al[56], Kuron et al[57]
Liver cancer	O-GlcNAcylation, HBP, canonical Wnt signalling pathway, oxidative stress, endoplasmic reticulum stress, EMT, YAP, mitochondrial biogenesis, mitochondrial networking, ATP synthase dimer stability, AMPK/mTOR pathway, STAT3 and AKT signalling pathways, NF-κB/GLUT1 signal	Zhang et al[58], Qiao et al[59], Chauhan et al[60], Chandrasekaran et al[61,62], Jiang et al[63], Li et al[64], Liu et al[65], Domenis et al[66], Lv et al[67], Li et al[68], Liu et al[69]
Cholangiocarcinoma	STAT3, O-GlcNAcylation	Saengboonmee et al[70], Phoomak et al[71]
Colorectal cancer	PTEN/Akt signal, EMT, MMP-9 signalling pathway, attenuate effect of 5-FU, modify adriamycin-induced cancer cell death, bromopyruvate resistance	Ran et al[72], Chen et al[73], Lin et al[74], Ma et al[75], Ganefi et al[76], Ideno et al[77]
Pancreatic cancer	Oxidative stress, p38 MAPK and ERK signalling pathways, mesenchymal and CSC-properties, JNK pathway, autophagy, EMT, increase LDHA activity and HK2, PFKP expression, AMPK signalling pathway, PI3K/AKT/GSK-3β signalling pathway, EGF/EGFR signalling pathway	Li et al[78], Ito et al[79], Rahn et al[80], Luo et al[81], Zhou et al[82], Han et al[83], Liu et al[84], Li et al[85,86], Cheng et al[87], Duan et al[88], Cao et al[89], Han et al[90], Li et al[91]
Prostate cancer	Oxidative stress, G1/S cell cycle transition, upregulate aerobic glycolysis, N-linked glycosylation, reduce docetaxel-induced cell apoptosis, reduce expression of IGFBP2	Rezende et al[92], Li et al[93], Huang et al[94], Fukami et al[95], Biernacka et al[96,97]
Bladder cancer	Wnt/β-catenin signalling pathway	Gao et al[98]
Endometrial cancer	EMT, overexpression of β-catenin, inhibit STAT3 expression	Gu et al[99], Han et al[100], Zhou et al[101], Wallbillich et al[102]
B-cell lymphoma	EMT, Wnt/β-catenin signalling pathway, abrogate etoposide chemotherapy effect	Wang et al[103], Shao et al[104]

cell cycle transition and cell proliferation. HG induces proliferation via STAT3 activation by increasing nuclear STAT3, p-STAT3, cyclin D1, vimentin and MMP270. Reema et al[111] found that HG promoted cell proliferation and clonogenicity by activating pro-oncogenic signalling. HG enhances the growth of cancer cell colonies by activating Akt[112].

HG and cancer cell apoposis

HG induces cell apoptosis through increased oxidative stress by increasing the intracellular ROS level, lipid peroxidation, protein carbonyl and 3-nitrotyrosine (3-NT) adduct formation and HG-mediated induction of alcohol dehydrogenase (ADH) and cytochrome P4502E1 (CYP2E1)[61,62]. HG triggers endoplasmic reticulum (ER) and oxidative stress, and integrates the signalling cascades into apoptosis signal-regulating kinase 1 (ASK1) and causes phosphorylation and activation of p38 and JNK MAPK signals, eventually leading to cell apoptosis[63]. It was also argued that HG enhances proliferation and inhibits apoptosis by JNK-mediated downregulation of the p53 pathway and increases p38 MAPK phosphorylation[55,113]. Zhu et al[43] found that HG enhanced cell proliferation, migration and invasion and suppressed apoptosis by increasing protein kinase C delta (PKCδ)-phosphorylation and proteasome activity.

HG and cancer cell invasion and metastasis

HG induces migration and invasion by monounsaturated fatty acids (MUFAs), suppressing PTEN/Akt signalling and regulating the epithelial–mesenchymal transition (EMT) mediated by stearoyl-CoA desaturase 1 (SCD1)[72]. HG upregulates high mobility group AT-hook 2 (HMGA2) and high mobility group box 1 (HMGB1) to induce EMT via the Wnt/β-catenin signalling pathway and production of hydrogen peroxide[85,103,114]. HG induces the binding of plasminogen to the cell surface and promotes the activation of plasminogen and

EMT[44]. HG activates the insulin-like growth factor 1 receptor (IGF1R)/Src axis and upregulates the expression of EMT, ERK, cyclin B1 and N-cadherin signalling pathways by mediating the downregulation of miR-9 expression[73]. HG increases the expression of glucose transport protein 4 (GLUT4) and glucose transporter 12 (GLUT12) and promotes EMT by upregulating vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) and oestrogen receptors (ERs). GLUT4 also supplies more energy for the growth of cancer cells by increasing glucose intake[45,99]. Lin et al[74] found that HG promoted the migration and invasion of cancer cells via the signal transducer and activator of transcription 3 (STAT3)-induced matrix metalloproteinase-9 (MMP-9) signalling pathway. HG increases expression of MMP-9 and MMP-2, downregulates E-cadherin expression, upregulates snail and induces higher malic enzyme 1 (ME1) activity[40,100,115]. Li et al[86] found that HG increased the production of ROS in a concentration-dependent manner. HG induces superoxide dismutase-dependent production of hydrogen peroxide, increases the expression of urokinase plasminogen activator (uPA), vimentin and fibronectin mediated by ROS and upregulates haem oxygenase-1 (HO-1) expression via ROS or the TGF-β1/PI3K/Akt signalling pathway[46,86,116]. HG modulates O-GlcNAcylation through the expression of glucosamine-fructose-6-phosphate amidotransferase (GFAT) and vimentin[71]. HG induces the establishment of a proinflammatory, pro-oxidant environment characterised by the cyclooxygenase-2 (COX-2)/PGE2 axis. Stromal-derived PGE2, acting as a stimulator of interleukin-1 (IL-1) epithelial expression, promotes the acquisition of motile properties by epithelial cells and the maintenance of COX-2/PGE2-dependent inflammation[47]. Cheng et al[87] found that the accumulation of hypoxia-inducible factor-1α (HIF-1α) induced by HG increased lactate dehydrogenase A (LDHA) activity and hexokinase 2 (HK2) and phosphofructokinase platelet type (PFKP) expression. Tomoka et al[48] found that HG induced Zn^{2+} transport via zinc transporters ZIP6 and ZIP10. Zhou et al[117] found that HG promoted cell migration via aquaporin 3 (AQP3).

HG and angiogenesis

Liao et al[56] found that HG increased the protein expression of receptor for advanced glycation end products (RAGE) and nicotinamide adenine dinucleotide phosphate oxidase-4 (NOX4) and affected angiogenesis and tumour metabolism via the RAGE-NOX-4 pathway. HG increased proliferation and angiogenesis and decreased apoptosis due to activation of the NF-κB pathway by increasing ROS[49]. Huang et al[94] found that HG led to lysophosphatidic acid (LPA) synthesis and upregulated aerobic glycolysis and VEGF-C production.

HG and cancer prognosis

Li et al[64] found the effect of maternally expressed gene 3 (MEG3) binding to miR-483-3p as molecular miRNA sponge. Overexpression of miR-483-3p suppressed ERp29 expression. HG negatively regulates the expression of endoplasmic reticulum protein 29 (ERp29) by inhibiting MEG3. ERp29 regulates the biological functions of carcinoma cells through EMT, which leads to a poor prognosis for hepatocellular carcinoma patients with HG64. In gastric cancer, a poor prognosis was associated with the multiplicative interaction of HG and long non-coding RNA (lncRNA) SNHG853. Yang et al[118] found that HG affected the outcome of colorectal cancer patients by inhibiting miR-16 expression and the expression of its downstream genes Myb and VEGFR2.

HG and abnormal molecular expression in cancer cells

Liu et al[65] found that HG enhanced the expression and O-GlcNAcylation of angiomotin (AMOT) and stimulated nuclear accumulation, transcription activity, interactions with transcription factors and transcription of target genes of YAP via AMOT. HG induces overexpression of β-catenin and subsequent transcription of the target genes by upregulating HBP and O-GlcNAcylation[101]. HG promotes the Wnt-stimulated formation of a lymphoid enhancer factor (LEF)-1/β-catenin complex that is associated with acetylase p300 and displaces SIRT1 deacetylase, leading to increased β-catenin acetylation, its nuclear accumulation and transcription activation119. HG increases expression of inhibitor factor 1 (IF1), decreases the level of transcriptional coactivator PGC-α and reduces mitochondrial biogenesis and ATP synthase dimer stability[66]. Duan et al[88] found that HG inhibits the expression of MHC class I chain-related protein A/B (MICA/B), promotes the expression of Bmi1 and weakens the cytotoxicity of natural killer cells in pancreatic cancer, contributing to immune escape by inhibiting the AMPK signalling pathway and activating the AMPK-Bmi1-GATA2-MICA/B axis. Fukami et al[95] found that HG induced N-linked glycosylation-mediated functional upregulation and overexpression of Cav3.2. Lee et al[120] determined that HG increased transcriptional activity and repressed the methylation of protein phosphatase 1 regulatory subunit 3C (PPP1R3C), and Briata et al[121] found that HG reduced c-myc expression.

HG and cancer chemoresistance or radioresistance

HG attenuated 5-fluorouracil (5-FU)–induced tumour growth inhibition by decreasing cell death and increasing DNA replication[54,75]. HG reduced the effect of metformin on cancer cell proliferation, cell death and cell cycle arrest and lost efficacy in inhibiting the mTOR pathway[50,111]. HG inhibited drug-induced p53 Ser46 phosphorylation, and mutual unbalance between p53-dependent apoptosis and damage-regulated autophagy modulator (DRAM) modified adriamycin (ADR)-induced cell death[76,122]. Kwon et al[57] found that HG-induced overexpressed inositol 1,4,5-trisphosphate receptor interacting protein (DANGER) bound to the death domain (DD) of death-associated protein kinase (DAPK) and inhibited ERK/DAPK-induced death, which accounted for radioresistance. HG suppressed bromopyruvate uptake and bromopyruvate-induced cell death by downregulating bromopyruvate carrier monocarboxylate transporter 1 (MCT1)[77]. HG-induced BCL-6 overexpression abrogated the effect of etoposide chemotherapy-induced cell death[104]. Wang et al[51] found that HG decreased carcinoma cellular sensitivity to 4-methylumbelliferone (4-MU)-inhibited cell proliferation. Biernacka et al[96] found that HG reduced docetaxel-induced cell apoptosis by upregulating insulin-like growth factor binding proteins 2 (IGFBP2). Liu et al[123] found that HG upregulated side population (SP, a key factor contributing to drug resistance) cells mediated by the Akt pathway. Nishiwada et al[124] found that 1% concentration sevoflurane in HG enhanced cell proliferation.

HG and cancer therapy

HG could reduce the sensitivity of cancer cells to docetaxel through a reduction in the expression of IGFBP2; however, metformin inhibits cell proliferation, reduces cell survival, promotes apoptosis of carcinoma cell induced by HG through activation of the AMPK/mTOR pathway, inhibits STAT3 and its target proteins stimulated by HG and negates the HG-mediated reduction in sensitivity to docetaxel[67,97,102]. Resveratrol played an important role in suppressing HG-driven ROS-induced cancer progression by inhibiting the ERK, p38 MAPK, STAT3, and AKT signalling pathways[68,89]. Indomethacin inhibited HG-induced proliferation and invasion by upregulating E-cadherin and activating the PI3K/AKT/GSK-3β signalling pathway[90]. Curcumin suppressed HG-driven EGF-induced invasion and migration by inhibiting the EGF/EGFR signalling pathway and its downstream signalling molecules, including ERK and Akt[91]. Aspirin inhibited cell proliferation by modulating abnormal glucose metabolism via NF-κB (or NF-κB/HIF1α)/GLUT1 signalling[69]. HG increased the cytotoxicity induced by carboplatin and 5-FU and decreased their IC50 because of the synergistic effect of the HG-mediated reduction in P-glycoprotein (P-gp) levels as well as increased drug accumulation, which enhanced ROS levels[52].

Conclusion

In summary, HG induced by various signals increases the risk of cancer. Studies of the role played by HG in cancer progression and therapy have revealed new connections between nutrient utilisation and the tumorigenic state. As interest in cancer and glucose metabolism grows, combining therapies of HG inhibitors with other modalities may be effective.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Xin Jia CAI, Jian Yun ZHANG, Ao Bo ZHANG and Xuan ZHOU analysed the data and drafted the manuscript; Drs Tie Jun LI, He Yu ZHANG, Jian Yun ZHANG and Xin Jia CAI designed the research; Drs Tie Jun LI, He Yu ZHANG and Jian Yun ZHANG obtained copies of studies and revised the manuscript. All authors read and approved the submitted version.

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