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REVIEW

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Proton pump inhibitors display anti-tumour potential in glioma

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Abstract

Objectives: Glioma is one of the most aggressive brain tumours with poor overall survival despite advanced technology in surgical resection, chemotherapy and radiation. Progression and recurrence are the hinge causes of low survival. Our aim is to explain the concrete mechanism in the proliferation and progression of tumours based on tumour microenvironment (TME). The main purpose is to illustrate the mechanism of proton pump inhibitors (PPIs) in affecting acidity, hypoxia, oxidative stress, inflammatory response and autophagy based on the TME to induce apoptosis and enhance the sensitivity of chemoradiotherapy.

Findings: TME is the main medium for tumour growth and progression. Acidity, hypoxia, inflammatory response, autophagy, angiogenesis and so on are the main causes of tumour progress. PPIs, as a common clinical drug to inhibit gastric acid secretion, have the advantages of fast onset, long action time and small adverse reactions. Nowadays, several kinds of literature highlight the potential of PPIs in inhibiting tumour progression. However, long-term use of PPIs alone also has obvious side effects. Therefore, till now, how to apply PPIs to promote the effect of radiochemotherapy and find the concrete dose and concentration of combined use are novel challenges.

Conclusions: PPIs display the potential in enhancing the sensitivity of chemoradiotherapy to defend against glioma based on TME. In the clinic, it is also necessary to explore specific concentrations and dosages in synthetic applications.

1 | BACKGROUND

Glioma is one of the most aggressive brain tumours. Histologically, the World Health Organization (WHO) classified the tumours of the central nervous system (CNS) into astrocytomas, oligodendrogliomas and ependymoma. In addition, gliomas are classified into four grades according to the degree of malignancy. Types I and II are low-grade gliomas and types III and IV are high-grade gliomas.[1–3] The clinical cure rate and 5-year survival rate of patients are all very low. The prognosis is very dismal and the average survival period is only about 1 year. One of the main reasons for the poor prognosis of patients is that glioma is prone to drug resistance to chemoradiation therapy resistance.[4,5] Therefore, it is urgent to explore new strategies for glioma treatment.

Pump proton inhibitors (PPIs) are a drug of choice for inhibiting gastric acid secretion. In clinical, they are the first-line option to treat peptic ulcers, gastroesophageal reflux disease, zoai syndrome and upper gastrointestinal bleeding.[6,7] It has become the first-line drug for abnormal gastric acid secretion and related diseases combined with amoxicillin, clarithromycin and other drugs to treat *Helicobacter pylori* infection.[8,9] PPIs have the advantages of fast onset, strong acid inhibition, long action time, low blood drug concentration and low

adverse reactions.[10] The first generation includes omeprazole, lansoprazole and pantoprazole; the second generation includes iprazole, rabeprazole and esomeprazole. Compared with the first-generation PPIs, in terms of drug properties, the second-generation PPIs have the advantages of higher bioavailability, less affected by food and antiacid drugs, slow plasma clearance, less first-pass effect after oral administration, higher stability, less adverse reactions and longer half-life. In clinical, the second-generation PPIs have better effects in inhibiting gastric acid secretion and *H. pylori*. Besides, they are more effective for relieving pain and the treatment of ulcers, especially, the coalescence of duodenal bulb ulcers. While combined with other medicines, the second-generation PPIs revealed higher security and effectiveness.[11–13]

Progression and invasion are the main causes of death in malignant tumour patients.[14] The tumour microenvironment (TME) is a multi-complex environment regulated by various cytokines, transcription factors and pathways.[15] One major cause of the progression and invasion is set off by the intimate relationship of glioma cells with the microenvironment. Recent therapeutic anti-tumour approaches focus on such critical components of TME.[16,17]

Thus, we searched Pubmed and Cnki conducting for this review. Our aim is to explain the specific relationship between TME and the progression of glioma. PPIs, the main force for treating the stomach, were found the proficiency to promote the sensitivity of glioma to chemoradiotherapy. Thus, associating with the mechanism of PPIs, another crucial purpose is to make clear the mechanism of PPIs in hypersensitization to inhibit proliferation and progression of glioma based on TME.[18]

2 | EPIDEMIOLOGY OF GLIOMA

Glioma is the most common and malignant primary brain tumour in the CNS caused by canceration of glial cells in the brain and spinal cord. Up to the present, glioma is the most invasive and incurable cancer.[19,20] In the worldwide, about 100,000 cases of diffuse glioma are recorded every year. The annual incidence rate is about 3–8 cases per 10,000 persons.[21] However, the incidence of glioma is increasing gradually. The peak incidence of primary glioma is between the ages of 55 and 60 years and the incidence rate is higher in men than women. Secondary GBMs tend to affect younger individuals about age 40 years old.[22,23] The main median survival is 15 months under treatment and 5 months without treatment, respectively.[24,25] However, the patients affected by low-grade gliomas may survive for more than 20 years.[26]

Up to date, the mainstay of treatment methods contains surgical excision, chemotherapy and radiotherapy.[24] According to the fifth edition of the WHO Classification of Tumours of the CNS (WHO CNS5), the standard of care and prognosis of glioma, circumscribed gliomas are usually benign and recommended for early complete resection, associated with chemotherapy if necessary. Diffuse gliomas and other high-grade gliomas according to their molecule subtype are slightly intractable, with the necessity of chemotherapy. However, for glioblastoma, feasible resection followed by radiotherapy and temozolomide chemotherapy is contained in the current standard of care.[27,28]

Glioma stem cells with the characteristics of stem cells and heterogeneous resident nerve cell spheres can promote the recurrence and progression of glioma.[29] In terms of progression, there are two main methods of recurrence after surgical resection. The first is to convert the apoptosis-related factor ligand (FasL) in astrocytes into the paracrine death signal pathway of cancer cells, or effect by inhibiting the axon Pathfinder L1 cell adhesion molecule (L1CAM) to promote the growth of glioma. Serine protease inhibitors (serpins) in glioma progression can inhibit the production of fibrinolytic enzymes and ensure the survival of cancer cells by protecting cancer cells from the biological process of death and promoting the growth of vessels.[30]

Moreover, with the extension of treatment time, chemoresistance occurs frequently. Also, it is inevitable for normal tissues adjacent to cancer to be damaged.[31] Due to the resistance to chemoradiotherapy and the aggravation of glioma, local recurrence and distant progression are prone to occur.[32] Moreover, because the glioma is prone to pass across the blood–brain barrier (BBB) adhering to the surface of capillaries and growing around capillaries, the delivery and penetration of therapeutic drugs passed into the brain are restricted resulting in the weakened therapeutic effects.[33]

As a result, the clinical therapeutic effect of glioma is deficient. Nowadays, it is an urgent problem to explore novel drugs with better curative effects to overcome the resistance and the physiological barriers.

3 | THE CLINICAL APPLICATION OF PPIS

PPIs are kinds of stomach medicine with minimal side effects, generally.[34] Clinically, they are used to remedy peptic ulcers, gastroesophageal reflux disease, zoai syndrome and upper gastrointestinal bleeding having become the first-line drugs for abnormal gastric acid secretion and related diseases.[35–38] However, different PPIs have different clinical application tactics and blood–brain barrier penetration (Table 1).[39–42]

PPIs are mostly derivatives of benzimidazole compounds.[43] They are mostly weakly basic drugs with low original drug activity. After being absorbed into the blood, it is transported to the gastric mucosal parietal cells and finally reaches the acidic cavity of the secretory tube where the pH < 4.[44] The technical drug is easy to be ionized and positively charged in this environment to play a preferable role.[45] Due to the low membrane penetration, the drug is continuously aggregated and converted into the form of bioactive hyposulfonic acid and hyposulfonamide under the catalysis of acid, and then mixed with the sulfhydryl (sh) of vacuolar ATPase (V-ATPase) dehydrating and coupling to produce an irreversible covalent disulfide bond to inhibit the H^+ transport mechanism of the enzyme and acid secretion.[46]

PPIs are also H^+-K^+ ATPase inhibitors which may act on the acid-secreting tubules on parietal cells. The acid-secreting tubules secrete acid in the way of H^+ and K^+ exchanging through H^+-K^+ ATPase on the membrane to pump H^+ out of the cells. PPIs cannot transfer the hydrogen of parietal cells to the gastric cavity and inhibit the formation of gastric acid.[44,47] Besides, PPIs bind to cysteine residues nearby the nucleotide-binding domain of subunit A covalently resulting in the

TABLE 1 Molecular weight, dose in clinic, blood–brain barrier (BBB) permeability of pump proton inhibitors (PPIs)

PPIs	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Esomeprazole
Molecular weight	345.416	369.362	383.370	359.44	367.398
Dose in clinic	20 mg/day	15–30 mg/day	40 mg/day	10–20 mg/day	0–40 mg/day
BBB permeability	Omeprazole was able to penetrate the BBB and the time to reach the maximum concentrations is about 60 min in brain. Lansoprazole could penetrate the BBB and is similar with omeprazole. The time to reach the maximum concentrations is about 40–60 min in brain. Pantoprazole is under trail. Rabeprazole is under trail. Esomeprazole is able to cross the BBB. The peak serum concentration is reached 90–180 min after oral administration.				

inactivation of V-ATPase to inhibit acid content secreted.[48] Only as new pump molecules are synthesized and inserted into the cell membrane can gastric acid secretion restart.[49] Besides the application in gastrosia, PPIs has the potential in curing tumour such as epithelial ovarian and breast cancer nowadays.[50–53] Till now, the most used PPIs are to treat late-stage tumours. Such as omeprazole could inhibit the progression of early colorectal adenoma to colorectal cancer and distal metastasis of advanced breast cancer.[54,55] However, there has been a study reporting PPIs administration could decrease the occurrence of the early-stage gastric cancer induced by ulcerative differentiation.[54] In addition to being used alone, PPIs are often used in combination with conventional chemotherapy drugs for cancer.

Omeprazole has the ability to inhibit V-ATPase to change the acidic microenvironment and enhance the sensitivity of drug-resistant cells to taxol. Besides, omeprazole combined with paclitaxel can significantly reduce the tumour volume in animal models with epithelial ovarian cancer.[50] V-ATPase is overexpressed in epithelial ovarian cancer compared with normal ovarian epithelial cells. YAP (Yes-associated protein) is one of the major transcription activation factors playing an important role in regulating cell proliferation and organ development. YAP is overexpressed and is connected with the progression and multi-drug resistance of the tumour. V-ATPase D1 also known as ATP6V0D1, is the D subunit of the V0 domain. YAP is associated with V-ATPase D1 to promote progression and MDA of the tumour. Esomeprazole could inhibit the expression of YAP and V-ATPase D1, also the combination of YAP and V-ATPase D1 to promote the sensitivity of tumour cells to conventional anticancer drugs such as PTX.[51] In terms of breast cancer, as the effective chemotherapeutic drugs for breast cancer, raloxifene and doxorubicin combined with omeprazole, lansoprazole and pantoprazole, the viability of breast cancer cells is decreased and the apoptosis is enhanced obviously, compared with raloxifene and doxorubicin solely.[52,53]

4 | TUMOUR MICROENVIRONMENT IS THE MAIN MEDIUM FOR THE PROLIFERATION AND PROGRESSION OF TUMOUR

Progression is the most common phenomenon for patients with glioma which may lead to death. Progression occurs when tumour cells spread from the site of origin to another part of the brain. Progression is a multifactorial process that depends on metabolic changes, gene mutations and TME. Tumour cells, cancer stem cells, cancer-associated fibroblasts (CAFs) and cytokines secreted by these cells, extracellular matrix proteins, blood vessels and various extracellular substances form a complex environment consisting of TME.[56,57] TME is a recognized significant key element affecting tumour occurrence, growth and progression considered as a unit so as to generate a dynamic communication with tumour cells.[58,59] Tumour cells can change and maintain their own survival and development conditions through autocrine and paracrine, so as to promote the growth and development of tumours.[60] TME not only includes the structure, function and metabolism of tumour tissues but is also related to the internal (nuclear and cytoplasmic) and external environment of tumour cells.[61] The main characteristics of the tumour microenvironment are acidification and hypoxia because of the imbalanced steady-state.[62] Therefore, tumours have intracellular alkaline pH and lower extracellular pH ranging from 7.2 to 7.4 and 6.5 to 7.1, respectively.[63,64] The acidic microenvironment strongly contributes to tumour progression by stimulating invasion and progression, inhibiting the immune surveillance of cancers and conferring chemoresistance.[65] The acidic extracellular environment is conducive to tissue damage and the activation of destructive enzymes in the extracellular matrix (ECM) increasing the potential for tumour progression and acquiring cell phenotype of multidrug resistance (MDR).[66] In order to maintain intracellular pH (pHi), the tumour cells have evolved powerful mechanisms to counteract cytoplasmic acidification and expel accumulated protons from cells, including Na^+/H^+ exchanger (NHE), carbonic anhydrase, monocarboxylic acid transporter (MCT) and proton pumps.[67]

Pump proton could keep the stability of H^+ in and outside the microenvironment, and evade the change of intracellular acidity caused by bioenergy conversion.[68] Proton pumps such as V-ATPase, NHE and the carbonic anhydrase are upregulated in cancer cells.[69] In tumours, V-ATPase can pump protons out of cells, alkalize the intracellular environment and acidify the extracellular environment, so as to resist apoptosis and promote tumour aggressiveness.[70] Increased activity of these pH regulators protects cells from changes in cell phenotype caused by pHi fluctuations by squeezing H^+ in the extracellular space.[71]

The metastatic potential of tumour cells is affected by the relationship between tumour cells and ECM. Low pH activates and

triggers the secretion of proteolytic enzymes including matrix metalloproteinase-2 (MMP-2), MMP-9, a tissue serine protease, adamalysin-related membrane protease, cysteine protease, cathepsin and gelatinase leading to the degradation and remodelling of ECM, so as to promote tumour invasion and progression.[72]

It is reported that the acidic environment after the metabolism of tumours is not conducive to normal cells and results in the immune escape of tumour cells.[73] PPIs can directly change the quantity of T-cell receptors (TCR) or major histocompatibility complex (MHC) so as to improve the recognition and elimination of tumour cells by T cells.[74] Alkalizing the acidic environment of tumour cells can also improve the activity of other effector cells such as natural killer cells (NK) or natural killer T cells (NKT).[75] Under the acidic environment, tumour cells can use the nutrition provided by autophagy of normal cells to meet the needs of tumour cell growth.[76] PPIs can also inhibit autophagy resulting in the lack of nutritional supply for tumour cell proliferation and the death of the tumour.[77] Compared with normal cells, the tumour cells could be more adaptable to the imbalanced pH environment.[78] Because the V-ATPase complex is mainly located at the edge of tumour cells which may induce the acidification of TME and furtherly promote the growth of cancer.[79] In addition, the acidic TME provides extremely suitable living conditions for the proteolytic activity of cathepsins especially the lysosomal cathepsins, since the activity of most of the cathepsins could be enhanced in an acidic condition.[80] And they could activate growth factors and proteases or degrade components of the extracellular matrix to promote progression. For instance, Cathepsin B (Cat B) can upregulate the function of MMPs which leads to the detachment of cells leading to the initiation of the cell migration.[81]

Akt (protein kinase B[PKB]) accumulates in mitochondria and phosphorylates pyruvate dehydrogenase kinase 1 (PDK1) on phospho-NDRG1 (THR346) to inactivate the pyruvate dehydrogenase complex. And then this pathway turns tumour metabolism to glycolysis to antagonize apoptosis, inhibit oxidative stress and maintain the proliferation of tumour cells.[82] Simultaneously, low pH could increase glycolysis to inspire progression. Glycolytic metabolites are the synthetic raw materials of biological macromolecules and the indispensable structural elements of new tumour cells. The increase of lactic acid produced by glycolysis will decompose and destroy ECM and promote progression.[83]

EMT is pivotal for wound healing, processes and its occurrence in cancer is known to aggravate invasion, migration and drug resistance in tumours. The occurrence of EMT causes the loss of epithelial characters of tumour cells and the transformation into mesenchymal-like cells and thus enhancing tumour cell proliferation and motility and decreasing cell apoptosis.[84] Transforming growth factor-β (TGF-β) has played a key role in deciding EMT.[85] V-ATPase may promote EMT induced by TGF-β. What is more, low pH is more conducive for tumour cells to produce more TGF-β and promote EMT which implies the growth of cancer.[86]

Hypoxia is another major feature of TME associated with malignant progression, therapy resistance and poor prognosis of glioblastomas (Figure 1). Hypoxia is a pathophysiological condition that generally arises as a consequence of the rapid proliferation of cancer cells as they outgrow their blood supply, therefore, depleting the cells of nutrients and available oxygen. Hypoxia always happens in late-stage tumours. Hypoxic tumours are found to be highly aggressive and resistant to chemoradiotherapy because hypoxic tumours require triple the normal radiation dose to achieve the desirable cell death effect as a normal irradiating dose which means that hypoxia is also a key factor in determining the growth of tumour-induced by MDR.[87,88] Previous studies have revealed that oxygenation in glioma is 10 mmHg compared with normal brain tissue which is 40 mmHg and which may arise from radiation resistance.

Moreover, compared with normal cells, the expression of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) in adjacent tissues was significantly higher.[89,90] Stably expressed HIF-1α drives gene expression of two metabolic enzymes lactate dehydrogenase A (LDH-A) and PDK1 which are vital in the conversion of pyruvate into lactate and inactivating pyruvate dehydrogenase (PDH) and subsequently prevent pyruvate oxidation in the mitochondria to promote glycolysis to improve the tolerance to hypoxia. This process could increase glucose to glycolysis while suppressing OXPHOS and mitochondrial respiration by decreasing the input into mitochondria to avoid apoptosis.[91] It is the classical Warburg effect. The hydrogen ions removed from sugar will not be oxidized into the water through the respiratory chain, but will accumulate in large quantities in the cells, such as lactic acid.[92] This altered glucose metabolism not only enables tumour cells to use glucose-derived carbons for the synthesis of essential cellular ingredients but also rapidly provides ATP to fuel cellular activities. In addition, this metabolic shift contributes significantly to chemoradiotherapy resistance. Tumour cells can promote the Warburg effect, enhance acid secretion and increase extracellular pH (pHe) furtherly promoting the survival of tumour cells.[93] Lactate accumulation also promotes cancer cell migration by facilitating the interaction of fibroblasts and escaping immune surveillance.[94] At the same time, a large number of metabolites such as lactic acid and pyruvate can further improve the transcription and expression activity of HIF-1α, and finally, form a positive feedback expression of HIF-1α in a hypoxic environment (Figure 1).[95] HIF-1α degrades extracellular matrix and upregulates collagen expression genes promoting collagen fibre synthesis. HIF-1α promotes the reconstruction of ECM under hypoxia based on proline 4-hydroxylase A1 (P4HA1), P4HA2 and procollagen lysine oxoglutarate dioxygenase 2 (PLOD2) to increase directional migration.[96] HIF-1α regulates VEGF, TGF-β and prospero homeobox-1 (Prox-1) to mediate the proliferation and progression of lymphatic endothelial cells and to disrupt the cellular barrier around existing blood vessels, pulling endothelial cells away to form new capillaries with fenestrations and fewer tight junctions. This results in an enhanced infiltration of cellular and plasma components into the brain, further inducing the reconstruction of TME, as well as maintaining the stem cell phenotype of tumour cells promoting progression and drug resistance.[97,98]

In addition, nitric oxide synthases (NOS), widely expressed in gliomas, use L-arginine to produce primary RNS type NO that interacts with $O2^{-}$, generating $ONOO^{-}$. NO is more effective in quenching

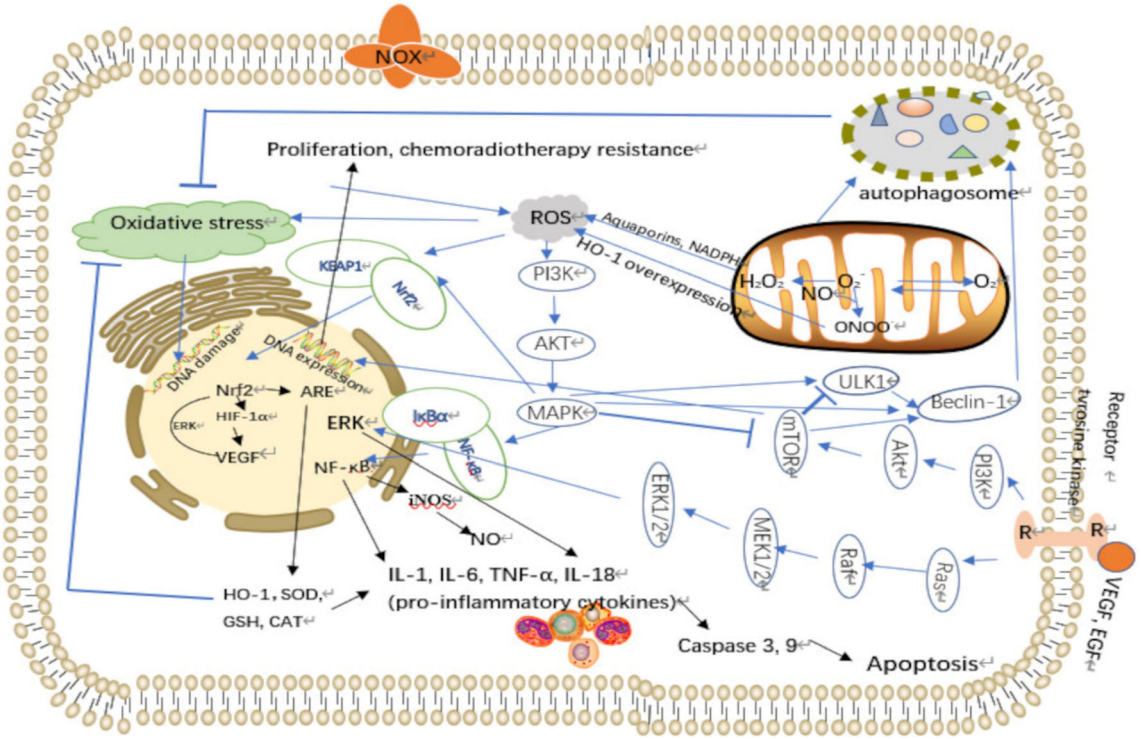

FIGURE 1 Schema depicting sources of ROS and antioxidant defences reported for glioma cells

superoxide and reacts with O_2 to form other nitrogen oxides such as NO_2, as a free radical, which in turn may react with NO to yield N_2O_3 reacting with biomolecules (lipids, proteins and DNA), potentially leading to cell death (Figure 1).[18,99] NO plays a role in the activation of NF-κB which is a major transcription factor in glioma progression. IκB kinase-independent NF-κB activation may involve NO-induced IκB nitration. RNS may disrupt the Keap1-Nrf2 complex which can prolong the activation of Nrf2 and promote the antioxidant state inducing survival of tumour cells.[100] RNS also inhibits wild-type p53 through cysteine (Cys) oxidation and tyrosine (Tyr) nitration contributing to glioma genesis furtherly.[101]

Another reason promoting progression and recurrence is MDR. A formidable obstacle for MDR is the blood-tumour barrier (BTB) and blood–brain barrier (BBB), filtering barriers of capillaries. They exclude most compounds except highly lipidized small molecules of less than 400 daltons, rendering potentially powerful anti-cancer drugs impotent for GBM treatment. Thus, breaking the BTB or BBB will significantly impact GBM treatment.[98] Actually, the BBB is composed of non-fenestrated brain endothelial cells (BECs) of the capillary wall, which is surrounded by pericytes, astrocytes, perivascular neurons, a basal membrane and an extracellular matrix, forming the highly organized neurovascular unit.[102] Besides the nitrosourea compounds carmustine (BCNU) and lomustine (CCNU) as well as the platinum agents cisplatin and carboplatin, the most widely used chemotherapeutic drug is temozolomide (TMZ), an imidazotetrazine derivative of dacarbazine. TMZ could penetrate into the CNS and has 96%–100% bioavailability.[103] However, the concentration of TMZ is far away efficient. TMZ is one of the substrates of P-glycoprotein (P-gp), an important efflux pump which locates on the apical membrane side of endothelial cells forming BBB and serves as a maintainer of the integrity and the polarity of BBB. P-gp not only hinders brain entry of a large number of xenobiotics including potentially toxic substances and therapeutic agents but also transports the compounds that have crossed the BBB back into the circulation (Figure 2).[104] Due to the overexpression of P-gp at the BBB of glioma, only 20% of TMZ regarding a systemic dose is able to enter the cerebral parenchyma.[105] In addition, BBB also accounts for the limited efficacy of other chemotherapeutic agents in GBM, such as etoposide, irinotecan, vincristine and cisplatin. Undeniably, BBB and BTB greatly contribute to the MDR.[106] The mechanisms of MDR in tumour cells which is in the TME include four aspects: (1) The amplification or overexpression of transmembrane transporter gene leads to the high expression of encoded transmembrane transporter, so as to promote drug efflux and the change of drug subcellular distribution, resulting in the decrease of drug concentration in cells[107] (2) the change of metabolic transformation, such as the change of some proteases in cells, result in the enhancement of cell detoxification (3) the change of drug action target, such as the decrease topoisomerase (TOPO) content or the change of property leads to the resistance to anti-tumour drugs targeting TOPO (4) other mechanisms include the change of apoptosis-related pathways, cell proliferation speed, the enhancement of damage repair and the change of pharmacokinetic factors.[108] Several transmembrane transporter proteins may hinder drugs from reaching the target by reducing the concentration of drugs in tumour cells or changing the distribution of drugs in cells, such as drug efflux P-glycoprotein (P-gp), multidrug resistance protein (MRP). P-gp is an

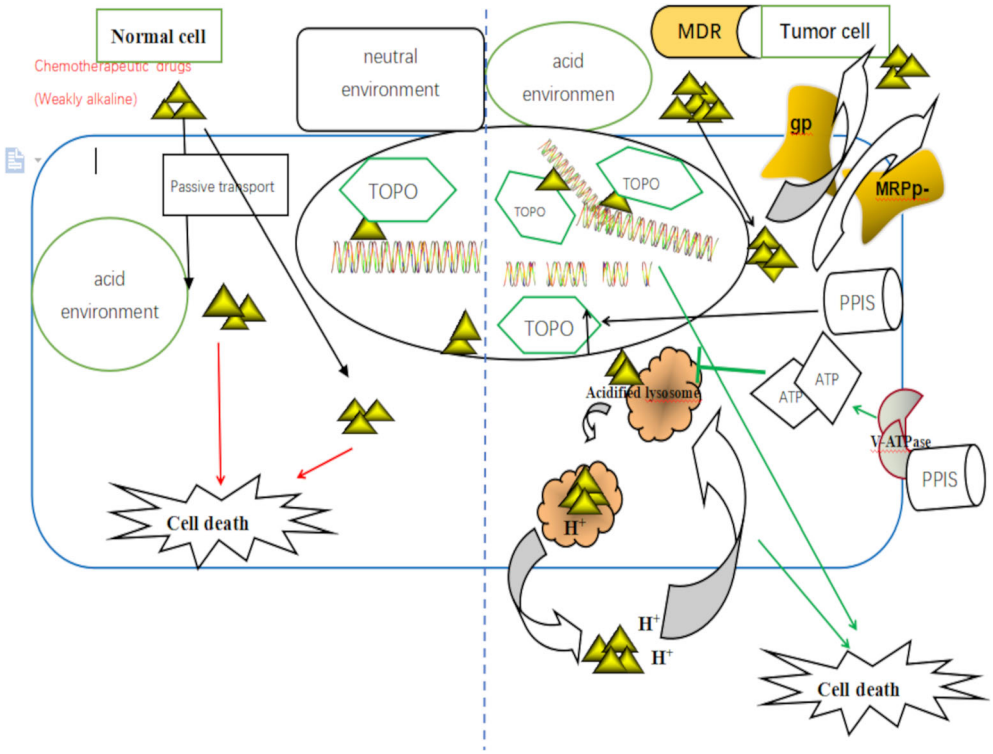

FIGURE 2 The mechanism of pump proton inhibitors (PPIs) for defending multidrug resistance

efflux drug transporter associated with multidrug resistance gene-1 (MDR-1) expression in the cell membrane, which is responsible for expelling various drugs from tumour cells to form multidrug resistance.[109] Weakly alkaline drugs can lead to capturing ions based on being protonated in an acidic extracellular environment, which hinders the effects of anti-cancer chemotherapy drugs. In general, most chemotherapy drugs are weakly alkaline and the characteristics are prone to ionize in an acidic environment and with high polarity, so it is not suitable to pass through the cell membrane.[110,111] Once entering tumour cells, drugs are encapsulated in acidic organelles and the efficacy will be reduced or ineffective. Even several chemotherapy drugs induce the production of V-ATPase in tumours maintaining the acid environment. Lysosomal vesicle or endosomes style structures in the acid environment can further expel drugs out of cells or eliminate drugs by activating relative secretory pathways. And then these structures can be further reused to enhance drug resistance limiting the drug's effects on its molecular targets (mainly DNA). Therefore, the concentration of chemotherapeutic drugs that can play a toxic and anti-cancer role in cancer cells is still very low.[112] In the hypoxia and glucose deficient tumour microenvironment, the expression of mRNA and protein of Topo is decreased and associated with decreased DNA breakage leading to the decreased cytotoxicity of chemotherapy drugs. At the same time, the content of complexes and chemotherapy drugs-TOPO-DNA is decreased resulting in MDR.[113]

The immune system's response to the tumour can impact the glioma's survival, proliferation and invasiveness.[114] Tumour-associated macrophages (TAMs) are formed by peripheral blood monocytes infiltrating into solid tumour tissues accounting for a large proportion of tumour stromal cells. TAMs are an important component of TME. It has been reported that *macrophages* are related to immunosuppression and immune escape.[115] In the early stages, tumour cells release chemokines to attract macrophages and other inflammatory cells reaching the extracellular matrix. Then TAMs can penetrate the basement membrane so that tumour cells escape the bondage of the basement membrane and reach the surrounding normal tissue matrix.[116] At the same time, TAMs and tumour cells can promote angiogenesis by releasing enzymes to generate angiogenesis, such as MMP2, MMP-7, MMP-9, MMP-12 and cyclooxygenase-2 (COX-2) to improve the invasiveness and motility of cells.[117,118] Neovascularization can provide nutrition and oxygen for tumour growth and provide a path for tumour cell progression.[119] TAMs also could release cytokines and growth factors directly to promote growth, such as VEGF, tumour necrosis factor-α (TNF-α) interleukin-8 (IL-8) and so on.[120] Hypoxia in TME can further induce macrophages to produce HIF-1α and promote angiogenesis.[121]

CAFs exist in the stroma of tumour cells which are associated with EMT and angiogenesis.[122] Fibroblasts activate HIF-1α and NF-κB signalling pathways to stimulate oxidative stress, autophagy and glycolysis. These decomposition products create nutrient support for tumour growth.[123] Besides, CAFs produce a variety of cytokines and extracellular matrix proteins including stromal cell-derived factor 1 derived factor 1 (SDF1), hepatocyte growth factor (HGF), VEGF, platelet-derived growth factor (PDGF) and TGF-β to provide a basis for the progress and progression.[124]

Mast cells (MC) secret fibroblast growth factor 2 (FGF-2), VEGF and TGF-β to promote the progress and progression.[125] A variety of cytokines produced by tumour cells can induce the proliferation of myeloid-derived suppressor cells (MDSCs), such as COX-2, IL-6 and

granulocyte-macrophage colony-stimulating factor (GM-CSF) and VEGF can further enhance the immunosuppression of myeloid suppressor cells and enhance immune escape together.[126,127]

This kind of neuro-inflammatory TME can lead to the loss of BBB integrity.[128] The consequences of a compromised BBB are deleteriously exposing the brain to potentially harmful concentrations of substances from the peripheral circulation, adversely affecting neuronal signalling and abnormal immune cell infiltration.[129] All of these can lead to disruption of brain homeostasis.

Autophagy also displays a key role in the growth of glioma. Autophagy is an important catabolic process of substances in cells.[130] It wraps the wrong proteins or damaged organelles through autophagy vesicles with double-layer membrane structure, fuses with lysosomes and hydrolyzes with lysosomal acid hydrolases to produce biological molecules such as amino acids which are finally reused by cells to realize the circulation of substances in cells.[131] In the early stage of tumour progression, autophagy will inhibit tumour progression. In the middle and late stages of tumour progression, autophagy will protect the tumour from stimulating and anoikis apoptosis so as to promote progression.[132] Anoikis is a special form of programmed cell death induced by the loss of contact between cells and extracellular matrix and other cells. Usually, tumour cells gather together and closely adhere to the extracellular matrix to form a 'home' for self-function and survival. When they break away from the cell adhesion matrix and lose the connection between cells, anoikis apoptosis will generate.[133] Moreover, tumours will produce extensively damaged proteins, organelles and other harmful components after chemotherapy and radiotherapy. At this time, the activity of autophagy is improved to remove harmful substances in time and provide emergency and raw materials for DNA damage repairing which may result in a poor prognosis of tumour treatment.[134]

With the long-term administration of chemistry, autophagy could gather the tumour cells to assemble into blocks promoting progression. Moreover, autophagy may induce the movement of damaged proteins, mitochondria and stressors including ROS to maintain the activation of advanced glioma.[135] Chemotherapy could activate the autophagy genes like autophagy-related protein 5 (Atg5), LC3 and others involved in autophagic pathways inducing progression.[136,137] PI3K-Akt-mTOR is a key signalling pathway that is related to autophagy.[137] mTOR acts as the main regulator of autophagy containing two complexes called mammalian target of rapamycin complex 1 (mTORC1) and mammalian target of rapamycin complex 2 (mTORC2). MAPK inhibits mTORC1 activity, which leads to suppression of autophagy activating unc-51-like kinase 1 (ULK1). ULK1 induces the Beclin-1 phosphorylation, which can result in autophagy.[138–140] At the same time, autophagy is an adaptable response under the stimulation of the endoplasmic reticulum (ER). Under ER stress, Ca^{2+} is released into the cytoplasm and triggers autophagy by activating the MAPK-TOR signal pathway. In addition, in the tumour microenvironment, cancer cells experience hypoxia resulting in the exposure of hydrophobic regions of misfolded/unfolded proteins and accumulation largely in the ER inducing the upregulation of unfolded protein response (UPR) and the expression of autophagy genes inducing invasion and progression. In addition to canonical UPR, proteotoxicity also stimulates the selective, autophagy-dependent, removal of discrete ER domains loaded with misfolded proteins to further alleviate ER stress. These mechanisms can favour the progression and long-term survival of advanced glioma cells.[141,142]

It has been evidenced that autophagy could increase the expression of NF-κB to activate MMP inducing invasion and progression.[143] MMP plays a key role in the invasion process by degrading many elements of ECM, including collagens, fibronectin and laminin.[144] It was reported that MMP is localized in vasculature cells and tumour cells of malignant astrocytomas.[145] MMP inhibition significantly decreases invasion, migration and tumour progression in advanced glioma cells.[146] All of the tumour cells would upregulate glycolysis to reduce the energy supplied by mitochondrial. Autophagy provides a source of energy in this process to promote the survival and progression of advanced glioma.[76,147]

In terms of the pathological of gliomas, some mutations will indeed cause cells to continuously enter the cell cycle for mitosis, escape apoptosis, contact inhibition and immunosuppression and make cells continuously obtain energy so as to cause metabolic abnormalities and induce angiogenesis, hypoxia and necrosis of brain tumours, such as IDH mutation, H3K27M mutation, TERT mutation, MGMT mutation and so on. These mutations will activate the expression of various signal pathways and form the basis for the occurrence and development of glioma.[148]

4.1 | PPIs can induce apoptosis by changing the acidic tumour microenvironment

More and more studies have proved that the acidic environment outside the tumour cells plays an important role in the development, infiltration, dissemination and drug resistance of the tumour (Figure 3).[149] PPIs inhibit the activity of V-ATPase in the acidic environment outside the gastric cancer cells to hinder the proton transport, so as to change the pH gradient of gastric cancer cells and cause cell inactivation (Figure 3). The changed pH affects the structure and activity of almost

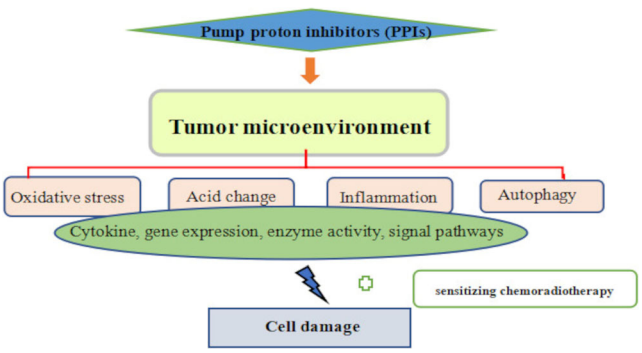

FIGURE 3 Mechanism of pump proton inhibitors (PPIs) inducing glioma cell damage

every enzyme, then, these active enzymes affect various signals and pathways of cells.[150] For example, V-ATPase is involved in the Wnt/β-Catenin signalling pathway which promotes tumour development and progression. Pantoprazole can inhibit V-ATPase so that this pathway is blocked.[151]

The concrete mechanism of V-ATPase is to maintain the balance of abnormal pH gradient inside and outside the cell.[152] After being acidified outside the cell, V-ATPase can activate proteolytic enzymes, including MMPs, tissue serine proteases and bone morphogenetic protease type 1 metalloproteinase (BMP-1), to degrade ECM. V-ATPase can also remove various toxic molecules, such as H^+ and ROS.[153–155] In addition, M-ATPase and P-ATPase play a similar role to V-ATPase. These all exist on the cell membrane, mitochondrial membrane, lysosomal membrane, endosomal membrane and Golgi membrane, so as to maintain an acidic environment outside the cell membrane and inside the organelle membrane in gastric tumours.[156] Omeprazole could cause the disorder of the lysosomal function of gastric tumour cells, further causing the activation of caspase-3.[157] The activated caspase-3 cleaves the corresponding cytoplasmic and nuclear substrates, resulting in the apoptosis of the tumour finally.[158] One research report that the rate of immune cell infiltration (M1 macrophages, neutrophils, CD103 cells and NK cells) is high, and the antitumor effectors (iNOS, INF-γ, IL-1α) are enhanced after using the inhibitor of V-ATPase.[159] At the same time, the number of cancer cell-positive cells and the activity of caspase are all decreased.[155] The role of PPIs is exactly similar to the inhibitor of V-ATPase in suppressing the progression of the tumours. Likewise, esomeprazole, as an inhibitor of V-ATPase, can reverse EMT by inhibiting IκB protein and furtherly inhibiting the expression of TGF-β and thus countering tumour.[86]

The balance of acidity inside and outside cells can maintain the survival of normal cells. However, the acid–base imbalance is the main induced element of cell canceration. The main pH value is 7.2 and 7.4 in and outside the normal cells, respectively. However, the main pH value in and outside the tumour is 7.4 and 6.3, respectively.[85] The tumour could balance this kind of microenvironment through the functional expression of several different molecular types of machinery. The migration and growth of solid tumours rely on the supplement of glucose.[160] In the short term, the tumour cells could adapt to the decreation of glucose. But the long-term reduction of glucose would increase the apoptosis of cancer cells. In order to combat the reduction of glucose, the change in the microenvironment may produce more lactic acid which may reduce the death of cells induced by a shortage of glucose.[161] The increase of lactic acid could downregulate the G1/S transition process in the cell cycle and inhibit tumour cells in the G0 phase, so as to reduce the demand of tumour cells for energy and nutrients. At the transcriptional level, the G2/M checkpoint was also down-regulated which could further aggregate tumour cells in the G0 phase.[162] Lactic acid could also activate the autophagy process of cells to reuse intracellular substances to maintain cell survival.[163,164] At the same time, several studies illustrate that lactic acid also inhibits the apoptosis of tumour cells by maintaining the content of NADPH and high expression of anti-apoptotic protein.[165,166] In a word, lactic acid can be the main reason leading to tumour cells escaping apoptosis. PPIs could harbour acid production to invert the proliferation induced by lactic acid.[167]

4.2 | PPIs can induce apoptosis by changing the anoxic tumour microenvironment

Oxidative stress is a popular research factor to recover the tumour even the glioma. In general, the damage induced by oxidative stress is mainly due to the imbalance between the antioxidant defence system and the excessive formation of ROS.[168] In the normal functional states, the production and removal of ROS are in a dynamic balance. However, if the production of ROS exceeds the removal as given an acute stimulation, then, the excessive free radicals will cause irreversible oxidation damage to the body.[169] The main resources of ROS are mitochondria and cytoplasm.[170,171] Mitochondria mainly produce oxygen-free radicals and non-oxygen-free radicals, such as O_2^- and H_2O_2.[172] Of course, other cells are the secondary source of ROS in TME. Macrophages, neutrophils and tumours are the main generated resources of ROS. ROS generated by macrophages is considered as defending and phagocytosing tumours.[173] Studies also show that activated monocytes contacting with tumours in TME could generate a high quantity of ROS producing more impact on DNA damage, metabolic activity, membrane structure and relative protein synthesis.[174] A low level of ROS may activate cell proliferation and inhibit cell senescence and death. The high quantity of ROS may lead to the oxidative modifications of DNA, protein and lipid, finally, harming cells.[175] A large amount of nitric oxide (NO) will produce peroxynitrite with a stronger oxidation effect with a superoxide anion. $ONOO^-$ can irreversibly damage mitochondria by inhibiting the mitochondrial respiratory function and the activity of Na^+/K^+ ATPase and reduce the biological activity of NO participating in the enhancement of cell adhesion, proliferation, vasoconstriction accelerating the injury of arteriosclerosis.[18] ROS oxidizes or peroxidases unsaturated fatty acids of which the function is to support the fluidity of the cell membrane damaging the permeability of cell membranes, such as membrane receptors, membrane proteins and ion channels.[176] Furthermore, the nutrients absorbed by cells are reduced, such as vitamins, amino acids and inorganic salts, resulting in immunopathologic injury. ROS can break the N-glycosidic bond on nucleotides and produce base-free sites leading to the breaking of the main chain.[177] It could also promote DNA to produce pyrimidine dimer.[178] In addition, modification of base groups occurs, such as acetylation which further affects protein synthesis, cytoskeleton and DNA damage repair.[179] When taking protein into consideration, ROS can break and crosslink protein or polypeptide chains resulting in protease inactivation and metabolic disorder.[180] Besides, due to the high expression of SOD and catalase enzymes in glioma; there is an accelerated conversion of superoxide to hydrogen peroxide in tumour cells which makes astrocytes particularly sensitive to damage induced by ROS.[181]

PPIs have been used to modulate the pHi, disturb the mitochondrial membrane potential and produce excessive ROS leading to

apoptosis (Figure 3).[182] Several studies implied the ROS in the TME may promote more macrophages to inhibit the progression of tumour.[183] In addition, PPIs have been applied to enhance the secretion of gastrin, and then enhance the secretion of insulin by islet cells, further inhibiting glycolysis and strengthening oxidative stress.[183]

Studies concluded that P-ATPase plays a crucial role in defending against ROS.[184] Glycolysislar V-ATPase is overexpressed in tumour cells and metastatic cells to inhibit the generation of ROS in the tumour acidic microenvironment.[50] PPIs could inhibit P-ATPase and V-ATPase to enhance the sensitivity of tumour cells to oxidative stress.[185] Mild up regulation of mammalian target of rapamycin (mTOR) pathway activity can promote the production of cellular antioxidants, in turn, while over-activation will promote the production of ROS. PPIs, such as esomeprazole, could reduce the over-transduction of mTOR signals furtherly inhibiting the growth of cancer cells and prolonging lives.[186]

The activity of cytochrome c oxidase (COX) is associated with the survival period of glioma. The median survival time of patients with low tumour COX activity is short, while the median survival time of patients with high tumour COX activity is long.[187] Because COX promotes the switch from glycolytic to OXPHOS metabolism. Increased COX activity in tumours has been associated with tumour progression after chemotherapy failure.[188,189] Recently, a variety of studies have considered the activity of COX as a prognostic indicator of glioma.[190,191] Pantoprazole blocked the level of COX inducing the increased depolarized mitochondria ($\Delta\psi$ m) and ROS levels.[149] Moreover, PPIs, as the inhibitor of pump proton, have the potential of inhibiting the activity of mitochondrial electron transport complex, electron transport to reduce mitochondrial respiration and energy supplement so that promoting tumour cell death.[192]

Different PPIs own different mechanisms of inducing apoptosis. Bax and Bcl-2 genes play an important role in apoptosis.[193] Pantoprazole can inhibit the activation of the STAT3 pathway and downregulate its downstream cyclin D1 and Bcl-2 accordingly so as to inhibit the proliferation of tumour cells and induce apoptosis.[194] Omeprazole is different from pantoprazole. Experimental research shows omeprazole cannot induce the apoptosis of SGC-7901 (from lymph node progression from a 56-year-old female patient with gastric adenocarcinoma) through the expression of Bax and Bcl-2 related genes, but, through the decreased mitochondrial membrane potential after the action of ROS and caspase pathway. Apoptosis signalling pathways related to caspase activation include mitochondrial/cytochrome c (Cyt-c) pathway, death receptor pathway and ER pathway. After the action of omeprazole, the expression of caspase-3 in SGC-7901 cells increased as time goes on indicating that omeprazole may activate caspase-3 through the mitochondrial/cyt-c pathway to induce apoptosis.[195]

4.3 | PPIs can enhance oxidative stress based on NF-κB, MAPK, Keap1/NRF/ARE, PI3K/Akt signal pathways

ROS affects metabolism mainly based on NF-κB, mitogen-activated protein kinases (MAPK), Keap1/NRF/ARE and PI3K/Akt signal pathways (Figure 1).[71] At first, NF-κB and MAPK pathways exert an essential implication in oxidative stress.[196] Under no stimulations, the main components P50/65 and IκBα are active in the cytoplasm with the limitation of an inhibitor of κB (IκB) protein.[197] While accepting a stimulation, IκB is phosphorylated by IκB kinase (IKK) and IκB detaches from NF-κB, enabling NF-κB dimers to enter the nucleus and express relative target genes actively, such as cytokines, COX-2 and pro-inflammatory proteins.[24]

The three main subfamilies of MAPKs are extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK which may modulate gene expression of nuclear Nrf2 and antioxidants enzymes mediated by ARE.[198,199] Moreover, ERK could be activated in cell growth and differentiation. P38 was involved in cell apoptosis and stress signal pathway.[200,201] PPIs selectively inhibited the phosphorylation of ERK and stimulated the phosphorylation of p38 in a time and dose-dependent manner to sensitize apoptosis.[201] When the above three enzymes are activated, they can further promote the phosphorylation of NF-κB and stimulate the release of TNF-α and IL-6 which would promote the proliferation of tumours.[202] Omeprazole has been proved to inhibit the activity of MAPK and NF-κB and subside with the downregulation of TNF-α, IL-6 and SOD2 which may suppress the growth of tumours.[195] MAPK pathways are downstream pathways of different growth factor receptors such as epidermal growth factor (EGF). EGF activates protein kinase C (PKC) thereby activating the Ras/Raf/MEK/ERK pathway. It has been reported that the Ras/Raf/MEK/ERK pathway is involved in mediating H_2O_2-induced apoptosis in human glioma cells.[203–205] It is well known that KRAS mutations contribute to cell proliferation and survival in numerous cancers, including glioma. One pathway through which mutant KRAS acts is an inflammatory pathway that involves the kinase IKK and activates the transcription factor NF-κB. BRAF is a kinase that is downstream of KRAS and is predictive of poor prognosis and therapeutic resistance.[206] However, there has been evidence that the inhibitor of V-ATPase can inhibit the mutation of B-Raf and the subsequent MAPK–ERK pathway to promote tumour apoptosis.[207] IDH (Isocitrate dehydrogenase) mutations were mainly distributed in II, and III-grade gliomas and secondary gliomas defined by WHO. It is closely related to methylguanine methyltransferase (MGMT) promoter methylation and TP53 mutation.[208] IDH mutations can prevent cells from resisting γ Radiation, singlet oxygen, UVB radiation and other emergency damage, promoting the progression of glioma. In terms of mechanism, IDH mutations will affect the affinity of the enzyme, resulting in the decrease of the affinity between the enzyme and substrate. IDH mutants will compete with wild-type IDH for substrate, and mutant IDH is more likely to combine with the substrate to form a dimer, leading to the accumulation of HIF- α and activation of downstream target genes including VEGF so as to promote tumour progression.[209] IDH mutations are often used to predict early glioma. In classifying lower-grade gliomas with IDH mutation, the V-ATPase is overexpressed. It is also mentioned that the use of V-ATPase inhibitors can inhibit the expression of the neurodevelopmental core transcription factor POU3F2, thereby reducing IDH mutations and inhibiting tumour proliferation and anti-radiation.[210] Therefore, PPIs

have the possibility of inhibiting IDH mutation in glioma, thus reducing the occurrence of glioma. Till now, a clinical epidemiological survey has shown that esomeprazole can inhibit the methylation of tumour suppressor gene APC and increase the expression of APC in oesophageal cancer.[211] With regard to glioma, some studies have shown that PPIs can inhibit MGMT promoter methylation, thereby increasing the sensitivity of glioma to radiotherapy and chemotherapy.[212] Mutations in H3.3 often occur in glioma, resulting in decreased H3 histone methylation and increased H3 histone acetylation with subsequent activation of transcription promoting progression.[213] Studies have shown that acetylation inhibitors can inhibit the pump protons and down-regulate the effective components of the MAPK–ERK-BRaf pathway so as to inhibit tumour proliferation. However, in terms of tumours resistant to acetylation inhibitors, the activity of related drug metabolic enzymes increases so as to promote anti-tumour, after the administration of omeprazole, lansoprazole and pantoprazole. These further indicate that PPIs have the potential to inhibit tumour progression.[214–216] One of the serious risks of glioma is epilepsy. Up to 75% of LGG patients have seizures during the course of the disease.[217] Epilepsy is a transient interruption of normal electroencephalogram activity, which significantly affects the quality of life. The mass effect of glioma mainly refers to the excessive proliferation of brain white matter, which leads to the gradual increase of tumour volume.[218] With the increased volume of tumours, it is easy to compress the surrounding brain tissue, and it is easy to cause the loss of stability and uncoordinated discharge of neurons during the growth of glioma. The two main reasons are IDH mutation and abnormal activation of the mTOR pathway.[219] However, PPIs have the potential to suppress the IDH mutation and mTOR pathway. Besides, it has been proved by an experiment that the proportion of myelinated axons increased after omeprazole treatment. In vitro incubation with omeprazole significantly promoted the differentiation and maturation of oligodendrocyte precursor cells. In vivo, Omeprazole treatment (10 mg/kg) for 2 weeks significantly improved the motor coordination function of demyelinated mice.[220] PPIs also could prolong action potential.[221] Thus, PPIs may play a crucial role in preventing seizures.

Nrf2 is a key transcription factor regulating gene expressions of several antioxidant enzymes, such as NAD(P)H quinone acceptor oxidoreductase 1 (NQO1), SOD, catalase, glutathione peroxidase (GPX), glutathione reductase (GR) and haeme oxygenase-1 (HO-1), which play important roles in protecting cells against oxidative damage.[222] Nrf2 also plays an important role in the tumour environment to promote the proliferation of glioma and protect glioma from anti-tumour therapies.[223] Tumour cells lose the heterozygosity of gene through Nrf2 or Keap1 mutation so that Nrf2 and Keap1 cannot be combined normally resulting in Nrf2 accumulation in tumour cells and then activating downstream genes increasing the level of detoxifying enzymes in tumour cells, promoting the formation and growth of tumour cells, enhance the resistance of tumour cells to radiotherapy and chemotherapy. Thus, blocking-up Nrf2 could suppress glioma.[224,225] The microenvironment serves as the basis for indirect mechanisms of Nrf2 in the treatment of glioma. The mechanism of downregulating Nrf2 is mainly about two aspects: direct and indirect ways. Indirect mechanisms include three main aspects of the microenvironment: perivascular, hypoxic and immune microenvironment.[226] Angiogenesis plays a key role in providing energy so as to activate the proliferation of glioma. Nrf2 was found to significantly increase microvessel density (MVD) and expression of small vessel marker CD31.[227] Nrf2 could also regulate angiogenesis based on HIF-1α and VEGFs.[228] HIF-1α is a downstream molecule of Nrf2 to regulate hypoxia. Activation of HIF-1α could activate numerous perivascular compounds, such as angiopoietin, endothelin-1, inducible nitric oxide synthase (iNOS), adrenomedullin and erythropoietin. Furtherly, in turn, VEGF can also activate Nrf2 according to activate ERK1/2 and induce the production of antioxidative enzymes.[229,230] The glioma is addicted to an anoxic environment. The overexpression of Nrf2 exerts antioxidant function and further promotes the expression of HIF-1α and HO-1(HO-1 is a molecule to resists hypoxia) to inhibit the migration and invasion of tumours in a hypoxic microenvironment finally.[231] HO-1 also plays a key role in fighting against inflammation via ERK/Nrf2 signal cascade induced by oxidative stress.[232]

Glioma could evade immune surveillance to decrease the response between the tumour cells and immune surveillance cells. Nrf2/ARE pathway regulates tumour immune surveillance based on regulating the secretion of cytokines and the function of immune cells.[233] Nrf2 regulates the secretion of a variety of cytokines, such as INF-γ, IL-5 and IL-13.[234] INF-γ induces the production of cytokines affected by immunosuppression and growth factors, which is conducive to the growth and progress of tumour cells. Besides, it may downregulate Alpha-fetoprotein (AFP) and melanoma antigen (MAGE) to promote antigen modulation of tumour cells so as to escape immune surveillance.[235] At the same time, Nrf2 could induce the transformation of CD4 (+) T cells into the T helper cells 2 (Th2) to secret IL-4 and IL-10 in order to inhibit immune protection.[236] The above indirect mechanisms all rely on vascular endothelial cells, fibroblasts and immune cells which are all existed in TME.[19] Nrf2 may active proteasome protective genes such as Phase II detoxification enzyme gene, proteasome gene, ubiquitinase gene, antioxidant protein gene and multidirectional drug-resistant protein 2 (MRP2) gene which have been proved to inactive external substances and detoxify and be associated with MDR.[237] Besides, under low oxidative stress, overexpressed Nrf2 will reduce the sensitivity to cytotoxic chemotherapeutic drugs by promoting the detoxification of anti-cancer drugs and enhancing the antioxidant capacity.[238,239] Based on the above mechanisms, PPIs have been proven to inhibit the activation of Nrf2 and downregulate the expression of genes or enzymes regulated by Nrf2 to suppress the growth of glioma, such as SOD, GPx, catalase (CAT), HO-1 which may inhibit antioxidation.[240]

The acidic microenvironment can inhibit the production and function of CD4, CD25, factor Forkhead box P3 (FOXp3) and iT-regs through the PI3K/Akt/mTOR signal pathway.[241] IL-10 produced by iT-regs decreased the production of ROS in the vascular wall, the activity of NADPH and improved vascular endothelial dysfunction.[242] However, it has been proven that omeprazole and pantoprazole have the ability to reduce the iT-regs differentiation in an acidic microenvironment so as to suppress the glioma.[241]

4.4 | PPIs can inhibit tumour progression by inhibiting tumour-related inflammation

Enhanced inflammation is a risk factor for many cancers. Immunosuppression caused by inflammation is one of the main reasons for poor prognosis and the short survival of glioma patients.[238] Macrophages are natural immune cells that can be found in most TMEs.[243] Research reported that macrophages produce a small number of tumorigenic factors in vitro, and their ability to inhibit T-cell activation and proliferation is reduced and associated with the decreased of Dew sugar receptor-1 (CD206), IL-10, TGF-β, the expression of arginase-1, matrix metalloproteinase and vascular endothelial growth factor after using sh-V-ATPase.[244,245] Being similar to the inhibitor of V-ATPase and sh-V-ATPase, PPIs may play a similar role in inhibiting tumour progression.

In different microenvironments, there are different macrophage subtypes containing pro-inflammatory and anti-inflammatory. M1 subtype could promote macrophage phenotypes to inhibit tumour. M2 subtype could suppress macrophage phenotypes to promote tumour.[246,247] Research has proved that pantoprazole may enhance recruitment of TAM in TME showing augmented expression of CD11c, phagocytosis and macrophage morphology.[248,249] Phagocytosis and expression of CD11c are considered important signature markers of macrophages with M1 phenotype.[250] Additionally, pantoprazole displays increased anti-tumour activity with an augmented expression of anti-tumour molecules, such as IL-1, TNF-α, IL-2R and NO. Experiments show that pantoprazole could counter the tumour as exposed in vitro. Thus, PPIs may not directly enhance the anti-tumour activity, but rely on the cytokines secreted by macrophages indirectly.[251]

Inflammatory mediators can change the local environment of tumours, and chronic inflammation can lead to DNA damage.[252] Clinically, anti-inflammatory drugs can reduce the incidence of cancer.[85] Especially, PPIs have been studied to target TNF-α monoclonal antibodies, anti-sensory targeting Smad7, and non-steroidal anti-inflammatory drugs to prevent cancer based on inflammation (Figure 3).[253] Some inflammatory mediators and chemokines are special inflammatory mediators. PPIs directly inhibit epithelial cells and neutrophils or the production of relative chemokines playing an anti-inflammatory role through suppressing the secretion of INF-α and proinflammatory mediators such as IL-1 and translationally controlled tumour protein (TCTP) so as to inhibit cancer-related symptoms and progress.[254] Besides, STAT3 plays an important role in maintaining and promoting the tumorigenic inflammatory environment, the transformation and progression of malignant tumours based on NF-κB and IL-6/GP130/JAK pathways.[255] There has been a research reporting that pantoprazole can inhibit the activity of the IL-6/STAT3 pathway in gastric cancer cells.[192]

TNF-α and IL-6 are two kinds of cytokines that play an important role in the process of cancerous cachexia.[256,257] IL-6-like cytokines independently mediate the excessive lipolysis and metabolism in cancerous cachexia.[258] TNF-α downregulates the PLIN pathway by upregulating the MAPK pathway so as to promote lipolysis. Abnormal metabolism of fat has a lot to do with the progression of tumours.[259] Several relative experiments showed that TNF-α and IL-6 declined apparently in the serum of cancer cells in mice after intragastric omeprazole which implied that PPIs inhibit the tumour progression caused by fat metabolism.[254] Besides, PPIs may decrease the quality of IL-4 directly and furtherly stimulate the production of TNF-α.[260] Omeprazole and pantoprazole have been already proved to decrease pro-inflammatory factors such as TNF and IL-6, and increase anti-inflammatory factors such as IL-10 implying the potential for anti-tumour.[193] As a result, PPIs may give play to anti-inflammatory and cancer clearance. Furthermore, PPIs could transfer M2 macrophages to M1 macrophages to fight cancer.[261] Also, PPIs have a direct effect on neutrophils, monocytes, endothelial cells and epithelial cells, so as to exert an anti-inflammatory effect and inhibit INF-α, secretion of proinflammatory mediators such as IL-1 and TCTP.[262] The anti-cancer activity of PPIs is based on the fact that it can significantly reduce the production of acid-active substances, IL-6 and nitric oxide, especially TNF-α, expression of inducible NOS and COX-2. PPIs can act in an acidic environment by inhibiting inflammatory factors to further inhibit cancer.[263]

4.5 | PPIs display an anti-tumour effect through autophagy

V-ATPase is the main proton pump that acidifies vesicles such as lysosomes. PPIs can disrupt the lysosomal localization of V-ATPase leading to lysosomal dysfunction, thus contributing to the lysosomal storage disorders in order to counter tumours.[264]

The mammalian target of rapamycin (mTOR) is a highly conservative serine/threonine-protein kinase that belongs to the PI3K-related protein kinase family.[112] MTOR can phosphorylate Atg13 preventing it from interacting with complexes containing Atg1 and Atg17, and inhibiting autophagy assembly so as to reduce radiation resistance.[265] The activation of mTOR could induce aerobic glycolysis through upregulating Pyruvate kinase M2 (PKM2), as well as the activation of OXPHO.[266] MTOR can also stimulate the metabolism of lipids, nucleotides and other components to promote tumour progression. Moreover, mTOR can activate HIF-1α promoting the regeneration of blood vessels.[267] MTORC2 can also directly promote tumorigenesis by activating Akt or Serum- and glucocorticoid-inducible kinases (SGK) promoting the growth of tumours.[268]

Hypoxia plays a crucial role in regulating autophagy since the absence of oxygen leads to inhibition of mTORC1 and subsequently decreased inhibition of the unc-51 like Ulk1 complex finally resulting in activation of autophagy.[269] PPIs depolarize mitochondrial membrane potential by increasing the opening of mitochondrial permeability transition pore (MPTP), resulting in excessive production of ROS which further stimulates lipid peroxidation and reduces glutathione levels.[270] This process could generate excessive ROS leading to lysosomal chamber instability which will affect mitochondrial membrane potential and mitochondrial energy supplement to suppress hypoxia and autophagy in advanced glioma promoting the anti-glioma.[270] In

addition, more ROS will promote the release of pro-apoptotic molecules into the cytoplasm and further promote autophagy.[271] It has been reported that PPIs can induce autophagy by activating ERK and JNK and inhibit mTOR signalling by activating MAPK.[201,272] There is also evidence showing that PPIs mediate the strong upregulation of Beclin-1 by activating NF-κB which is responsible for the ROS-induced autophagy making the foundation for anti-tumour.[273,274]

Besides, PPIs could moderate the acidic microenvironment to inhibit the activation of lysosomal cathepsins to suppress MMP increasing sensitivity to TMZ. Finally, the progression of the tumour was inhibited.[275] PPIs may activate MAPK kinase, reduce blood glucose levels and block glycolysis induced by TNF-α so as to invert the Warburg effect which could activate the autophagy promoting progression.[276]

5 | PPIS SENSITIZE CHEMORADIOTHERAPY PROMOTING APOPTOSIS

Chemoradiotherapy resistance is an important element to early recurrence, treatment failure and dismal prognosis of glioblastoma.[277] With growing amounts of evidence that chemoradiotherapy may induce the more normal cells to glioma leading to recurrence and progression.[278,279] Even if the concentration of drugs entering plasma and cerebrospinal fluid is enough to inhibit the progression of the tumour, the drug resistance and progression of glioma also happen from time to time.[280] Thus, hoping to make use of PPIs and chemoradiotherapy together to play a good effect.

The radiation may lead to the mutation of mitochondrion respiratory chain complex I and II and DNA which will lead to more ROS in glioma.[281] Excessive ROS could damage DNA containing mitochondrion DNA leading to respiratory chain dysfunction, even higher levels of free radicals in the cells, and the disbalance of O_2^- in and outside the cells, and, further, block oxygen supplement.[282] In addition, ionizing radiation (IR) will produce more free radicals which combine with oxygen and further lead to permanent DNA damage.[283] Thus, radiotherapy can irreversibly damage DNA through reactive oxygen species. However, the tolerance of normal cells to radiation dose is limited, and the radiation dose cannot be increased continuously.[284] Hypoxic tumour cells continue to exist after radiation and transform into a more invasive phenotype.[19] PPIs such as esomeprazole could generate more ROS persistently to make up for the deficiency of oxidative stress caused by limited radiation.[285] The inhibitory effect of many chemotherapeutic drugs depends on the oxygen partial pressure of the TME. In general, the sensitivity of chemotherapy was the strongest at the peak of oxygen partial pressure.[286,287] Because of the ability to enhance oxygen partial pressure through enhancing oxidative stress, PPIs could increase the sensitivity to chemotherapy. However, we need to explore the dose and concentration of different PPIs with the maximum oxygen partial pressure in TME.

The inverted pH gradient of cell membrane inside and outside tumour is an important mechanism leading to drug resistance.[288] The acidic extracellular microenvironment makes a chemical and physical shelter for the anti-tumour effect of weakly alkaline chemotherapeutic drugs. Once the chemotherapeutic drugs are protonated and alkalized, they cannot pass through the plasma membrane.[241,272] Chemotherapeutic drugs in tumour cells enter lysosomes, acidic organelles, and acidic vesicles through protonation and neutralization, and are further discharged out of cells.[289] PPIs changing cell microenvironment can inhibit the intracellular P13K/Akt/mTOR signal pathway and bypass the TSCL/2-Rheb signal pathway to inhibit its downstream mTOR molecules, and then inhibit the expression of HIF-1α, MDR protein and P-gp.[290,291] In glioma, MDR protein and P-gp gene are overexpressed.[292] P-gp could combine with chemotherapeutic drugs to pump the substrate out of the cell by hydrolyzing ATP, so as to inhibit the effect of chemotherapeutic drugs. Being similar to P-gp, overexpressed multidrug resistant-associate protein-1(MRP1) pumps the drug out of cells.[293] Research implied that PPIs may inhibit the expression of MRP1 and P-gp to reverse chemoresistance. The excessive PPIs could be cultured in vitro by the alkalizate microenvironment of cancer cells so that increasing chemosensitivity.[294] PPIs can reverse the Warburg effect of tumours by inhibiting pyruvate dehydrogenase kinases and subsequently activating mitochondrial OXPHO or changing anaerobic digestion and ATP binding box (ABC) transcription factors, so as to increase the sensitivity of cancer cells to chemoradiotherapy inducing apoptosis.[86,295]

PPIs can prevent the occurrence of EMT by interfering with the expression of the TGF-β/Smad signal pathway and NF-κB in the acidic microenvironment.[296–299] It also has been proved that rabeprazole administration induced cell death and reduced cell migration together with EMT by inhibiting Akt and Gsk-3β phosphorylation, which in turn suppressed the EMT. In addition to molecular aberrations and hypoxia, pump protons may facilitate epithelial to mesenchymal transition by modulating the pH of the TME. We found rabeprazole could play a better role in the unbuffered acidic environment to inhibit EMT.[300] What is more, pantoprazole inhibits breast cancer resistance protein (BCRP) and has a chemo-sensitizing activity, thereby contributing to improved delivery of imatinib (a kind of drug for treating leukaemia) into the CNS.[299] It has been proved that treatment of the cancer cells with the PPIs resulted in order of magnitude reduction in the half-maximal inhibitory concentration (IC_{50}) values.[301] Esomeprazole enhances radiosensitivity in radiation-resistant squamous cell carcinoma of the head and neck.[285] PPIs could also increase chemotherapeutic drug uptake by the tumour cells.[302] PPIs, as the small molecules, could pass through BBB and BTB (Table 1).

In the clinic, PPIs have been proven the ability to overcome the resistance of conventional chemotherapeutic drugs for breast cancer and radiation. The use of PPIs in 6754 patients suffering from breast cancer significantly not only improved the overall survival rate of these patients and reduced the disease recurrence rate but overcome the resistance of conventional chemotherapy drugs and radiation.[303] Besides, based on clinical epidemiological comparative trials, PPIs can assist radiotherapy and chemotherapy to delay the overall survival of 206 patients with rectal cancer.[56] What is more, Omeprazole not only improved the effect of radiotherapy and chemotherapy but also delayed the recurrence and complications of 125 rectal cancer

patients.[304] The combined use of PPIs in the treatment of laryngeal cancer can reduce the incidence of pharyngeal reflux and mucositis.[305] Although there has been no relative research studying the synergistic effect of chemoradiotherapy and PPIs in glioma, based on the above-mentioned relevant clinical epidemiological study about the administration of PPIs in other cancers and preclinical pharmacologic or toxicologic metabolism and mechanism analysis. Of course, improper dosage selection of PPIs and chemoradiotherapy will also lead to the aggravation of adverse reactions. A clinical study showed that the inappropriate dose of PPIs led to the further aggravation of radiation pneumonia after radiotherapy for lung cancer.[306]

In general, PPIs may be a potential valuable anti-cancer drug to promote chemoradiotherapy sensitivity so as to block the growth of glioma.

6 | THE ACUTE SIDE EFFECT OF PPIS AND THE NECESSITY OF COMBINING PPIS WITH CHEMORADIOTHERAPY

The basic side effects of PPIs contain nausea,[307] diarrhoea or headache,[308] and even more serious side effects such as subacute cutaneous lupus erythematosus,[309] and interstitial nephritis and pneumonia.[310] After a long period of the epidemiological follow-up survey, patients with long-term use of PPIs may get complications of suppurative liver abscess, pulmonary tuberculosis and inflammatory bowel disease.[311] Inflammatory mediators can cause metabolic disorders as being with PPIs for a long time, such as IL-1, IL-6, TNF-α, INF-γ and prostaglandin E2 (PGE2) which may induce an increase in muscle decomposition and a decrease of muscle synthesis lead to the decrease of muscle mass and muscle strength, even furtherly subside with decreased physical function, polymyositis and rhabdomyolysis.[312] Besides, mitochondrial would be impaired and intestinal microbial would change based on the proximal pH of the intestine increases.[313] It has been proved that PPIs elevate the pH of the stomach and upper gut causing more bacteria, even pathogenic bacteria, to survive in the gastrointestinal tract and enter the gut gradually.[314] Vitamin B12, vitamin C, vitamin D, magnesium, calcium, iron, β-carotene and zinc will be reduced due to the decreased relative quality of food release and body absorption.[315–319] Suppressing magnesium may inhibit the absorption of Vitamin D implying the release of adipocytokine which is involved in the regulation of glucose levels and fatty acid breakdown inducing insulin resistance so that the appearance of obesity and contribute to an increase of the inflammatory state.[315] Based on a reported real case, PPIs may be associated with several mental diseases.[320] Thus, it is urgent to design specific and efficient combined medication or united anti-glioma therapies to treat glioma.

7 | CONCLUSIONS AND FUTURE DIRECTIONS

The tumour microenvironment is the main medium for proliferation, progression and multidrug resistance of tumours. Acidity and hypoxia, as well as the relative inflammatory response and autophagy, are the main influencing factors for tumour progression and progression in TME. PPIs could promote apoptosis and sensitize chemoradiotherapy through altering the release of inflammatory factors and cytokines of inflammatory cells, autophagy and promoting oxidative stress based on NF-κB, MAPK, Keap1/NRF/ARE, PI3K/Akt signal pathways in TME. PPIs could be considered as an adjuvant treatment strategy to be combined with medication to fight glioma. In order to better predict the therapeutic effect, COX can be considered a prognostic indicator.

In terms of the practical application scope of PPIs nowadays, many kinds of PPIs have been used for different cancer, such as liver, and breast cancer. Nowadays, there is little known about its possible glioma protective effects and relatively few studies on practical application in glioma. Therefore, it is necessary to put PPIs into practice to determine the real advantages and disadvantages of PPIs.

AUTHOR CONTRIBUTIONS

Bihan Li collected, read relevant literature and wrote the article. Ying Liu collected relative literatures and guided this article. Shilong Sun collected relative literatures and guided the mentality and this article. [Correction added on 22 March 2023, after first online publication: Author Contributions have been amended.].

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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