Journal of Translational Medicine

REVIEW

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Autophagy in brain tumors: molecular mechanisms, challenges, and therapeutic opportunities

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Abstract

Autophagy is responsible for maintaining cellular balance and ensuring survival. Autophagy plays a crucial role in the development of diseases, particularly human cancers, with actions that can either promote survival or induce cell death. However, brain tumors contribute to high levels of both mortality and morbidity globally, with resistance to treatments being acquired due to genetic mutations and dysregulation of molecular mechanisms, among other factors. Hence, having knowledge of the role of molecular processes in the advancement of brain tumors is enlightening, and the current review specifically examines the role of autophagy. The discussion would focus on the molecular pathways that control autophagy in brain tumors, and its dual role as a tumor suppressor and a supporter of tumor survival. Autophagy can control the advancement of different types of brain tumors like glioblastoma, glioma, and ependymoma, demonstrating its potential for treatment. Autophagy mechanisms can influence metastasis and drug resistance in glioblastoma, and there is a complex interplay between autophagy and cellular responses to stress like hypoxia and starvation. Autophagy can inhibit the growth of brain tumors by promoting apoptosis. Hence, focusing on autophagy could offer fresh perspectives on creating successful treatments.

Highlights

- Autophagy has a dual function in cancer acting as pro-survival or pro-death mechanism.
- Brain tumors are among malignant cancers with high mortality and morbidity worldwide.
- Autophagy can interact with other cell death pathways such as apoptosis in brain tumors.
- Autophagy can regulate progression of various brain tumors including glioma, glioblastoma and ependymoma, among others.
- Autophagy can control metastasis and drug resistance in brain tumors.

Keywords Autophagy, Glioblastoma, Brain tumor, Cancer progression

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Introduction

General background

Brain tumors originating from glial cells, which are more common in the brain and central nervous system compared to other types of brain cells, posing challenges in their treatment due to their distinct growth patterns [1, 2]. Chemotherapy, radiation, and surgery are typical therapeutic choices; however, the blood–brain barrier hinders the efficiency of chemotherapy [2]. The progression of tumors can differ, yet shared characteristics can still be recognized. Identifying key characteristics and growth factors of brain tumors, differentiating from other tumors, exploring treatments, and studying drug resistance for improved are of importance. Malignant brain tumors are the cause of the second highest number of cancer-related deaths in the US, accounting for 2.4% of cases [3–5]. Approximately 1,310 individuals are projected to undergo death from primary brain tumors in the US in 2011, with around 1,344 new diagnoses expected. Glioblastomas (GBM), accounting for 54% of gliomas, are the most prevalent and aggressive form of brain tumor [5]. Despite advancements in multimodal treatment, the typical lifespan of GBM patients has only increased by 12–14 months, indicating a minimal enhancement of under 5% [6]. The low survival rate of GBM is due to their aggressive nature, making surgical removal challenging, and their resistance to traditional cancer therapies including radiation and chemotherapy designed to target tumor cells [7–9]. Targeting pro-survival and non-apoptotic death pathways is essential to combat cancer and chemoresistance, as impaired apoptosis plays a role in both conditions. Autophagy is a cellular process that involves moving cytoplasmic materials to lysosomes for degradation and reuse by enclosing them in autophagosomes [3, 10]. Its roles now include tumorigenesis, maintaining organelle and protein quality, and ensuring genomic stability. More than two decades ago, reduced autophagy activity was discovered in rat hepatocytes [11, 12]. In 1999, the oncogenic gene *BECLIN1* was shown to have a tumor suppressor function [13]; in mice with mutations in autophagy-related genes, tumors developed more quickly in a spontaneous manner [14, 15]. Recent studies have associated reduced autophagy flux with the development of astrocytic tumors and decreased levels of autophagy-related proteins in high-grade gliomas [16, 17]. Controlling autophagy could potentially improve how tumor cells react to chemotherapy and radiation [18–23]. Autophagy has a dual function in cancer development [24] and is also associated with immune escape and the adjustment of immune cell activity [25]. The present study focuses on investigating the role of autophagy in the advancement of brain tumors, with an emphasis on the molecular pathways that control this mechanism.

Brain tumors: an overview of various types

There are two main categories for the approximately 150 various types of brain tumors including primary and metastatic [1, 2, 26]. GBMs are the primary brain tumors primarily made up of glial cells. Nerves, blood vessels, glands, and other cells that form the body's structure may also be present. While most brain tumors that spread to other parts of the body originate in the brain, some tumors can develop elsewhere and spread to the brain through the circulatory system. This symptom commonly appears in patients with breast or lung cancers. Classification of brain tumors is determined based on tumor types, their metastatic potential, and prognosis. The complexity and prognosis of brain tumors are determined by their origin, development, and advancement. To understand the development, outcome, treatments, resistance to drugs, and return of brain tumors, it is essential to investigate their source, including the formation of cancer stem/progenitor cells [1]. During embryonic development, a variety of brain cells, such as neuronal cells and glial cells, are produced from a single pluripotent stem cell. Brain cells differentiate and divide rapidly after their lineage is determined at around day 16 until birth. There is a drastic change in the way genes related to growth or differentiation are expressed at this point. This quick alteration in gene expression is regulated by both internal and external signaling mechanisms, as well as stromal cell participation. Whenever the process is not properly regulated, a cancer stem cell can be formed. Various brain tumors are a result of various phases of brain growth that lead to the generation of progenitor cells. Development and specialization are dependent on various factors such as fibroblast growth factor (FGF) [2, 26, 27], along with changes in histone modification and DNA methylation for epigenetic modification [27–30]. During the formation of tumors, a number of signaling pathways take place, with involvement of FGF being observed. Certain research indicates that signaling pathways regulate epigenetic processes, while other studies suggest the contrary [31]. Nonetheless, brain tumor development varies significantly between children and adults. Various different gene mutations can be identified in adult brain tumors. Tumors in children's developing brains, like those caused by the H3K27me3 mutation, might be more frequently linked to epigenetic alterations. Their reversible epigenetic changes involve differences in levels of histone acetylation and methylation, along with modifications to upstream gene regions [30, 32, 33].

Brain tumors can develop in both children and adults, with variations in their severity as either benign or malignant. It is unexpected to learn that brain tumors in adults and children may vary in terms of location, origin, prognosis, and treatment, but also have some similarities.

Initially, brain tumors were classified based on histological and physiological characteristics [32, 34]. Eventually, these classifications have grown to include indicators of genetic and molecular changes. The metastatic capacity has been used to differentiate between malignant and benign brain tumors [30, 35]. The categorization has also been enhanced by the genomic data [36, 37]. In general, categorizing brain tumors as either malignant or benign helps in determining prognosis and guiding treatment plans. This classification is based on the metastatic potential of tumors. In this scenario, the presence of malignant brain tumors like glioblastoma can be distinguished by their infiltration of nearby tissue and their capacity to metastasize in the central nervous system or other areas. Conversely, benign brain tumors like meningiomas show gradual growth and have limited capability to invade surrounding tissues. Advancements in biology have allowed for the comprehension of how specific genomic mutations, chromosomal changes, and expression patterns contribute to the spread of tumors. Additionally, alterations in onco-suppressor or oncogenes can specifically promote metastasis. Hence, focusing on the genetic makeup can offer fresh perspectives on brain tumor progression and spread that are useful for categorizing these tumors. Further details regarding metastasis-associated differentiation can be located in these research papers [38–40].

Mutations in genes that act as tumor suppressors or oncogenes are widespread in brain tumors and other cancers. The dominant opinion suggests that tumors can be more effectively formed through gradual mutations [41]. The creation of cancer progenitor cells through epigenetic processes is the main trigger for the initial phases of carcinogenesis [42, 43]. Due to significant differences in causes and development of brain tumors in children and adults, this idea is relevant. While children typically have better treatment responses, they could still face long-term issues from chemotherapy. Adult brain tumors have a grim outlook and are prone to spreading. Epigenetic changes are needed in children's tumors because cells divide faster in younger patients, allowing various cell types to potentially become cancerous cells [27]. Due to their high level of specialization, adult cells require mutations instead [44]. Mutations cause tumors to develop and advance at a faster pace, with epigenetic alterations also capable of inducing the production and advancement of cancer progenitor cells [41–43, 45]. For example, a mutation in IDH is often identifiable in glioblastoma tumors [46]. Alternatively, pediatric tumors exhibit mutations in H3K27me3, indicating mutations in the histone 3 gene or enzymes responsible for histone 3 tail amino acid methylation [32]. When cancer cells metastasize, they go through epithelial-mesenchymal transition (EMT) followed by mesenchymal-epithelial transition (MET). Because EMT-MET can be reversed, it is logical to consider that epigenetic mechanisms could play a role in these changes [47]. Metastasis involves transition from epithelial to mesenchymal and back. Epigenetic processes might have an impact on the second transition. The EMT-MET transition mechanisms are not commonly seen in childhood brain tumors, which limits their spread. Various factors, including developmental stage, genomic and epigenetic landscape, and tumor microenvironment, contribute to the disparity between childhood and adult brain tumors. Further details are available in these studies [48–51].

Autophagy flux

Yeast and mammalian cells have over 30 autophagy-related genes (ATGs) that regulate the autophagy process [52]. ATG proteins closely control cargo selection, vesicle formation, elongation, docking, fusion with lysosomes, and breakdown. A significant number of routes that manage cellular stress can induce autophagy. These signals comprise nutrients, growth factors, energy levels, oxygen levels, oxidative stress, ER stress, and pathogen infection [53]. The mTOR regulates autophagy to suppress it in environments with high nutrients [54]. Due to growth factor signaling, the class I phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) pathway facilitates the activation of TOR by the GTPase Ras homolog abundant in the brain (Rheb) [55]. AMPK and EIF2α help inhibit TOR, leading to the activation of autophagy [55, 56]. Moreover, increased levels of tumor suppressor PTEN, which functions as a inhibitor of the PI3-K/AKT pathway, can promote the initiation of autophagy [57]. The tumor suppressor protein TP53 boosts the transcription of negative regulators like AMPK and PTEN, subsequently controlling autophagy indirectly [58, 59]. The creation of a PI3K complex is required for vesicle formation. This complicated structure is comprised of PI3K/Vps34, Beclin-1 (the human version of ATG6), and p150 (the yeast myristoylated serine/threonine kinase Vps15) [60]. Multiple binding partners like Beclin-1-UVRAG [61, 62], ATG14L/Barkor [63, 64], and AMBRA1 [65] positively regulate Beclin-1 in autophagy, while BCL-2 and BCL-xL from the anti-apoptotic BCL-2 family inhibit autophagy. These components physically bind to Beclin-1 and inhibit the formation of the PI3K core complex [66]. Despite this, BNIP3, a member of the pro-apoptotic group BCL-2/adenovirus E1B 19kd-interacting protein 3, binds with BCL-2 and releases Beclin-1, interrupting the BCL-2/Beclin-1 interaction [67]. Rubicon, a newly discovered molecule, interacts with Beclin-1 to lower its levels. However, the MAPK/ERK pathway can increase Beclin-1 levels [64, 68].

Two processes similar to ubiquitin are involved in vesicle elongation [69, 70]. The complex ATG5-ATG12 is created in the initial system through the activity of ATG7, functioning like E1, and ATG10, functioning like E2. ATG16 binding to the ATG5-ATG12 complex leads to the creation of a large multimeric ATG16L complex. In another situation, LC3/ATG8 is cleaved by the protease ATG4, and then ATG7 and the enzyme ATG3 similar to E2 attach the cleaved ATG8 to the lipid PE. The soluble LC3/ATG8 (LC3-1) is transformed into LC3-II and then moved to the autophagosomal membrane's internal and external surfaces during the recruitment phase. The ATG16L complex expands the lipidation of LC3/ATG8 by serving as an E3 (Fig. 1) [71, 72]. The autophagosome merges with the lysosome to create the autolysosome, where cellular components are broken down and recycled by enzymes.

Autophagy in tumor progression

Autophagy's important role in cellular balance and disease progression makes its alterations significant. Noticeably, the improper regulation of autophagy is linked to the advancement of different illnesses in humans, such as cardiovascular diseases [74, 75], cancer [76–78], diabetes mellitus [79, 80], fibrosis [81, 82], neurological diseases [83, 84] and cataract [85, 86], among others. The crucial role of autophagy in the development of cancer has been significant. Hence, numerous research studies have centered on exploring the impact of autophagy on cancer growth [87], spread [88], drug resistance [89, 90], radioresistance [91, 92] and immune evasion [25], as well as other aspects. Furthermore, phytochemicals [93] and nanoparticles [94] have been utilized to control autophagy in the treatment of cancer. Recent research has brought attention to the possible impact of molecular pathways on the regulation of autophagy during the development of cancer. ONC206 has the ability to induce cell death and inhibit growth of liver cancer. Furthermore, ONC206 induces a type of autophagy that promotes cell survival, and inhibiting this process can increase the potential for cell death caused by ONC206 [95]. SNX10 downregulation can induce autophagy to suppress metastasis, EMT, and PI3K/Akt in cervical cancer [96]. Increased TSTA3 levels have been shown

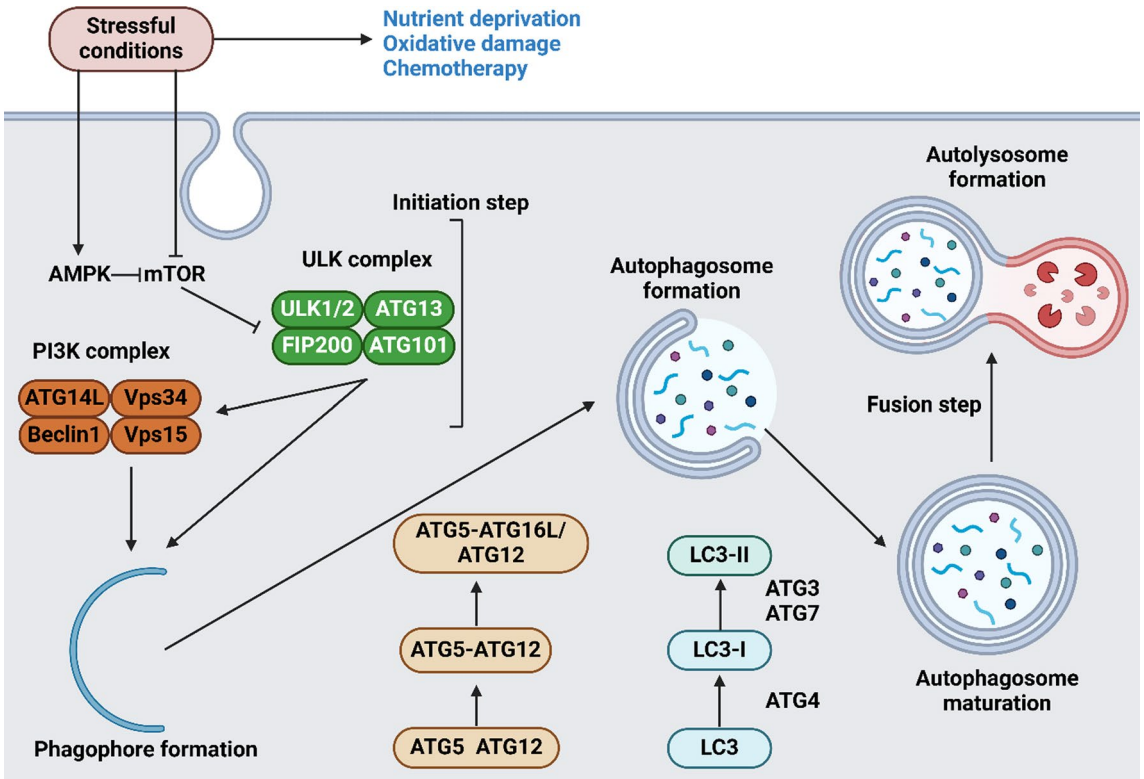

Fig. 1 A schematic representation of how autophagy works in cells [73]. The presence of stressful conditions including starvation and oxidative damage along with chemotherapy can stimulate autophagy through AMPK upregulation and mTOR downregulation. Then, ULK complex stimulates PI3K to induce autophagy. Then, ATG5-ATG16L and ATG12 complex along with the formation of LC3-II can improve the autophagosome expansion. Autophagy has been comprised of four stages including initiation, autophagosome formation and expansion, autophagosome-lysosome formation and degradation of cargo by autolysosomes

to enhance the aggressiveness of LUSC by controlling autophagy through LAMP2 and leading to a negative prognosis [97]. HDAC2 has been shown to increase the expression of LAPTM4B, leading to the advancement of hepatocellular carcinoma through autophagy [98]. Additionally, triggering autophagy can overcome resistance to chemotherapy [99]. As a result, autophagy has a crucial role in promoting the development of human cancers.

In the specific context of epithelial-to-mesenchymal transition, autophagy-related reactions boost tumor growth and advancement by reducing responsiveness to cellular and environmental cues [100–103]. Faults in the process of autophagy machinery can hinder the spread and growth of cancerous cells, as well as their ability to metastasize. Enhanced autophagy flux in advanced human malignancies generally leads to the invasive/metastatic phenotype, high nuclear grade, and poor clinical prognosis [104, 105]. During the proliferation of autophagy-capable hepatocellular carcinoma cell lines, lentiviruses that consistently lower BECN1 or ATG5 levels make these cell lines almost unable to survive in the metastatic environment [106]. Additionally, the strong antimetastatic effects of N-myc downstream regulated 1 (NDRG1) are due to its ability to suppress stress-induced autophagy responses [107]. During the advancement of BRAFV600E-driven carcinogenesis, the elimination of Atg7 in the lungs causes the development of small oncocytomas rather than adenocarcinomas, leading to a buildup of faulty mitochondria and a heightened dependence on external glutamine [108].

Genetic treatments focused on autophagy machinery do not lessen tumor growth in specific models of natural mammalian cancer development because of the $Trp53^{-/-}$ genotype [109–111]. On the other hand, if TP53 loss-of-heterozygosity occurs, pancreatic cancer cells, xenografts, and autochthonous adenocarcinomas driven by KRASG12D will keep growing regardless of autophagy inhibition through genetic or pharmacological means [112, 113]. Pancreatic adenocarcinoma cells with $KRAS^{G12D}$ mutation go into a dormant state after oncogene removal, triggering autophagy to combat metabolic stress [114]. Breast cancer stem cells that form mammospheres have a high level of autophagy activity and can efficiently develop tumors in vivo [115, 116]. Autophagy can enhance cancer growth by maintaining the survival of cancer stem cells and/or enhancing the survival of inactive cancer cells, as blocking BECN1 or ATG4A genetically can prevent tumor development [114]. Cancer cells that cannot undergo autophagy are more susceptible to chemotherapy and radiation therapy and are less resistant to external stimuli [101, 117, 118]. In mice with a healthy immune system, a meaningful immune response can only occur if cell death happens before autophagy responses [119, 120]. The occurrence of senescence in cancer cells after treatment can potentially lead to disease recurrence due to the release of pro-inflammatory and mitogenic cytokines in the surrounding environment [121]. In experimental models of lymphoma, cells depend greatly on autophagy processes for survival. Inhibition of autophagy with drugs has been shown to work together with other chemotherapeutic agents in inducing senescence-associated secretory phenotype (SASP) (Fig. 2) [122, 123].

Understanding the protective role of autophagy can lead to the development of GBM treatment by targeting this molecular pathway. It is worth mentioning that NEO214 can induce cell death and suppress autophagy [124]. In contrast, cannabidiol has been demonstrated to increase ERK expression and stimulate ROS production to enhance autophagy and ferroptosis in GBM [125]. This shows that autophagy plays roles in both promoting survival and inducing cell death as glioblastoma progresses. The anti-cancer function is not provided by the induction of autophagy through pharmacological compounds. Actually, medications can facilitate pro-survival autophagy. Casticin, for instance, triggers cell death and self-cleansing mechanisms, but at the same time inhibits stem cell properties by decreasing Akt/mTOR and JAK2/STAT3 [126]. VLX600, among other types of medications, has been demonstrated to promote mitophagy and autophagy-induced cell death in GBM as an iron chelator [127]. Hence, the role of autophagy may vary due to the influence of pharmaceutical substances on its regulation. Another factor is Aloperine, which has been demonstrated to regulate late autophagy and induce cell death through apoptosis and paraptosis in GBM [128]. Throughout GBM advancement, several autophagy-associated factors such as PARP1, ARSB, and CANX show an increase, whereas ATG3, KIF5B, and EDEM1 show a decrease in expression [129]. The increase of CMTM6 as a factor related to autophagy can activate the Wnt axis to enhance GBM development [130]. While the majority of research has concentrated on controlling autophagy when it is triggered, a new approach for treating GBM is being considered. This idea relies on regulating autophagy before it starts. A recent development is the creation of a pharmacological compound called Eltromopag, which can inhibit autophagic lysosomal genes at the transcriptional level by suppressing TFEB, preventing protein biosynthesis. Evidence suggests that this medication enhances how GBM cells react to temozolomide treatment [131]. Autophagy plays a flexible role in the development of GBM, impacting both proliferation and metastasis [132]. Hence, autophagy has the ability to control advancement of GBM [133, 134]. Furthermore, the role of autophagy in governing the advancement of

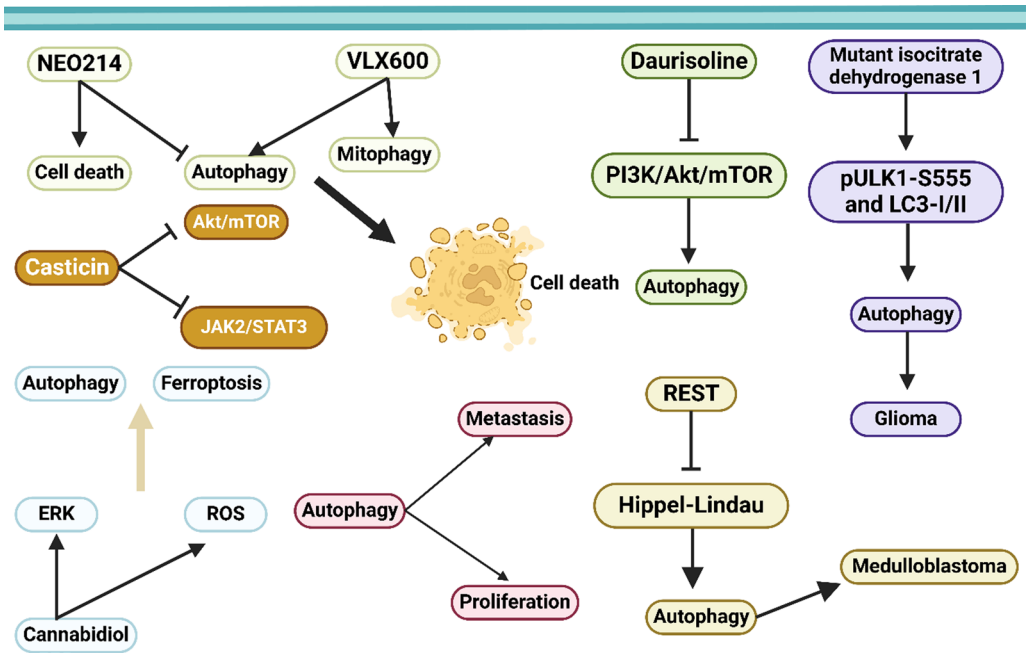

Fig. 2 The function of autophagy in the regulation of brain tumor progression. NEO214 suppresses autophagy, while it enhances cell death in brain tumors. Moreover, VLX600 promotes both autophagy and mitophagy to promote cell death. Therefore, autophagy exerts dual function in the regulation of brain tumor progression

glioma has been examined alongside GBM. The mutant isocitrate dehydrogenase 1 found in glioma can elevate the levels of pULK1-S555 and LC3-I/II to induce autophagy [135]. Therefore, controlling autophagy in glioma may open up opportunities for its treatment. Daurisoline has been shown to inhibit autophagy by decreasing PI3K/Akt/mTOR signaling, enhancing tumor cells' sensitivity to temozolomide [136]. Bacoside a has the ability to induce apoptosis and autophagy in order to hinder the advancement of glioma [137]. Hence, autophagy plays a two-fold role in controlling the advancement of glioma. Amantadine has shown promise in boosting ROS levels to trigger apoptosis, as well as promoting the start of autophagy while inhibiting the merging of autophagosomes with lysosomes [138]. Hence, growing evidence emphasizes the role of autophagy in controlling the advancement of glioma, serving as a biomarker and a possible target for treatment [139–143]. Autophagy has also been extensively recorded in controlling the development of different brain tumors including medulloblastoma [144]. REST can decrease the level of expression of Hippel-Lindau to boost autophagy in medulloblastoma [145]. The inhibition of autophagy with 3-MA has proven advantageous for protecting astrocytoma cells from the toxicity induced by pyocyanin and 1-hydroxyphenazine [146]. In relation to these conversations, the modulation of autophagy as a potential factor in the advancement of brain tumors and its manipulation (whether triggered or blocked) could be considered in the therapy for these malignancies. Figure 2 highlights the role of autophagy in the progression of brain tumors.

Autophagy and cancer metastasis

Factors like invasion, resistance to anoikis, and colonization present challenges to the establishment of distant colonies by metastatic tumor cells [147, 148]. Autophagy is essential for the advancement of metastatic tumor cells when they encounter environmental stimuli such as hypoxia and starvation [101, 149–152]. Evidence suggests a connection between increased levels of autophagy and the metastasis of cancer. In human breast cancer, increased levels of LC3B were associated with lymph node metastasis and unfavorable survival outcomes [104, 153]. In melanoma metastases, the levels of LC3B staining were greater when compared to primary tumor samples that were matched [104, 154, 155]. The presence of a specific set of autophagy genes was linked to a more aggressive and invasive nature in human glioblastoma [156]. Nutrient pathways regulate autophagy through both post-translational and transcriptional mechanisms [101, 157–159]. The precise connection between increased autophagy and the advancement of aggressive cancer is not well understood, but it could be attributed to a deficiency of resources in the tumor's surrounding environment. Macropinocytosis is just one of the surprising methods that tumors have developed to gather

nutrients from their environment [160]. Autophagy genes in pancreatic cancer were found to be upregulated due to the constant activation of MiT/TFE transcription factors, which shield them from mTORC1's inhibitory effects [157]. In the presence of nutrients, mTORC1 phosphorylates TFE transcription factors and they gather at the lysosome [161]. While most research has concentrated on the role of autophagy in brain tumor proliferation and drug resistance, several studies have emphasized its effects on brain tumor metastasis. It is important to comprehend the role of autophagy in regulating invasion, as metastasis is responsible for up to 90% of cancer-related deaths. Disrupting autophagy can hinder the spread of cancer cells [162]. Inhibiting MALAT1 can hinder autophagy to decrease the spread of glioma cells [163]. While one set of research underscores the importance of autophagy in promoting the spread of brain tumors, a separate study shows that the decrease in glioma metastasis caused by decorin is due to increased autophagy and lowered TGF-β levels [164]. Besides, the MCOLN1/TRPML1 axis can interfere with autophagy in order to reduce the invasion of tumor cells[165]. In the past few years, the role of nanoparticles in regulating autophagy has been significant in cancer treatment [166–168]. Incorporating curcumin into layered double hydroxide nanostructures can promote autophagy to reduce the spread of glioma cells [169]. EMT induction is a key mechanism in cancer metastasis and can trigger drug resistance as well [170, 171]. Future research should concentrate on exploring the involvement of autophagy in regulating EMT in brain tumors.

Autophagy and cancer drug resistance

Autophagy, a crucial process within cells, enables tumor cells to endure carcinogenesis by reusing organelles and proteins [172]. Conversely, cell death independent of caspase can lead to drug resistance when activated autophagy is involved. Extended or continuous autophagy can lead to autophagy-induced cell death. Regardless of necrosis and apoptosis, this form of cell death involves significant cytoplasmic vacuolization due to autophagy. Increased expression of autophagy genes can have a substantial impact on the process of cell death. For example, the expression of Beclin-1 in human synovial sarcoma cells can enhance cell death by promoting excessive autophagy [173]. The role of autophagy in enhancing cell death is crucial for enhancing the sensitivity of cancer cells to chemotherapy. Resveratrol, a plant phytoalexin, causes p62/SQSTM1 accumulation, leading to autophagy-mediated cell death in imatinib-resistant CML cells [174]. Furthermore, ovarian cancer cells treated with metformin experience cell death associated with autophagy when they encounter the ATG5-ATG12 complex [175]. Higher amounts of cancer-causing Ras are linked to aging and cell death related to autophagy. Increased levels of Ras lead to the activation of autophagy through the upregulation of proteins like Noxa and Beclin-1 [176]. The excessive expression of prolidase leads to a series of actions that result in cell death by boosting the quantities of ATG7, LC3A/B, and Beclin-1 [177]. The anticancer flavonoid baicalein induces cell death related to autophagy by activating AMPK/ULK1 and reducing components of the mTORC1 complex [178]. To avoid autophagy-induced cell death, myeloma cells upregulate caspase-10 and cFLIPL expression, leading to the cleavage and inactivation of BCLAF1 [179].

There has been a thorough assessment of the role of autophagy in controlling drug resistance in brain tumors. Enhancing autophagy during low oxygen levels can enhance resistance to chemotherapy in GBM and astrocytoma. The fundamental molecular mechanism includes the activation of HIF-1α, which boosts ATG5 expression by reducing miR-224-3p levels [180]. Epigenetic factors can also control autophagy in GBM. miR-93 is able to reduce the levels of Beclin-1, ATG5, ATG4B, and p62 in order to inhibit autophagy and enhance the effectiveness of therapy in GBM [181]. Yet, stimulating autophagy may aid in enhancing drug responsiveness in brain malignancies. A case is CN-3, able to enhance the sensitivity of temozolomide and support apoptosis and autophagy driven by ROS in GBM [182]. Additionally, valproic acid has the ability to decrease p62 and Akt levels in order to promote apoptosis and autophagy, thus improving the luteolin response in glioma cells [182]. TOPK inhibiting autophagy by phosphorylating ULK1 can increase glioma resistance to temozolomide [183]. A fascinating study revealed that combining autophagy suppression with inhibition of tyrosine kinase activity can have a synergistic effect in treating glioma [184]. Hence, along with drug resistance, enhancing toxic autophagy or inhibiting protective autophagy may enhance the effectiveness of chemotherapy in brain tumors. Sitagliptin acts as a cancer inhibitor, inhibiting glioma cell viability, stemness, and autophagy, while also enhancing sensitivity to temozolomide [185]. Thioridazine is a cancer-fighting agent that hinders autophagy and enhances the responsiveness of GBM to temozolomide treatment [186]. LINC00470's downregulation of PTEN in glioma can hinder autophagy and speed up cisplatin sensitivity [187]. Wnt is another controller of autophagy that can initiate protective autophagy to increase resistance to temozolomide in GBM [188]. Hence, there is growing evidence indicating that autophagy plays a role in regulating drug resistance in brain tumors [189–195]. While many studies have concentrated on cancer's resistance to chemotherapy, several studies have emphasized the significance of autophagy in

resisting radiotherapy. Linc-RA1 can inhibit autophagy and enhance radioresistance in glioma by reducing H2Bub1/USP44 levels [196]. Additionally, inhibiting autophagy flow and interfering with DNA damage repair in GBM may enhance the efficacy of radiotherapy [197]. Figure 3 shows the function of autophagy in brain tumor metastasis and chemoresistance.

Autophagy in brain tumors

The failure to treat brain tumors is due to the ineffectiveness of conventional methods in causing cell death. This has resulted in the exploration of autophagy as another way to induce glioma cell demise. Common brain tumor alterations such as p53, PTEN, AKT, NF1, and EGFR regulate autophagy [3, 198]. According to the Cancer Genome Atlas consortium, glioblastoma (GBM) tumors can be classified into four molecular subtypes: neural, classical, mesenchymal, and proneural. Variations in autophagy vulnerability in xenograft subtypes may stem from variances in baseline levels of LC3 protein expression. Enhanced therapies tailored to specific GBM subtypes could result from combination approaches that focus on autophagy and lysosomal systems. The activation of autophagy by certain experimental treatments for glioma may play a role in either cell death or survival, but its exact impact is still not completely clear and varies depending on the situation. Recognizing these distinctions is essential when developing possible combination treatments [199]. Furthermore, the majority of gliomas typically exhibit EGFR vIII mutant expression, EGFR amplification, and deletion of NF-1 and PTEN genes [199]. Mutations in the PI3K-Akt-mTOR pathways drive glioma survival and resistance to chemotherapy by inducing abnormal signaling [200]. Consequently, targeting receptor tyrosine kinases (RTKs) with monoclonal antibodies or chemical inhibitors is a favored treatment approach. Moderate success has been seen in the treatment of gliomas in preclinical research using particular mTOR and PI3K inhibitors [201]. The cytotoxic effects in gliomas may increase when late stage autophagy blockers are mixed with other medications that enhance autophagy. For instance, the glioma cell death was increased by combining chloroquine (CQ) with AKT-1/2 and PI-103, two inhibitors of PI3K/mTOR/AKT [202, 203]. Some variables, like the specific compounds targeting different autophagy phases, have not been thoroughly studied and could explain the varied outcomes of autophagy suppression in various situations. Some therapy trials are currently testing the combination of autophagy-blocking medications with autophagy-promoting therapies, showing promising results. Glioma cell death linked to autophagy may also happen due to

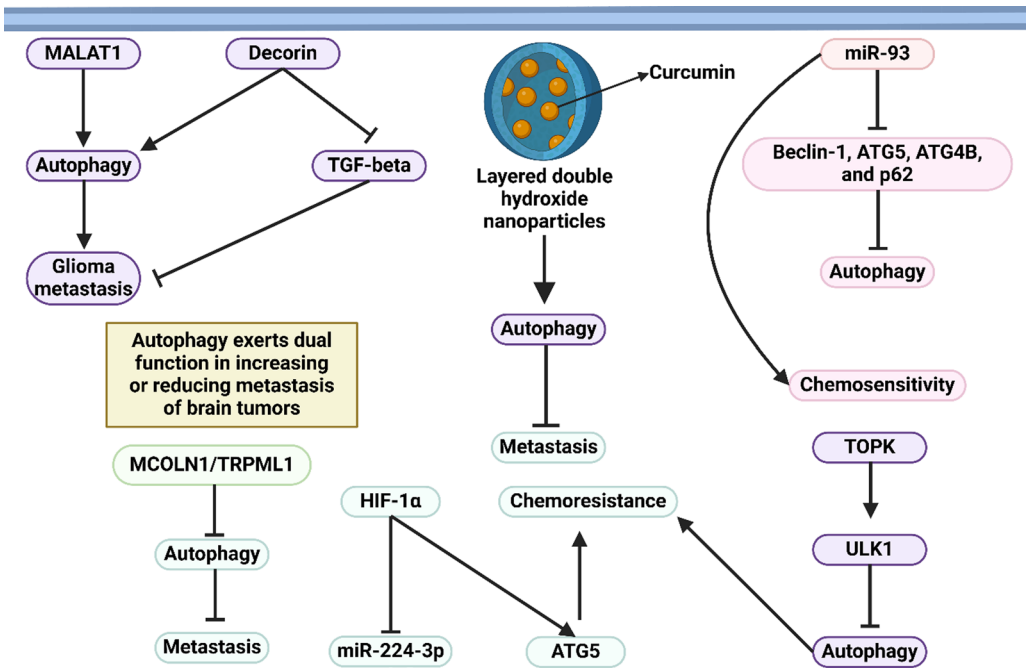

Fig. 3 The role of autophagy in the regulation of drug resistance and metastasis in brain tumors. Silencing MALAT1 can suppress autophagy to impair glioma metastasis. Decorin is able to mediate autophagy, while it downregulates TGF-β to disrupt invasion. Loading curcumin on layered double hydroxide nanostructures can stimulate autophagy to reduce metastasis. HIF-1α-mediated downregulation of miR-224-3p can increase ATG5 levels to mediate drug resistance

different therapies. To demonstrate, the inclusion of an autophagy inducer in specific chemotherapy treatments may enhance cytotoxicity.

Glioma

Tumor cells may acquire resistance to therapies, leading to stress-induced autophagy activation that promotes tumor growth and recurrence [3, 204]. Hence, it can be inferred that the role of autophagy might go beyond controlling tumor advancement and impact the recurrence of glioma. During the initial phases of glioma progression, autophagy is crucial and is linked to the advancement of gliomas, particularly high-grade ones. LC3 and p62, proteins associated with autophagy, have been connected to a poorer outlook in gliomas [205]. In addition, high expression levels of ATG4C are linked to a decreased survival period in high-grade glioma patients [206]. Therefore, autophagy-related factors as biomarkers can diagnose and predict glioma patient outcomes. Inhibiting ATG4C leads to cell cycle arrest and apoptosis, highlighting autophagy's importance in cell survival. Reduced ATG4C levels slow glioma growth in mice [206].

Noncoding RNA MALAT1 suppresses miR-101, reducing autophagy-related gene expression, inducing autophagy, and promoting cell growth [207]. Biopsy samples taken from gliomas illustrate higher rates of MALAT1 in comparison to normal tissue, suggesting the potential of MALAT1 as a biomarker for cancer diagnosis. HIF-1α expands autophagy through the transcription of autophagy genes [207–209]. It also aids in the creation of blood vessels, regulating VEGF to provide oxygen and nutrients for tumor cell viability [210]. The levels of angiogenic and hypoxia markers are associated with tumor grade and unfavorable outcome in patients with brain tumors [211]. Increased levels of pKDR/VEGFR-2 and ATG5, along with a negative outcome, are associated with enhanced vasculogenic mimicry (VM) development in individuals with glioma. Furthermore, the activation of the PI3K-AKT pathway and generation of ROS during autophagy can stimulate vasculogenic mimicry in glioma stem cells [212]. Thus, aside from controlling different characteristics of glioma such as growth, cell death mechanisms, and growth, autophagy can be seen as a predictive and diagnostic marker.

Autophagy is vital for the survival of tumor cells in the hypoxic glioma region and contributes to its aggressiveness. It additionally aids in the growth of cells within the tumor's surrounding environment. Oxidative stress in tumor cells promotes the degradation of Caveolin-1 and activation of autophagy, boosting pro-autophagy proteins such as BNIP3L, LC3, BNIP3, ATG16L, HIF-1α, and NF-κB. Prolonged exposure to TMZ results in glioma cell line dormancy, which is controlled by H2BK, EphA5, and IGFBP5. Obtained stemness is linked to a state of inactivity, controlled by indicators of stem cells like OCT4, KLF4, and SOX2 [213]. Therapeutic strategies that control tumor dormancy might postpone or stop glioblastoma reappearance after surgery [214]. Autophagy plays a crucial role in treating cancer by blocking the start of tumors and destroying cancer cells as they advance. Gliomas show reduced levels of autophagosome initiation and elongation genes like Beclin-1, FIP200, and Bif1 [215, 216]. Glioma patients with elevated levels of these genes experienced improved survival outcomes [156, 217]. Heightened AKT and mTOR activity in high-grade gliomas enhances the growth and stem cell characteristics of glioma stem cells [218–220], which play crucial roles in regulating autophagy. MiR-224-3p inhibits ATG5 and FIP200, which helps to inhibit autophagy and GBM cell carcinogenesis [221]. During low oxygen levels, increased BNIP3 in glioma cells induces autophagy, potentially reducing cancer development by clearing p62-labeled clumps [222]. Furthermore, patients with glioblastoma multiforme who exhibit high levels of p62 experience a more negative outlook [156]. Sinomenine hydrochloride triggers the JNK pathway and inhibits the AKT/mTOR axis, leading to autophagy-mediated cell death in glioma cells through ROS generation [223]. Autophagy also plays a role in regulating senescence and preventing cancer development [122]. Resveratrol enhances the toxicity of TMZ by increasing ROS production, activating AMPK, and blocking the mTOR pathway [224]. Flovokawain slows down cell growth in glioma cells by triggering autophagy and senescence, while deactivating the AKT/mTOR pathway [225]. Autophagy could potentially stop the growth of tumors by triggering apoptosis through the ATG protein [226, 227]. Beclin-1 might induce cell death by inhibiting the anti-apoptotic actions of Bcl-xL and Bcl-2. Beclin-1 induces glioma cell apoptosis by binding to Bcl-xL and Bcl-2, leading to the release of Bak and Bax, both activators of caspases-3/−9 [228].

The regulation of cell death mechanisms, including autophagy, is one of the ways in which 3beta androstene 17alpha diol (17alpha-AED) exerts its anti-cancer effects on glioma. Significantly, 17alpha-AED has been proven to inhibit growth, while promoting the creation of autophagosomes and activating autophagy by increasing Beclin-1 and ATG5 [229]. β-asarone is another anti-tumor compound capable of inducing autophagy in glioma by increasing Beclin-1 levels [230]. Increased phosphorylated Beclin-1 levels in glioma stem-like cells also regulate autophagy during starvation, along with anti-cancer compounds [231]. CISD2's ability to prevent Beclin-1-induced autophagy enhances glioma growth [232]. The decrease in α-l fucosidase 1 expression may elevate levels of Beclin-1 and ATG12 to trigger

autophagy in inhibiting glioma malignancy [233]. A fascinating study found that the elimination of Beclin-1 can reduce the formation of vasculogenic mimicry caused by hypoxia [234]. Thus, Beclin-1 has a substantial impact on controlling autophagy in glioma [235, 236].

Glioblastoma

Significant stress indicators in the GBM surroundings associated with autophagy activation are necrosis and acidic stress. Tumor necrosis will develop in 90% of people with grade IV astrocytic tumors [237–240]. The areas of rapidly dividing tumor cells encircling areas of cell death are called perinecrotic niches (PNN). Metabolic alterations are necessary for the survival of GBM cells in PNN, where periods of low oxygen and lack of nutrients happen from time to time [241, 242]. This setup is connected to unfavorable results for patients and is related to resistance to radio and chemotherapy treatments [210, 243]. The PNN enhances angiogenesis, re-expresses markers of glioma stem cells, and activates anti-apoptotic and pro-migratory transcriptional programs to stabilize hypoxia-induced factors. Furthermore, hypoxia induces GBM cells to shift towards aerobic glycolysis, leading to the creation of an acidic environment [241, 244–249]. This acidity might promote tumor invasion by activating proteinases like heparanases and cathepsins, which rely on pH levels [250]. Heparanase (HPSE), an endo-β-D-glucuronidase, has enzymatic and non-enzymatic functions that vary according to pH. HPSE expression is inherently linked to a poor outlook [251], cell spreading [252], and the progression of GBM. Autophagy is another cellular process that is controlled by HPSE activity in brain tumors and other malignancies [253]. Additional molecules derived from vascular endothelial cells (vEC), such as osteopontin (OPN), similarly support autophagy and are associated with stem-like properties in GBM cells [254, 255]. Possible advantages of OPN-triggered autophagy include increased glioma aggressiveness and ability to migrate, reduced sensitivity to chemotherapy drugs, and improved survival of cancerous cells [256]. The majority of treatments for glioma, such as radiotherapy, temozolomide, and bevacizumab, are more potent activators of the autophagy pathway. Studies have linked increased autophagy activity to unfavorable outcomes in several types of cancers and to the reduced sensitivity of GBM cells to therapy [257]. On the other hand, if autophagy processes become too intense, it can result in cell fatigue and ultimately death [258–260]. While therapy-induced autophagy in GBM cells may serve two purposes, most evidence suggests that it primarily functions as a protective mechanism and adaptive response. Autophagy can be triggered by TMZ in glioma cells and reactive astrocytes of glioma patients [261]. The autophagy inhibitors CQ and HCQ decrease the autophagy process in glioma cells exposed to TMZ, causing an accumulation of proautophagy proteins and strain on the endoplasmic reticulum [262]. Blocking autophagosome synthesis is an effective strategy to enhance TMZ cytotoxicity in GBM cells if the autophagy system provides protection against TMZ-induced cytotoxicity [262, 263]. The combination of CQ and TMZ greatly raised cleaved PARP levels, supporting the idea that autophagy plays a role in adaptive phenotype and cell flexibility [264]. Autophagy is proposed as the primary factor in the cytotoxic effects of TMZ and inhibiting it significantly impacts TMZ's anti-tumor effects in vitro [265]. Ionizing radiation is the most efficient adjuvant therapy for GBM. Another consequence of radiation therapy is the enhanced autophagy in GBM cells cultured in vitro [266]. Radiation can induce cell death in GBM cells through apoptosis, but GBM cells do not undergo apoptosis and instead activate autophagy, which may serve as a protective response [266, 267]. This shows that autophagy interacts with apoptosis as an additional cell death pathway in GBM cells. Moreover, the combination of radiotherapy and CQ treatments can enhance radiosensitivity in GBM cells and induce apoptosis in GSCs in a synergistic way [263, 268]. Therefore, combining CQ as an autophagy blocker with radiation therapy can effectively inhibit the advancement of cancer. Also, BVZ, an antiangiogenic medication, is an instance of a treatment that can enhance autophagy in GBM, leading to increased progression-free survival without impacting overall survival [269]. Protective autophagy helps GBM cells resist and survive in a hypoxic microenvironment created by BVZ at the level of the TME. In addition, BVZ induced autophagy in GBM cells by inhibiting the Akt-mTOR pathway directly [270]. IRF1 expression is essential for autophagy in gliomas [271]. Autophagy is triggered, allowing GBM cells with CD133 and Sox2 expression to remain viable by absorbing BVZ via micropinocytosis [272]. Silencing ATG7 can reverse autophagy to enhance GBM sensitivity to BVZ treatments [273].

The GBM cells engage in autophagy due to both internal and external triggers. Internal stimuli could be oncogenic proteins or alterations in ATG. 16 ATGs have been detected in humans, with four of these genes experiencing significant mutations in hepatocellular carcinoma, gastric and colorectal cancers, as well as other types of cancers possibly due to dysregulation of autophagy. However, thorough genomic research has revealed that core autophagy genes are generally not mutated in GBM and eleven other human malignancies, suggesting that the autophagy process is active in these conditions. Significant predictive factors for GBM patients have been identified through numerous ATG signatures showing that

high autophagy scores are linked to unfavorable results [274, 275]. Moreover, increased levels of ATGs have been associated with the aggressiveness of glioma, leading to reduced survival rates and the advancement of tumors [205, 206, 276]. The primary GBM is caused by three key molecular signaling pathways: p53, Rb, and PI3K [277]. The PI3K/Akt/mTOR pathway plays a crucial role in regulating autophagy in human cancers and serves as a vital detector of nutrient and growth factor rates [278, 279]. Mutations in PI3CA, PIK3R1, and PTEN, along with increased upstream activator expression, activate the PI3K/Akt/mTOR cascade in most GBM cases. Blocking PI3K inhibits tumor growth, prolongs survival in mice, and enhances autophagy while inhibiting invasion and angiogenesis in GBM cells [280–282]. The decrease in AKT and increase in JNK/Beclin-1 axis can trigger autophagy in GBM which is then induced by phloretin [283]. Hypoxia leads to elevated HIF-1A levels, which in turn promotes Beclin-1 upregulation in GBM radioresistance through autophagy activation [284]. However, miR-30a reduces Beclin-1 levels to inhibit autophagy and enhance temozolomide responsiveness in GBM. Hence, autophagy controlled by Beclin-1 in GBM [285], has dual roles in promoting survival and inducing cell death.

Astrocytoma

Autophagy helps in the removal of protein build-up [286, 287]. This is particularly evident with Alexander disease, a rare neurological disorder characterized by dominant mutations in the glial fibrillary acidic protein, GFAP. The accumulation of GFAP in Rosenthal fibers leads to a series of symptoms such as abnormal movements, delayed development, epilepsy, and seizures [288]. The ability to recreate autophagy in cell lines and mice has been achieved by generating GFAP mutants, a phenomenon initially noticed in the brains of individuals with Alexander disease. It is worth mentioning that the autophagy process has the ability to remove GFAP [289, 290]. Moreover, experiments conducted in live mice with tau pathology have shown that drugs that boost autophagy, such as rapamycin or trehalose, assist in removing tau [291, 292]. This effect has also been observed in laboratory-grown primary neurons [293]. Research lacking on autophagy in glial tau. Rapamycin reduces reactive astrocytes, tau tangles in P301S tau transgenic mouse model [291]. More research required to clarify if rapamycin affects reactive astrocytes directly or through reduced neuronal degeneration related to autophagy. Both astrocytes and neurons in the brains of deceased PD patients possess α-synuclein cytoplasmic inclusions [294, 295]. Study on human glioma cell lines revealed that increasing BAG3-dependent autophagy by reducing levels of the minor heat shock protein CRYAB enhanced α-synuclein clearance. Additionally, an increase in α-synuclein aggregation throughout the entire brain resulted from CRYAB overproduction in astrocytes in a mouse model that expressed the A30P mutation of human α-synuclein [296]. Study shows boosting autophagy could manage α-synuclein in astrocytes [296], lessening toxicity from buildup. LC3B and Beclin-1 also linked to astrocytoma patient outcomes [297–299]. CD133, which is a marker of cancer stem-like cells, was also investigated in this group [300]. Astrocytoma cancer stem-like cells showing LC-3B protein are more resistant to radiation and chemotherapy. Patients with high expression levels in both CD133 and LC-3B showed shorter survival periods, and strong staining of LC-3B was a sign of a negative prognosis. These results suggest that astrocytoma cancer stem-like cells, along with enhanced autophagy, may be responsible for the resistance to radiation therapy and chemotherapy. Additionally, activated autophagy provides protection for neurons and astrocytes against bilirubin-induced cytotoxicity [301]. TFP induction enhances the survival of rat hippocampal primary neurons following UCB treatment, by inhibiting cleaved caspase-3 protein expression and decreasing HO-1, CHOP, and IL-8 mRNA levels in SH-SY5Y cells. Activation of autophagy prevents UCB-induced damage to neuronal cells by utilizing mTOR/ER-stress/PKC/calcium signaling pathways, therefore shielding neurons from UCB toxic effects. The HIF-1α/miR-224-3p/ATG5 axis regulates hypoxia-induced autophagy in GBM and astrocytoma, impacting cell behavior and response to chemotherapy [180]. In glioma LN229 and astrocytoma U-251MG cells, HIF-1α levels rise under hypoxia while miR-224-3p decreases. ATG5 is targeted by miR-224-3p. Decreased ATG5 levels increased hypoxia-driven chemosensitivity in glioblastoma cells by limiting cell movement. Furthermore, overexpression of miR-224-3p led to increased chemosensitivity of glioblastoma cells, thereby limiting their ability to move. Blocking autophagy with 3-methyladenine safeguards 1321N1 astrocytoma cells from the toxic effects of pyocyanin and 1-hydroxyphenazine [146]. Autophagy is identified by the accumulation of acidic vesicular organelles; 1321N1 astrocytoma cells showed protection from cell harm induced by pyocyanin and 1-hydroxyphenazine when given the autophagy inhibitor 3-methyladenine (5 mM). Furthermore, autophagy might contribute to cellular injury caused by pyocyanin and 1-hydroxyphenazine, instead of apoptosis and senescence. HHV-6A infection disrupts the regular equilibrium of autophagy and the UPR, resulting in increased beta amyloid formation and tau phosphorylation in primary neurons and astrocytomas [302]. This study was the first to demonstrate that HHV-6A infection in astrocytoma cells and primary neurons reduces autophagy,

raises Aβ production, and triggers ER stress/UPR, leading to increased tau protein hyper-phosphorylation. Compared to IDH wildtype glioma, IDH mutant astrocytomas exhibit increased synergistic toxicity due to elevated ROS production and autophagy induced by both LonP1 and CT-L inhibition [303]. In other words, BT317 is a recently developed small compound derived from coumarinic compound 4 (CC4) using structure–activity modeling. It blocks the functioning of LonP1 and CT-L proteasomes, leading to autophagy-related cell demise and the buildup of ROS in advanced IDH1 mutated astrocytoma cell lines. The commonly used chemotherapy TMZ not only blocked autophagy induced by BT317 in vitro but also showed enhanced synergy with BT317.

Ependyoma

An ependymoma (EPN), a type of neuroepithelial tumor, has the potential to form in various parts of the neuroaxis such as the spinal cord, posterior fossa (PF), and supratentorial area (ST) [304, 305]. Around 90% of ependymomas in children develop within the skull, with 63% located in the posterior fossa and 33% in the superior temporal lobe [306]. Discovering successful therapy for EPNs is extremely challenging because of their significantly diverse clinical characteristics. Another factor to take into account is that the rate of oversight survivorship (OS) after a decade remains steady at about 64% in pediatric medicine [307–309]. Additionally, DNA methylation profiling was used to categorize EPNs into nine subgroups, with three subgroups identified in each anatomical region of the CNS where EPNs are located. In addition, analysis of clinical and demographic data showed that the majority of high-risk patients were part of either ST-EPN-RELA or PF-EPN-A molecular subgroups, out of the nine recognized subgroups [310]. This highlights the importance of a precise molecular classification in the clinical setting. Up to now, no specific research has looked into the role of autophagy in ependymoma. Scientists started investigating the link between nucleoporin TPR overexpression and autophagy in this tumor because there is a proven association between TPR depletion and autophagy initiation in HeLa cells [311]. Dewi and colleagues' study explored the mRNA expression levels of autophagy-related proteins and found that ependymoma patients show a significant decrease in the expression of ATG3, ATG5, ATG12, and Beclin 1 [312]. Examination of LC3 and p62 proteins supports these results, providing credibility to the notion that autophagy is being hindered. Furthermore, TPR knockdown can also lead to restoration of gene levels and activation of autophagy in a more general sense. In particular, it is believed that the depletion of TPR leads to the formation of nuclear membrane blebs, suggesting that an abundance of TPR may hinder nucleophagy, a type of selective autophagy that breaks down nuclear elements [313], ultimately promoting ependymoma tumorigenesis. TPR downregulation in a xenograft mouse model also inhibits tumor growth [312]. The data demonstrates that enhancing nucleophagy is essential in reducing the tumorigenicity of ependymoma, as shown by the discovery that mTOR inhibitors can reduce tumor growth in vivo by restoring nucleophagy. This perspective suggests that triggering autophagy might offer a treatment option for ependymoma.

Oligodendroglioma

Malfunctions in the autophagy-lysosome pathway (ALP) and the ubiquitin–proteasome system (UPS) may also result in the buildup of aggregates in MSA brain oligodendrocytes. An elevated level of macroautophagy has been noted during the advancement of MSA, hinting at a potential involvement in eliminating protein clumps [314]. The existence of autophagy-related proteins in GCIs of MSA, like MAP1LC3/LC3 and SQSTM1/p62, provides additional evidence of the ALP potentially playing a role in the advancement of the disease [315]. Mavroeidi and colleagues demonstrated that in models of multiple system atrophy, oligodendroglial SNCA/alpha-synuclein and TPPP/p25A are eliminated through autophagy [316]. The research showed that ALP primarily breaks down endogenous SNCA and TPPP/p25A in oligodendroglial cell lines from rats and primary oligodendrocytes from mice. In the rat brain lysosomes, TPPP/p25A is eliminated via chaperone-mediated autophagy (CMA) in a manner resembling KFERQ. Moreover, the data also shows that boosting autophagy may be a successful strategy for removing SNCA and/or TPPP/p25A in MSA. In patients with Nasu-Hakola disease, the oligodendrocytes in the brain show the presence of LC3, which is a characteristic feature of autophagosomes [317]. NHD brains with Nogo-A and CNPase also showed oligodendrocytes producing LC3, ubiquitin, ubiquilin-1, and HDAC6, with no detection of Beclin-1 or sequestosome 1. LC3 was found in axonal spheroids in NHD brains as well. The findings suggest that dysregulation of autophagy control may be responsible for oligodendrogliopathy, a brain disorder that leads to leukoencephalopathy in NHD patients. Autophagy mediates the secretion of amyloid peptide by oligodendroglial precursors [318]. NG2 cells, a newly discovered cell type, can eliminate β-amyloid peptides through endocytosis and autophagy processes. Mice with Alzheimer's disease showed the gathering and grouping of these cells around the amyloid plaque. In NG2 cells, β-amyloid peptides caused the autophagic pathway to activate, and actin-dependent macropinocytosis aided in their engulfment.

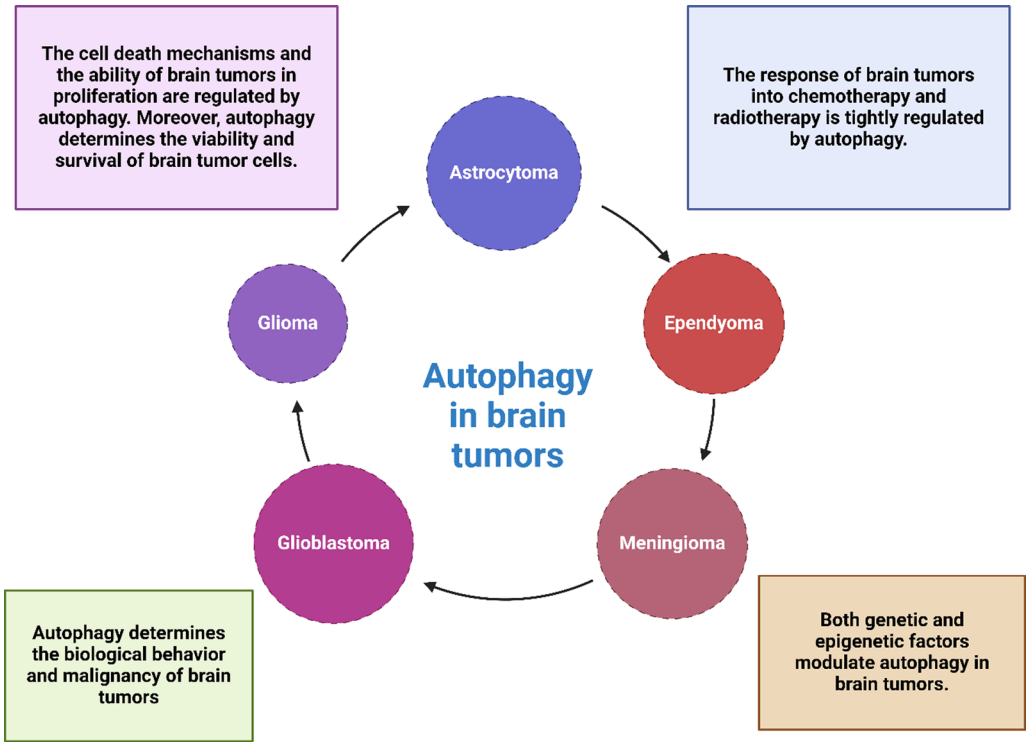

Fig. 4 The versatile function of autophagy in brain tumors. Autophagy can regulate the progression of glioma, glioblastoma and other rare brain tumors including astrocytoma, ependymoma and meningioma. Autophagy has dual function in brain tumors and therefore, both induction and inhibition can be followed in brain tumor therapy

According to the findings, NG2 cells show potential as a therapy for Alzheimer's disease. The microRNA-101 controls autophagy and the buildup of alpha-Synuclein in oligodendroglial cells in multiple system atrophy [319]. In individuals with MSA, there was an increase in levels of miR-101 in the striatum, while gene expression of RAB5A was decreased. Overexpressing miR-101 in oligodendroglial cell cultures resulted in a significant increase in α-syn buildup and impaired autophagy functions. The opposite effect was observed with the use of an antisense construct targeting miR-101. Administering anti-miR-101 in MSA mice reduced α-syn accumulation in oligodendroglial cells, enhancing autophagy. This suggests miRNA dysregulation could contribute to MSA pathogenesis by impacting autophagy via miR-101 alterations. Mitochondrial dysfunction and oxidative stress hinder α-syn clearance in oligodendrocytes [320]. Autophagy efficiently degrades both externally added α-syn and internally produced α-syn without affecting the overall process. Disruption of the autophagic pathway occurs when mitochondria are damaged, leading to an accumulation of α-syn and promoting aggregate formation.

Meningioma

Diosgenin induces cell death pathways and cell cycle arrest in optic nerve sheath meningioma cells, reducing proliferation, migration, invasion, and HBL-52 cell survival [321]. The reason for this was because autophagy was activated, LC3 II and Beclin-1 expression increased, and cell cycle was halted in the sub-G1 phase. Diosgenin also inhibited cell migration and invasion, and induced cell death through mitochondria-dependent apoptosis. This implies that diosgenin could be a promising candidate for an anticancer drug in optic nerve sheath meningioma cells. The effectiveness of Farnesol for treating optic nerve meningioma was assessed by studying its ability to inhibit cell growth in HBL-52 cells [322]. Farnesol has a significant impact on HBL-52 cell viability, reducing it by 50% at a concentration of 25 μM. This occurred because autophagy was activated, LC3 II and Beclin-1 expression increased, and cell cycle was halted at the G2/M phase. Farnesol inhibited the expressions of MMP-2 and 9, thereby reducing cell migration and invasion. This indicates that Farnesol could be helpful in the treatment of optic nerve sheath meningioma [323]. The relationship between ILK and AKT regulates the miR-21 expression in vertebular schwannoma and meningioma [326]. Put simply, OSU-T315 greatly reduces miR-21

Table 1 Evaluating the function of autophagy in brain tumors

Brain tumor	Remark	References
Glioblastoma	Reducing HMGB1 levels or blocking autophagy decreases these effects and is linked to better outcome in GBM; enhancing YAP expression increases glioma cell proliferation and autophagy by enhancing HMGB1 transcription and movement	[325]
Glioma	Hypoxic glioma-derived exosomes facilitate autophagy and M2-like macrophage polarization through an IL-6-pSTAT3-miR-155-3p-autophagy feedback loop, furthering the immunosuppressive environment and supporting glioma progression.	[326]
Glioma	By blocking lysophagy and cathepsin, the impact of pimozide and loperamide is lessened. These medications trigger glioblastoma cells to experience autophagy and lipotoxicity through ATG5 and ATG7, resulting in the buildup of sphingolipids and ultimately cell death and lysosomal membrane damage	[327]
Glioma	Celastrol induces cell cycle arrest in G2/M, apoptosis, and autophagy in glioma cells through the activation of JNK, generation of ROS, and inhibition of Akt/mTOR. Autophagy and apoptosis exhibit a reciprocal feedback loop	[328]
Glioma	PHLDA2, elevated in glioma, boosts cell survival and growth while inhibiting cell death and self-degradation processes. Silencing it results in higher autophagy levels, triggering apoptosis, and reducing levels of phosphorylated AKT and mTOR	[329]
Glioma	Rapamycin slows down the growth of glioma cells, triggers cell death, and enhances self-degradation by increasing miR-26a-5p and decreasing DAPK1 levels. On the other hand, contradictory outcomes are observed when miR-26a-5p is suppressed or DAPK1 is increased in expression	[330]
Glioma	MiR-124-3p hinders glioma cell growth and enhances cell death and self-digestion by targeting CREBRF and inhibiting the AKT pathway	[331]
Glioma	The interaction between DANCR, miR-33b, DLX6, and ATG7 promotes glioma cell growth and autophagy, inhibiting apoptosis by sequestering miR-33b and increasing DLX6 and ATG7 levels, offering new perspectives for glioma treatment	[332]
Glioblastoma	COPZ1 contributes to the advancement of glioblastoma by interfering with iron metabolism. In contrast, downregulating COPZ1 induces ferroptosis through the COPZ1/NCOA4/FTH1 pathway, resulting in reduced tumor growth and improved survival rates	[333]
Glioma	Chaperone-mediated autophagy (CMA) regulated by LAMP2A affects the behavior of glioblastoma stem cells and tumor formation. Reduced levels of LAMP2A decrease GSC characteristics and cancer growth, while increased levels boost GSC formation and correlate with poor outcome in GBM	[334]
Glioblastoma	SW33, a compound derived from sinomenine, hinders the advancement of glioblastoma by reducing cell growth, movement, and infiltration. It triggers cell death controlled by mitochondria and enhances cellular recycling via the PI3K/AKT and AMPK/mTOR pathways	[335]
Glioblastoma	Increased expression of PAK1 accelerates the advancement of glioblastoma by inducing autophagy under low oxygen conditions, through acetylation at K420. This modification boosts PAK1's function, leading to the phosphorylation of ATG5 and ultimately fostering the formation of autophagosomes and tumor expansion	[336]
Glioma	Deprivation of glucose triggers AMPK, leading to the phosphorylation of ACSS2 at S659. This alteration boosts the movement of ACSS2 to the nucleus and its connection with transcription factor EB, leading to increased acetyl-CoA production from acetate. This process helps with histone acetylation, autophagy, and the advancement of glioma	[337]
Glioma	The extended non-coding RNA lnc-NLC1-C boosts glioma advancement by enhancing cell multiplication, movement, and penetration, while also inhibiting cell death and self-cleansing through the miR-383/PRDX-3 pathway	[338]
Glioma	The lengthy non-coding RNA lnc-NLC1-C promotes the advancement of glioma by enhancing cell growth, movement, and infiltration, while also inhibiting cell death and self-cleansing through the miR-383/PRDX-3 pathway	[339]
Glioma	LncRNA H19 boosts glioma growth and movement by regulating autophagy through the mTOR/ULK1 signaling pathway. Increased levels of H19 suppress autophagy by blocking mTOR phosphorylation and boosting ULK1 phosphorylation, while reducing H19 expression encourages autophagy	[340]
Glioma	Nicardipine enhances GSCs' responsiveness to temozolomide (TMZ) by promoting cell death and inhibiting self-digestion through activation of the mTOR pathway. Findings from tests in the laboratory and in living organisms show that nicardipine could be used as a supplement to block autophagy in GSCs, ultimately improving the effectiveness of TMZ treatment	[341]
Glioma	A risk assessment model, based on six autophagy-related genes, shows a strong predictive power for low-grade glioma prognosis and is closely linked to survival outcomes. High and low-risk groups showed variations in key pathways, immune infiltration, and checkpoint differences	[342]
Glioma	Timosaponin AIII, found in Anemarrhena asphodeloides, has antitumor effects on glioma cells by reducing cell viability and inducing cell death along with mitochondrial dysfunction. It also triggers autophagy and hinders tumor growth in mice models, promoting apoptosis by inhibiting autophagy	[343]
Glioblastoma	In glioblastoma (GBM), the compound PI-103, which inhibits both PtdIns3K and mTOR, induces autophagy to support survival in therapy-resistant, PTEN-mutant glioma. Autophagosome maturation inhibition boosts apoptosis, but inhibitors like rapamycin do not trigger apoptosis because Akt is activated as part of a feedback loop	[344]
Glioma	Matrine reduced U251 cell viability, triggered apoptosis and autophagy, and decreased circRNA-104075 expression. The effects were reversed by circRNA-104075 overexpression through activation of the Wnt/β-catenin and PI3K/AKT signaling pathways and by reducing matrine's inhibition of BCL-9 expression	[345]

Table 1 (continued)

Brain tumor	Remark	References
Glioma	LY3023414, a strong inhibitor of PI3K-AKT-mTOR pathway, successfully decreased glioma cell viability and growth, triggered apoptosis, and initiated autophagy. Significantly, blocking autophagy increased its ability to fight tumors in both laboratory settings and living organisms, particularly in glioma cells lacking Beclin-1	[346]
Glioma	Dexamethasone improved cell viability after exposure to radiation in U373 (with PTEN mutation) and LN229 (with normal PTEN) cells. Autophagy had differing effects on the two cell lines, as inhibiting autophagy reversed the protective effects in U373 cells but not in LN229 cells	[347]
Glioma	High-grade gliomas exhibited increased TLR2 levels, which were positively associated with tumor grade, LC3, and Beclin1 expression. Increased levels of TLR2 were associated with worse results and heightened activity of glioma cells, aiding in cell cycle advancement and encouraging autophagy by boosting LC3-II conversion and increasing phosphorylated p38 levels	[348]
Glioma	Treatment with Prucalopride decreased the growth, movement, and ability to spread of glioma cells, raised cell death by increasing Bax and cleaved caspase-3 levels while lowering Bcl-2 levels, and promoted autophagy by increasing Beclin 1 and LC3-II levels, reducing p62 levels, and blocking key components in the AKT-mTOR pathway like p-AKT, p-mTOR, and p-P70S6K	[349]
Glioma	The induction of autophagy by AZD8055 and rapamycin treatment blocked the self-renewal and tumorigenicity of glioma-initiating cells by degrading Notch1, a crucial factor in maintaining their properties	[350]
Glioma	Increased levels of decorin were found to suppress the movement, invasion, and change in cell structure of glioma cells by enhancing autophagy through the c-Met/Akt/mTOR pathway. Furthermore, lower levels of decorin in glioma tissues were associated with worse patient survival rates	[351]
Glioma	The presence of certain autophagy-related genes (ARGs) such as ATG5, BCL2L1, CASP3, CASP8, and GAPDH is linked to a negative outlook and a suppressive immune environment. GSEA suggests links to DNA repair, hypoxia, and immunosuppression, while CMap has discovered 14 potential medications for individuals at high risk	[352]
Glioma	Baicalein activates AMPK to induce autophagy and apoptosis in glioma U251 cells, leading to elevated LC3II levels and apoptosis markers, which are reversed when AMPK phosphorylation is blocked	[353]
Glioma	This study created and confirmed a predictive marker associated with autophagy, composed of six genes, able to forecast survival results in low-grade glioma (LGG) patients. High-risk patients showed an increase in pathways related to autophagy and cancer	[354]
Glioma	Corilagin inhibits the growth of glioma cells by enhancing apoptosis and autophagy through decreased expression of NRF2	[355]
Ependymoma	TPR plays a role in the development of ependymoma by controlling the movement of HSF1 mRNA and sustaining MTORC1 activity, which ultimately prevents the activation of autophagy. Therapeutic possibilities for ependymoma treatment could be found by focusing on the TPR-HSF1-MTOR axis	[311]
Meningioma	Farnesol significantly reduced HBL-52 cell survival by promoting autophagy, increasing LC3 II and Beclin 1 levels, causing G2/M cell cycle halt, and hindering cell movement and penetration by suppressing MMP-2 and MMP-9 expression	[322]
Meningioma	Diosgenin significantly decreased the viability of HBL-52 cells, with an IC50 of 15 μM. It triggered autophagy by increasing LC3 II and Beclin 1, caused cell cycle arrest in sub-G1 phase, hindered cell migration and invasion, and started apoptotic cell death through mitochondria	[321]
Astrocytoma	In individuals with astrocytoma, there was a notable link between the presence of LC3B protein and the resistance to radiation and chemotherapy, with higher levels of LC3B signaling a worse prognosis. Moreover, patients with high levels of both CD133 and LC3B had significantly shorter survival times, suggesting that the combination of cancer stem cells and enhanced autophagy contributes to resistance to treatment	[356]
Astrocytoma	In low oxygen levels, glioblastoma and astrocytoma cells show increased levels of HIF-1α and decreased levels of miR-224-3p, which leads to the promotion of autophagy through the regulation of ATG5. The interaction between HIF-1α, miR-224-3p, and ATG5 affects cell movement and response to chemotherapy by controlling hypoxia-induced autophagy. Overexpressing miR-224-3p decreases cell movement and enhances sensitivity to chemotherapy, while triggering autophagy reverses these outcomes	[180]
Astrocytoma	In 1321N1 astrocytoma cells, toxicity is mainly caused by autophagy, not oxidative stress, and the autophagy inhibitor 3-methyladenine can protect cells from this toxicity. Autophagy-induced cell death plays a significant role in toxicity	[146]

levels, resulting in increased expression of PTEN, BTG2, TIMP1, and PDCD4. Studies have demonstrated that AKT regulates miR-21, which in turn enhances tumor development in meningiomas and vestibular schwannomas by blocking AKT activation inhibitors like BTG2 and PTEN. OSU-T315 inhibits AKT and induces cell death through autophagy dysregulation in both VS and meningioma, indicating an upregulation of ATG5. Osteoglycin enhances the growth of meningioma by blocking NF2 and stimulating mTOR [324]. Meningiomas are identified by an increase in OGN mRNA levels, which then stimulates cell growth, activation of cell cycle, and formation of colonies. Cells with higher levels of OGN displayed decreased NF2 mRNA and protein levels, as well as increased activity of the mTOR pathway and AKT. Meningioma cells experienced an increase in cell death and

self-degradation following a reduction in OGN expression caused by an AKT inhibitor. Blocking AKT might be a potential treatment for meningiomas, suggesting that OGN is a novel oncogene contributing to their advancement. Figure 4 illustrates the role of autophagy in brain tumors. Table 1 outlines the function of autophagy in brain tumors.

Conclusion

The development of new treatment strategies for brain cancer patients has been of importance in the recent years. Their treatment is urgent, as a number of brain tumors such as GBM demonstrate poor prognosis. The abnormal levels of autophagy can increase the progression of brain tumors. The new therapeutics can be developed based on targeting autophagy for accelerating therapy and improving response to conventional therapeutics, including chemotherapy. Since autophagy has both carcinogenic and anti-carcinogenic functions, the regulation of autophagy should be performed in a cautions way. Therefore, both induction and suppression of autophagy have been followed for the treatment of cancer. Research has demonstrated that autophagy is clinically relevant in brain tumors. Both promoting and blocking autophagy are proposed as potential therapies for brain tumors. Brain tumors use autophagy for growth and treatment resistance. Drugs like chloroquine and hydroxychloroquine are tested in clinical trials for autophagy inhibition. chloroquine (CQ) and hydroxychloroquine (HCQ) are compounds that can disrupt the final phase of autophagy by inhibiting lysosomes. Clinical trials are being conducted with CQ and HCQ for the treatment of brain tumors either by themselves or along with temozolomide and radiotherapy. Dual PI3K/mTOR inhibitors are also available to suppress autophagy upstream regulators, and have been used in GBM patients to inhibit tumor growth and resistance to drugs. If autophagy is found to have harmful effects, promoting it could hinder the development of brain tumors. mTOR inhibitors and natural compounds have been utilized to trigger autophagy. Rapamycin and everolimus, which are mTOR inhibitors, are able to stimulate autophagy and have a synergistic effect when combined with other treatments. Furthermore, the treatment of brain tumors involves regulating autophagy in conjunction with immune checkpoint modulation. The combined use of CQ and bevacizumab can effectively work together to inhibit GBM and control autophagy and angiogenesis in a synergistic manner. Nevertheless, there are multiple hurdles present in the clinical research. Tumor heterogeneity in GBM poses difficulties in understanding the benefits of autophagy-related treatments. It is important to establish the best timing and amount of autophagy regulators. Furthermore, brain tumors can induce resistance to autophagy modulators in developing brain tumors.

Abbreviations

ATGs	Autophagy-related genes
ER	Endoplasmic reticulum
AMPK	Adenosine monophosphate-activated protein kinase
EIF2α	Initiation factor 2α
PI3-K	Phosphatidylinositol 3-kinase
NDRG1	N-myc downstream regulated 1
CSCs	Cancer stem cells
SASP	Senescence-associated secretory phenotype
EPN	Ependymoma
PF	Posterior fossa
OS	Oversight survivorship
CNS	Central nervous system
LC3B	Light chain B
MiT/TFE	Microphthalmia/transcription factor E
EPI	Epirubicin
P-gp	P-glycoprotein
HMGB1	High-mobility group B1
DAMP	Damage-associated molecular pattern
TRAIL	TNF-related apoptosis-inducing ligand
GBM	Glioblastoma
PNN	Perinecrotic niches
OPN	Osteopontin
IRF1	Interferon regulatory factor 1
TFP	Trifluoroperazine
ROS	Reactive oxygen species
CC4	Coumarinic compound 4
FGF	Fibroblast growth factor
EMT	Epithelial–mesenchymal transition
MET	Mesenchymal–epithelial transition

Acknowledgements
The figures were created by Biorender.com (Biorender.com).

Author contributions
Jiarui Zhang and Chen Yang analyze data, draw charts and write manuscripts. Jinan Zhang helped collect data and references and provided technical support. All authors contributed to the article and approved the submitted version.

Funding
This work did not receive specific funding.

Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that there are no competing interests regarding the publication of this paper.

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Received: 20 July 2024 Accepted: 27 December 2024
Published online: 13 January 2025

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