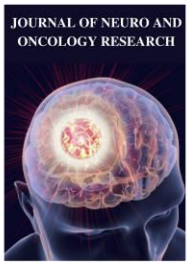

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Review Article

Brain Tumor Autophagy: A New Breakthrough in Cancer Research

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Abstract

Autophagy is the inherent, preserved cell breakdown that removes undesirable or imperfect factors through a lysosome- correspondent definite media. It slows down necrosis in cancer cells, which in ramble slows down the inflammation that comes before necrosis, which is understood to speed up neoplasm growth but whose exact cause is intimately unclear. Hence, autophagy is nowadays noted as a pivotal element since it stops the advancement of tumor by precluding cancer cells from ageing and turning on cell death. Yet, some autophagic pathways, alike the PI3K- AKT- mTOR pathway, also amplify tumor production. This pathway has steps like inauguration, nucleation, extension and conformation of double membrane vesicles understood as autophagosomes, which fuse with lysosomes in mammals and vacuoles in yeast and plants, for the degeneration of the intravascular cargo. Because, autophagy contributes to both tumorigenesis and tumor suppression, it isn't easy to distinguish if it results in a positive or negative stasis for cell survival. So, autophagy should be acclimated in the molecular, cellular and epigenetic environment, to deduce variety of tumor cells, in high- grade gliomas. In this review, we talk over the aim of pathways, modulators and genes of autophagy in brain neoplasms.

Keywords: Autophagy; Tumor Development; Cancer Cells; Glioblastoma Multiforme; Brain Tumors

Abbreviations:

GBM: Glioblastoma Multiforme; MAPK: Mitogen-Activated Protein Kinase; RAS: Rat Sarcoma; RAF: Rapidly Accelerated Fibro sarcoma; PTEN: Phosphatase and Tensin Homolog Deleted on Chromosome 10; NF- κB: Nuclear Factor Kappa B; mTOR: Mammalian or Mechanistic Target of Rapamycin; TMZ: Temozolomide

Introduction

Brain Tumors and Their Types

A brain tumor is an assemblage, or mass, of aberrant cells in your brain. Brain neoplasms can be cancerous or benign. Approximately 150 different brain tumors have been proved, but the two main groups of brain neoplasms are nominated which are primary and metastatic. Primary intracranial growths of the brain structures, carrying meninges, are exquisite with an overall five- time survival rate of 33.4% they're inclusively called primary brain tumors [1]. Metastases are the most common neoplasms of the Central Nervous System (CNS) [2]. Brain metastases affect 15-30 of cancer cases, particularly primary growths of the lung, bone, colon and kidney and melanoma. Despite upgrades in multimodal molecular targeted remedy and immunotherapy that don't secure long- term treatment, malignant brain neoplasms and metastases contribute significantly to cancer bonded mortality (Fig. 1, Table 1) [3].

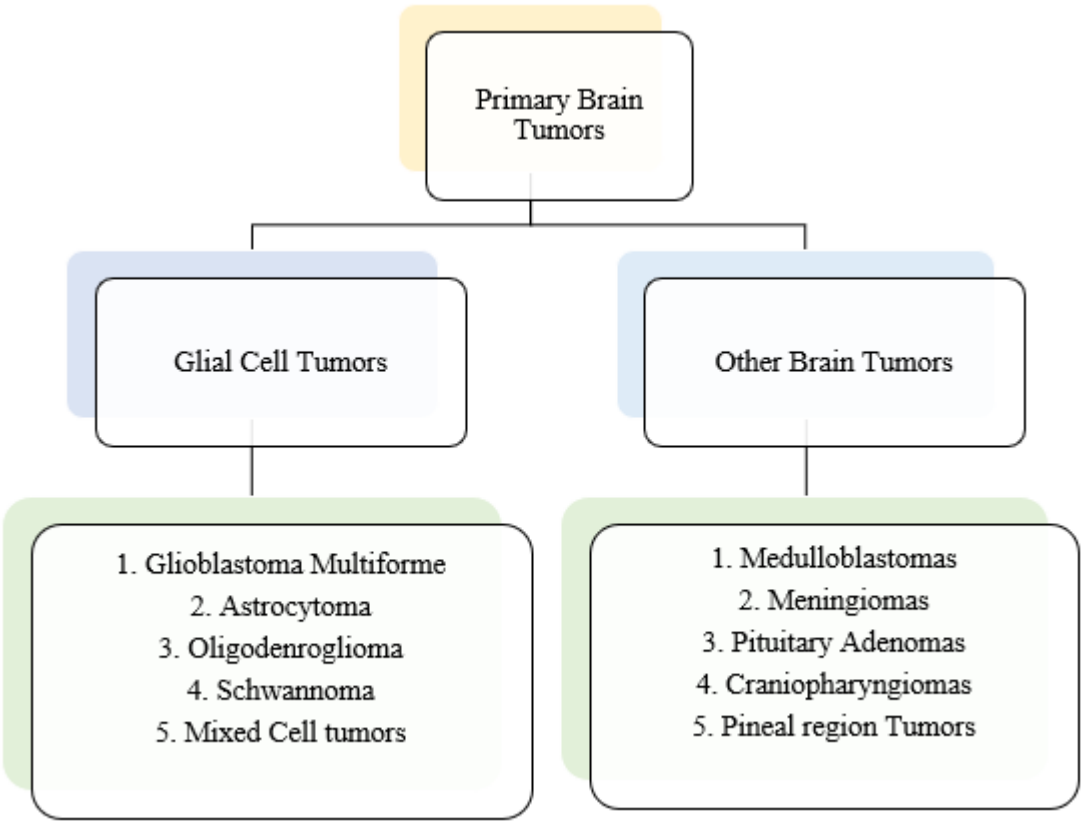

Figure 1: The Following figure consists of flowchart showing some important types of primary brain tumors, which are divided in two parts, some are the tumors originating from different types of glial cells and others that originate in different regions of brain.

Sr. No	Types of Brain Tumors	Description	Global Incidence
1.	Glioblastoma Multiforme	Glioblastoma, are the most aggressive and most frequent class of cancer that originates in the brain and has actually poor prognostic for survival. The median overall survival of GBM cases is around 15 months [4]	From 3.19 cases per 1,00,000 person to 4.17 per 1,00,000 person in year
2.	Astrocytoma	Astrocytoma originates in astrocytes kind of star- shaped glial cells in the brain. Most common glioma found in the adults, generally affecting the brain and occasionally the spinal cord. They advance to form the glioblastoma multiforme [5]	4.7 per 1,00,000 person in year
3.	Oligodenroglioma	Oligodendrogliomas are a rare type of diffusely infiltrating glioma brain tumour that develops from glial cells called oligodendrocytes. They frequently affect the cortical grey matter and are most typically caught in the frontal lobes.	The prevalence of oligodendrogliomas is around 5% of all central nervous system neuroepithelial neoplasms.
4.	Schwannoma	Schwannoma is a rare kind of tumor that forms in the nervous system. Schwannoma grows from cells called Schwann cells. Schwannoma neoplasms are frequently benign, but in rare cases, they can become cancerous.	4.4 to 5.23 cases per 1,00,000 person in year; in children and adolescents, it's 0.44 cases per 1,00,000 person in year.
5.	Medulloblastoma	Medulloblastoma is a cancerous brain tumor that starts near brainstem, in cerebellum. The tumor is rapid growing and can	5 cases per 1,00,000 person in year for

		circulate to diverse regions of brain and spinal cord. Medulloblastoma s are more frequent in youths than adults. Medulloblastoma accounts for roughly 20 of all childhood brain tumors and 63 of intracranial embryonic tumors.	pediatric population.
6.	Meningiomas	A meningioma is a tumor that arises from the meninges the membranes that surround the brain and spinal cord. Most of these tumors are grade 1, which means that they're benign. Meningioma is the most frequent type of tumor that forms in the head. Most meningioma grows very slowly.	About 8 cases per 1,00,000 person in year
7.	Pituitary Adenomas	Non-cancerous tumours in the pituitary gland that do not circulate beyond the skull.	Roughly 1 case per 1000 of the general population in a year.
8.	Craniopharyngiomas	Craniopharyngiomas are rare, benign tumors of the central nervous system. Craniopharyngiomas are epithelial tumors that generally rise in the suprasellar region of the brain, elongating to affect the hypothalamus, optical chiasm, cranial nerves, third ventricle and major blood vessels.	1.3 per 1,00,000 person in year
9.	Pineal region Tumors	Pineal region tumors are primary central nervous system tumors. These neoplasms begin in the pineal gland but can spread to the spinal cord. They happen most frequently to children and to adults younger than 40.	Pineal gland tumors are exceedingly rare and account for 0.4-1.0 of brain tumors.

Table 1: This above table represents the classes of primary brain tumors and their incident rates globally, per year.

What is Autophagy?

Autophagy is a basic function of eukaryotic cells and is well conserved from yeast to humans. The most emphatic character of autophagy is the amalgamation of double membrane- bound chambers that isolate materials to be downgraded in lytic chambers, a procedure that seems to be mechanistically diverse from conventional membrane traffic [6]. Autophagy likewise has oncogenic or onco- suppressive goods turning on the sort of excrescence, cell viability and intracellular environment.

Autophagy refers to a batch of catabolic pathways that govern cellular homeostasis by recycling and demeaning cytoplasmic rudiments similar protein summations, damaged or uninvited organelles and infections that hold raided the core [7]. An offbeat organelle grasped as the phagosome mediates autophagy. Autophagy is generally perceived as a unselective breakdown pathway because phagosomes devour a portion of cytoplasm [8]. This proceeding lookouts against injury and sickness while conserving cellular homeostasis [9]. Cellular conservation is transported out via the evolutionary preserved lysosomal declination path understood as autophagy.

Autophagy is an evolutionary well- saved recycling medium that is activated in reaction to stressful pictures, analogous as an extension in the configuration of Reactive Oxygen Group (ROS). ROS damage significant cellular macromolecules at high statuses. In array to break fresh ROS affair, autophagy is only in that it eliminates not right oxidized or compromised proteins but also big ROS- redeeming organelles like mitochondria and peroxisomes [10]. Macro-autophagy, micro-autophagy and chaperone- intermediated autophagy are three distinct kinds of autophagy that all cultivate the proteolytic breakdown of cytosolic factors at the lysosome [11].

Steps of Autophagy

Various autophagy pathways can be distinguished by grading the contents of the autophagosome. These pathways include, lipid droplets, ER, secretory granules, mitochondria and indeed some corridor of the nexus. Furthermore, proteins that are prone to aggregation, ribosomes and pathogens, can be specifically targeted and degraded by autophagic processes [12]. The five aspects that frame up the autophagy procedure are inauguration, extension, development, emulsion and declination [13].

In yeast macroautophagy, induction of autophagosome conformation is controlled by the Atg1- Atg13- Atg17- Atg31- Atg29

kinase complex. In mammalian cells, this complex is framed up of an Atg1 homolog from the Unc-51-like kinase family (either ULK1 or ULK2), the mammalian homolog of Atg13 and RB1- inducible curled- coil 1 (RB1CC1/ FIP200), which is needed for the induction of macroautophagy and may be an ortholog of yeast Atg17. The second step of autophagy which is Autophagosome elongation and maturation, involves two ubiquitin-like conjugation systems such as the microtubule- associated protein 1 Light Chain 3 (LC3) and the Atg12 systems. The autophagosome fuses with a lysosome to form an autolysosome, which degrades macromolecules into amino acids, fatty acids and nucleotides [14]. ULK1- Complex This is a largely regulated complex responsible for the inauguration of autophagosome conformation [15]. Autophagosomes are formed by expansion of a precursor cube known as the phagophore, which initiates the insulation of the weight. Upon completion autophagosomes are formed by expansion of a precursor cube known as the phagophore, which initiates the insulation of the weight. Upon completion, the autophagosome fuses with the vacuole, releasing the inner autophagosome vesicle into the vacuole lumen, where it's now nominated an autophagic body [16]. During autophagy initiation a portion of the cytosol is girdled by a flat membrane sheet known as the isolation membrane or phagophore. The isolation membrane also elongates and seals itself to form an autophagosome. The autophagosome fuses with normal endocytic traffic to develop into a late autophagosome, before fusing with lysosomes (Fig. 2) [17].

Figure 2: Steps of autophagy: Autophagy begins with the conformation of the phagophore which leads to the proliferation of the phagophore into an autophagosome with the aiding of peculiar proteins. The autophagosome contains some distinctive damaged organelles, which can fuse with a lysosome forming an autolysosome. It also depicts the ATG protein assembly and interaction between the cargo and LC3 molecule.

Autophagy in Cancer

Cancers can over govern autophagy exertion to upgrade tumor, aggression and to suffer micro environmental pressure. Two mechanisms by which autophagy causes cancer are the preservation of mitochondrial energy metabolism and the forestallment of the function of the p53 excrescence suppressor protein. The abecedarian autophagy gene ATG6/ BECN1 existed mono-allelically deleted in 40 to 75 of mortal prostate, bone and ovarian malice, cohering to primitive examinations [18].

Ras- expressing cells collect abnormal mitochondria and hold lesser oxygen consumption as an aftermath of indecorous macro phagosome product or weight delivery. This" autophagy dependence " indicates that regulating autophagy and mitochondrial metabolism are important novel styles for handling this rigid malice, as tumors with Ras mutations have a dismal outlook [19]. RAS- driven neoplastic irruption is backed by autophagy. deduction of autophagy- bonded genes inhibits overrunning in three-dimensional culture, lowers cell motility and lowers pulmonary metastasis *in-vivo* in epithelial cells modified with carcinogenic RAS [20].

Lack of autophagy encourages tumor development and necrosis. Tumor susceptibility is associated with allelic loss of the critical autophagy regulator beclin1, while the exact mechanism is unknown [21].

Autophagy Signaling in Cancer

At current, two significant autophagy regulation mechanisms ATG5/ 7-dependent and-self-dependent are accessible. The Unc-51-Like Kinase (ULK) complex, which includes the proteins ULK1/2 (mammalian orthologs of incentive ATG1), FIP200(FAK-family interacting protein of 200 kDa), ATG13 and ATG101, initiates traditional ATG5/ 7-dependent autophagy [22]. A crucial element of starvation- convinced autophagy is the Atg1/ ULK1 complex, which integrates flags from upstream detectors like MTOR and AMPK and transmits them to the autophagy pathway downstream [23].

Atg13's mammalian homologue as easily as the mammalian Atg1 homologues ULK1 and ULK2 are phosphorylated by mTOR. The commerce of the ULK proteins with FIP200 is intermediated by the mammalian Atg13, which binds to both ULK1 and ULK2. Atg13 list stabilizes and activates ULK and makes it effortless for ULK to phosphorylate FIP200, whereas Atg13 knockdown prevents the product of macro phagosomes. ULK1, ULK2 and Atg13 are dephosphorylated as a consequence of the autophagy-converting goods of rapamycin or leucine privation, which correspondingly spark ULK to phosphorylate FIP200. These conclusions exhibit that the ULK- Atg13- FIP200 facilities are mTOR's primary marks and expressive autophagy controllers in reaction to mTOR signaling [24].

Autophagy in Brain Tumors

The phosphatidylinositol 3- kinase to Akt to mammalian mark of rapamycin (PI3K- Akt- mTOR) trace, which encourages angiogenesis, accumulation and viability, is intoxicated in several malice, encompassing glioma [25]. The exertion of all 3 autophagy- bonded proteins LC3, beclin 1 and p62 as well as the posture of autophagy are explosively identified with the histology of the excrescence and are comparatively more current in high stage gliomas than low stage gliomas. A poor prognostic is largely related with positivity for LC3, p62 and autophagy [26]. In *in-vitro* studies, Glioma cells command been shown to constitutively spark NF- κB through exploration. proliferation of the protein that controls glucose 78 (GRP78) autophagic exertion at a position denoted by phosphorylated CHOP/ eIF2 AKT/ mTOR/ P70S6B pathway activation results in fate for glioma [27].

Autophagy in Glioblastoma

In glioblastoma, Epidermal Growth Factor Receptor (EGFR) gene modification constantly occurs, which activates downstream kinases similar as Phosphatidylinositol 3 ′- Kinase (PI3K), Akt and mammalian Target of Rapamycin (mTOR) [28]. The PTEN/ PI3K/ Akt/ mTOR alliance takes center stand among the several signaling pathways that command the elaboration of GBM due to its part in the excrescency, accumulation and metabolism of excrescence cells. In peculiar, PTEN excrescence suppressor gene differences are proved in over 80% of GBM cases [29].

By cranking downstream signaling pathways involving RAS- RAF- MAPK (containing ERK, JNK and p38) and PI3K- AKT-mTOR, PDGFR, EGFR and VEGFR are amped. These pathways also impart signals to spark recap agents like AP- 1, NF- B, Forkhead box class O(FOXO), HIF- 1, and- catenin. These nuclear recap factors constrain the formulation of genes necessitous for irruption, angiogenesis, apoptosis and the enhancement of the cell cycle [30]. It has been exposed that autophagy prevents the growth of tumors by ravaging cancer cells at the excrescence's primordial stages. There have been snaps of crucial genes for macro phagosome inauguration and extension (Beclin- 1, FIP200, blood- converting factor 1(Bif1), UVRAG, Atg4c and Atg5) subsisting deleted or vented at downgraded situations in gliomas [31].

Autophagy Targeted Therapy in Glioblastomas

A largely shifted genome and an over activation of tyrosine kinase receptors, similar as the Epidermal Growth Factor Receptor (EGFR), the Platelet Deduced Growth Factor Receptor (PDGFR) and the Vascular Endothelial Growth Factor Receptor (VEGFR), which possess subsisted set up regulated in glioblastoma multiform, are the main reasons of GBM defiance to a diverseness of curatives, because and inhibiting EGFR-signaling also promotes autophagy in Glioblastomas [32].

With the misplacement (37% of all GBM cases) or deduction (80% of all GBM cases) of the reception of phosphatase and tensin homolog, roughly 85% of GBM cases parade an overregulation of the RAS/ MAPK and PI3K/ AKT pathways (PTEN). Tumor

suppressor genes (PTEN, P16, RB and TP53) are inactivated in the nasty cells of GBM, which promotes cell multiplication and autophagy through the down- regulation of apoptosis caused by an boost in anti- apoptotic proteins (Bcl- 2, Mcl- 1, Bcl- xL, HIAP- 1, HIAP- 2 and XIAP) and a drop in pro- apoptotic proteins (shot, Bak, Bax, Bad, Bim, PUMA, NOXA, caspases- 8,-10,-9, Apaf, DR4, Fas and FADD). The serine/ threonine protein kinase and the 5 '- AMP- Actuated Protein Kinase (AMPK) are the immediate autophagy controllers (mTOR) [33].

Retinoblastoma protein knockdown averted autophagy and produced glioblastoma cells further liable to apoptosis. Amalgamations of chemotherapy and autophagy impediments retain existed substantiated to amplify the conclusiveness of treatment for glioblastoma. Simvastatins are FDA- approved impediments of the Mevalonate (MEV) waterfall, effortlessly comprehended for their goods on dwindling Cholesterol (CH) and extensively exercised for the immediate and secondhand forestallment of knots from cardiovascular complaint. Simva causes MEV waterfall- self-sufficient sensitization of GBM cells to TMZ- convinced cell expiration and it identifies the repression of macro- phagolysosome emulsion as a feasible remedial path for the treatment of GBM [34].

In the case of cancer, mutant p53 promotes tumorigenesis and inhibits autophagy, forming it a feasible remedial mark. Radio-defiance is degraded when the CTSD gene is stilled by pepstatin A, the gene's asset, or by small snooping RNA (siRNA). assimilated to U251 cells, the radio- resistant glioblastoma sub-clone cells parade advanced situations of autophagy. In radio-resistant cells, the position of CTSD protein formulation is equally hooked with p62 and appreciatively identified with LC3 II/ I. As autophagy situations declined, performing in radio- sensitization, CTSD repression escalated the neoplasm of macro-phagosomes while dwindling the product of autolysosomes [35].

Correspondingly, the medicine Hydroxychloroquine (HCQ) shows implicit to heal glioblastomas because HCQ can inhibit autophagy by blocking the fusion of autophagosome with lysosomes [36,37].

Conclusion

Cases with grade IV gliomas parade veritably meaningful pAKT, pmTOR and p- p70S6K formulation, which is too remarkable than in grade I or grade II tumors. In end, mortal glioblastoma of all malice orders vent the mTOR pathway proteins pAKT, pmTOR and p- p70S6K. Advanced attention of these proteins, still, were connected to tumors with advanced nasty malice grades. The vulnerability of GBM cells to TMZ remedy was enriched by miR- 519a. Autophagy might be a raceway through which miR-519a's salutary goods travel. also, by stopping the STAT3/ Bcl- 2 pathway, miR- 519a overexpression can beget autophagy. thus, a treatment route for GBM that combines miR- 519a and TMZ may be flourishing. These treatments only have managed to extend the survival of GBM cases, but after an original response, the antitumor effect is flash and utmost tumors ultimately progress with a high migrant and invasive capacity, followed by rush and resistance to colorful curatives. The lack of effectivity or cure and the adverse goods of these drugs are substantially due to a binary effect of autophagy, which may be both an excrescence-suppressing medium and a tumorigenic debaser, since an increase in autophagy may be salutary by precluding excrescence conformation and progression, while autophagy inhibition could be profitable to promote a complete retrogression. Thus, more autophagy targeted therapies should be established by carrying out extensive research on the genes and pathways of autophagy, which are responsible for the survival and tumor suppression in glioblastoma mainly and also in other aggressive brain tumors.

Conflict of Interest

The authors have no conflict of interest to declare.

References

1. Perkins A, Liu G. Primary brain tumors in adults: diagnosis and treatment. Am Family Physician. 2016;93(3):211-7B.
2. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. J Neurooncol. 2005;75:5-14.
3. Tyagi A, Wu SY, Watabe K. Metabolism in the progression and metastasis of brain tumors. Cancer Lett. 2022;539:215713.
4. Batash R, Asna N, Schaffer P, Francis N, Schaffer M. Glioblastoma multiforme, diagnosis and treatment; recent literature review. Curr Med Chem. 2017;24(27):3002-9.
5. Aljendi R, Knifaty MA, Amin M, Diab S, Ali MS, Alshehabi Z. A recurrent pleomorphic xanthoastrocytoma in the cerebellum in a young adult: a case report and review of the literature. Case Rep Neurol. 2023;15(1):54-62.

6. Cao W, Li J, Yang K, Cao D. An overview of autophagy: Mechanism, regulation and research progress. Bulletin Du Cancer. 2021;108(3):304-22.
7. Nakatogawa H, Suzuki K, Kamada Y, Ohsumi Y. Dynamics and diversity in autophagy mechanisms: Lessons from yeast. Nat Rev Mol Cell Biol. 2009;458-67.
8. Kocak M, Ezazi Erdi S, Jorba G, Maestro I, Farrés J, Kirkin V, et al. Targeting autophagy in disease: Established and new strategies. Autophagy. 2022;18(3):473-95.
9. Mizushima N. Autophagy: Process and function. Genes Dev. 2007;21(22):2861-73.
10. Yang X, Zhong X, Tanyi JL, Shen J, Xu C, Gao P, et al. mir-30d Regulates multiple genes in the autophagy pathway and impairs autophagy process in human cancer cells. Biochem Biophys Res Commun. 2013;431(3):617-22.
11. Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. J Pathol. 2010;221(1):3-12.
12. Pourhanifeh MH, Mahjoubin-Tehran M, Karimzadeh MR, Mirzaei HR, Razavi ZS, Sahebkar A, et al. Protein homeostasis in amyotrophic lateral sclerosis: Therapeutic opportunities? Front Mol Neurosci. 2017;2;10:123.
13. He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annual Review of Genetics. 2009;43:67-93.
14. Grasso D, Renna FJ, Vaccaro MI. Initial steps in mammalian autophagosome biogenesis. Frontiers in Cell and Developmental Biol. 2018;6:146.
15. Reggiori F, Klionsky DJ. Autophagic processes in yeast: mechanism, machinery and regulation. Genetics. 2013;194(2):341-61.
16. Grasso D, Renna FJ, Vaccaro MI. Initial steps in mammalian autophagosome biogenesis. Frontiers in Cell and Developmental Biol. 2018;6:146.
17. White E. The role for autophagy in cancer. J Clin Investig. 2015;125(1):42-6.
18. Guo JY, Chen HY, Mathew R, Fan J, Strohecker AM, Karsli-Uzunbas G, et al. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. Genes Dev. 2011;25(5):460-70.
19. Gorjizadeh N, Poudineh S, Barghgir B, Eghbali M, Sarlak A. The crosstalk between autophagy and MicroRNAs in esophageal carcinoma. Galen Med J. 2023;23;12:e2903.
20. Deretic V, Saitoh T, Akira S. Autophagy in infection, inflammation and immunity. Nat Rev Immunol. 2013;13(10):722-37.
21. Jung CH, Jun CB, Ro SH, Kim YM, Otto NM, Cao J, et al. ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. Mol Biol Cell. 2009;20:1992-2003.
22. Fan QW, Cheng C, Hackett C, Feldman M, Houseman BT, Nicolaides T, et al. Akt and autophagy cooperate to promote survival of drug-resistant glioma. Sci Signal. 2010; 3(147):ra81.
23. Lin L, Baehrecke EH. Autophagy, cell death and cancer. Mol Cell Oncol. 2015;2(3):e985913.
24. Feng F, Zhang M, Yang C, Heng X, Wu X. The dual roles of autophagy in gliomagenesis and clinical therapy strategies based on autophagic regulation mechanisms. Biomed Pharmacother. 2019;120:109441.
25. Fan QW, Cheng C, Knight ZA, Haas-Kogan D, Stokoe D, James CD, et al. EGFR signals to mTOR through PKC and independently of Akt in glioma. Sci Signal. 2009;2(55):ra4.
26. Ryskalin L, Gaglione A, Limanaqi F, Biagioni F, Familiari P, Frati A, et al. The autophagy status of cancer stem cells in gliobastoma multiforme: From cancer promotion to therapeutic strategies. Int J Mol Sci. 2019;20(15):3824.
27. Li XY, Zhang LQ, Zhang XG, Li X, Ren YB, Ma XY, et al. Association between AKT/mTOR signaling pathway and malignancy grade of human gliomas. J Neurooncol. 2011;103:453-8.
28. McCubrey JA, Steelman LS, Chappell WH, Abrams SL, Wong EW, Chang F, et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta - Mol Cell Res. 2007;1773(8):1263-84.
29. Pottier C, Fresnais M, Gilon M, Jérusalem G, Longuespée R, Sounni NE. Tyrosine kinase inhibitors in cancer: Breakthrough and challenges of targeted therapy. Cancers. 2020;12(3):731.
30. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee SU. Glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment. Asian Pac J Cancer Prev. 2017;18(1):3.
31. Liu X, Sun K, Wang H, Dai Y. Knockdown of retinoblastoma protein may sensitize glioma cells to cisplatin through inhibition of autophagy. Neurosci Lett. 2016;620:137-42.
32. Li H, Chen L, Li JJ, Zhou Q, Huang A, Liu WW, et al. miR-519a enhances chemosensitivity and promotes autophagy in glioblastoma by targeting STAT3/Bcl2 signaling pathway. J Hematol Oncol. 2018:1-6.
33. Shojaei S, Koleini N, Samiei E, Aghaei M, Cole LK, Alizadeh J, et al. Simvastatin increases temozolomide-induced cell death by targeting the fusion of autophagosomes and lysosomes. FEBS J. 2020;287(5):1005-34.

34. Zheng W, Chen Q, Wang C, Yao D, Zhu L, Pan Y, et al. Inhibition of Cathepsin D (CTSD) enhances radiosensitivity of glioblastoma cells by attenuating autophagy. Mol Carcinog. 2020;59(6):651-60.
35. Xu R, Ji Z, Xu C, Zhu J. The clinical value of using chloroquine or hydroxychloroquine as autophagy inhibitors in the treatment of cancers: A systematic review and meta-analysis. Medicine. 2018;97(46).
36. Khan I, Baig MH, Mahfooz S, Rahim M, Karacam B, Elbasan EB, et al. Deciphering the role of autophagy in treatment of resistance mechanisms in glioblastoma. Int J Mol Sci. 2021;22(3):1318.
37. Escamilla-Ramírez A, Castillo-Rodríguez RA, Zavala-Vega S, Jimenez-Farfan D, Anaya-Rubio I, Briseño E, et al. Autophagy as a potential therapy for malignant glioma. Pharmaceuticals. 2020;13(7):156.