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Review Article

Brain Tumor Autophagy: A New Breakthrough in Cancer Research

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Abstract

The term autophagy originates from a brace of Greek hitches, auto and phagy, where auto relates to one's own tone, and phagy refers to ingesting. Through a lysosome- suspended constrained medium, autophagy is the congenital, preserved crack-up of the cell that eliminates unwanted or imperfect factors. It enables the controlled cellular element breakdown and recycling. In cancer cells, autophagy prevents necrosis, which in amble reduces the preceding inflammation, which is accepted to hasten excrescence tumor, the medium causing this is quietly unknown. therefore, autophagy is presently appertained to as to command binary part as it prevents excrescence progression by precluding cancer cells from weathering and causing cell grave but, there are given autophagic pathways like PI3K- AKT-mTOR pathway which extend excrescence product. Collectively, it's set up that a blights in autophagy can usher to glioblastoma multiform, gliomagenesis, medulloblastoma, neural stem cells and numerous unlike excrescences in brain. In this review, we bandy the signification of pathways, modulators, and genes of autophagy in brain excrescences.

Keywords: autophagy; tumor development; cancer cells; glioblastoma multiforme; brain tumors

Abbreviations:

GBM - Glioblastoma Multiform

RAS - Rat Sarcoma

RAF - Rapidly Accelerated Fibrosarcoma

MAPK - Mitogen-Activated Protein Kinase

mTOR - Mammalian or Mechanistic Target of Rapamycin

NF- κB - Nuclear Factor Kappa B

TMZ - Temozolomide

PTEN - Phosphatase and Tensin Homolog Deleted on Chromosome 10

Introduction

What is Autophagy?

Autophagy, gut event of eukaryotic cells is initially delivered from incitement to humans. The concoction of double membrane- bound cells that entrap paraphernalia to be degraded down in lytic chambers — a methodology that appears to live mechanistically tone- reliant from journal membrane custom is the most emphatic aspect of autophagy [1].

The stint" 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 [2]. 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 [3]. Cells command a low rudimentary position of autophagy, which can be amplified in reaction to environmental pressure. This proceeding lookouts against injury and sickness while conserving cellular homeostasis [4]. Cellular conservation is transported out via the evolutionary preserved lysosomal declination path understood as autophagy. Autophagy likewise has oncogenic or onco- suppressive goods turning on the sort of excrescence, cell viability, and intracellular environment.

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. The instantaneous redox-sensitive marks, which are protein cysteinyl thiols ornon- protein thiols, thereby produce up the earliest string of defense. 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 [5].

Rough endoplasmic reticulum without ribosome appendage, falling off of the double- sub caste membrane, gradationally crossing a portion of the cytoplasm, organelles, proteins, and disparate cell- degradable accoutrements are all exemplifications of precise exemplifications of autophagy [6]. Picky or adaptable(non-selective) autophagy is achievable. corridor of the cytoplasm is packaged into auto- phagosomes via general autophagy and transmitted to lysosomes for wastage. Alternately, picky autophagy capacities by relating individualized targets similar harmed cell organelles, protein groups, and intracellular infections [7].

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. Through the application of a macro phagosome, a double membrane- bound vesicle that merges with the lysosome to produce an autolysosome, macro-autophagy transports cytoplasmic weight to the lysosome. conversely, in micro-autophagy, the lysosome itself straightway absorbs cytosolic factors through invagination of the lysosomal membrane. bulky structures can be consumed via macro- and micro-autophagy applying both picky and on-selective styles. Targeted proteins are transmitted across the lysosomal membrane during chaperone- intermediated autophagy (CMA) in a sophisticated with chaperone proteins (similar as Hsc- 70) that are honored by the lysosomal membrane receptor lysosomal- associated membrane protein 2A (Beacon- 2A), directing to the unfolding and declination of the targeted proteins.[8]

Discussion

Steps of Autophagy

The five aspects that frame up the autophagy procedure are inauguration, extension, development, emulsion, and declination [9].

The original stage of autophagy inauguration is the translocation of the ULK1 inauguration complex to the phagophore. By curbing mTOR, the ULK1 complex is fabricated and made available for activation and translocation. The Class III PI3 kinase complex mediates extension of the phagophore membrane. The autophagy receptors p62/sequestosome- 1 and optineurin intervene weight reclamation to the developing phagophore. The ubiquitin- suchlike (Ubl) disciplines on autophagy substrates and the LC3- II on the developing phagophore are used by autophagy receptors to bind both poly- ubiquitin progressions and LC3-II (LIRs). finalized auto phagosomes are redeemed to empower emulsion with the lysosome after substrate reclamation and check. As an effect of the auto phagosome- lysosome emulsion, the lysosome's acid hydrolases can downgrade the autophagic substrates. Nutrients can be reclaimed back into the cytosol thanks to declination [10].

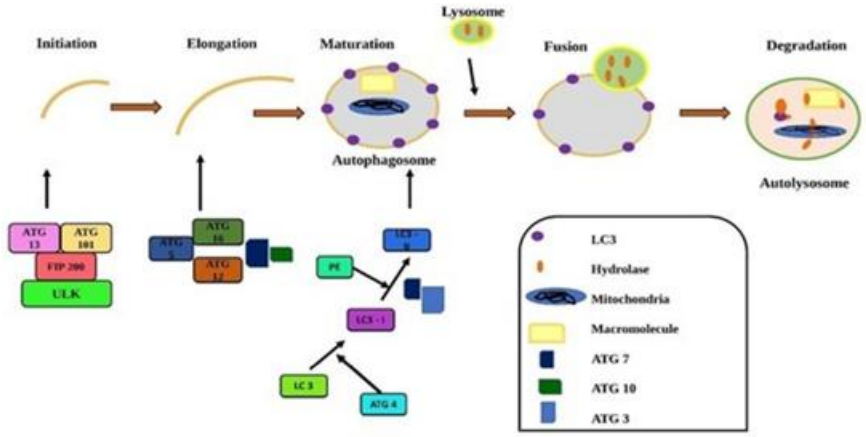

Figure 1: Steps of Autophagy

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

By gumming the apoptotic operation, autophagy securities some cancer cells from anticancer curatives. distinct cancer cells, on the other aspect, expertise autophagic cell death postdating cancer treatments [11].

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 [12].

Ras- expressing cells collect abnormal mitochondria and hold lesser oxygen consumption as an aftermath of indecorous auto phagosome product or weight delivery. The tricarboxylic acid cycle product and energy loss in appetite are likewise caused by autophagy abnormalities. This" autophagy dependence " indicates that regulating autophagy and mitochondrial metabolism are important novel styles for handling this rigid malice, as excrescences with Ras mutations have a dismal outlook [13]. 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 [14].

Breast cancer mammary excrescence inauguration and tumor are covered when FIP200 is knocked off. The expiry of mammary excrescence cells and Ras- converted embryonic fibroblasts (MEFs) was unaffected by the FIP200 omission, although both systems' proliferation was markedly dropped. FIP200 therefore, can be a promising thing in the treatment of cancer [15]. 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 [16].

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 [17]. 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 [18].

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 auto 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.[19]

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 [20].

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 [21]. 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 [22].

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) [23]. 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 [24].

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 excrescences. 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 excrescences with advanced nasty malice grades [25].

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 [26]. It has been exposed that autophagy prevents the growth of excrescences by ravaging cancer cells at the excrescence's primordial stages. There have been snaps of crucial genes for auto 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 [27].

Autophagy targeted therapy in brain tumors

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 [28].

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 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) [29].

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 [30]. In the case of cancer, mutant p53 promotes tumorigenesis and inhibits autophagy, forming it a feasible remedial mark [31].

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 [32].

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 auto-phagolysosome emulsion as a feasible remedial path for the treatment of GBM [33].

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 auto-phagosomes while dwindling the product of autolysosomes [34]. Correspondingly, the medicine hydroxychloroquine (HCQ) shows implicit to heal glioblastomas [35].

The mechanisms preliminarily mentioned have exhibited that autophagy can spark apoptosis as the response is farther boosted, which has the capability to acclimatize excrescence cells and boost the prognostic of cases with glioma and, eventually, offers an optimistic roadway to unfold new tactics.

Conclusions

Glioblastoma cells' class of autophagy would alter grounded on the characteristics of the excrescence medium. In array to effectively target survival autophagy, a remedial route should be evolved while featuring on the quantum of autophagy activation in excrescence tissues.

Future Focus

The mechanisms previously mentioned have shown that autophagy can trigger apoptosis as the reaction is further intensified, which has the ability to sensitize tumor cells and boost the prognosis of patients with glioma and, finally, offers a promising avenue to develop novel tactics.

Utilizing autophagy as an additional tool to enhance established and novel therapies may improve patient outcomes in difficult-to-treat cancers like glioblastoma. This may also lessen the occurrence of chemo-resistance and radio-resistance, which are common in this disease, and improve prognosis for many glioblastoma patients.

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