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Unfolding the role of autophagy in the cancer metabolism

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ABSTRACT

Autophagy is considered an indispensable process that scavenges toxins, recycles complex macromolecules, and sustains the essential cellular functions. In addition to its housekeeping role, autophagy plays a substantial role in many pathophysiological processes such as cancer. Certainly, it adapts cancer cells to thrive in the stress conditions such as hypoxia and starvation. Cancer cells indeed have also evolved by exploiting the autophagy process to fulfill energy requirements through the production of metabolic fuel sources and fundamentally altered metabolic pathways. Occasionally autophagy as a foe impedes tumorigenesis and promotes cell death. The complex role of autophagy in cancer makes it a potent therapeutic target and has been actively tested in clinical trials. Moreover, the versatility of autophagy has opened new avenues of effective combinatorial therapeutic strategies. Thereby, it is imperative to comprehend the specificity of autophagy in cancer-metabolism. This review summarizes the recent research and conceptual framework on the regulation of autophagy by various metabolic pathways, enzymes, and their cross-talk in the cancer milieu, including the implementation of altered metabolism and autophagy in clinically approved and experimental therapeutics.

1. Introduction

Autophagy is a self-regulatory catabolic process that maintains cellular integrity and eradicates toxic molecules such as intracellular pathogens, misfolded proteins, cancerous molecules, and damaged organelles including mitochondria, endoplasmic reticulum, and peroxisomes [1,2]. In addition, it functions diversely as Chaperone-Mediated Autophagy (CMA), microautophagy, and macroautophagy. All these pathways end up in lysosomes [3]. However, the journey of the target cargo towards the lysosome varies in these pathways. In CMA, Lysosomal-Associated Membrane Protein 2A (LAMP 2A) is a receptor present on the membrane of lysosomes that recognizes the proteins attached with a chaperone protein HSC70 and allows the complex to invade inside the lysosomal membrane [4,5]. Microautophagy drives the elimination of toxins by directly engulfing them by lysosomes. Macroautophagy (thereafter considered as autophagy), however, delivers the cytosolic cargoes by engulfing them in double-membrane vesicles called autophagosomes, which eventually fuse with lysosomes and form autolysosomes (Fig. 1) [5]. Despite the non-selective role of autophagy in recycling and degrading the toxins as mentioned above, autophagy can also function selectively due to its ability to detect diverse substrates in severe conditions. Selective autophagy specifically targets cargoes with the required receptors, including SQSTM1(p62) [6], NBR1 [7], and leads to its degradation. These are named according to the particular degraded cargo, such as ferritinophagy for ferritin, mitophagy for mitochondria, reticulophagy for ER, and xenophagy for bacteria [8].

Through the combined work of many scientists, the complex autophagic machinery has become preferably comprehensible, which suggests that ablating any step or factor in the autophagic incidence will eventually give different outcomes [9]. Therefore, its contribution is observed in many complicated diseases such as neurodegenerative diseases, cardiovascular disease, pathogenic infections, cancer and metabolic defects. Defective autophagy is prominently found in many neurodegenerative diseases including Alzheimer's, Parkinson's, Huntington's disease [10] and pathogenic infection including *Streptococcus pyogenes* infection [11]. Additionally, increased autophagy is found in many patients with cardiovascular diseases, including congestive heart failure, coronary artery disease, hypertension, and aortic valvular disease [12]. Indeed, a specific autophagic gene ablation can have severe pathological consequences, such as in Crohn's disease, the deleted Atg16L hinders the initiation of autophagosome formation [13]. Accumulated evidence has shown the foremost role of autophagy in cancer. Initially, autophagy being a catabolic process, was considered as a tumor suppressor [5]. However, recently many scientists introduced the pro-survival nature of autophagy in cancer progression, which was the paradigm shift [1,14]. They found that autophagy assists in sustaining

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Abbreviations:

CMA	chaperone-mediated autophagy
ROS	Reactive Oxygen Species
Atgs	Autophagy Regulator Genes
GEMM	genetically engineered murine mice
PINK1	PTEN-induced putative kinase 1
NSCLCs	non–small cell lung cancers
TKI	tyrosine kinase inhibitors
ROS	reactive oxygen species
Atgs	Autophagy Regulator Genes
GEMM	Genetically Engineered Murine Mice
3-MA	3-methyladenine
Cav- 1	caveolin-1
CAFs	cancer-associated fibroblast
2-DG	2-deoxyglucose 5-thioglucose
3-BrPA	3-bromopyruvate
TSCC	Tongue Squamous Cell Carcinoma
SIRT1	sirtuin1
PtdIns	Phosphatidylinositol 3-phosphate
NAA10	*N*-alpha-acetyltransferase 10
PEP	phosphoenolpyruvate
PK	pyruvate kinase
PKM	pyruvate kinase M
YAP1	Yes- Associated Protein 1
AKT1S1	AKT substrate1
PKCλ/ι	Protein kinase Cλ/ι
MERCs	Mitochondria-Endoplasmic Reticulum Contact Sites
PDAC	Pancreatic Ductal Adenocarcinoma
RRAG	Ras-related GTP binding
FFA	Free Fatty Acid
NCoR1	Nuclear Receptor co-Repressor 1
CTGF	Connective Tissue Growth Factor
ANKRD37	Ankyrin Repeat Domain Protein
p-STAT3	Phospho-Signal Transducer and Activator of Transcription 3
JNK1	c-Jun *N*-terminal Kinase 1
LKB1	Liver Kinase B1
PPP	Pentose Phosphate Pathway
TIPRL	TOR Signaling Pathway Regulator-Like
ANKDD1A	Ankyrin Repeat and Death Domain-Containing 1A
HCQ	Hydroxychloroquine
TMZ	Temozolomide
EC	endothelial cells
CSCs	cancer stem cells
NAC	*N*-acetylcysteine
CQ	chloroquine.

stressful conditions occurring during tumor development. The best-studied are nutrient starvation and hypoxia that are tightly regulated by AMPK-mTOR [15] and BNIP3 and BNIP3L [16] pathways respectively, which is explained later in the review (Fig. 2). Defects in metabolic functions are one of the hallmarks of cancer. During the development of a tumor, the metabolic state gets altered due to change in glucose, lipid and iron metabolism in the cancer milieu. Autophagy actively participates in regulating these metabolic pathways and can be induced by a plethora of stimuli such as nutrient starvation, reactive oxygen species (ROS) and hypoxia. Although, various stresses that induce autophagy can also be considered as one of the consequences of aberrant metabolic pathways that concomitantly participate in cancer

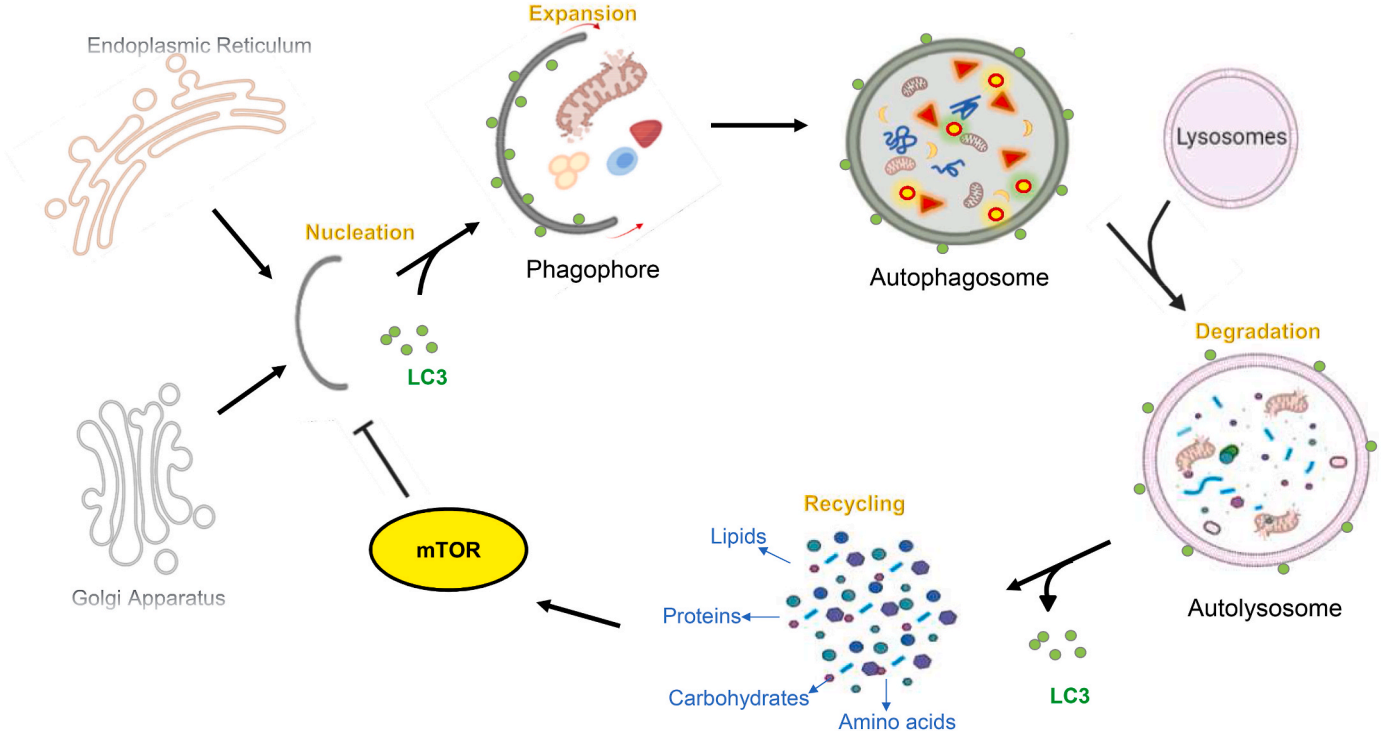

Fig. 1. The Autophagy undergoes recycling of Macromolecules. The Nucleation of the autophagic membrane emerges from the Endoplasmic reticulum and Golgi apparatus, which further converges degraded organelles, misfolded proteins, carcinogenic molecules and undergoes elongation forming Phagophore. The Phagophore expands and matures, forming autophagosomes. The fusion of lysosomes produces autolysosomes which undergo degradation and further recycle the macromolecules. The fulfillment of nutrients activates mTOR that negatively regulates autophagy by inhibiting the nucleation of the autophagy.

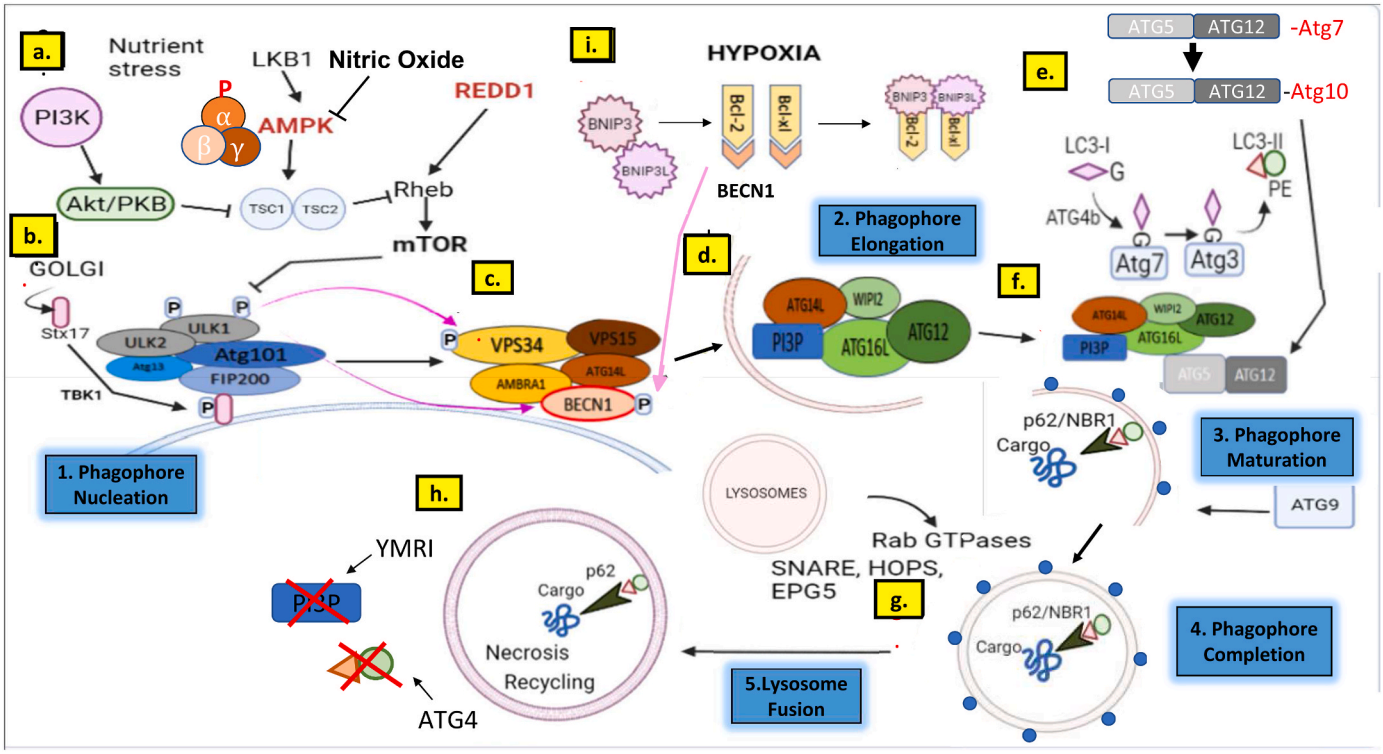

Fig. 2. The mechanism of autophagosome formation. **a.** Different factors induce Autophagosome initiation and nucleation. Under nutrient stress, LKB1 specifically phosphorylates α-AMPK of heterotrimeric AMPK, Nitric oxide inhibits by dephosphorylating AMPK and REDD1 increased in hypoxia upregulates TSC1-TSC2 complex that abstains the Rheb mediated activation of mTOR, whereas PI3K increasesphosphorylation of Akt and upregulates mTOR. **b.** Phagophore nucleation. AMPK phosphorylates ULK1 and promotes phagophore nucleation. The ULK1-complex includes ULK1, ULK2, Atg 101, FIP200, Atg 13. The complex binds to the membrane by phosphorylated Stx 17, Stx17 released from Golgi apparatus and undergoes tbx1 mediate phosphorylation. **c.** ULK1 phosphorylates VPS34 and BECN1 and activates Class 2I phosphoinositide 3-kinase complex I (PI3KC3–C1). PI3KC3–C1 complex includes PI, VPS34, Atg14L, VPS15, AMBRA-1, and BECN1. The complex results in the formation of PI3P on the membrane derived from the Endoplasmic Reticulum. **d.** Phagophore elongation. PI3P recruits additional autophagy-specific PI3P effectors, such as WIP2I. WIP2I concomitantly recruits the Atg 12–Atg16L conjugation complex and promotes phagophore expansion. **e.** Elongation requires ubiquitin-like proteins Atg12-Atg5 and LC3B phosphatidylethanolamine (PE). Atg12-Atg5 conjugation activates E1 like enzyme Atg7 and E2 like enzyme Atg10 and forms a supramolecular complex with Atg16L; meanwhile, LC3B gets lipidated to PE by an E1 like Enzyme Atg7 and E2 like Atg 3 that club with the Atg12-Atg5-Atg16L complex and forms a membrane-bound LC3B-II. Atg4B, a cysteine protease, activates LC3B–I by cleaving the *C*-terminal of glycine and exposing it for binding to PE. The complex is recruited by WIPI and acts as an E3 ligase for LC3B-PE. **f.** Phagophore maturation. LC3B acts as a docking site for autophagy receptor p62 and NBRI. Atg 9 requires a lipid membrane from the Endoplasmic reticulum, Golgi apparatus, and Mitochondria to complete the autophagosome. **g.** Phagophore completion. Docking and fusion of lysosomes occur by Rab GTPases and recruits SNARE, HOPS complex. Atg 4 and YMIR degrade the LC3 and PI3P, respectively. Recycling of MPP7 activates YAP1, and cytosolic MDH1 regulates ULK1 levels, thereby activating autophagy. **i.** Bcl-2 and Bcl-xl are negative autophagy regulators; however, in hypoxic conditions, HIF1α activates BNIP3 and BNIP3L, subsequently binds the Bcl-2 and Bcl-xL consequently releases BECN1. The released BECN1 resumes autophagy. (**Abbreviations-** AMPK- AMP-Activated Protein Kinase, REDD1- Regulated In Development And DNA Damage Response 1, TSC1/2 -Tuberous sclerosis proteins 1/2, ULK1/2- Unc-51 like autophagy activating kinase, FIP200- Family Interacting Protein of 200 kD, Stx1/2- Shiga toxins, Tbx1-T-box transcription factor, VPS34-kinase vacuolar protein sorting 34, AMBRA1-autophagy and BECN1 regulator 1, PI- Phosphoinositide, PI3P- Phosphatidylinositol 3-phosphate, WIP2I -WD-repeat domain PI-interacting protein 2, PE-Phosphatidylethanolamine, SNARE- Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor, HOPS-Homotypic fusion, and protein sorting, MMP7- MAGUK p55 subfamily member 7, MDH1-malate dehydrogenase 1).

progression [8]. For instance, disruption in glycolytic pathway results in starved conditions and dysfunction in oxidative phosphorylation results in ROS accumulation. This review will comprehensively explain the indispensable presence of autophagy during cancer progression which involves the specific cross-talk between the autophagy and metabolic pathways. The review is partitioned into three parts. The first part of the review has summarized the essential metabolic pathways involved in autophagy which altogether alters tumor progression. The second part includes the rewiring of autophagy and metabolism in specific cancers, and the third part summarizes autophagy as the potential therapeutic target.

2. Autophagy and cancer

The involvement of autophagy in various diseases has sought many scientists' attention and is keenly investigated in the diseases mentioned above. Due to the involvement of autophagy in distinct signalling pathways altering the cancer progression, its role in cancer has been-subjected to intense investigation in the past several years. The uncontrolled proliferative cancer cells spread with the continuance of unpredictable moves and are the leading cause of death worldwide. The cancer cells within the restricted tumor microenvironment utilize autophagy to sustainsturdy responses.The established cross-talk of autophagy with metabolism, results in the availability of essential survival substances in the cancer milieu [8].

The peculiarity of autophagy engraved a distinct position in the management of cancer cell progression [9]. It works as a helping hand with cancer cells to maintain metabolism for nutrient availability, scavenging ROS, and exacerbating dysfunctional mitochondria. However, autophagy works in a context-dependent and site-specific manner either by promoting or demoting cancer cells' proliferation, motility, and invasive properties. The detection of autophagy is confirmed with the increased expression level of LC3B-II (formed by lipidation of LC3B–I during autophagosome formation) [17], BECN1 [18], Autophagy

Regulator Genes (Atgs) [19] in various cancer cell lines. Additionally, the expression level of selective autophagy receptors such as optineurin and degradation of p62 is also considered for detecting autophagy.

The cancer-initiating factors, including DNA damage, ROS production, and genomic instability, are all strictly under the surveillance of autophagy. BECN1 is a multi-domain protein with an *N*-terminal BCL2 homology (BH)-3 domain that binds with Bcl-2 and effectively suppresses autophagosomes formation. In contrast, the central coiled-coil domain (CCD) binds with UVRAG or ATG14 and contributes to PI3K complex [18]. In many tumor cells such as ovarian, breast, and testicular cancer, the monoallelic deletion of BECN1 is observed. Thus, cancer cells harboring a functional copy of BECN1 revealed its role as a haploinsufficient tumor suppressor gene as it maintains partial augmentation of autophagy [20]. However, mosaic deletion of Atg5 in liver tumor cells completely impaired autophagy, and Atg7 deficiency results in benign oncocytomas in Genetically Engineered Murine Mice (GEMM) of $KRAS^{G12D}$-driven lung cancer [21]. Several pieces of evidence reveal the presence of tumor cell-autonomous autophagy where tumor proliferation includes either wild-type or impaired autophagy regardless of intact host autophagy [21]. Selective autophagy viz, mitophagy maintains mitochondrial flux and oxidative stress as dysfunctional mitochondria activate PTEN-Induced Putative Kinase1 (PINK1), which eventually ubiquitinates it by tumor suppressor E3 ligase Parkin (Parkin 2) [22]. Thereupon, it is imperative to comprehend the versatile nature of autophagy in the progression of cancer cells.

Autophagy is orchestrated with limited nutrients and oxygen in the tumor microenvironment, promoting cancer cell progression by recycling macromolecular complexes and supplying raw materials to metabolic pathways. For example, autophagy augments the TCA cycle through anaplerotic reactions, and initiates oxidative phosphorylation that maintains ATP levels without extracellular resources [23]. Similarly, hypoxia-induced autophagy either by BNIP3 and BNIP3L or AMPK activation and mTOR inhibition promotes survival mechanisms [24]. In contrast, BECN1 ablation results in tumor progression in lung and hepatocellular cancer cells, and induction of autophagy promotes cell death in breast cancer cells [25] which also showed the tumor-suppressive role of autophagy. Targeting autophagy at distinct steps confers different outcomes, such as inhibiting autolysosome formation accumulates autophagosomes that impede tumor-promoting apoptosis and necroptosis [2]. The context-dependent activation and coordination of autophagy at various stages of tumor progression are therefore still obscure. However, the understanding of certain stages where autophagy participates contrastingly as a tumor suppressor or promoter becomes a paramount study that will surely simplify complementing the autophagy with various metabolic pathways.

Furthermore, how the selection of a particular metabolic pathway proceeds and defines autophagy towards tumor progression is essentially investigation worthy and one of the subjects of this review.

3. Glycolysis

This metabolic pathway essentially provides ATP, independent of the availability of total oxygen present. The glycolytic pathway preferably occurs in the cytoplasm and includes ten consecutive steps that convert glucose into pyruvate. Pyruvate is further metabolized in the TCA cycle followed by oxidative phosphorylation and eventually produces 36/38 ATP; however, in low oxygen availability (anaerobic condition), pyruvate is processed to lactate and produces only 2 ATPs [26]. The accumulation of lactate results in a decreased pH and renders NADH recycling for the perpetuation of glycolysis. Otto Warburg, in the 1920s, explained the preferable metabolic shift to glycolysis and lactate production in cancer cells, despite enough available oxygen. This phenomenon was coined as the Warburg effect. As only 2 ATPs are produced in each cycle, it renders the cancer cells to function innumerous times to fulfill their energy requirements [27]. Although nutrient starvation, hypoxia, and oxidative stress are known to induce autophagy; however, these factors are considered one of the consequences of diversion during the glycolytic pathway [28]. Moreover, autophagy works in both directions with glycolysis either by complementing or by overcoming the whole pathway. Autophagy complements glycolysis by providing raw material after digesting complex proteins and lipids. However, autophagy overcomes glycolysis by switching it towards oxidative phosphorylation or pentose phosphate pathway (Table .1) [26]. The induction of glycolysis during tumorigenesis, which augments autophagy, was verified in Ras mutant cancer cells. Ras is a mutationally active and potent oncogene that promotes adhesion independent transformation and facilitates glycolysis. Genetic or siRNA-mediated knockdown of Atgs during Ras transformation resulted in reduced proliferation and decreased glucose metabolism. Thereby, autophagy promotes Ras-driven tumor growth in a glycolytic context [29]. Lei Duan and Ricardo E. Perez investigated the active participation of p53 during glycolysis and autophagy cross-talk in MCF7 and U2OS cell lines. Nutlin-3a (p53 activator) treatment resulted in apoptotic resistance with the maintenance of glycolysis and p53 directed induction of AMPK, which elevated prosurvival autophagy. However, when U2OS cells were treated with Nutlin-3a along with 2DG (glycolytic inhibitor), it explicates decreased MDC fluorescence (late autophagosome detection), which indicates the regulation of autophagic flux by glycolysis in response to Nutlin-3a [30]. Autophagy also triggers glycolysis with NF-κB by performing non-canonical functions. When NF- κB translocates to the nucleus, it elevates HIF1α mRNA and protein expression level which increases both autophagy and glycolysis (Table .1) [31]. Competent cancer cells exploit autophagy as per the stress conditions. The glycolytic inhibition can also activate autophagy with the increased AMPK level to surpass the nutrient deprivation and maintain mitochondrial activity for perpetual ATP production [32]. In glioma cells, Xuan Zhong Wang et al. astonishingly revealed autophagy's participation with RSL3 (induces ferroptosis by inactivating glutathione peroxidase 4), which causes glycolysis dysfunction and promotes cell death [33]. Autophagy is also associated with other metabolic pathways, so at times inhibition of autophagy switches a metabolic shift from oxidative phosphorylation to aerobic glycolysis and promotes resistance towards applied therapy, as observed in gastric cancer, where inhibition of autophagy promotes epithelial to mesenchymal transition and metastasis [34].

Due to the emergence of EGFR mutation in cancer and developing resistance against tyrosine kinase inhibitors, autophagy manifested an imperative role in maintaining ATPs level and promoting EGFR-mutant tumor survival. In Human Non–Small Cell Lung Cancers (NSCLCs) with activating mutations in EGFR, resistance against erlotinib (EGFR-targeted tyrosine kinase inhibitors) is induced. Experiments dispense a substantial increase in glycolysis with an increased level of GLUT1, MCT4, AKT pathway, and glycolytic enzymes such as Hexokinase II in NSCLCs. However, targeting only glycolysis by erlotinib results in starved conditions which sporadically induces autophagy through AKT activation instead of AMPK and this activated autophagy develops resistance. Surprisingly, when glycolysis was inhibited along with autophagy by the AKT inhibitor, it sensitized Erlotinib-resistant cells towards the targeted therapy [35]. Lijun Jia et al. shows that quercetin, a bioactive flavonoid, suppresses breast cancer progression by inhibiting glycolysis. Further, the 3-methyladenine (3-MA) application and activation of the Akt/mTOR pathway by IGF-1 (insulin-like growth factor) inhibits autophagy and results in breast cancer proliferation [36]. Concluding, quercetin inhibits glycolysis and induces autophagy by inhibiting the Akt/mTOR pathway and decreased tumor progression. Till now the exact mechanism of glycolysis through which it regulates autophagy is still obscure; however, different combinatorial options of targeting autophagy with glycolysis have given promising results towards decreased resistance development during the applied therapy. The context-dependent and site-specific role of autophagy rewiring metabolism and cancer progression was also observed while understanding the Reverse Warburg Effect, as described in upcoming topic.

Table 1
Effect of autophagy inhibitors on drug resistant cancer cells.

Cancer	Drug-resistance mediated by autophagy induction	Autophagy Inhibitor	Mechanism of targeting drug-resistant cancer cells
Breast Cancer	Tamoxifen	LDHA inhibitor/3-methyladenine	Inhibits induced autophagy due to LDHA expression [61].
Gastric Cancer	Oxamate	Chloroquine	Inhibition of autophagy triggered due to oxamate induced inactivation of LDHA [62].
Colorectal Cancer	PFKFB3 inhibitor, 3PO	3-methyladenine/Chloroquine	Inhibition of autophagy induced due to PFKFB3 inhibition [16].
Colon Cancer Cells	$CoCl_2$	3-methyladenine	Inhibits hypoxia-induced autophagy [101].
Colon Cancer	Inhibition of ANKRD37	Chloroquine	Inhibition of autophagy induced due to ANKRD37 translocation to the nucleus [106].
Lung Cancer	Cisplatin	3-methyladenine	Inhibition of hypoxia-induced activation of BNIP3 and BNIP3L and autophagy [108].
Colon adenocarcinoma	Oxaliplatin	SP600125	JNK inhibition prevents hypoxia-induced autophagy [109].
Hepatocellular carcinoma	Cocl2 (hypoxia)	Atg4bC74A	Inhibition of autophagosome formation prevents the supply of ATP through β-oxidation [92].
Colon Cancer	–	3-methyladenine	Inhibits the supply of FFA from adipocytes [93].
Acute myeloid Leukemia	–	3-methyladenine	Inhibition of autophagy Prevent oxidative phosphorylation [70].
Gastric Carcinoma	Irinotecan	Gossypol and phenformin	Inhibits oxidative phosphorylation and NADH production, thus inhibiting autophagy [166].
Melanoma $BRAF^{V600e}$ driven Cancer	Vemurafenib/dabrafenib	Atg7 deficiency/Chloroquine	Inhibits autophagy induced by BRAF inhibitor [167].
Colorectal Cancer	Cabozantinib XL184	SBI0226365/Chloroquine	Inhibition of autophagy-dependent metabolism [153].
Lung Cancer KRAS mutant	Deltarasin	3-methyladenine and *N*-acetylcysteine (NAC)	Inhibits reactive oxygen species-induced autophagy [115].
EGFR mutated Non-small Lung cancer	Erlotinib	Chloroquine	Inhibition of erlotinib induced autophagy [165].
Lung Cancer	Crizotinib	Chloroquine	Inhibition of Akt/mTOR induced autophagy during crizotinib resistance.
Acute myeloid leukemia with mutated NMP1	–	Inhibition of PKM2/ Chloroquine	Inhibition of PKM2 induced autophagy [54].
Lung Cancer	Iso deoxyelephantopin (ESI)	3-methyladenine	Inhibition of ESI induced translocation of Nrf2 to nucleus and activation of p62 induced autophagy [168].
Glioblastoma	Bevacizumab (Anti-angiogenic therapy)	Chloroquine	Inhibition of hypoxia induced autophagy due to bevacizumab [169].
Pancreatic ductal adenocarcinoma	BPTES (glutamine inhibitor)	Chloroquine	Induce apoptotic cell death upon autophagy inhibition [78].
Gastric Cancer	*N*-acetyl cysteine	Drug targeting BECN1	ROS inhibits HIF1α and NFκB induced autophagy [31].
Liver Cancer	bromopyruvate (3-BrPA), 2-deoxy-D-glucose (2-DG), and lonidamine	Atg5 knockdown/Bafilomycin treatment	Inhibits upregulated glycolysis due to impaired autophagy [26].

4. Reverse warburg effect

The controversial role of autophagy becomes more comprehensible when understood in the context of metabolic coupling where two specific cell types communicate by their metabolism while being associated with autophagy. The tumor microenvironment comprises core cancer cells with unlimited proliferative capacity and other surrounding stromal cells. The tumor stroma includes immune cells, myofibroblasts/cancer-associated fibroblast (CAFs) (stromal cells), and vasculature. In addition, stromal caveolin-1 (Cav-1), a tumor suppressor, frequently deleted in several cancers including breast, neck, colon, and ovarian cancer, is considered a marker of stromal glycolysis and autophagy. The CAFs increase proliferation of nearby oxidative cancer cells (epithelial cells) via the paracrine secretion of recycled nutrients. Furthermore, the Warburg Effect occurs specifically in stromal cells instead of epithelial cells. However, the oxidative cancer cells (epithelial cells) undergo the ''Reverse Warburg Effect,'' where cancer cells receive glucose parasitically from neighboring stromal cells and concomitantly activate the tricarboxylic acid cycle (TCA cycle) that releases NADH and generate sufficient amounts of ATP via oxidative phosphorylation and also promote metastasis. In return, the epithelial cells transfer the ROS produced in them and create oxidative stress in the adjacent stromal cells. They also upregulate autophagy, stromal oxidative stress, along with activation of crucial transcription factors such as HIF1α (aerobic glycolysis) and NFκB (inflammation) in CAFs. The induced autophagic glycolytic fibroblasts in stromal cells secrete both recycled and high-energy nutrients such as ketone bodies, L-lactate, as well as glutamine which is again utilized by epithelial cancer cells to fuel oxidative mitochondrial metabolism and protect themselves against apoptosis. At the same time, the stromal cancer cells mount an antioxidant defense by overexpressing specific essential antioxidant proteins, such as the peroxiredoxins and TIGAR. Thus, inhibiting autophagy in stromal cells abstains from transferring pyruvate to epithelial cells resulting in tumor suppression. In contrast, activation of autophagy in epithelial cells impedes tumor progression due to their inability to utilize recycled nutrients [27]. This explicitly revealed the tissue-dependent operation of autophagy that eventually creates contrasting outcomes when governed under a specific metabolic pathway and tumor microenvironment. Autophagy in specific cancer cells can also influences other cells for survival and growth.

5. Glycolytic enzymes regulating autophagy-

5.1. Hexokinase (HK)

Among the four isoforms of Hexokinase (HKI, II, III, and IV), HK II is prominent in regulating glycolysis in cancer cells. Hexokinase converts glucose to glucose-6- phosphate, consumes ATP and perpetuates the glycolytic pathway. There is a significant increase in HK II expression along with glycolysis in the tumor microenvironment. The role of autophagy in glycolysis is controversial; however, HK II reveals another avenue for regulating glycolysis and autophagy. Glucose deprivation and HK II overexpression upregulate the autophagic mechanism, whereas attenuation of autophagy is observed on HK II inhibition. In addition, HK II affects autophagy, independent of AMPK, by directly targeting mTOR. Under glucose deprivation, autophagy is activated by HK II only if its substrate is phosphorylated but it is not able to proceed

with the glycolysis. For example, HK binds to 2-deoxyglucose 5-thioglucose (2-DG) which impedes glucose phosphorylation and thereby inhibits glycolysis.

HK II specificity was confirmed with the failure of HK I in affecting autophagy progression. Compared to HK I, HK II consists of the TOS motif (Fig. 2), as present in mTORC1 substrate which is critical for raptor binding andmTOR inhibition. Additionally, Glucose-6-phosphate inhibits the binding of HK II to mTOR, exhibiting negative feedback (Fig. 2). HK II has shown a diverse role in targeting tumor progression for example in liver cancer, an inhibitor of HK II, 3-bromopyruvate (3-BrPA), gave a potent tumor-suppressive role in the SMMC7721 cell line transfected with Atg5 shRNA.

As autophagy inhibits glycolysis and selectively ubiquitinates HK II by the TRAF6 (E3 ligase) which promotes its recognition by the autophagy receptor SQSTM1 (p62), thereby, according to this study, targeting glycolysis can be a new therapeutic target in autophagy impaired liver cancer (Fig. 2) (Table .1) [26]. Also, in Tongue Squamous Cell Carcinoma (TSCC), HK II under hypoxia upregulates both glycolysis and autophagy that simultaneously promotes epithelial to mesenchymal transition. Thus, siRNA-mediated inhibition of HK II shows tumor cell death besides decreasing glycolytic flux and autophagy [37]. Thereby understanding HK II functions in regulating autophagy and glycolysis opens new avenues of targeting cancer.

5.2. 6-Phosphofructo-1-kinase 3 (PFKFB3)

Fructose 2,6 bis-phosphate is an allosteric activator of the glycolytic enzyme 6- phosphofructo-1-kinase (PFK). One of the isoforms, PFKFB3, is commonly overexpressed in human cancers and contributes mainly to the Warburg Effect [38]. In breast cancer cell lines, MDA-MB-231, with increased AMP/ATP ratio during mitotic arrest, results in activation of AMPK that further phosphorylates ULK1 and ULK2 (essential autophagy inducing components). AMPK also, while sensing the loss of ATP, upregulates glycolysis by phosphorylating the PFKFB3, which was verified by using compound C (AMPK inhibitor) that eventually prevents PFKFB3 phosphorylation. Thus, AMPK plays a dual role during mitotic arrest and triggers mitotic cell death by inducing autophagy and inhibiting PFKFB3 [39]. Siyuan Yan et al. revealed that the subcellular localization of PFKFB3 inside the nucleus regulates H2O2 induced autophagy as siRNA mediated silencing of PFKFB3 suppresses basal H2O2 induced autophagy and AMPK activity. Thus, nuclear PFKFB3 promotes H2O2 induced autophagy through the AMPK signaling pathway [40]. In conclusion, PFKFB3 can serve as a crucial player in regulating tumor progression via altering autophagy.

5.3. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)

GAPDH is involved in the conversion of glyceraldehyde-3-phosphate to D-glycerate-1,3- bisphosphate (1,3-BPG) [41]. The non-glycolytic role of GAPDH includes physio-pathological functions such as regulation of gene expression, DNA repair and replication, neurodegeneration, virulence in bacteria, tubular bundling, protein-protein interactions, RNA export, and autophagy [42]. During glucose starvation, AMPK activation phosphorylates GAPDH (Fig. 2) that eventually activates sirtuin1 (SIRT1) and stimulates autophagy. SIRT1 belongs to a class of histone deacetylase (HDAC) that plays a critical role in drug resistance and also disturbs the metabolic machinery. The subcellular localization of GAPDH inside the nucleus directly interacts with SIRT1, removes its repressor, and increases SIRT1 deacetylase activity. SIRT1 additionally induces autophagy by deacetylating the critical component of autophagy, i.e., LC3B in the nucleus, to redistribute it to the cytoplasm, which further associates with autophagic membranes [43]. Moreover, GAPDH also interacts with the member of Ras superfamily of GTPases Rheb, which prevents binding of Rheb to mTOR and thereby inhibits mTOR signaling. Thus, GAPDH inhibits mTOR and acts as a prosurvival factor in cancer through the induction of autophagy to support the energy consumption of rapidly proliferating cancer cells (Fig. 2) [42]. However, the studies to understand exact mechanism of GAPDH regulating autophagy and simultaneously driving tumorigenesis need further investigation.

5.4. Phosphoglycerate kinase (PGK1)

PGK1 is an essential regulator of glycolysis that catalyzes the chemical reaction of 1,3- bisphosphoglycerate to 3-phosphoglycerate [44]. The autophagy process is altered by post-translational modification of PGK1. It was speculated that acetylation of PGK1 at Lys 388 is required for induction of autophagy in low glutamine conditions. This is accompanied by activating *N*-alpha-acetyltransferase 10(NAA10) that enhances the activity of Atg14-associated PIK3C3-BECN1-PIK3R4 pathway and leads to Phosphatidylinositol 3- phosphate(PtdIns) production marked with an increase conversion of LC3B–I to LC3B-II. The acetylated PGK1 interacts with BECN1 by phosphorylating it at Ser 30.

Furthermore, the conformational change of PIK3C3 induced by BECN1 phosphorylation triggers the binding of PtdIns to PIK3C3 (responsible for autophagosome formation) to produce more PtdIns3P which further promotes autophagy and prosurvival glioblastoma cancer cells. However, in nutrient-rich conditions, mTOR destabilizes NAA10 by phosphorylating it at Ser 228 and eventually inactivates autophagy [45]. Thereby, targeting PGK1 in glycolysis effectively alters the autophagy in the context of cancer progression.

5.5. PK isoenzyme M2 (PKM2)

PKM is a rate-limiting glycolytic enzyme that plays a significant role in metabolic reprogramming. In glycolysis, it catalyzes the conversion of phosphoenolpyruvate (PEP) to pyruvate and releases energy in the form of ATP [46]. The mutually exclusive alternative splicing of the pyruvate kinase M (PKM) gene produces two isoforms termed as PKM1 and PKM2. Unlike PKM1, which is generally expressed in normal cells, the alternatively spliced PKM2 is expressed predominantly in various cancer cells and contributes mainly towards the Warburg Effect. The preferred expression of PKM2 isoform of pyruvate kinase (PK) over its constitutively active splice variant M1 isoform is deemed as an essential factor perpetuating aerobic glycolysis in cancer cells [47]. PKM2 is found in two forms, the tetrameric form has a higher affinity for PEP than the dimeric form, however this dimeric form is highly preferred in cancer cells [48]. Accumulated evidence has suggested the involvement of PKM2 in modulating autophagy in the cancer milieu. PKM2 knockdown in alveolar adenocarcinoma and pancreatic carcinoma cells, disrupts glycolysis and induces prosurvival autophagy where PKM2 regulates autophagy either by AMPK or PI3K/AKT pathway [49,50]. Hwan Tae et al. reveal the role of SIRT1 in regulating autophagy via targeting PKM2. They verified it by using MHY2245, a SIRT1 inhibitor that targets PKM2 metabolism and mTOR in human ovarian cancer cells which aggravates autophagy and impedes cancer progression [51]. Moreover, PKM2 can also reinforce metastasis and target autophagy for promoting tumor cell death. As observed in human prostate cancer cells, knockdown of PKM2 disrupts the Warburg Effect and its association with protein kinase B(PKB)/mTOR that eventually augments autophagy culminating in cancer cell death [52]. However, in another study, shRNA-mediated knockdown of PKM2 inhibits autophagy by stimulating JAK/STAT3, which further promotes tumor-suppressor activity in hepatocellular carcinoma [53]. In this context, PKM2 role in mutated Nucleophosmin Acute Myeloid Leukemia (NMP1-AML) was investigated where elevated PKM2 contributes profoundly to tumor survival by activating autophagy. Here, PKM2 activates BECN1 induced autophagy by phosphorylating Thr119 of BECN1 that consequently disrupts the Bcl-2-BECN-1 complex [54].

The involvement of epigenetic regulators in modulating metabolic pathways is highly appreciated; however, their role in altering autophagy was understood by deciphering the cross-talk between Yes-

Associated Protein 1 (YAP1) and PKM2 where dephosphorylation of YAP1 enhances autophagic flux. Besides, siRNA-mediated G9a (nuclear histone lysine methyltransferase) inhibition upregulates PKM2 by Akt/HIF1α axis and efficiently rewires these events promoting proliferation in glioma cells [55]. In certain conditions, the introduction of other biological factors effectively modulates the regulation of autophagy by PKM2. For example, in PKM2 knockdown lung carcinoma, the introduction of LBK1, a

Serine/threonine kinase which acts upstream of AMPK and inhibits it by phosphorylating at Ser-172 and thereby inhibits autophagy [56]. Similarly, Yanling Feng and Jingwei Liu deciphered that complex of Atg7 (key autophagy component) and Fibroblast Growth Factor Receptor 1 (FGFR1) blocks the phosphorylation of PKM2 at its Tyr-105 site and concomitantly suppresses the ROS formation. Here, both the mentioned conditions eventually promote cancer cell death [57].

Interestingly, Chang-Liang He et al. elucidated that overexpression of PKM2 phosphorylates Ser 202/203 of mTORC1 inhibitor AKT substrate1 (AKT1S1) that activates mTORC1 and impedes autophagy albeit independent of nutrients availability and led to accelerated oncogenic growth in renal carcinoma and breast cancer cells [58]. Moreover, breast cancer samples lacking stromal Cav-1 revealed PKM1 and PKM2 expression in the tumor stroma. PKM1 when confirmed by CD-45 immunostaining induced tumor inflammation and showed upregulated aerobic glycolysis, in contrast, PKM2 augments non-canonical NFκB dependent autophagy and drives mitochondrial respiration in tumor cells [48]. Thereby, both PKM1 and PKM2 promote tumor progression via a different mechanism.

5.6. *Lactate dehydrogenase (LDH)*

LDH, a key glycolytic enzyme that extends glycolysis in limited oxygen conditions. The two isoforms of lactate dehydrogenase are known as LDHA, and LDHB, which work oppositely in the cellular microenvironments. LDHA with a net charge of −6 has a higher affinity for pyruvate and promotes the conversion of pyruvate to lactate. In contrast LDHB, with a net charge of +1, has a higher affinity for lactate and converts it to pyruvate, NADH, and H+ [59]. When compared to normal cells, LDHA expression is found elevated in various types of spontaneous cancer cells, while in fact, LDHB expression varies among different types of cancer cells. Many scientists reveal that, with the accumulation of protons, LDHB regulates autophagy in a pH-dependent manner (Fig. 3). The close interaction of LDHB and lysosome promote V-ATPase-dependent lysosomal acidification and thus autophagy. Furthermore, the induced autophagy comes with the consequences of alteration in tumor progression [60].

Acquired tamoxifen-resistant breast cancer cell lines such as MCF-7 (MCF-7/TAM-R) and T47-D (T47-D/TAM-R) significantly showed higher apoptotic resistance accompanied by the induction of prosurvival

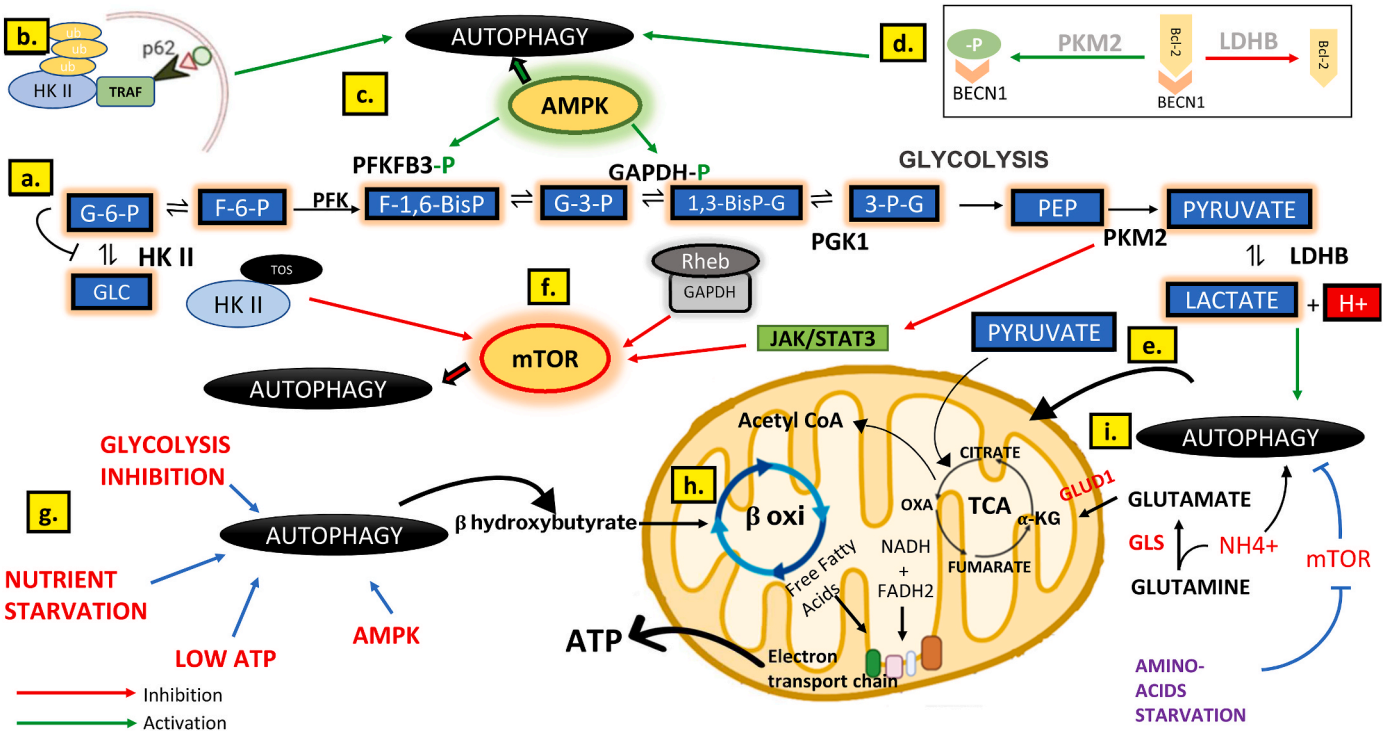

Fig. 3. Autophagy maintains the ATP production and energy supply in tumors. Induction of autophagy by glycolysis. **a.** HK II consists of the TOS motif, inhibits mTOR by binding to it via its TOS motif, and induces autophagy. However, Glucose-6- phosphate inhibits that complex and prevents autophagy. **b.** The E3 ligase TRAF6 ubiquitinates HK II and promotes its recognition by the autophagy receptor SQSTM1 (p62), causing selective degradation, eventually inhibiting glycolysis. **c.** AMPK induced under starvation conditions stimulates phosphorylation of PFKFB3 and GAPDH, promoting glycolysis and simultaneously autophagy. **d.** PKM2 phosphorylates BECN1 at Thr-119, whereas LDHB inhibits Bcl-2, disrupts the Bcl-2-BECN-1 complex, and promotes autophagy. **e.** The elevated pyruvate can switch towards the TCA cycle and promote ATP production or further move towards the lactate production and release protons, although accomplished by LDHB converting Pyruvate to lactate. The proton increases the acidification of autophagosomes and promotes autophagy. **f.** Inhibition of mTOR promotes autophagy. GAPDH forms complexes with Rheb and inhibits mTOR; PKM2 promotes JAK/STAT3 and inhibits mTOR. **g.** Under glycolysis inhibition, nutrient starvation, and low ATP, AMPK induces autophagy and various other pathways. **h.** Autophagy supplies free fatty acids to the electron transport chain via activating β-oxidation and overcomes the starved conditions. i. Autophagy promotes glutaminolysis and server's glutamine to tricarboxylic cycle through anaplerotic reactions. TCA cycle provides NADH and FADH2 to the electron transport chain and eventually produces enormous amounts of ATP. Amino acid starvation inhibits mTOR. Additionally, GLS (glutaminase) converts glutamine to glutamate, and glutamate further deaminated by the enzyme GLUD1 (glutamate dehydrogenase 1) undergoes a blunt entry as αKG, which replenishes the TCA cycle. (**Abbreviations-**TRAF6- Tumor necrosis factor receptor (TNFR)-associated factor 6, HK2-Hexosekinase II, PFKFB3- 6-phosphofructo-1-kinase 3, GAPDH-Glyceraldehyde 3-phosphate dehydrogenase, PKM2-Pyruvate kinase 2, BECN1- Beclin1, LDHB- Lactate Dehydrogenase B, GLS- glutaminase, GLUD1-glutamate dehydrogenase 1, αKG- α-ketoglutarate).

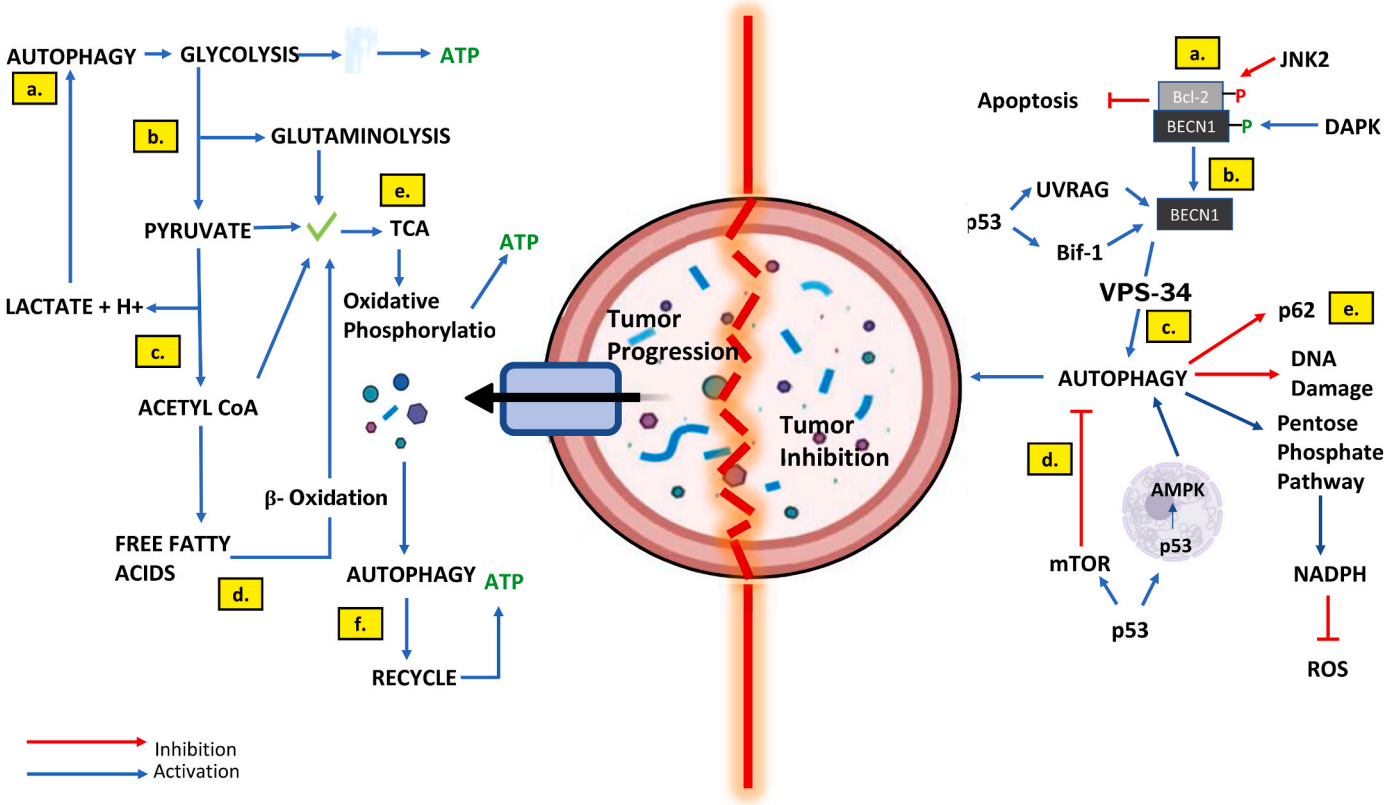

Fig. 4. Autophagy participating in tumor progression and tumor inhibition. **1.** Autophagy nurtures tumor progression by providing ATP to tumor cells. **a.** Autophagy directs glycolysis for ATP production. **b.** However, if glycolysis is not fully completed, it can be diverted to either glutaminolysis or pyruvate, and both can converge to the TCA cycle. **c.** Pyruvate can also be diverted to lactate and H+ production in anaerobic conditions or acetyl CoA production in aerobic conditions. Further, acetyl CoA can either be directly involved in the TCA cycle or undergo Free fatty acids (FFA) production. **d.** FFA is simplified by entering β-oxidation and eventually converges to the TCA cycle. **e.** The activated TCA cycle with provided raw materials from different stages of metabolic pathways produces NADH and ATP, which fuels oxidative phosphorylation and gives rise to ATP production. **f.** The complex macromolecules are recycled by autophagy and produce ATPs. **2.** Autophagy inhibits tumor progression. **a.** JNK1 phosphorylates and deactivates Bcl-2, whereas DAPK phosphorylates and activates BECN1, thereby disrupting the Bcl-2-BECN1 complex and releases BECN1. **b.** p53 upregulating either UVRAG or Bif-1 that form multiprotein complex BECN1. **c.** the activated BECN1 further complexes with VPS-34 and promotes autophagosome formation. **d.** p53 subcellular localization gives contrasting results as p53 inside the nucleus activates AMPK promoting autophagy whereas in cytoplasm promotes mTOR, which inhibits autophagy.**e.** Autophagy promotes tumor inhibition by preventing p62 (SQSTM1) accumulation, DNA damage and activating the pentose phosphate pathway. NADPH activates the enzymes glutathione and impedes ROS production. (**Abbreviations-** FFA-Free fatty acids, JNK1- c Jun N Terminal Kinase, DAPK-Death Associated Protein Kinase, UVRAG-UV radiation resistance-associated gene, Bif-1-Bax-interacting factor-1, AMPK- AMP-Activated Protein Kinase, the mTOR-mechanistic target of rapamycin).

autophagy. Here, the association of LDHA with BECN1 profoundly disrupts the Bcl-2-BECN-1 complex and is responsible for the mentioned condition. Thereby targeting LDHA opened a novel strategy to interrupt autophagy which inhibits the inevitable tamoxifen resistance (Table .1) [61]. Interestingly, the mechanism behind oxamate resistance in gastric cancer cells was shown by Zhi Zhao et al. (Table .1). Oxamate inhibits LDH by competitively binding to its pyruvate binding site which interrupts aerobic glycolysis. The inhibited LDH further induces protective autophagy by inhibiting the PI3K-Akt-mTOR pathway (Table 1) [62]. Moreover, Liang Shi et al. reveal that LDHB regulates autophagy by post-translational modification. Mass spectroscopy revealed that the deacetylation of LDHB at Lys-329 by Sirtuin5 favorably shows higher LC3B-II/LC3B–I ratio and promotes tumorigenesis with activated autophagy [63]. Therefore, the literature evidence reveals that lactate dehydrogenase participates in regulating autophagy and thus can be exploited as a potential therapeutic target.

6. Nitric oxide (NO)

NO is a ubiquitous, short-lived, and diffusible messenger formed from L-arginine. NO functions diversly in regulating signaling pathways, blood flow regulation, neurotransmission, and cancer. In addition, it can participate either directly or indirectly in tumor progression [64]. NO is capable of inducing autophagy in a multitude of ways, as few are mentioned here. In Caveolin deficient stromal cells, substantial NO release promotes mitochondrial dysfunction and ROS production, driving oxidative stress that mimics hypoxia and eventually induces autophagy [27]. Evidently, the diffusible nature of NO and its multiple blunt entry points in the autophagic pathway, regulate autophagy in a context-dependent manner by preferentially exploiting the specific autophagic mechanisms for tumor progression. For example, NO impedes induction of autophagy in HEK293 cells, whereas it preferentially induces it in melanoma cells [65]. Moreover, in hepatocellular carcinoma, an increase in iNOS (inducible Nitric oxide synthase) and eNOS (endothelial Nitric oxide synthase) promotes NO production that disrupts the BECN1-Vps34 complex whereas promotes Bcl-2-BECN-1 complex which disrupts the autophagosome formation and thus suppresses tumor progression. NO is well known to be maintained by the cGMP pathway. However, it can target autophagy by *S*- nitrosylating JNK1 and IKKβ, which further activates mTOR via TSC2, thereby inhibiting autophagy in a cGMP independent regulation [66]. Therefore, it is concluded that NO substantially regulates autophagy in site-specific and context-dependent manner.

7. Oxidative phosphorylation

While autophagy regulates glycolysis in the realm of cancer cells by diverse mechanisms; one can also speculate the function of autophagy as a driving force of oxidative phosphorylation that opens a new avenue of nutrient availability in the cancer milieu. Thus, cancer cells fulfill their nutrient demands by exploiting autophagy-mediated shifts towards oxidative phosphorylation, often reducing their dependence on glycolysis [67]. Oxidative phosphorylation in mitochondria employs NADH, FADH2 that passes through the four complexes with concomitant formation of H+ gradient across the intermembrane space, where distortion in the gradient eventually produces ATP [68]. Yotaro Kudo et al. reveal that Protein kinase Cλ/ι (PKCλ/ι) acts as a tumor suppressor by inhibiting both autophagy and oxidative phosphorylation. Mechanistically, they used the proximity-dependent biotin method (BioID2) and identified the interaction of p62 and PKCλ/ι by PTB1 domain, where PKCλ/ι phosphorylates LC3B at Ser 12 and impairs the LC3B's ability to interact with p62. Also, PKCλ/ι knockdown unleashes autophagy and triggers oxidative phosphorylation while ROS production activates NRF2 which promotes cell-autonomous proliferation. Thereby, it concludes that the PKCλ/ι deficient cells promote autophagy-induced cell survival in hepatocellular carcinoma [69]. Interestingly, the subcellular localization of autophagy at Mitochondria-Endoplasmic Reticulum Contact Sites (MERCs) triggers cell proliferation by maintaining oxidative phosphorylation. Autophagy governs lipid catabolism and provokes autophagosome formation by regulating the supply of free fatty acids (FFA) at MERCs that eventually perpetuate the supply of ATP [70]. Evidently, it is known that autophagy is distinctly triggered by inhibition of mTOR pathway. However, Jae-Seon et al. suggest that the degradation of macromolecules and recycling of intracellular substituents by autophagy eventually activates mTOR. In return, mTOR releases proto-lysosomal proteins that further terminate autophagy by reforming it to lysosomes, thereby initiating feedback loop. The feedback loop usually is terminated by blocking oxidative phosphorylation which results in ATP depletion and mTOR inactivation [23]. BRAF-driven cancers are exquisitely sensitive to autophagy where $BRAF^{V600E}$ signals as a monomer while RAS causes dimerization of BRAF. Autophagy becomes requisite by supplying glutamine with a direct entry in the TCA cycle to perpetuate mitochondrial metabolism and promote tumor cell survival. Therefore, BRAF inhibitors failed to promote antitumor effects due to the circulation of glutamine and the recycling of fuels by oxidative phosphorylation through the autophagic process [71]. Similarly, Jessie Yan et al. showed that cancer cells with the Ras mutation maintain a basal level of autophagy. It sustains a pool of functional mitochondrial oxidative phosphorylation that supports cancer cell growth [72]. Thus, autophagy provides an alternate pathway for cancer cells to fulfill their required nourishment.

8. Glutaminolysis

Glutamine is a non-essential and the most abundant amino acid. Cancer cells utilize glutamine that serves as a significant anaplerotic precursor of α-KG and replenishes the TCA cycle (Table 1) [74]. Autophagy supply TCA intermediates by producing oxo-acids from glutamine [75] and recycles non-essential cellular compounds during starvation due to the inhibition of the mTOR pathway. In breast cancer cell line MCF7, CAFs lacking Cav-1 secrete an enormous amount of glutamine that maintains elevated oxidative phosphorylation in epithelial cancer cells which further releases glutamate and ammonia [22]. Further, the released by-product ammonia diffuses back to fibroblast and induces autophagy. On the other side, fibroblast protects MCF7 (epithelial cancer cells) from autophagic cell death and secrets TIGAR that inhibits glycolysis, apoptosis along with autophagy [27]. Additionally, glutamine metabolism was observed to be triggered by c-Myc via miR23a/b and transcription factor, Foxo which triggers autophagosome formation in a glutamine synthetase-dependent manner, helping cancer cells to survive in nutrient and growth factor-deprived conditions [76].

However, glutamine starvation conditions activate various biological factors that modulate autophagy towards tumor progression. In human colon cancer cells, upon glutamine starvation, X-Box-Binding Protein-1u (XBP-1u) limits autophagy by 20S proteasome-mediated degradation of transcription factor FoxO1.However, the interaction between XBP-1u and FoxO1 is increased by phosphorylation of XBP-1u specifically on Ser 61 and Ser 176 by ERK1/2. The increase in Transcription Factor EB (TFEB), specifically under glutamine deprivation instead of glucose, results in its translocation from the cytoplasm to the nucleus and eventually augments macropinocytosis-associated autophagy which was verified with increased LC3B-II level (Table .1) [78]. Ju-Won Seo et al. also added that the augmented autophagy in Pancreatic Ductal Adenocarcinoma (PDAC), in return, maintains glutamine levels. Inhibiting either glutamine metabolism or autophagy subsequently activates the other pathway as a compensatory mechanism by perpetuating the TCA cycle through anaplerotic reaction. Thus both, the glutamine metabolism and autophagy are essential to maintain intracellular glutamine levels in PDAC [79]. $BRAF^{V600E}$ driven lung tumorigenesis and tumor cell survival are substantially sustained by Atg7 and mitochondrial glutamine metabolism which is independent of ROS production. At later stages of tumorigenesis, aberrant autophagy accumulates defective mitochondria, prevents glutamine metabolism, and converts adenomas and adenocarcinomas to oncocytoma [80]. During high glutaminolysis, α-KG promotes EGLN1 (α-KG dependent hydroxylation of target proteins) and activates mTORC1. RRAG (Ras-related GTP binding) proteins further promote the translocation of mTORC1 to the lysosome surface, where mTORC1 interacts with Rheb and terminates autophagy in cancer cells [81]. Seung Min Jeong et al. reveals that DMKG (dimethyl-αKG) treatment, increases mitochondrial glutamine metabolism with enhanced mitochondrial glutamine anaplerosis and activates mTORC1 that limits autophagy and suppresses pancreatic cancer growth [74]. The role of Sirtuin5 was appreciated, when during glutamine metabolism, it supplies ammonia and eventually regulates autophagy. In the breast cancer cell line MDA-MB-230,

When Sirtuin5 is repressed by MC3482, it succinylates glutaminase that elevates glutamine metabolism and ammonia-induced autophagy, which, however, is mTOR independent but Atg dependent [82]. Thereby the accumulated evidence explains the contribution of glutamine in tumor progression regulated by autophagy.

9. Lipolysis

During cancer progression, degradation of lipids becomes necessary to fulfill the purpose of energy generation, biosynthesis of membranes, and synthesis of other biomolecules [83,84]. The characteristic metabolic plasticity of autophagy is seen with its sheer participation during the regulation of lipid homeostasis [85]. Autophagy substantially acts as lipolysis machinery for the degradation of lipids. It releases FFA, which contributes in serving as an efficient source of energy relative to amino acids or carbohydrates during cancer progression. Lipids are found in the form of Lipids droplets (LDs) [86]. During autophagy, lysosomes receive LDs, encapsulated in double-membrane autophagosomes, and further undergoes degradation on the formation of autolysosomes. The degradation of LDs generates free-fatty acids that serve as a substrate for β-oxidation in mitochondria, although lysosomal acid lyases (LAL) also generate free-fatty acids directly by lipolysis. The autophagy-mediated selective degradation of lipids called lipophagy serves as a dual anti- and pro-cancer role [87]. The lipophagy impairment results in poor patient prognosis, and its tumor suppressive role was highlighted during LAL deficiency that results in aggressive hematopoiesis and accumulation of immature myeloid-derived suppressor cells (MSDCs). Accumulated MSDCs in tumor efficiently evades host immunity by skipping immune surveillance. Moreover, reports suggest the LAL's role in reducing metastasis in lung and liver cancer. In contrast to the mentioned tumor-suppressive role, the production of FFA also serves as

an energy substrate for proliferating cells or provides intermediates for the

Synthesis of biomolecules. This collective information reflects the plasticity and flexibility of autophagy-mediated lipolysis for cancer progression [88]. A separate study has reported that FoxO 6 and FoxO1 transcription factors play a significant role in regulating hepatic lipid metabolism. Moreover, FoxO1 is also known to mediate autophagy by protein-protein interaction with Atg-7, and acts as a tumor suppressor by targeting autophagy-mediated cancer cell death. In that context, the significance of subcellular localization of FoxO1 in the cytoplasm is merely comprehended for impeding cancer cell growth. This suggests the role of lipid metabolism in cancer cell rewired by FoxO1 mediated autophagy [89].

The role of mTORC1 has been well established in promoting protein synthesis with simultaneous inhibition of autophagy under amino acid starvation, however, it is also emerging as a central regulator of lipid homeostasis. mTORC1 signaling is responsible for the accumulation of fatty acids in adipocytes and impedes lipolysis. Interestingly, the connection of mTORC1 mediated autophagy and lipid homeostasis was observed when adipose-specific *Atg7* knockout mice, show a substantial decrease in adipocyte lipolysis. This explains the inhibitory effects of mTORC1 on lipolysis due to the attenuation of autophagy. Although, one can further pursue in investigating mechanistically the role of mTORC1 mediated autophagy in regulating lipolysis and its further impact on different cancers [90]. Nevertheless, several reports have provided preliminary insight into the significance of lipid metabolism and autophagy in regulating cancer progression. However, there are still many questions unanswered regarding the selectivity and specificity for degradation of LDs by autophagy and its context dependent role in cancer milieu.

10. β-oxidation

β-Oxidation is a catabolic process that simplifies fatty acids into acetyl CoA [91]. Accumulated evidence suggests that β-oxidation serves as a new source of nourishment which is smartly exploited by autophagy to metabolically fuel and nourish the growing cancer cells [86]. Autophagy by inducing β-oxidation imparts (FFA) that serves as a raw material for oxidative phosphorylation or TCA cycle intermediates. Although, it also selectively removes damaged mitochondria while maintaining the β-hydroxybutyrate level and accesses the transportation of FFA, fulfilling the ATP requirement for cancer growth and promoting survival [92]. Yang-An Wen et al. further confirmed the role of FFA in triggering autophagy in colon cancer cell survival. Adipocytes in the tumor microenvironment activate mitochondrial β-oxidation by providing FFA that activates AMPK induced autophagy by phosphorylating ULK1 and ULK2 (Table 1) [93]. Here autophagy augments the ability of cancer cells to utilize FFA and unblocks the growth-promoting potential of adipocytes. The role of Nuclear Receptor Co-Repressor 1 (NCoR1) in the regulation of autophagy by lipid metabolism was also investigated. Due to the presence of a potential LC3-Interacting Region (LIR)/GABARAP-interacting motif (GIM) in NCoR1, it actively interacts with GABARAP under starved conditions, which results in its degradation via induction of autophagy and further promotes the nuclear receptor Peroxisome Proliferator-Activated Receptor (PPRα) accumulation, thereby activating lipid metabolism. However, in nutrient-rich conditions, NCoR1 interacts with ribosomal protein S6 kinase 2 (S6K2) which is phosphorylated by an active mTORC1 that translocates to the nucleus and inhibits β-oxidation. Besides, mTOR also activates TFEB which retains specific autophagic genes in the cytoplasm. Thereby, NCoR1 acts as a substrate of autophagy which effectively promotes β-oxidation in response to physiological fasting [94]. Moreover, in acute myeloid leukemia, autophagy promotes oncogenesis by promoting β-oxidation for clearing lipid droplets that further support oxidative phosphorylation. However, the cross-links between the two processes are regulated at MERCS which control autophagy and finally tunes the proliferation and growth in leukemia cells [70]. Thus, β-oxidation with the assistance of autophagy, opens a new door for supplying nutrients to cancer cells by supporting oxidative phosphorylation.

11. Hypoxia

It is evident that the hypoxia milieu present in the core of tumor cells aids cancer progression. Although, previous studies have also suggested the substantial role of autophagy under hypoxia in the realm of cancer. Under adequate oxygen, HIF1α is hydroxylated and interacts with Von Hippel-Lindau tumor suppressor (VHL), which consequently ubiquitinates and degrades HIF1α, whereas the hypoxic condition dehydroxylates VHL and stabilize HIF1α [95]. Besides, hypoxia regulates autophagy by modulating various biological factors, for example, it phosphorylates AMPK which either activates TSC2 dimer or BNIP3 that eventually inhibits mTORC1 [96]. Further phosphorylated AMPK also targets ULK1 and LC3, which altogether activate autophagy [97]. The HIF1α upregulated under hypoxic conditions, actively binds the promoter of BNIP3 and REDD1 and further begins their transcription [98,99]. REDD1 targets TSC2 dimer and further inhibits mTOR, whereas BNIP3 complements with Nix (BNIP3L) and they competitively bind with Bcl-2 via their weak BH3 domain and disrupts the Bcl-2-BECN-1 complex. The released BECN1 further promotes autophagosome formation [99]. Hypoxia also triggers an unfolded protein response that activates ATF4 and transactivates Atg7 and LC3 [100]. Although the research to date has investigated many oncogenes and metabolic enzymes targeted by HIF1α that drive malignancy, these are found in defined coordination with autophagy in tumor specific manner. However, whether and how it turns the fate of a cancer cell either towards progression or cell death still lacks clarity. The fulfillment of the desired ATP in glioblastoma is attained by recycling cellular components and metabolic precursors through autophagy induced under hypoxia [100]. Interestingly, inhibiting hypoxia-induced autophagy by 3-MA markedly increases hypoxia-induced apoptosis and proves an effective strategy for adjuvant chemotherapy of human colon cancer (Table 1). [101]. However, activation of hypoxia-induced autophagy may also contribute to tumor suppression, as seen during Salidroside treatment [102]. Despite targeting only autophagy, hypoxia is also involved in

Concomitant activation of glycolysis with autophagy for tumor progression. In TSCC and multiple myeloma cells, hypoxia activated autophagy was observed besides the increased rate of glycolysis and lactate production. Here, HK II complements hypoxia and regulates glycolysis along with autophagy rendering cell survival phenotype (Table 1) [37,103]. Autophagy can also be induced in dysfunctional glycolysis and HIF1α conditions. As Fengsen Duan and Chunlei Mei revealed that autophagy induces cell death in bladder cancer by utilizing vitamin K2. During the suppression of PI3K/HIF1α and glycolytic dysfunction, vitamin K2 induces AMPK under starved conditions, and eventually induces autophagy [104].

Connective Tissue Growth Factor (CTGF) is a target of TGF-β, which is induced in breast cancer stromal cells lacking Cav-1. It represents tumor microenvironment-dependent execution of HIF1α mediated autophagy and glycolysis which together promotes tumor growth in fibroblast via recycling nutrients. However, in oxidative epithelial cells, induction of autophagy metabolically suppresses tumor growth via self-digestion in tumor cells. This concluded the compartment-specific role of hypoxia-induced autophagy by CTGF [105]. Recently, Minzi Deng et al. showed the role of subcellular localization of Ankyrin Repeat Domain Protein (ANKRD37) in hypoxia-induced autophagy. The high expression of ANKRD37 reduces the survival rates of colon cancer, however, the translocation of ANKRD37 into the nucleus activates HIF-1α and shows opposite results. ANKRD37 inside the nucleus augments HIF-1α-induced autophagy which consequently increases colon cancer cell proliferation (Table 1) [106]. Juan Zhang et al. interpreted that the Gene Associated with Retinoid-Interferon-Induced Mortality-19

(GRIM-19) impedes hypoxia-induced invasion and EMT of colorectal cancer by ameliorating the accumulation of HIF-1α accompanied by inhibiting Phospho- Signal Transducer and Activator of Transcription 3 (p-STAT3) expression with the eventuality of hypoxia-induced autophagy (Table 1) [107].

Other than the role of BNIP3 and BNIP3L to impel hypoxia-induced autophagy; it is also identified as apoptotic mediators under hypoxia. In lung cancer, cisplatin-resistance is observed which promotes cell survival. The augmentation of autophagy under hypoxia above the threshold was confirmed when cisplatin significantly induced MDC (a specific auto-phagolysosome marker) localization in vacuoles of both A549 and SPC-A1 cells but simultaneously suppresses apoptosis induced by BNIP3 and BNIP3L. In this scenario, BNIP3 and BNIP3L promotes cell death by inducing apoptosis instead of cell survival autophagy [108]. The c- Jun *N*-terminal Kinase 1 (JNK1) preferentially sustains the intricate cross-talk between autophagy and apoptosis. JNK1 phosphorylates Bcl-2 and Bcl-xL that augments BECN1 release. Furthermore, it also activates transcription factor Foxo, which promotes Atgs and altogether converges to augment hypoxia-induced autophagy for sensitizing HT29 colon adenocarcinoma cells towards chemotherapy (Table 1) [109]. In conclusion, hypoxia plays an important role and regulates autophagy via different upstream and downstream regulators of metabolic pathways in compartment-specific manner. Thereby unravelling the hypoxia assistance in modulating autophagy can open new therapeutic avenues.

12. Involvement of autophagy in different cancers

Given the diversity of metabolic pathways and numerous metabolic isoforms involved in cancer, the necessity of autophagy in cancer progression will likely remain obscure and intensely debatable. Moving forward, it becomes imperative to comprehend the controversial and multifaceted role of autophagy in distinct stages of cancer and the alteration of metabolism while regulating autophagy during tumorigenesis (Fig. 4). Thereby prioritizing these key points, the review further continues summarizing autophagy using appropriate examples of cancer (viz. lung cancer, glioblastoma, breast cancer, and prostate cancer) to accurately determine the cross-talk of autophagy with different metabolic

Pathways during tumorigenesis. Later, this review precisely abridges the inhibition and activation of autophagy which can reveal new avenues in therapeutic targets.

13. Lung cancer

Lung cancer is a prominent seed for cancer mortality worldwide, and NSCLC is most prevalent among all lung cancers, accounting for poor prognosis and diagnosis. RAS protooncogene encoded oncoproteins are the common mutations in NSCLC. Among the three RAS isoforms, HRAS, NRAS, and KRAS, KRAS is the most frequently mutated RAS isoform, and patients harboring this mutation develop more aggressive lung tumors with limited treatment options [111]. Autophagy regulates $KRAS^{G12D}$-driven lung tumurosis while regulating mitochondrial function, lipid metabolism, and growth [112]. It was invested that loss of p53 in Ras driven tumors utilize autophagy for mitochondrial function and lipid catabolism as defective autophagy cause oncocytoma, lipid accumulation and results in tumor cell metabolic catastrophe [112]. The role of tumor suppressor Liver Kinase B1 (LKB1) in KRAS-driven NSCLC and GEMM for modulating autophagy was investigated by Vrushank Bhatt et al. The LKB1 acts upstream of AMPK and phosphorylates it, that eventually induce autophagy which further activates lipolysis, recycles TCA intermediates, maintains the mitochondrial metabolic process, and sustains cellular and tissue homeostasis under starvation [113]. However, they found that ablation of autophagy results in an increase in de novo FA synthesis with decrease in FA elongation. This indicates that autophagy ablation rewires the lipid metabolism, which could be a metabolic bypass for KL tumors to manage defective autophagy. Thereby, combinatorial interruption of autophagy and lipid metabolism serve as an effective therapy for LKB1-deficient RAS-driven lung cancer [113]. Similarly, deletion of an SRC activator and Nedd9 (scaffolding protein) in KRAS and Trp 53 mutated NLCSC showed elevated LKB1 and AMPK, which eventually induces autophagy with a tumor growth advantage [114]. Autophagy and apoptosis can either complement each other towards tumor progression or tumor cell death or function individually with contrasting

Results. This combination, however was observed when lung cells were treated with deltarasin. Elaine Lai Han Leung et al. investigated the efficacy of deltarasin which induces apoptosis and inhibits KRAS-RAF signaling by inhibiting the interaction of KRAS with Phosphodiesterase 6 Delta Subunit (PDEδ) protein. Besides, the elevated AMPK induced autophagy was observed with a significant increase in GFP-LC3 puncta in deltarasin-treated A549 cells. Thus, deltarasin induces both apoptosis and autophagy to disrupt $KRAS^{G12D}$-driven lung tumors however, inhibition of autophagy alone elevates ROS production that promotes cancer survival (Table 1) [115].

Similarly, several bioactive molecules such as Bisdemethoxycurcumin [116] and D-limonene [117] showed antitumor properties with the concomitant increase in both autophagy and apoptosis. Much remains to be learned about how autophagy targets metabolic alterations that are prioritized in a particular circumstance and allows cancer cells to escape given therapies. In this context, few examples are mentioned that explains the role of autophagy during targeted therapy. The autophagy via Akt/mTOR pathway contributes to crizotinib resistance in ALK-positive lung cancer cells (Table 1) [118]. Whereas, Erlotinib (Tyrosine kinase inhibitor) resistant NSCLC cells H1650 showed GATA6-upregulating autophagy which was more distinguished than the basal level autophagy and consequently increased tumor cell survival [119]. However, Paclitaxel resistance development is associated with an increased BECN1 production that augments the autophagy process. Interestingly, Paclitaxel indirectly targets BECN1 which restricts the inhibitor, i.e., miR-216b, that specifically targets 3′UTR of BECN1. Thus, increasing the miR-216b expression or inhibiting autophagy can improve the paclitaxel treatment in NSCLC therapy [120]. When human lung adenocarcinoma cells were incubated with Glu-plasminogen (plasminogen with glutamic acid) and analyzed spectrophotometrically, it was investigated that plasminogen conversion to plasmin (concentration up to 1.0 μM) induces autophagy as a survival response. Moreover, autophagy by upregulation of TIGAR, switches glycolysis towards the Pentose Phosphate Pathway (PPP). Further, increased NADPH production from PPP gradually scavenges ROS and prevents apoptosis [121]. Notably, many compounds are identified that functionally regulate tumor growth by rewiring metabolism and autophagy. For example, Chromium induces ATF-4 mediated autophagy, induced ATF-4 along with the ER stress augments aerobic glycolysis and simultaneously hinders apoptosis in A549 cells [122]. Similarly, Cadmium induces tumor cell growth in A549 and HELF cells via autophagy-dependent glycolysis [123]. Lastly, Final-2 also diminishes tumor proliferation by inhibiting the GLUTs that downregulate glycolysis. It induces G0/G1 cell cycle arrest and inhibits autophagy [124].

Until now, it was mentioned that mTOR pathway regulates autophagy; however, autophagy can also function mTOR independently. Su-Jin Jeon et al. reveal that TOR Signaling Pathway Regulator-Like (TIPRL) induces autophagy and glycolysis independent of the mTOR pathway. This was approached through the phosphorylation of eukaryotic Initiation Factor 2α (eIF4) and its subsequent interaction with TIPRL that activates ATF4 and transactivation of Atgs. Although treatment with 2-DG in shRNA-mediated TIPRL knockdown A549 cells showed growth inhibitory effects and thereby revealed the ability of cancer cells to resist metabolic stresses and promote tumorigenesis through autophagic machinery [125]. The emerging role of fatty acids and its association with autophagy was comprehended by Qinghua Yao, et al., where they showed the tumor-suppressive nature of

Docosahexaenoic acid, and Eicosapentaenoic acid (ω-3 long-chain polyunsaturated fatty acids) which attenuates autophagosome formation by phosphorylating Akt and activating mTOR in A549 cells [126]. Thus, multimodal functions of autophagy divert cancer cells in various directions, including both aggressive tumor growth and tumor deterioration.

14. Glioblastoma (GBM)

GBM is the most aggressive adult glioma and invasive form of central nervous system (CNS) malignancy with a median survival of only 14 months [127]. It is characterized by severe metabolic alterations and stressful conditions such as hypoxia which results in a poor prognosis [16]. Although the treatments of brain tumors have been intensely studied, however much remains to be investigated about the treatments with regard to the precise mechanism of autophagy involved. While many stress conditions and metabolic enzymes are involved in the regulation of autophagy, the emergence of autophagy under hypoxic conditions and their specific role in glioblastoma was comprehended by Sihua Huang et al. They revealed that miR-224–3p constrains tumor growth by negatively regulating Atg5 expression and thus autophagy; however, the elevated HIF1α under hypoxia impedes miR-224–3p action while upregulating Atg5. Atg5 is involved in Atg 12- Atg5 complex, which promotes the elongation of autophagosomes during autophagic processes [128]. In continuance, Xing Feng et al. investigated acetylation at Lys 420 with attenuation of PAK1 (p21 [RAC1] activated kinase 1) dimerization under hypoxia which further phosphorylates Atg5 and stimulates prosurvival autophagy [129]. Also, Jianbo Feng et al. demonstrated the tumor-suppressive nature of Ankyrin Repeat and Death Domain-Containing 1A (ANKDD1A) in hypoxic conditions which inhibits transactivation of HIF1α by hydroxylating the *C*-Terminal-Activating Domain (*C*-TAD) with the assistance of HIF1α Subunit Inhibitor (FIH1) resulting in cell autophagy inhibition in addition to suppressed GBM cells adaptation to the hypoxic stress [130]. Accumulated evidence suggests that the inhibition of autophagy at more upstream levels divulges its anticancer properties. The treatment of Hydroxychloroquine (HCQ) and Temozolomide (TMZ), an inhibitor of autophagy and a chemotherapeutic drug, respectively, showed decreased lactate production and disrupted the complex I of oxidative phosphorylation, they altogether restrict the tumor growth and explains that resistance associated with given chemotherapy was due to activation of autophagy [131]. This was further verified by Julie Sesen et al., as they use Metformin, a biguanide molecule used for Type-2 diabetes, that sensitizes glioblastoma towards TMZ treatment. Mechanistically, Metformin increases glycolysis and lactate production which intensifies the acidification during autolysosome formation and simultaneously inhibits mitochondrial respiration which all together increases the autophagic process that suppresses the tumor-initiating potential of GBM [132]. Later, Lara Macchioni et al. introduces the alkylating agent Bromopyruvate which inhibits ATP production via targeting both mitochondrial and glycolytic pathways with an increased autophagic process that prevents tumorigenesis [133] whereas Changhong Liu and Yan Zhang discovered a cytoplasmic long noncoding RNA, LINC00470 that activates Akt and increases glycolytic flux. This impedes cell autophagy that results in GBM tumorigenesis and poor patient prognosis [134]. Lipid reprogramming have evidenced in malignancies due to formation of Lipid droplets in GBM. The energy homeostasis in GBM under starvation was revealed when Xiaoning Wu et al. and team through Immunofluorescence imaging and time-lapse videos deciphered that autophagy hydrolyzes LDs to release FFA and eventually undergoes energy production in mitochondria [135]. Glioblastomas are refractory to conventional treatment, including surgery, chemotherapy, and radiation therapy; however proper comprehensive regulation of autophagy promises to reduce aggressive cancer growth and provides a new supplemental therapeutic approach.

15. Breast cancer

Like most other cancers, breast cancer is profoundly variable with significant clinical heterogeneity [136]. Breast cancer ranks second among the most dreadful cancer-related deaths in women. It is often diagnosed with a poor prognosis and remains a major public health issue on a global scale. Accumulated evidence have indicated the active participation of autophagy during breast cancer progression, which further aids in resistance development against the given therapy [137]. However, multifaceted autophagy has been implemented occasionally for impeding tumor progression. The link between autophagy and breast cancer was highly appreciated when BECN1, a potent driver mutation, was found adjacent to the tumor suppressor BRCA1 (a known deletion in breast cancer). Moreover, subsequent studies reveal the rewiring of autophagy with various

Metabolic pathways. For example, LDHA elicits survival of the tamoxifen-resistant ER-positive breast cancer cells by sustaining glycolysis and BECN1-induced autophagy. However, pharmacological and genetic inhibition of LDHA promotes rehabilitation of apoptosis and EMT-like phenotype that sensitizes the cells towards the therapy [61]. The cross-talk between the Akt and glycolytic flux which modulates the autophagic incidence in breast cancer cells was deciphered by Yajun Chen et al. . They revealed the overexpression of (PRMT2β), which is a novel Protein Arginine *N*- Methyltransferases (PRMT2) splice variant isolated from the breast cancer cells MCF7 and T47D, and is responsible for inhibition of autophagy, Akt pathway, and glycolytic flux [138].

Surprisingly, Chang-Fang Chiu et al. revealed the antitumor effect with a concomitant activation of autophagy and apoptosis by Hydroxamate-Based Histone Deacetylase (HDAC) 8-selective Inhibitor (HMC) and showed that epigenetic treatment is a viable strategy for breast cancer treatment. HMC promotes anticancer properties by inhibiting the Akt-mTOR pathway that encourages apoptosis by upregulating the Bax expression level which further produces ROS and induces autophagy [139]. Plant-based chemical compounds have also been investigated for rewiring autophagy and metabolic pathways. Ursolic acid, a plant-derived pentacyclic triterpenoid, suppresses glycolysis and augments AMPK induced autophagy while activating apoptosis by depolarization of mitochondrial membrane potential. Thus, activated apoptosis inhibits breast cancer cell proliferation and progression [140].

Recently, Sujin Lee et al. investigated the involvement of Nuclear factor Erythroid 2-like-2 (NFE2L2; NRF2) mediated induced expression of miR-181c in cancer regulation. miR-181c overexpression in NRF2-silenced breast cancer cells showed hindrance in HIF1α accumulation which consequently mismanaged the hypoxia-induced glycolytic enzymes and autophagy. Thus, prevents HIF1α orchestrated metabolic adaptation of hypoxic cancer cells [141]. Moreover, autophagy regulated by Glutamate Pyruvate Transaminase 2 (GPT2) manifests the tumor-suppressive role. It is prominent in aggressive triple-negative breast cancer cells and pivots between glycolysis and glutaminolysis by providing TCA cycle intermediates and managing altered nutrient levels. However, GPT2 via mTOR activation negatively regulates autophagy and promotes tumor progression [142]. Interestingly, leptin, a hormone derived from adipose tissue, plays a predominant role in breast cancer. Leptin is responsible for both FFA oxidation and FFA release, indicating its multifaceted role in lipid metabolism. This multifaceted role of leptin is further controlled and managed by autophagy. Duc-Vinh Pham and team showed an interesting dual role of leptin mediated autophagy that regulates cancer cell specific lipid metabolism. They explain that autophagy maintains SREBP1, a master regulator of FA synthesis and results in accumulation of LD. Meanwhile, leptin mediated autophagy activation initiates lipolysis of the accumulated LD that mobilize to mitochondria and provide ATP to the growing breast cancer cells. Thereby, autophagy and SREBP1 along with leptin could be regarded as a promising therapeutic target [143]. Considering the above-mentioned participation of autophagy in a nutshell, its functions

vary with different drugs, enzymes, plant compounds and stress conditions in the context of breast cancer regulation.

16. Prostate cancer (PCa)

PCa is a non-cutaneous, highly intensive disease in men worldwide. It remains a significant issue of durable responses in tumors because of the elevated cross-talk between metabolism and autophagy towards the targeted therapy [144]. Here, the insensitivity of intensive multimodal therapy explains a lot about autophagy being critical with metabolic adaptation and helping tumors to adapt with induced stress. Propranolol, a widely used non-selective beta-adrenergic receptor blocker, attenuates the late stage of autophagy. Thus, complementation of propranolol with 2-DG results in autophagosome accumulation and initiation of apoptosis with inhibition of mitochondrial bioenergetics and glycolysis with augmented tumor suppression [145]. Moreover, Y. Ma et al. deciphered the tumor suppressor nature of miR-361–5p. It inversely regulates Sp1 and PKM2, which are responsible for emergence of castration-resistant PCa cells by enhancing aerobic glycolysis, hypoxia-induced autophagy and G1 cell cycle arrest. Similarly, the dual nature of autophagy was deciphered by miR-96, as at either extreme end of the threshold, miR-96 can promote or abolish autophagy by hypoxia, mTOR, or Atg7 [146]. Interestingly, Jeong Yong Jeon et al. revealed the tight regulation of autophagic flux with glycolysis in cancer cells. The application of 2-DG induces autophagy in a short-term treatment which gradually decreases with its long-term treatment. Thereby autophagy affects PCa cells in a dose-dependent action of 2-DG [147]. The proliferation and migration of PC-3 cells have increased in hypoxia due to the promotion of Atg5 by direct binding of HIF1α to its promoter. Thus, Kaiyuan Yu et al. delved into the complementary relationship between Atg5 and HIF1α and their contribution towards the tumor progression in PCa [148].

Additionally, autophagy mediates LD degradation and promotes lipolysis in androgen-sensitive PCa cells which aids the survival of PCa cells during hormone therapy [149]. Harri M Itkonen et al. showed that Enoyl-CoA delta isomerase 2 (ECI2), an enzyme involved in degradation of unsaturated lipids, is a novel androgen receptor target that promotes prostate cancer cell survival. The inhibition of ECI2 results in accumulation of lipid with decrease in autophagy mediated lipolysis. This impedes the supply of essential ATP to prostate cancer cells for survival and eventually activates cell death response [87]. In context with lipid metabolism, Prashanta Kumar Panda et al. discussed the role of Abrus agglutinin (AGG)-induced senescence through autophagy in prostate carcinoma cells (PC3) that leads to ablated proliferation. The AGG treatment inhibits autophagy which inhibits lipolysis and further accumulates FFA. The facilitation of senescence is achieved due to accumulation of FFA and formation of reactive oxygen species [150]. Thereby understanding the autophagy mechanism with variable outcomes in PCa development and progression, uncover innumerable therapeutic interventions.

17. Other cancers

The complex networking between metabolism and autophagy has participated in different other cancers such as pancreatic cancer, hepatocellular carcinoma, breast cancer and colorectal cancer. The cross-regulation in these processes is also uncovered in other cancers. Scientific evidence supports both tumor-promoting and tumor-suppressive functions of autophagy and deciphers that the outcome of autophagy depends on tumor type, context, and stage. However, the multifaceted role of autophagy has spread its influence in most cancers. Andrea Viale et al. showed the role of mutant KRAS in PDAC. When explored on a mouse model with developed inducible mutated KRAS ($KRAS^{G12D}$) in a p53 (LoxP/WT) background, the results showed cell survival along with tumor relapse that depends on oxidative phosphorylation rather than glycolysis and further increases genes of autophagy and lysosomes regulators which consequently promotes tumor cell progression [151]. Additionally, Dong-Eun Lee et al. revealed the participation of NEDDL4 in autophagy regulation. It is an E3 ubiquitin kinase, which suppresses autophagy and mitochondrial metabolism by targeting ULK1 and glutamine transporter ASCT2. The NEDDL4 further impedes pancreatic cancer cells' survival and progression via targeting autophagy [152]. However, Aaron J Scott et al. investigated the lethality in colorectal cancer cells due to autophagy. Cabozantinib, an inhibitor of receptor tyrosine kinases (RTKs), induces autophagy with the reduction of the PI3K/AKT/mTOR pathway. Tumor cells decline the uptake of glucose as measured by 18 [F] FDG-PET in the presence of cabozantinib and thereby induce autophagy with acquired resistance and survival [153].

Compiling all the other examples, it is evident that autophagy skilfully connects metabolism and cancer, which introduces a fresh perspective for future therapeutic approaches.

18. Role of autophagy in cancer-related therapeutics

Intensive multimodal therapy has been found insensitive due to the lethality of metastatic cancer cells. This lethality has prolonged due to the ascending of resistance in the targeted therapy [154]. With prolonged research many scientists have found the hidden role of autophagy in it. A myriad of studies has also shown that tumor cells under stress conditions like hypoxia induces autophagy and become radiation and chemo-resistant. Therefore drug-induced autophagy inhibition will overcome the above-mentioned drawback. For example, in B16–F10 melanoma cells, autophagy was activated in hypoxic areas, and blocking of autophagy by HCQ or by BECN1 depletion caused increased tumor inhibition and restored cytotoxic T-cell activity [155]. Owing to the tumor inhibitory role of autophagy, its induction will also aid in eradicating tumors, as many autophagy inducers have preferentially been used and accepted in clinical trials. It has been observed in several studies that mTOR signaling inhibition is capable of inducing autophagy. On treatment with mTOR inhibitor rapamycin, there was a prominent reduction in tobacco carcinogen-induced lung carcinoma in a murine model [156].

The registered antimalarial drug chloroquine (CQ) and its derivative HCQ prevent the final step of autophagy and limits acidification of lysosomes. Till now, only these two drugs have been approved for clinical trial either in combinatorial fashion with other drugs or individually. Although for clinical trials, HCQ is preferred over CQ for inhibiting autophagy due to its less toxicity than CQ at peak concentrations. In the realm of tumor metabolism, HCQ targets macropinocytosis along with autophagy. However, the use of HCQ at high doses for longer period of time shows complete inhibition of autophagy with repercussions of huge side effects. Other drugs including 3-MA which targets class-III PI3K undergoing autophagosome formation, are also under clinical trials to fight cancer by targeting autophagy [2]. Targeting autophagy alone does not affect cancer effectively as studied earlier; therefore, autophagy inhibitors complementing conventional cancer therapy are highly preferable [157]. Combinatorial approach of HCQ with vorinostat, show a reasonable progression-free survival (PFS) and safety profile for highly treatment-refractory colorectal cancer. A phase I/II trial of HCQ with everolimus for advanced clear cell renal cell carcinoma show dose-limiting toxicity (Table .2). Similarly, a phase I/II trial of HCQ with neoadjuvant gemcitabine in patients with borderline resectable pancreatic adenocarcinomas is well tolerated in the neoadjuvant setting (Table .2) [158,159]. Verteporfin is another novel drug that acts at an earlier stage of the process to prevent the early stage of the formation of the autophagosome. In combination with the anti-metabolite gemcitabine, verteporfin attenuates pancreatic tumor growth in a pre-clinical setting [159]. Other combinations such as HCQ and doxorubicin, CQ and radiation or CQ, temozolomide, and radiation are also given positive results.

In the xenograft model, proteasome inhibitor bortezomib and CQ suppressed tumor progression more efficiently than either of them

Table-2
Recent combinatorial autophagic inhibitors with other drugs in Clinical Trials.

Combinatorial Drug	Cancer	Clinical Phase
HCQ + everolimus [170]	Advanced clear cell renal cell carcinoma	I/II
HCQ + tamoxifen [170]	Breast cancer	I
HCQ + vorinostat [159,170]	Malignant solid tumor, Colorectal cancer	I/II
HCQ + gemcitabine [159]	Advanced adenocarcinoma, small cell lung cancer	I/II
HCQ + Sunitinib malate [159,170]	Adult solid neoplasm	I
HCQ [159]	ER + Breast Cancer, Prostate Cancer	I/II
HCQ + Abraxane and gemcitabine [159]	Pancreatic carcinoma	II
HQ + Dabrafenib and Trametinib [170]	Low grade and high-grade gliomas	I/II
CQ with concurrent chemoradiation + Temozolomide [170]	Glioblastoma, GBM	I
CQ + bortezomib [170]	Hematologic malignancy	.

alone, indicating inhibition of both autophagy and proteasome degradation pathways could constitute a better strategy for cancer control [160]. Plentiful autophagy-specific drugs for example HCQ, 3-MA, Wortmannin, spautin-1 etc when synergized with conventional cancer therapy, effectively promotes anticancer effects [2]. Based on CQ and quinacrines, a series of more potent dimeric compounds have been generated, including Lys 05, DQ661, and DC661. These compounds inhibit lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1) by binding to it. These progressively regulate many autophagy, mTOR, metabolic enzymes by palmitoylation. Although these compounds show better drug delivery than HCQ due to better cell penetration and lysosomal localization in the acidic tumor microenvironment [161]. Moreover, the adaptive role of autophagy in cancer cells is complex and paradoxical. It is thereby still obscure whether induced autophagy helps to survive the cancer cells or direct towards their inhibition. The same is observed when chemotherapy or radiotherapy is given, where autophagy is usually activated after these treatments. A study performed in myc-induced lymphoma revealed the advantage of using CQ along with apoptotic activators in relieving the cancer burden with activated autophagy. However, the tumor burden decreased when autophagy inhibitor CQ or Atg5 shRNA were given [157]. Additionally, in combination with HDAC inhibitor Suberoylanilide Hydroxamic Acid (SAHA), CQ has been shown to promote cancer cell death in Chronic Myelogenous Leukemia (CML) cell lines expressing imatinib-resistant mutant forms of Bcr-Abl and is suggested for future clinical trials. This regimen has enhanced the SAHA-induced superoxide generation causing relocalization and production of lysosomal protease cathepsin D. Also, Cathepsin knockdown has reduced the efficacy of this combination, suggesting the process is lysosome-driven [162]. Similarly, autophagy inhibition by 3-MA has also given significant results in cancer therapy, when used along with deltastarin, by elevating its anticancer property in KRAS-driven lung cancer cells and appear highly desirable for enhancing anti-cancer effects in future clinical applications. However, 3-MA promotes apoptosis by increasing ROS production, which can be collectively retarded with *N*- acetylcysteine treatment (a ROS inhibitor) [115]. Interestingly, the treatment of 3-MA with hypoxia preferentially enhances the tumor-suppressive nature of colon cancer cells. In HCT116 cells, hypoxia solely increases autophagy and apoptosis, which elevates cancer cells' survival. However, the application of 3-MA selectively obstructs hypoxia-induced autophagy, which markedly escalates hypoxia-induced apoptosis and altogether prevents tumor progression [101]. The tumor under metabolic stress specifically depends on autophagy for its survival; therefore, inhibiting autophagy in such tumors will be an excellent strategy for cancer therapy. Evidently, disparate regimes were used containing autophagy inhibitors with metabolic stress inducers (angiogenesis inhibitors, 2-DG). In PCa, therapeutic starvation with 2-DG induced autophagy by upregulating the level of BECN1; thus, using an autophagy inhibitor along with 2-DG could be a novel approach to target tumor cell metabolism that causes their death [164].

The presence of 2-DG and the inhibition of autophagy by MK2206 (AKT inhibitor) sensitized Erlotinib-resistant cells to the targeted therapy [165]. Determination of the specific role of autophagy in cancer progression depends on the cancer stage, cell type, and genetic content, which is essential for deciding the therapeutic strategy. Also, for improved cancer-based therapy, the molecular markers for autophagic flux in tumors and specific mechanisms by which autophagy confers treatment resistance need to be deeply explored. Further insights are also required for the proper use of autophagy modulators in cancer-specific therapeutic targets.

19. Conclusion

Autophagy has sought immense attention in the scientific world due to its flexibility and compatibility with relatively every circumstance during cancer development. Cancer cell manifestation indeed includes autophagy as a tool for cell proliferation through the availability of survival essentials and therefore protects against stressful conditions. A great deal of increased evidence reveals the tumor-specific expression of the metabolic isoforms exhibiting distinct and proliferation-enhancing enzymatic activity with substrate preference. The involvement of autophagy in the metabolic regime helps the cancer cells to collaborate among themselves and with the host microenvironment. In addition, autophagy supplies reservoirs by producing metabolic fuel sources to help cope with extreme stresses and ever-changing metabolic requirements. Appreciating the essential role of autophagy during cancer progression, however, whether the induction of autophagy activates a particular metabolic pathway, or the tumor itself narrows down to a certain metabolic pathway that further complements autophagy and intensifies tumor progression. This likely continues to remain ambiguous and entail further investigation.

Despite the huge progress made in the field of autophagy, numerous events still remain to be elucidated. Further, investigation is required to comprehend the outcomes of autophagy under different tumor growth stages. The importance of therapeutic targets based on metabolic-specific isoforms is now recognised and made diminishing of tumor progression easier. Targeting a specific metabolic isoform to which the tumor is addicted, restricts the cancer milieu from fulfilling its nourishment. However, the applied chemotherapeutics still develop resistance and promote proliferation by compensatory responses of metabolic pathways, escaping from the stress conditions, or hindered apoptosis which are all indeed easily managed by autophagy. Certainly, the double-edged sword nature of autophagy in the realm of cancer has often turmoil many to conclude its definite role. Thereby, better mechanistic understanding of autophagy during treatment will increase the effectiveness by closing avenues of resources that aid in cancer cell survival. Furthermore, future clinical trials can use therapeutic combinations by exploiting the flexible nature of autophagy in tumor metabolism. Co-targeting autophagy and metabolic enzymes during chemotherapy supports the notion of an effective therapeutic target and keeps us one step ahead in diminishing cancer growth.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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