BBA - Molecular Basis of Disease 1868 (2022) 166400

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Role and regulation of autophagy in cancer

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ARTICLE INFO

Keywords:
Autophagy
Homeostasis
Cancer
Hypoxia

ABSTRACT

Autophagy is an intracellular self-degradative mechanism which responds to cellular conditions like stress or starvation and plays a key role in regulating cell metabolism, energy homeostasis, starvation adaptation, development and cell death. Numerous studies have stipulated the participation of autophagy in cancer, but the role of autophagy either as tumor suppressor or tumor promoter is not clearly understood. However, mechanisms by which autophagy promotes cancer involves a diverse range of modifications of autophagy associated proteins such as ATGs, Beclin-1, mTOR, p53, KRAS etc. and autophagy pathways like mTOR, PI3K, MAPK, EGFR, HIF and NFκB. Furthermore, several researches have highlighted a context-dependent, cell type and stage-dependent regulation of autophagy in cancer. Alongside this, the interaction between tumor cells and their microenvironment including hypoxia has a great potential in modulating autophagy response in favour to substantiate cancer cell metabolism, self-proliferation and metastasis. In this review article, we highlight the mechanism of autophagy and their contribution to cancer cell proliferation and development. In addition, we discuss about tumor microenvironment interaction and their consequence on selective autophagy pathways and the involvement of autophagy in various tumor types and their therapeutic interventions concentrated on exploiting autophagy as a potential target to improve cancer therapy.

1. Introduction

The term autophagy was first coined in 1963 by Christian de Duve and it is referred to as an intracellular evolutionally conserved cellular degradative pathway [1]. The primary role of autophagy is to tag damaged organelles, cytoplasmic macromolecules and aggregated proteins and deliver it to the lysosomes which is subsequently degraded by lysosomal hydrolases to produce organic molecules like amino acids, nucleotides, sugars and ATP which is finally recycled back into the cytoplasm [2]. Autophagy is crucial as it acts as a cytoprotective mechanism by technically avoiding the accumulation of damaged intracellular components thereby maintaining cellular homeostasis and energy metabolism thus ensuring cell survival during stress and nutrient starvation conditions [3]. In terms of both morphology and protein constituents that are involved in the core machinery, autophagy is manifested as an extremely conserved intracellular process ranging from yeast to mammals [4,5]. Based on the distinguishing features, three types of autophagy namely macroautophagy, microautophagy and chaperone-mediated autophagy (CMA), the latter which was found to be present only in mammalian cells have been identified [6].

1.1. General autophagy mechanism

The selective and nonselective nature of micro and macroautophagy has been broadly characterized in yeast [7]. Selective autophagy specifically targets damaged proteins, impaired organelles including mitochondria, endoplasmic reticulum, chloroplast, peroxisomes and infectious microbes for degradation, whereas nonselective autophagy can be activated as a result of stress especially under starvation state therefore converting bulk cytoplasmic contents into energy rich molecules which could be utilized by the cells for recovery [8,9]. Microautophagy involves sequestration of the cargos by direct invagination of the vacuole membrane in yeasts, plants and lysosomes in mammalian cells [10]. The mechanism of macroautophagy is distinct compared to that of microautophagy in which the former involves the sequestration of double membrane bound phagophore to transport the cargo to lysosomes [11]. It is also clear that the vesicle formed, termed as autophagosomes, take up de novo pathway for their synthesis rather than

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https://doi.org/10.1016/j.bbadis.2022.166400
Received 18 October 2021; Received in revised form 17 March 2022; Accepted 18 March 2022
Available online 25 March 2022

membrane budding. The identification of more than 40 different ATG genes has led to the transition from morphological to molecular understanding of the mechanism [12].

The initiation and expansion of phagophore is regulated by series of proteins. In yeasts, Atg1-Atg13-Atg17-Atg31-Atg29 kinase complex and in mammals, Unc-51 like autophagy activating kinase 1 (ULK1) complex regulates the induction and formation of initial phagosome components [13]. The functional activity of this complex is further controlled by the association of mechanistic target of rapamycin complex 1 (MTORC1), the master regulator of autophagy, whose activation ultimately depends on the nutrient status of the cell [14]. Under metabolically normal state, MTORC1 associates with the induction complex (ULK1 and Atg13) and phosphorylate them thereby rendering their activity [15]. This prevents the induction of phagophore, thus the formation of autophagosome is inhibited. However, when cells are in nutrient deprived state or increased nutrient demand, MTORC1 is deactivated as a result of reduced signalling from Mitogen Activated Protein Kinase (MAPK) and phosphoinositide3 kinase (PI3K)/Akt pathway and dissociates from the complex [16,17]. This results in dephosphorylation of induction complex therefore activating further downstream pathways of autophagy.

The expansion of phagophore requires two ubiquitin-like (UBL) conjugation system. ATG12–ATG5-ATG16L1 conjugation complex is formed when ATG12 covalently binds to ATG5 with the help of ATG7 and ATG10 [18]. ATG12 was the first UBL system identified in the autophagy machinery. The ATG12-ATG5 complex dimerize with ATG16L1 in a noncovalent manner to form a larger complex. The resulting ATG12–ATG5-ATG16L1 complex is conserved across different domains and plays a major role in the formation of autophagosome [19]. The second UBL system involves the recruitment of microtubule-associated protein 1 light chain 3 (MAP1LC3) by ATG12–ATG5-ATG16L1 complex [20]. LC3, a member of ATG8 family is first converted into its cytosolic isoform LC3 1 by a cysteine protease, ATG4B. The E1 like-enzyme Atg7 and E2 like enzyme Atg3 helps in the activation of the processed LC3 1 in the subsequent steps [21]. Henceforth, by the association of phosphatidyl ethanolamine (PE), a class of glycerophospholipids, LC3 1 is converted to the membrane bound form LC3 II [22]. LC3 II is found to be present in either side of the membrane (outer and inner) of the expanding phagophore and helps in substrate selection for degradation by the autolysosome. Eventually, the matured phagophore wraps around the destined cargo and fuses to form a double membrane phagosome [23]. The microtubule mediated movement of autophagosomes to lysosomes is the crucial phase in the delivery of cargo and formation of autolysosome. The inner membrane of the autophagosome along with the cargo is subsequently degraded owing to the presence of resident hydrolytic enzymes in the lysosomes. The degraded components such as amino and fatty acids are exported back to the cytoplasm through lysosomal permeases where it can be utilized for energy generation or biosynthesis [24].

1.2. Chaperone mediated autophagy

CMA is very distinct from other autophagy types since it does not involve any vesicle formation and the proteins that are to be degraded seem to directly cross the lysosomal membrane to reach the lumen. The mechanism of CMA involves binding of chaperone complex to the target motif in the substrate protein after which it is brought to the surface of lysosomes [25]. Once the substrate reaches the lysosome, it interacts with the cytoplasmic tail of the lysosomal-associated membrane protein type 2A (LAMP-2A), which later promotes the formation of a translocation complex via LAMP 2A multimerization [26]. Upon binding, the substrate gets translocated to the lysosomal matrix by crossing the membrane mediated by luminal chaperones where they undergo complete degradation [26]. Moreover, CMA is highly selective compared to other autophagy types and allows selective removal of damaged or altered proteins under prolonged starvation or oxidative stress conditions [27].

Over the past few years, several researches have reported that defects in autophagy machinery can lead to genomic instability and metabolic stress which can give rise to pathological conditions including infections, neurodegeneration, heart disease, aging and cancer [28]. Additionally, the intrinsic role of autophagy in cancer is considered to be both tumor suppression and tumor promotion depending on the cell context, tumor stage and type [29]. In this review, we establish our focus on the mechanism of autophagy, their role in tumor progression, their typical interaction with the tumor-microenvironment and selective autophagy components involved in tumor progression. Additionally, we discuss the involvement of autophagy machinery and their role as tumor promoter in different tumor types. Finally, latest findings in the area of autophagy modulators as a therapeutic target in cancer treatment and their future development will be the focus of this review.

2. Autophagy and cancer

The homeostatic and protective nature of autophagy is relatively obvious considering its accommodating role during conditions like oxidative stress, nutrient deprivation and energy insufficiency. Moreover, the basal expression of autophagy is significant for key functions such as protein and organelle turnover [30]. However, data suggests that when the self-digestion process crosses a quantitative threshold due to prolonged growth factor, glucose or oxygen deprivation, it could result in cytotoxicity [31]. Additionally, the intricate connection between autophagy and apoptosis related pathway still needs to be uncovered [32]. However, studies have demonstrated that neuron-specific knockdown of atg5 reduced the survival of mice by upregulating bax-mediated apoptotic cell death [33]. This indicates that the autophagy may directly or indirectly be involved in deciding the fate of the cell, either survival or death. Therefore, autophagy dysfunction or pro-survival and self-cannibalistic nature of autophagy could be deleterious and detrimental to the cell in many cases and can serve as a causative factor for a wide variety of diseases. Till date, the involvement of autophagy is reported in several pathological conditions including myopathies, neurodegenerative disorders, infectious diseases, autoimmune diseases, heart disease, cell death, aging and cancer [34].

In cancer biology, autophagy is often represented as a double-edged sword where it plays dual roles as inducer of oncogenesis and as tumor suppressor and may contribute to tumor development and proliferation [35]. This paradoxical function of autophagy in tumorigenesis depends on different stages of cancer development and is further determined by environmental conditions such as nutrient availability, status of immune system, pathogenic conditions and microenvironmental stress [36]. During the initial phase of tumor development, autophagy exhibits suppressor role by degrading or inhibiting essential oncogenic molecules such as p62 protein [37]. Moreover, several indirect researches emphasize the tumor suppression role of autophagy. The participation of p53 in tumor suppression is highly complex. Inhibition of proteosomal degradation of cytoplasmic p53 prevented the activation or suppressed the basal levels of autophagy [38]. Therefore, pharmacological activation of p53 which are usually mutated in cancer cells could restore tumor suppressive function and inhibit tumor progression [39]. Moreover, several studies conducted on murine models concluded that the functional loss of many autophagy execution proteins such as Beclin1 and ATG5 predisposed mice to a wide range of tumors including lung adenocarcinoma, B cell lymphomas and hepatocellular carcinomas [40,41]. These results are few of the direct evidences that encourages the tumor suppression role of autophagy.

However, several factors are responsible for tumor suppression by autophagy during the initiation phase and alterations in their function which could possibly result in tumor progression. Autophagy response is considered as one such factor in which adequate level of autophagy is essential for tumor suppression. Abnormal or reduced autophagy fails to break down damaged organelles and proteins and lead to the development of cancer [40]. On the other hand, high-basal levels of autophagy

were observed in several cancer types including pancreatic cancer. Mutations in important tumor suppressor genes such as UV radiation resistance-associated gene (UVRAG) and Beclin 1 (BECN1) also results in the same effects which showed reduced clearance of damaged components and thereby providing favourable conditions for tumor development and progression [42]. The depletion of UVRAG and decrease of BECN1 are associated with increased cellular proliferation in several cancers such as gastric, colon, breast, prostate cancers and cervical squamous-cell carcinomas and hepatocellular carcinomas [43]. Additionally, autophagy related genes (ATGs) also play crucial role in controlling tumor progression. The deletion of ATG5 and ATG7 showed induction of liver cancers as a result of damaged mitochondria and oxidative stress in knockout mice models. Numerous studies also concluded that the deficiency of ATG3, ATG5 and ATG7 results in tumorogenesis [41]. In addition, the increased level of reactive oxygen species (ROS) correlates with cancer induction and progression [44] Autophagy prevents tumor generation by regulating excessive ROS production originated due to damaged mitochondria [45]. Therefore, basal autophagy with proper functioning of its protein machinery is considered to be an essential factor required for tumor suppression.

3. Role of autophagy in cancer progression and tumor suppression

During the initial discovery of the molecular machinery of autophagy, several proteins involved were found to have oncogenic properties. Autophagy associated genes such as oncogenic Bcl-2/Bcl-XL, Akt, PI3KCI, and mTORC1 and tumor suppressive proteins Beclin-1, PI3K-CIII, Bif-1, p53, DAPKs, UVRAG and phosphatase and tensin homolog (PTEN) serves as a direct link between autophagy and cancer [46]. Although autophagy plays a tumor repressive role during the initial stages of tumor, several studies suggest that autophagy is involved in cancer progression in the later stages once the cancer has established [47]. Oncogenes that are involved in tumor are known to interfere with signalling pathways essential for cellular metabolism. In this regard, numerous reports suggest that the autophagy machinery gets activated by tumor in response to stress conditions. Moreover, the survival characteristic of autophagy helps tumor to overcome extreme stressful conditions including hypoxia and nutrient deprivation [48]. In addition to this, high metabolic demand of cancer cells is supplied by autophagy by increasing the rate of degradation of defective proteins and organelles without affecting the functional integrity thereby maintaining viability of cancer cells [49]. Because of this dichotomous role, any attempt in regulating the autophagic process by the use of anticancer drugs could possibly skew the response to be fatal and could largely affect the overall patient survival. Studies have reported that autophagy in tumor cells induced by stress can result in treatment resistance which will subsequently result in tumor regrowth and progression. Most prominently, in cancer cells that survive chemotherapy or radiation therapy activation of autophagy may enable a state of dormancy in residual cancer cells which contribute to tumor recurrence and progression [50]. Another plausible role of cancer progression by autophagy has been implicated to exosome secretion. Some proteins involved in the extracellular vesicle secretion, like VCP and Rab7, are also associated with autophagy pathways at the same time crucial ATG proteins, such as ATG12/3 and ATG5, are identified as crucial regulators of exosome biogenesis. Therefore this suggests a possible link between autophagy and extracellular vesicle (EVs) machinery, that may contribute to cellular communication and signalling in the tumor microenvironment thereby acting as modulators of tumor progression and aggressiveness [51,52].

4. Role of autophagy in cancer progression and tumor suppression in response to RAS activation

RAS GTPase, a product of RAS gene is a GDP/GTP-binding guanine triphosphatase which plays a significant role in signalling pathways related to cellular growth, survival, proliferation and metabolism [53]. RAS protein once synthesized undergoes post-translational modifications which aids them to associate with plasma membrane [54]. Henceforth, a wide array of growth factors including epidermal growth factor (EGF), insulin-like growth factors (IGF), nerve growth factors (NGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and the ephrins and angiopoietins can activate RAS protein indirectly through receptor tyrosine kinases (RTKs) [55]. The auto phosphorylated RTK binds to growth factor receptor-bound protein 2/SOS exchange factor (Grb2/SOS) complex which directly interacts with RAS protein and renders them active [56]. The type of cofactors they bind to determine the activity of RAS. When it is bound to GTP with the help of guanine nucleotide exchange factors (GEFs), protein domains that catalyze the exchange of GDP for GTP becomes active and initiates one of many downstream signalling pathways by interacting with specific RAS effectors [57]. RAF kinase, phosphatidyl inositol 3-kinases (PI3Ks), RAL guanine nucleotide dissociation simulator (RALGDS) and phospholipase Ce are the main classes of RAS effectors which produce appropriate signals and activate signalling pathways for survival, cell proliferation and other physiological functions [58]. Whereas, in GDP bound state, the RAS protein become inactive. This is carried out by GTPase-activating proteins (GAPs), which propel the hydrolysis of GTP to GDP [59].

Initially, KRAS and HRAS were the two RAS genes that were identified during studies conducted in rats for understanding the two cancer-causing viruses, the Kirsten sarcoma virus and the Harvey sarcoma virus [60]. Subsequently, a third RAS gene was identified and was named as NRAS for their association with human neuroblastoma cells. Till date, several genetic and epigenetic factors were identified that are known to induce mutation in RAS gene. Studies confirmed that mutation in one of these genes convert them into active oncogenes which are very common constituting approximately 30% of all human cancers including colon, pancreatic and lung cancer with mutation in KRAS being more prevalent [61]. In particular, point mutation at 12, 13 or 61 residues in RAS protein produces an aberrant binding pattern with GTP. This conformational shift renders GAP insensitive and making it inaccessible for the hydrolysis of GTP. This anomalous alteration results in prolonged activation of GAP protein and consequently over stimulating downstream MAPK, PI3K and other signalling pathways ultimately leading to cancer cell proliferation, apoptosis, metabolism and angiogenesis [62].

RAS plays a highly complex and multifaceted role in autophagy, determined by the cellular context and cancer type. RAS mediated modifications in the regulation of autophagy depends largely on the signalling pathways it activates. Since the RAS effectors are diversified in nature, more than one signalling pathway can regulate autophagy. Raf-1, Rac1 and PI3K are the three most important pathways that enable the crosstalk between RAS and autophagy [63,64]. RAS positively regulates autophagy through the induction of Raf-1/MEK/ERK pathway and upregulates the expression of BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) [64]. BNIP3 promotes autophagy by obstructing the association of Beclin-1 and Bcl-2, allowing the former to bind with vsp34 or vsp15 forming an active complex necessary for autophagosome formation [65]. The upregulation of BNIP3 and subsequent promotion of autophagy is associated with several cancers including human breast carcinomas and uveal melanoma (UM) [66]. In one study, upregulation of BNIP3 stimulated the induction of autophagy which in turn contributed to the acquisition of anoikis resistance of hepatocellular carcinoma (HCC) cells, thus favouring the survival of cancer cells [67]. RAS was also shown to foster autophagy via Rac1/MKK7/JNK pathway which mediates the upregulation of ATG5 and ATG7 respectively, which is crucial in the elongation step of autophagosome formation [68]. The c-Jun NH2-terminal kinase (JNK) signal transduction pathway is also known to promote autophagy by phosphorylation of Bcl-2 and subsequent activation of BECN1 expression [69]. On contrary to the autophagy promoting role, RAS also negatively

regulates autophagy by activating anti-autophagic (i.e. class I PI3K/Akt/mTOR1) signalling pathway and subsequently preventing the activation of ULK1/Atg13/FIP200 complex [70]. Autophagy induced by Ras can, in turn affect tumor progression by modulating cell death, cell proliferation, mitochondrial integrity and sensitivity to matrix detachment and metabolic stress [71].

Although RAS partly plays tumor suppressive role through the induction of autophagy, the oncogenic RAS mutations and the mutations in other components of the RAS mediated signalling pathways are exclusively found in most tumors and lead to cancer development and proliferation. A study conducted on MCF10A cells overexpressing KRAS showed increased transcriptional and translational levels of ATG5 and ATG7 followed by malignant cell transformation in nude mice [72]. Subsequent knockdown of ATG5 and ATG7 reduced tumor formation indicating the tumor promoting role of autophagy. In another study, apoptosis-stimulating property of p53 protein 2 (ASPP2) suppresses autophagy induced cellular tumorigenicity in MEF cells with overexpressed oncogenic HRAS [73]. Moreover, murine model with mutated KRAS indicates the requirement of autophagy for tumor development in pancreatic cancer [74]. All these findings indicate the pro-oncogenic role of RAS mediated autophagy and the development of several deadly cancers, including colon, lung and pancreatic cancer. Although RAS mediated autophagy can suppress tumor during its initial manifestation, as the cancer progresses to later developmental stages, it becomes more aggressive and eliminates the toxic effect of autophagy. At this scenario, autophagy can assist tumor growth and serve as a cell-protecting mechanism thereby leading to cancer progression. Additionally, several approaches on the inhibition of autophagy-related proteins showed an increased accumulation of damaged mitochondria and later decreased cell growth [75]. These results combinedly stipulate that the RAS-mediated autophagy plays a vital function in the survival and growth of several tumors.

5. Hypoxia-induced autophagy in cancer progression

Hypoxia, a condition characterized by low oxygen availability is a familiar feature of several disease conditions including myocardial ischemia, chronic heart and kidney diseases, metabolic and reproductive diseases, stroke and cancer [76]. In cancer, oxygen demand is greater than oxygen supply because of the pronounced distance between cells and the existing blood vessel due to the hyperproliferating nature of cancer cells [77]. The level of hypoxia largely depends on the size, location and stage of the tumor, with brain tumors being extremely sensitive to hypoxia [78]. The cellular survival and proliferation of tumor in response to hypoxia is induced by the overexpression of complex signalling pathway including hypoxia inducible factor (HIF) pathway, PI3K/AKT/mTOR, MAPK and the NFκB pathway [79–81].

HIFs are transcriptional factors that respond to hypoxic conditions and modulate cellular response to oxygen availability. HIFs are activated in the presence of hypoxia and also through hypoxia independent-pathway by a number of receptors including G protein-coupled receptors (GPCR), toll-like receptors (TLR), and alarmin receptors [82]. Out of several members, HIF-1 is known for its important function in local and systemic tumor progression. Once activated HIF-1, targets the expression of more than 60 genes that are necessary for cell survival, cell invasion, angiogenesis and glucose metabolism. Over-expression or activation of HIF-1 correlates with several cancer types including cervical, endometrial, ovarian and breast cancer [83]. The mechanism of activation of HIF-α subunits (HIF-1 α, HIF-2 α and HIF-3α) is regulated by prolyl hydroxylase domain-containing proteins (PHD) and factor inhibiting HIF (FIH) enzymes [84]. PHD and FIH-1 are present upstream to HIF-α and are activated when oxygen is present [84]. In this case, the activity of PHD and FIH-1 regulates hydroxylation of HIF-α subunits which is further carried forward for polyubiquitination tagging by von Hippel-Lindau (VHL) tumor suppressor protein and subsequent proteolytic degradation of HIF-α [85]. However, when the level of oxygen is low, PHD and FIH-1 becomes inactive and HIF-α escapes hydroxylation and proteolytic cleavage by proteasome [86]. Now, the active HIF-α can translocate from cytoplasm to nucleus, dimerize with HIF-β subunit and initiates transcription of various adaptive pathways [87]. The effector functions of HIF-α involves enhancing cell survival and inhibition of anti-apoptotic pathway, formation of blood vessels by vasculogenesis through a number of regulators including iNOS, VEGF, VEGF receptors and COX-2 and facilitates cell migration through matrix degrading enzymes.

In tumor microenvironment, as a result of hyperproliferation of tumor cells, the blood vessels are more evidently found in the periphery surrounding the tumor, nourishing them with supplied oxygen and therefore promoting their proliferation. Meanwhile, cells that are present in between remains undernourished as a result of improper blood vessel formation. In this case, activation of HIF promotes blood vessel formation by inducing vasculogenesis and angiogenesis [88,89]. This function promotes previously stalled tumor cells to proliferate which yet again demands oxygen supply, recreating hypoxic microenvironment and HIF activation. This reactivated HIF further enhances tumor proliferation, metastasis and resistance [90]. Thus, the cross-talk between tumor progression and HIF activation is a never-ending phenomenon which is further worsened by the involvement of autophagy.

In order to promote hypoxia resistance, both HIF-1 and non-HIF-1 pathways can incorporate several alternative pathways such as autophagy and apoptosis depending on the severity of hypoxia. Several available literatures confirm the participation of hypoxia-induced autophagy in tumor survival and progression. The interaction between hypoxia-induced autophagy and cancer cell proliferation is coordinated by several stress response pathways such as mTOR, HIF-1 and the unfolded protein response (UPR) [91]. Importantly, hypoxia activated HIF-1 regulates autophagy by interacting with core autophagic proteins including BCL2, BNIP3, Beclin-1, BNIP3-like (BNIP3L)/Nix, phosphatidylinositol 3 kinase catalytic subunit type 3 (PIK3C3), ATG5 and ATG7 [92,93]. In this regard, hypoxia-induced AMPK and PTEN down-regulates mTOR which later enables autophagosome-lysosome fusion through ULK1 phosphorylation [94]. Besides this, HIF-1 indirectly triggers autophagy by modulating glucose metabolism. Recent data suggest that upon glutamate and oxygen deprivation, the autophagy is activated through direct binding of phosphoglycerate kinase 1 (PGK-1) to VPS34/Beclin1/ATGL14 [95]. Similarly, in acute myeloid leukemia (AML) cell lines, it was shown that the autophagy is regulated through association of pyruvate dehydrogenase kinase 1 (PDK1) with ULK1 [96]. Collectively, these studies indicate a strong connection between HIF-1 and mTOR pathways in regulating the activity of autophagy process.

Apart from HIF-1, hypoxia mediated mTOR inhibition is also known to stimulate autophagy in tumor cells. A recent data suggests that, in Crohn's disease patients, hypoxia ameliorated inflammation by down-regulating mTOR pathway and subsequently promoting autophagy [97]. Although, compelling evidence support the participation of mTOR pathway in autophagy regulation, the magnitude to which mTOR signalling participates in autophagy in tumor-hypoxia microenvironment is poorly understood. In the endoplasmic reticulum (ER), stress imposed due to hypoxia causes improper protein folding and prevents disulphide bond formation [98]. To manage this, affected cells recruit UPR integrated signalling networks which promotes cancer cell survival and offers resistance against anti-cancer therapies [99]. UPR mediated effector functions on mammalian cells are contributed by three main signalling pathways namely inositol-requiring enzyme 1 (IRE1), protein kinase RNA (PKR-like) ER kinase (PERK), and activating transcription factor 6 (ATF6) [100]. PERK regulated activation of transcription factor 4 (ATF4) and CCAAT-enhancer-binding protein homologous protein (CHOP) are known to optimize the survival of cancer cells by autophagy induction [101]. In turn, ATF4 and CHOP transcriptional factors regulates autophagy associated proteins namely microtubule-associated protein1 light chain 3β (MAP1LC3B/LC3B) and ATG5 [102]. Alongside this, emerging studies target the activity of IRE1 and its subsequent

downstream effector X-box binding protein (XBP1) against tumor growth and hypoxia in regulating autophagy [103]. Recent study conducted on breast cancer cell lines with downregulated XBP1 showed substantial inhibition of hypoxia gene expression, indicating the activity of XBP1 in promoting tumorigenesis by controlling HIF1α pathway [104]. However, the interconnection between autophagy and XBP1/HIF-1 in tumor progression under hypoxic condition still needs to be evaluated. Furthermore, the role of ATF6 arm of UPR-induced autophagy in hypoxia is least studied and there is an urgent need to be deeply investigated.

In addition to hypoxia-induced cellular cytotoxicity, hypoxia is also known to modulate the metabolic profile of the affected cell [105]. In this context, available researches suggests the involvement of autophagy in degrading cellular components including mitochondria (mitophagy), ER (ERphagy or reticulophagy), lipids (lipophagy), nucleus (nucleophagy), ribosomes (ribophagy) and peroxisomes (pexophagy) under hypoxic stress [9,106]. However, the relevancy and the exact mechanism controlling the selective autophagy types under hypoxic stress are poorly understood and still need to be uncovered.

6. Role of selective autophagy in cancer progression

Selective autophagy is a specialized type of autophagy, which is responsible for specifically removing dangerous cellular components such as dysfunctional proteins, damaged organelles, and intracellular pathogens. Selective autophagy regulates the degradation of number of specific cellular components through specialized autophagic receptors including p62/SQSTM1, nuclear dot protein 52 kDa (NDP52), neighbor of breast cancer 1 gene (NBR1), optineurin, and valosin-containing protein (VCP) [107]. Autophagy receptors specifically recognize ubiquitinated cargos and enables elimination by interacting with LC3/GABARAP/Gate16 protein on the phagophore membrane [108]. Though selective autophagy exhibits a tumor-suppressive functionality in the initial phase of cancer development, the pro-survival mechanism of autophagy promotes tumor survival and offers protection in established tumors. An overall summary of the different types of autophagy which includes macroautophagy, microautophagy and selective autophagy and their main proteins involved are depicted in the Fig. 1.

In macroautophagy, phagophore formation occurs which interacts with the organelles that are carried out by LC3-II forms autophagosome. This autophagosome carries the damaged organelles inside the phagophore to the lysosome forms the fusion of autophagosolysosome. These damaged organelles are lysed by acid hydrolase present inside the lysosome.

In microautophagy, both selective and non-selective pathway of autophagy occurs. In selective, substrate protein binds with chaperones and enters into lysosome. In non-selective autophagy, both organelles and proteins enter into lysosome which is detoxified by acid hydrolase present in it.

In mitophagy, the body system eliminates defective mitochondria through Parkin dependent and independent pathway. In Parkin dependent pathway, PINK1 interacts with PARL which on ubiquitinylation interacts with p62 and MFN2. All these proteins are triggered by PARKIN and Ambra1 mediates mitophagy. In Parkin independent pathway, Atg13 interacts and phosphorylated by ULK1, Hsp30, and Cdc31. On phosphorylation, Atg13 activates ROS as well as ATP depletion. The depleted ATP activates AMPK which inhibits mTOR which was also inhibited by ROS. The inhibited mTOR inhibits LC3II which prevents autophagy.

In pexophagy, two different pathways are elucidated in yeast and in mammals. In yeast, Atg36, Atg30 and Pex3 bind with peroxisome. Hrr25 initiates the induction of autophagy and triggers the high expression of Atg36. Upon interaction, Atg36 interacts with Atg8 and Atg11 which combines with Pex11βp to form pexophagosome. In mammals, NBR1, SQSTM1 and p62 binds with peroxisome. Pex5 and ABCD1 protein induces the interaction of Pex10, Pex12 and LC3II with peroxisome enhances the formation of pexophagosome.

In ER-phagy, two different pathways are elucidated in yeast and mammals. In yeast, ER-phagy is induced by different autophagy regulators namely Atg40, Atg39, Sec23, Lst1, VAMP8 and Nvj1. In mammals, three different autophagy occurs in the endoplasmic reticulum. In the sheet of ER, autophagy occurs by various proteins such as TEX264, CCPG1, FAM134B and Sec62. In tubular ER, CCPG1, RTN3, ATL3 involves in autophagy. ATZ interacts with CNX and FAM134B and forms ER derived vesicle which combines with STX17 and VAMP8 to form phagosome.

6.1. Mitophagy

Mitophagy, a selective elimination of mitochondria is primarily identified in yeast, is induced by atg32, and in mammals it is mediated by NIP3-like protein X (NIX or BNIP3L) [109]. This process is critical for regulating their number and maintaining quality control even under nutrient rich conditions. This is important because mitochondria generates toxic by-products such as reactive oxygen species (ROS) as a part of their metabolic process leading to cytotoxicity and cell death and eventually resulting in the release of cytochrome *c* and activation of caspases, leading to apoptosis [110].

6.1.1. Ubiquitin dependent receptors

PINK1/Parkin pathway is a widely elucidated mitophagy pathway. The membrane-voltage dependent translocation of PTEN-induced putative kinase 1 (PINK1) is the decisive factor which regulates mitophagy by differentiating healthy and defective mitochondria [111]. In normal circumstances, PINK1 is translocated to the inner mitochondrial membrane (IMM) via translocase of the outer membrane (TOM) and translocase of the inner membrane (TIM) where it is subjected to cleavage by a serine protease presenilin-associated rhomboid-like (PARL), ultimately leading to its degradation by mitochondrial proteasomes [112]. This maintains a basal level of PINK1 in IMM. However, in defective condition, mitochondrial membrane becomes depolarized and ceases PINK1 translocation. Additionally, PARL is phosphorylated by PDK2 rendering them inactive and unable to cleave PINK1, resulting in their accumulation [113]. This increased accumulation of PINK1 triggers ubiquitination of mitochondrial proteins such as mitofusin-1 (MFN1), MFN2, Miro1 or VDAC1 via Parkin [114]. Ultimately, autophagic receptors recognize these polyubiquitinated mitochondrial proteins and will be subjected to degradation via autophagic machinery. Recent study confirms the participation of PINK1/Parkin in regulating iron metabolism in pancreatic cancer. Mice with PINK1 and Parkin knockout induce RAS driven pancreatic tumorigenesis as a result of mitochondrial iron accumulation.

6.1.2. Ubiquitin independent receptors

BNIP3/NIX-mediated mitophagy pathway depends on the proteins BNIP3 and BNIP3L/NIX that are able to directly bind to autophagy receptors in its phosphorylated state and enables mitophagy without involving ubiquitination process [115]. Although several evidences clearly suggest that the dysregulation of mitophagy components contributes to cancer progression, only limited number of studies is available to completely elucidate the mechanism involved in it. Few of those concentrated studies describe the potential mechanism of Parkin in regulating tumor progression by modulating mitophagy. Loss-of-function mutation in Parkin which is commonly found in various tumors inhibits mitophagy leading to tumorigenesis [116]. This is supported by studies conducted on Parkin knockout mice, which exhibited increase in tumorigenesis [117]. Once the tumor is established, hypoxia increased tumor cell survival by activating mitophagy via HIF1-α mediated induction of BNIP3 and FUNDC1 pathways. BNIP3 further exhibits a dichotomous role wherein both its activation and inactivation contribute to tumor survival [118].

In response to oxygen deprivation, tumor-mediated hypoxia

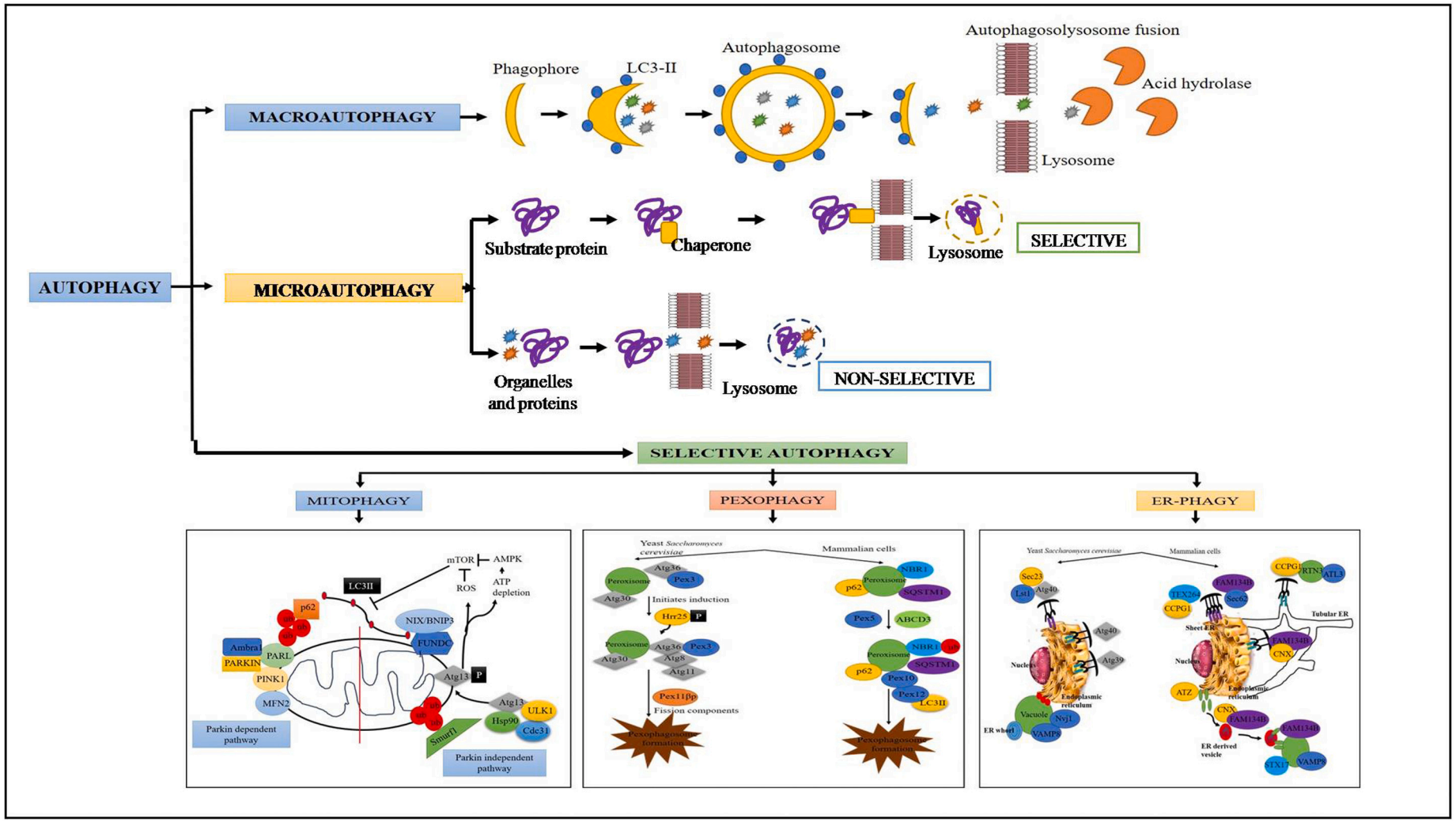

Fig. 1. Types of autophagy and proteins involved in the mechanism. There are three different autophagy: Macroautophagy, microautophagy and selective autophagy. Mitophagy, Pexophagy and ER-phagy are the three different forms of selective autophagy.

microenvironment induces mitophagy in the damaged cells. In cultured MEF cells, mitophagy is mediated by HIF1α dependent upregulation of BNIP3 triggering BNIP3 mediated mitophagy pathway [119]. Moreover, mitophagy promotes tumor cell survival by protecting them against ROS generated in excess quantity and by escaping apoptosis mediated cell death. Apart from this, most of the proteins that are involved in mitophagy are mutated in cancer patients, and can function as tumor promoter or suppressor considering the cancer type and context. For example, BNIP3 plays tumor suppressive role in breast cancer whereas in renal cell carcinoma and pancreatic cancer it is thought to have tumor promoting functions [120]. Alongside this, mitophagy contribute to the metabolic demands of tumor by engaging in Warburg effect which actively shifts the bioenergetic pathway from pyruvate to lactate generation meanwhile avoiding oxidative phosphorylation even in the presence of oxygen [121]. Moreover, PINK1/Parkin pathway which regulates quality control of mitochondria can also be linked to iron metabolism and influence tumorigenesis. Managing iron balance is essential for maintaining cellular integrity and any deregulation can promote tumor by excessive ROS production and oxidative stress [122]. Owing to the beneficial nature of mitophagy in cancer cells, any attempt in sensitizing cancer cell proliferation by inducing mitochondrial damage could result in increased activation of mitophagy thus offering resistance against anti-cancer therapies. Therefore, inhibition of mitophagy pathway is an active area of research in cancer therapy. In this context, knockdown of essential mitophagy components such as FUNDC1, PINK1 or AMBRA1 sensitized drug resistant cancer cells [123–125]. However, inhibiting key mitophagy components alone is not sufficient to mount an anti-tumor response since different mitophagy pathway may be involved in enabling resistance against therapy induced mitochondrial stress. For example, in prostate cancer, docetaxel therapy caused resistance against the treatment by inducing ULK1-independent mitophagy [126]. Additionally, in gastric cancer cells, overexpression of opa-interacting protein 5 (OIP5) activates MFN2/PINK1-mediated mitophagy and prevents docetaxel-induced cell death [127]. Therefore, further investigations are required to understand the clear-cut involvement of mitophagy in anti-cancer therapy.

6.2. Pexophagy

Peroxisomes are dynamic oxidative organelles found in most eukaryotic cells. They play a major role in modulating metabolic responses to different signals. Alongside this, they also control purine catabolism, beta-oxidation mediated fatty acid degradation, and ether phospholipid synthesis [128]. Moreover, thioredoxin-dependent peroxiredoxin (TPx-Q) are proteins that acts as disulphide reductase and regulates redox system. The presence of these proteins along with the proteins responsible for regulating oxidation process makes peroxisomes an important organelle regulating both generation and scavenging of ROS and reactive nitrogen species (RNS) [129]. Tight regulation of peroxisome biogenesis and degradation should be maintained to assure proper size, quality control, functional status, overall cellular homeostasis and to avoid peroxisome mediated disorders. Pexophagy is selective autophagy machinery that specifically targets peroxisomes for degradation [130]. Attempts in inhibiting pexophagy can result in impaired peroxisomes, kidney injury and redox imbalance indicating the significance of pexophagy [131]. Molecular regulatory mechanisms of pexophagy are also similar to mitophagy and other selective autophagy in which ubiquitination of membrane proteins triggers the induction of autophagy.

The molecular mechanism of pexophagy has been primarily elucidated in budding yeast *Saccharomyces cerevisiae*. In yeast, pexophagy can be induced by changing the nutrient conditions from oleic acid or methanol to a preferred carbon source such as glucose [132]. Atg30 and Atg36 are autophagy receptors with high functional similarity found in *Pichia pastoris* and *S. cerevisiae* respectively [133,134]. In yeast, Atg36 binds to peroxisomes via the C-terminal cytosolic domain of Pex3 (peroxisomal biogenesis factor 3) and initiates the induction of pexophagy. Formation of the pexophagosome is initiated once Atg38 binds at least one peroxin and Atg8 protein thereby linking peroxisome to the phagophore [134]. Pexophagosome formation also depends on the association of autophagic scaffold protein Atg11 with Atg36 which is triggered by Hrr25, an isoform of casein kinase 1. Hrr25 phosphorylates Atg36 which is required for the increased interaction of Atg36 with Atg8 and Atg11 [135]. The formation of this complex ultimately results in pexophagy-specific fission.

In mammalian cells, the regulation of peroxisome degradation was not clearly known. However, recently several studies uncovered the mechanism of regulating pexophagy in mammals. Various stress factors including hypoxia, nutrient deprivation, oxidative stress and peroxisomal dysfunctions are known to induce pexophagy in mammalian cells [136]. So far, overexpression of ubiquitin-binding autophagy receptors NBR1 and SQSTM1 or p62, are best described to induce degradation and aggregation of peroxisomes in mammalian cell lines [137]. Additionally, PEX5 and ABCD3 ubiquitination along with other peroxisomal membrane proteins (PMPs) in response to diverse stress factors lead to pexophagy in mammals [138].

Further on this discussion, the involvement of pexophagy in cancer progression and development is mostly concentrated on hypoxia-mediated pexophagy. Under hypoxic conditions, peroxisomes are targeted by pexophagy which reduces the number of peroxisomes drastically, thus decreasing the cells demand for oxygen and ultimately enabling cancer cells survival and proliferation in the advanced stage. The HIF-2a/EPAS1-dependent peroxisome degradation is also confirmed in the initial studies conducted in the liver further validating its occurrence. The increased expression of NBR1 and p62 is also associated with cancer progression. Notably, NBR1 is known to be expressed in the cytoplasm of low-grade non-muscle invasive urothelical carcinoma of the bladder [139]. On contrary, it was recognized that the expression of NBR1 is negatively regulated in clear cell renal cell carcinoma (ccRCC), stipulating that the activation of pexophagy is dependent on the cancer cell type and context [140]. Furthermore, PEX2 expression along with PEX10 and PEX12 is also significantly increased in hepatocellular carcinoma (HCC) cells. It was also identified that the tumor growth is directly proportional and ROS production is indirectly proportional to PEX5 expression in liver cancer cells [141]. In lymphoma cells, downregulation of PEX3 reduces its resistance to Vorinostat (Vor) by triggering apoptosis [142]. Additionally, loss of ataxia-telangiectasia mutated (ATM) kinase are highly oncogenic and accelerates tumor development by providing resistance towards many types of cancers including breast, colorectal, lung and hematopoietic cancer [143,144]. However, additional experimentations are required to understand the intrinsic role of individual pexophagy components in cancer development.

Although, individual components involved in pexophagy include NBR1, p62, ATM, PEX2, PEX3, PEX5, PEX10, PEX12 and those in ER-phagy include CCPG1, FAM134B, SEC62 which are critical regulators that are known to promote tumorigenesis however the overall mechanism that regulate tumor progression still needs to be uncovered [145–147].

6.3. ER-phagy

The endoplasmic reticulum (ER), a continuous membrane system in the cytoplasm is one of the most essential and complex organelles in the eukaryotic cell. These structures harbour several important functions including biosynthesis, folding, modification, and transport of proteins along with few processes related to calcium reserve, lipid and steroid hormone synthesis [148]. However, to efficiently maintain these dynamic functions and to cope with rapid metabolic demands in protein and lipid components, pharmacological defects, or pathogen attacks, ER components should be periodically restored to the pre-stress state in order to avoid stress induced by these processes. This is indispensable

owing to the fact that ER stress can result in damage or degradation of essential ER components and can subsequently affect normal physiological functions including protein misfolding [149]. ER-phagy is the mechanism which facilitates quality control and turnover of ER, characterized by lysosomal degradation of ER and its components [106]. Previously it was thought that the misfolded proteins in the ER lumen can be broken down only by the proteasome. However, intense research in the area of ER degradation showed compelling evidence in the participation of autophagy machinery [150]. Similar to mitophagy, ER-phagy also has the ability to discriminate between functional and damaged ER structures. Alongside this, ER-phagy can often target heterogenous and bulky materials for degradation. The identification of ER-phagy adaptor molecules has gained notable interest in determining the physiological significance of ER-phagy.

Similar to other selective autophagy pathways, the ER-resident receptors located on specific subdomains of the ER plays a critical role in mediating ER-phagy. Till date, five ER-phagy receptors have been recognized in mammals that act as selective autophagy receptors. These includes reticulophagy regulator 1 (RETREG1/FAM134B), reticulon-3 (RTN3), SEC62 cell cycle progression protein 1 (CCPG1) and atlastin GTPase 3 (ATL3) [106]. FAM134B is the first ER-phagy receptor to be identified and possess reticulon-homology domain (RHD), which is also found common in RTN3. FAM134B is localized at the curve edges of ER sheets and its activity is restricted to its resident subdomain and is responsible for the turnover of ER sheets [151]. RTN3 is found exclusively on ER tubules and is responsible for the selective degradation of ER tubules. Increased local concentration of RTN3 facilitates its oligomerization which in turn induces breakdown of ER tubules [152]. Meanwhile, SEC62, a part of SEC61/SEC62/SEC63 translocation machinery is confined to ER sheets following ER-stress. Despite its role in translocation of nascent polypeptides into the ER, SEC62 actively participates in ER-phagy to assist cellular recovery from ER stress [153]. ER subdomains containing molecular chaperones are the predominant target sites for SEC62-mediated ER-phagy [154]. Another ER-phagy receptor, CCPG1, a transmembrane protein located in the perinuclear ER and ER periphery locally restricts ER stress and is responsible for maintaining ER proteostasis by trimming areas of ER containing insoluble proteins [155]. ATL3, a novel ER-phagy receptor, belongs to a class of membrane-bound, dynamin-like GTpases plays a critical role in ER fusion. In response to starvation, ATL3 functions as ER-phagy receptor and promotes tubular ER degradation by interacting with GABARAP via GABARAP interaction motifs (GIMs) [156]. Though all these receptors can concurrently stimulate ER-phagy, they do not functionally coordinate with each other. Yet, all of these receptors trigger autophagy by interacting with LC3/GABARAP containing autophagic membranes via LC3-interacting region (LIR) domains [157]. Hereafter, the subsequent process of ER-phagy is similar to other selective autophagy pathways which include sequestration of cargo via interaction between LIR and LC3/GABARAP; wrapping of the isolation membrane surrounding the cargo forming autophagosome complex; autophagosome and lysosome fusion and subsequent degradation of the sequestered ER components by the action of lysosomal hydrolases and acidic pH environment.

Most of the proteins including receptors that are involved in ER-phagy are associated with cancer. In this context, FAM134B and SEC62 are directly related to different types of cancer, indicating that ER stress tolerance play a critical function in regulating tumorigenesis. However, studies confirmed that mutations or alterations in their functions are observed in several cancer types and can lead to tumor development. In colorectal adenocarcinoma cells, FAM134B was found to be inactivated via promotor methylation and as a consequence tumor aggressiveness as well as metastasis has been observed. Moreover, compared to healthy counterparts, FAM134B is mutated in more than half of the colorectal cancer samples. Additionally, mutation in FAM134B is also identified in colon cancer and oesophageal squamous cell carcinoma [158,159]. Under hypoxic conditions, increased expression of FAM134B plays a pro-tumor role in chronic myeloid leukemia (CML) cells thus mediating cancer cell proliferation and drug resistance [160]. Similarly, the mRNA and protein levels of SEC62 is highly elevated in prostate cancers whereas, downregulating these genes inhibits aggressiveness and migratory potential of various tumor cells including thyroid and non-small cell lung tumor [161]. Furthermore, SEC62 upregulation positively correlated with ER stress resistance and metastatic ability in almost 80% of cervical and thyroid cancers. Similarly, increased expression of SEC62 is linked with lymphatic metastasis in head and neck squamous cell carcinomas [162]. Despite its oncogenic capability, the actual mechanism of SEC62 in promoting tumor is poorly understood.

Another ER-phagy receptor CCPG1 has been associated with prostate cancer and was suggested as a predictive biological marker for this cancer type [163]. Moreover, CCPG1 was also recognized to directly affect autophagy initiation by physically interacting with FIP200 and ATG8 in lung cancer cells [155]. Furthermore, CCPG1 is downregulated in colon cancer and retinoblastoma cells [164]. In this regard, CCPG1 downregulation is associated with increased cell proliferation and decreased apoptosis in retinoblastoma cells [165]. Finally, the role of RTN3 in cancer still needs to be uncovered. However, recent studies suggest RTN3 as a possible prognostic marker for HCC cells as a consequence of its increased expression in such cancer type compared to healthy ones [166]. Furthermore, RTN3 upregulation in astrocytoma patients indicates its oncogenic role [167]. Conclusively, additional research is necessary to validate the exact mechanism of RTN3 in tumor progression.

7. Autophagy signalling in lung cancer

Lung cancer, the leading cause of cancer death is characterized by an abnormal cell growth in lung tissues. It can be broadly categorised as small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC), while the latter accounts for more than 85% of all lung cancers [168]. NSCLC is further divided into three main subtypes including squamous cell carcinoma, large-cell carcinoma and adenocarcinoma. The involvement of autophagy is found to be critical in the pathological manifestation of NSCLC. Autophagy can play both tumor-suppressive or tumor promoting role in the manifestation of NSCLC. Moreover, the most commonly mutated genes in NSCLC like p53, KRAS, EGFR, LKB1 and PTEN are closely linked to autophagy via mTOR signalling pathway [169].

7.1. P53 function and mutation

P53 has a dual role in regulating autophagy. Nuclear p53 induces autophagy alternatively cytoplasmic p53 downregulates autophagy [170]. Under stressful conditions, p53 translocate to the nucleus and activates transcription of sestrin1 and sestrin2 which ultimately stimulate autophagy via AMPK-TSC2-mTOR pathway [171]. Cytosolic p53 inactivates autophagy by associating with autophagy component focal adhesion kinase family interacting protein of 200 kDa (FIP200) [172]. P53 can also downregulate autophagy by inhibiting AMPK and activating mTORC1. Various studies conducted on mouse model indicate that blocking p53 expression can induce autophagy [173]. Furthermore, frequent mutations in p53 observed in the clinical cases of NPCLC suggest its involvement in the pathogenesis [174]. Moreover, mutant p53 alleles localized in the nucleus or cytoplasm can inhibit or stimulate autophagy depending on cellular context and microenvironment. Therefore, by targeting mutant p53 and restoring its normal function, potential anti-cancer therapies can be developed for treating NSCLC. Nutlin and RETRA are compounds that can potentially increase wild-type p53's anti-tumor activity by rendering its association with ubiquitin ligase MDM2 [175]. Moreover, smoking which is the primary risk factor of lung cancer prevalence increases the magnitude of p53 mutation compared to non-smoking patients. Moreover, mutant p53 induced by smoking exhibited lose in its tumor-suppressor role characterized by

aggressiveness and less survival rate of affected individuals [176]. Therefore, different strategies in the development of therapeutics must be undertaken for different p53 mutant subtypes.

7.2. mTOR pathway

Signalling pathways plays a pivotal role in sensing the environmental status including stress, hypoxia and nutrient deprived conditions [177]. The coordinated regulation of essential signalling pathways such as mTOR, MAPK, JAK/STAT, and AMPK will either activate or inactivate autophagy and also determines the intensity of the autophagic response to different cellular condition [178–180]. mTOR signalling pathway is responsible for regulating multiple cellular processes including protein synthesis, metabolism, cell growth, proliferation and survival [181]. In the context of autophagy, mTOR acts as a central regulator and modulates its activity depending on the cellular condition [182]. mTOR is a member of conserved serine/threonine kinase that is associated with various functions including cell cycle regulation, differentiation and proliferation. Two distinct protein complexes mTORC1 and mTORC2 are involved in the mTOR signalling pathway [183]. Several studies confirm that mTOR is a negative regulator of autophagy. In nutrient surplus state, mTORC1 directly phosphorylates and inhibits pro-autophagic proteins ULK1 and ATG13 and thus suppresses autophagy [184]. Whereas during starvation state, the activation of AMPK can indirectly inhibit mTOR activity and positively regulate the activation of ULK1 or VPS34/Beclin1/ATG14 complexes and elevate basal autophagy levels [185]. As previously mentioned, mutations in several genes including amplification of EGFR and PIK3CA, and PTEN deletion in NSCLC can result in deregulated mTOR signalling pathway and can lead to aberrant autophagy induction [186]. MAPK pathway gets activated by responding to various environmental signals and control complex cellular processes such as differentiation, development, proliferation and apoptosis [187]. MAPK/JNK signalling cascades participates in the regulation of autophagy. Once induced, JNK phosphorylates further downstream effectors ultimately activating and enhancing the transcription activity of Beclin-1, thus inducing autophagy [188]. Similar to MAPK, JAK/STAT pathway is yet another signalling network which mainly contributes to cellular growth, differentiation, proliferation and apoptosis [189]. STAT3 plays a dual role in autophagy depending on its subcellular localization. Nuclear STAT3 promotes autophagy by transcriptionally regulating BCL2 family members and other autophagy-related genes. Whereas, cytoplasmic STAT3 inhibits autophagy by sequestering EIF2AK2 (eukaryotic translation initiation factor 2 alpha kinase 2) and modulating FOXO1 (Forkhead box protein O1) and FOXO3 (Forkhead box protein O3) [190]. Furthermore, AMPK signalling cascades acts as a master regulator in maintaining cellular energy homeostasis by responding to environmental cues including nutrient deprivation and hypoxia [191]. AMPK is one of the crucial autophagy regulators which when activated induces autophagy by associating with ULK1 protein [192]. Altogether, these signalling pathways positively or negatively modulate autophagy by regulating autophagy related transcriptional factors [193].

7.3. EGFR and autophagy signalling in NSCLC

EGFR mediated tumor progression has been widely elucidated in several studies which includes the activation of various signalling networks that are associated with autophagy [194]. In addition to this, the interaction of EGFR with the core autophagy protein Beclin-1 provides possible evidence in determining the tumor promoting role of autophagy. Wei and his colleagues identified that the active EGFR mutant observed in NSCLC cells stimulated the association of EGFR with Beclin-1. The binding of EGFR with Beclin-1 promoted its phosphorylation at three tyrosine residues (Y229, Y233, and Y352) respectively [195]. The EGFR-mediated phosphorylation of Beclin-1 modified its interactome, thus preventing its binding with vps34. Meanwhile, the modified interactome of Beclin-1 increased its likelihood to bind with Bcl-2 and Rubicon complex, thereby suppressing autophagosome formation [196]. In contrast, treatment of EGFR-mutant NSCLC cells with erlotinib, an EGFR tyrosine kinase inhibitor, disrupted the formation of EGFR-Beclin-1 complex resulting in autophagy induction. Additionally, expression of Beclin-1 phosphomimetic mutant (Beclin-1 Y229/233/352E) induced autophagy by blocking the activity of erlotinib and preventing the disruption of EGFR-Beclin-1 complex. Furthermore, Beclin-1 phosphomimetic mutant conferred more resistance compared to the control or wild-type Beclin-1 xenografts upon erlotinib treatment [195]. Altogether, these data indicate that EGFR in association with Beclin-1 contributes to tumor progression by suppressing autophagy.

Several studies clearly suggest close association of NSCLC with epidermal growth factor receptor (EGFR) mutations, which makes up for about 10–40% of total adenocarcinoma [197]. In this regard, while the p53 mutations are primarily associated with smokers, EGFR mutations occurs more frequently in females and non-smokers with adenocarcinoma [198]. Though EGFR is generally present in the plasma membrane, it has also been found in the mitochondria and nucleus thereby indicating that the functionality of EGFR may be dependent on its subcellular localization.

In the plasma membrane, EGFR acts as a membrane-bound receptor tyrosine kinase. Upon ligand binding, EGFR undergoes homo or heterodimerization with ErbB2/neu, ErbB3/HER3, ErbB4/HER4 and subsequent phosphorylation of EGFR occurs [199]. The phosphorylated EGFR then activates a number of downstream signalling molecules that are crucial for cancer cell survival, growth and proliferation. MAPK, JAK/STAT, NCK/PAK/JNK, PLC/PAG/PKC and PI3K/AKT/mTOR are the major pathways triggered by EGFR activation which ultimately exert a potent stimulatory effect on autophagy (Fig. 2) [200]. Alongside this, recent evidence indicates that EGFR may also mediate autophagy through the activation of AMPK/mTOR and LKB1/AMPK pathway [201]. Each of these signalling pathways has a series of downstream effectors which ultimately leads to the expression of associated gene targets. For example, MAPK pathway activates a series of intermediate proteins, including Ras, Raf, MEK and ERK to transfer signal from the receptor to the nucleus [202]. Moreover, a recent study indicates that EGFR stimulates the activation of downstream protein c-Jun N-terminal kinases (JNK) whose effector function exerted a major protective effect by upregulating autophagy and is characterized by decreases apoptosis and ROS generation in A431 cells [203]. However, mutation in EGFR, such as Thr790Met (T790M), a gatekeeper mutation of the EGFR accounts for almost 50% of NSCLCs and provides resistance against autophagy inhibition drugs, gefitinib and erlotinib [204]. As previously mentioned, EGFR signalling is found to be amplified in NSCLCs as a result of mutation. However, this altered signalling did not affect any downstream pro-survival signalling cascades. Furthermore, inhibition of downstream signalling molecules did not modify the sensitivity of NSCLC cells with EGFR T790M mutation, suggesting the involvement of other types of signalling pathways activating autophagy and subsequently mediating acquired epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) resistance [205]. It is also hypothesized that the application of EGFR-TKI may enhance autophagy in lung cancer cells as a consequence of acquired EGFR-TKI resistance [206]. However, the exact mechanism by which EGFR-TKIs induce autophagy is still needed to be evaluated. Therefore, understanding the relationship between autophagy and EGFR-TKI resistance can provide promising therapeutic approach to enhance the effect of EGFR-TKIs in NSCLC patients.

8. Autophagy signalling in pancreatic cancer

Pancreatic cancer, the fourth highest cause of cancer mortality in the world is characterized by a malignant neoplasm formation, originating from the tissues containing transformed cells of the pancreas. Out of several types of pancreatic cancer, pancreatic ductal adenocarcinoma

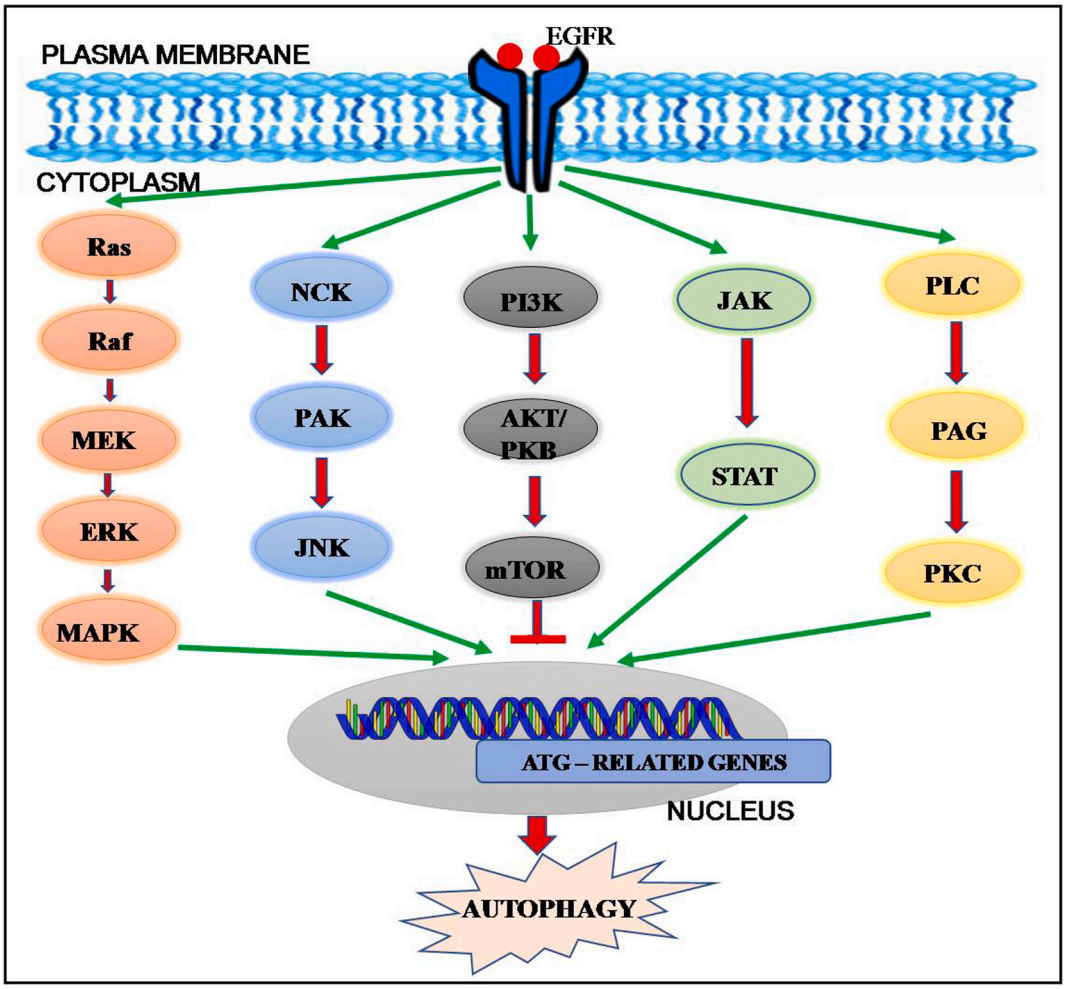

Fig. 2. EGFR mediated autophagy signalling pathway in NSCLC. Upon ligand binding, the plasma membrane-bound epidermal growth factor receptor (EGFR) gets phosphorylated via homo or heterodimerization with ErbB2/neu, ErbB3/HER3 and ErbB4/HER4. The phosphorylated EGFR then activates several downstream signalling pathways including MAPK, JAK/STAT, NCK/PAK/JNK, PLC/PAG/PKC and PI3K/AKT/mTOR that are crucial for autophagy regulation. Activation of the above-mentioned signalling cascades elicits a provoking effect on autophagy. Targeting these pathways could be a possible treatment strategy for NSCLC.

(PDAC) accounts for more than 85% of pancreatic cancer and is the most aggressive form with a 5 years overall survival rate of less than 8% [207]. The pathogenesis of PDAC is highly associated with acinar cell damage and dysfunction. One of the major functions of pancreatic acinar cells is to produce and secrete digestive enzymes and proteases. This process demands a very high protein production rate and thus requires an extensive rough endoplasmic reticulum network. As a consequence, acinar cells are usually prone to ER stress and accumulation of misfolded proteins [208]. The former can result in chronic pancreatitis which may lead to the development of PDAC by forming inflammation in the exocrine pancreas.

8.1. *Autophagy in PDAC survival and development*

Several data confirm the involvement and essential role of autophagy in PDAC survival and development. Moreover studies carried out in vivo showed the loss of ATG7 in pancreatic epithelial cells leads to pronounced loss and damage of acinar cell suggesting the requirement of autophagy for the maintenance of acinar cell physiology. Additionally, conditional ATG7 knockout in all pancreatic epithelial cells have showed impaired autophagy, increase in damaged mitochondria and ER stress, resulting in increased ROS generation in the pancreas [209]. This increased oxidative stress in turn is known to regulate autophagy. In PDAC cell lines, antioxidant-inhibited ROS showed significant reduction in basal autophagy levels and conversely, reduced autophagy triggered the generation of ROS, confirming the cross-regulation of ROS and autophagy in PDAC. Moreover, during early stages of PDAC development decrease in autophagy allow ROS to promote genomic instability required for transformation, whereas during later stage, increase in basal autophagy level protects the cells from ROS mediated cellular cytotoxicity. This indicates the biphasic role of autophagy and ROS in PDAC pathogenesis [29]. Another way in which autophagy can be regulated in PDAC is through vacuole membrane protein 1 (VMP1), a candidate marker for autophagosome formation [210]. VMP1 expression is induced by cell starvation and mTORC1 inhibition and function through interaction with beclin-1 and ultimately forming phagophore complex [211]. Furthermore, KRAS activating mutations are the defining features of PDAC in almost 90% of the patients. In this regard, in PDAC cells, VMP1 is overexpressed via KRAS-PI3K-AKT1-GLI3-P300 pathway and this additional VMP1 is necessary for oncogenic KRAS to induce autophagy [212]. These studies together indicate that VMP1 is likely to be an autophagy regulator in PDAC.

Furthermore, during later stages of PDAC development, increase in the LC3-II levels showed elevated basal autophagy levels compared to non-cancerous pancreatic cells. Immunohistochemistry analysis of human pancreatic tumor samples have shown an increase in autophagy levels as the premalignant pancreatic interepithelial neoplasms (PanINs) transformed to more advanced PDAC [29]. Moreover, aberrations of

RAS oncogene and TP53, along with KRAS activating mutations have found to be cooperative in their contribution to PDAC [213]. Sequence analysis of PDACs showed that TP53 have been mutated or inactivated in almost 75% of patients and this mutated TP53 have been shown to drive pancreatic cancer [214]. In addition to this, the pancreatic tumor microenvironment has been found to be hypoxic, stipulating the role of hypoxia in inducing autophagy and subsequent PDAC development. High expression of HIF-1α has been shown to correlate with poor prognosis in PDAC patients [215]. Hypoxia is known to induce autophagy in several ways in most tumor types including PDAC, in which elevated basal autophagy levels have been observed. As already mentioned, activated HIF-1α upregulates the expression of BNIP3 and BNIP3 like protein (BNIP3L). Activated BNIP3 and BNIP3L induce autophagy by subsequently disrupting the Bcl-2-Beclin-1 complex in a mTOR independent pathway [216]. This mechanism is stipulated in various cancer cell lines, including salivary adenoid cystic carcinoma and prostate cancer, and this process may also occur in PDAC [217]. Moreover, high level of LC3 expression associated with the increase in hypoxic marker carbonic anhydrase IX at the pancreatic cancer tissue serves as evidence for the connection between autophagy and hypoxia [218]. Recent research in PDAC patients revealed that the hypoxia induces ROS production which ultimately stimulates autophagy by subsequently inhibiting the pAKT/mTORC1 pathway [219]. Although there is significant correlation between hypoxia and autophagy in PDAC, the exact mechanism that regulates hypoxia-induced autophagy in PDAC is not fully understood.

8.2. *Impact of molecular pathways involved in autophagy on pancreatic cancer metabolism*

Although not all pathways involved in regulating and reprogramming autophagy in PDAC are fully understood, autophagy is thought to play a significant role in PDAC metabolism. In this context, transcriptional regulation of autophagy-lysosome function satisfies metabolic demands of pancreatic cancer. This extensive process is carried out by the MiT/TFE subclass of basic helix-loop-helix transcriptional factors which includes transcription factor E3 (TFE3), microphthalmia-associated transcription factor (MITF) and transcription factor EB (TFEB) [220].

In normal cells under nutrient stress conditions, MiT/TFE transcription factors control the biogenesis of autophagy-lysosome proteins [221]. RNA sequence analysis revealed that the high expression of these transcription factors correlated with increased lysosomal biogenesis in PDAC [220]. Furthermore, it was found that in PDAC cells, importin-8 (IPO8), a member of the importin-β family of nucleocytoplasmic transporters binds TFE3 and promotes the translocation of TFE3 into the nucleus resulting in the activation of its transcriptional functions in both normal and nutrient starvation conditions (Fig. 3). Although binding of IPO8 to MITF or TFEB is not experimentally proven, depletion of IPO8 decreased the expression levels of MITF and TFEB in PDAC cells. Moreover, depletion of MiT/TFE proteins in PDAC cells impaired autophagic flux and lysosomal catabolism indicating their potential in processing of cargo from autophagy thereby providing PDAC cells with

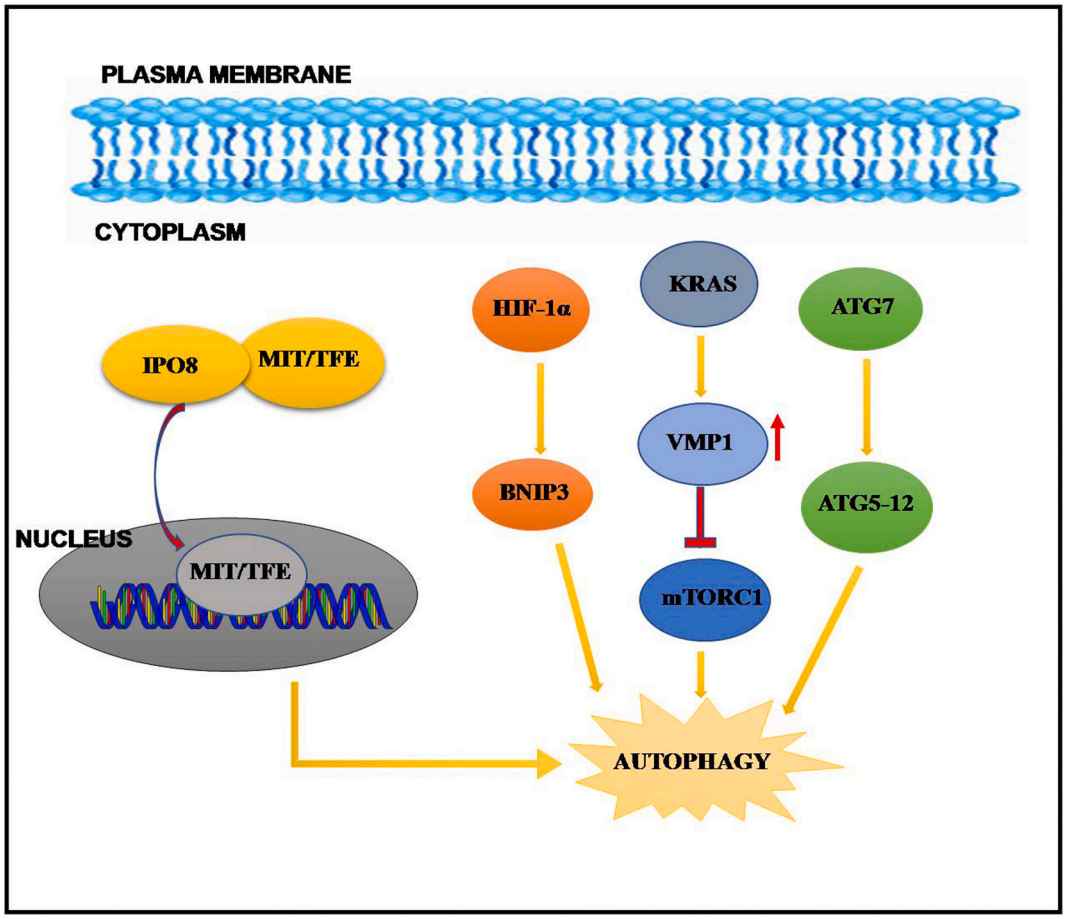

Fig. 3. Schematic representation of the molecular pathway involved in PDAC development. Under normal conditions, MIT/TFE transcriptional factors are inactivated by mTORC1. In PDAC cells, IPO-8 drives nuclear translocation of MIT/TFE by escaping mTORC1 inactivation of MIT/TFE. This process subsequently activates autophagy machinery and ensures cancer cell survival. Moreover, high expression of HIF-1α upregulates BNIP3 likes protein which activates autophagy in a mTOR independent pathway. Furthermore, KRAS activating mutation and ATG7 participation in PDAC increases autophagy levels by activating a wide range of downstream autophagy associated proteins.

intracellular nutrient supplies. In this regard, in vitro silencing of MiT/TFE transcriptional factors showed reduced growth of PDAC cells. Though their activity is not crucial as MiT/TFE proteins, TFE3 and MITF were also found necessary for in vivo xenograft growth of many PDAC cell lines [220].

Inhibition of autophagy is a possible strategy for therapeutic treatment of PDAC. However, employment of hydroxychloroquine (HCQ) as a monotherapy did not show significant reduction in PDAC development [222]. Further on this research, gemcitabine treatment increased susceptibility of cancer stem cells (CSCs) in vivo by autophagy inhibition. However, a combinatorial treatment containing both HCQ and gemcitabine can produce promising results by preventing pancreatic tumor formation [223]. Moreover, an interesting avenue involving combinatorial PDAC treatment with MAPK/NF-κB/autophagy inhibitors could be a promising strategy [224]. Furthermore, identification of suitable biomarkers in PDAC patients in respect to autophagy inhibition is yet to be studied.

9. Autophagy signalling in colorectal cancer

Colorectal cancer (CRC) is the third leading cause of cancer deaths in United States with a 5-year survival rate of 14% in later stages [225]. Genetic analysis has confirmed that the initial loss of adenomatous polyposis coli (APC) gene typically causes sporadic CRCs. APC is a cytoplasmic scaffold protein that acts as a negative regulator of β-catenin and leads to proteasomal degradation of β-catenin. APC gene mutations have been found in almost 80% of all human colorectal cancers. Therefore, loss of APC prevents proteasomal degradation and constitutively activates β-catenin which leads to uncontrolled epithelial cell proliferation [225]. This is subsequently followed by mutations in tumor protein p53 and KRAS leading to tumor development and proliferation [226]. Since, most of the genes that are mutated in CRC also regulate autophagy; the involvement of autophagy in CRC development has been widely elucidated. Several expression analyses have observed downregulation of ATG5 in CRC patients. Interestingly, increased expression of ATG5 correlated with increased evidence of lymphovascular invasion [227]. On contrary, expression of LC3B and SQSTM1 is associated with poor prognosis of CRC [228]. Moreover, mutation in receptor for activated C kinase 1 (RACK1) promotes tumorigenicity of colon cancer by inducing autophagy and inhibiting apoptosis [229]. Furthermore, upregulation of Beclin1 is observed in almost 95% of colon cancers compared to normal tissues [230]. Under starvation state, inhibition of KRAS showed decreased autophagic induction suggesting its positive regulatory role in inducing autophagy in CRC [231]. Similarly, loss of p53 increased the accumulation of LC3 thereby decreasing autophagic flux and activating apoptosis-mediated cell death in human colorectal cancer cells. [232] All these proteins are crucial in triggering autophagy and modulating or inhibiting the activity of these proteins can possibly reduce the severity of CRC.

The rapid progression of tumors leads to the decrease in the

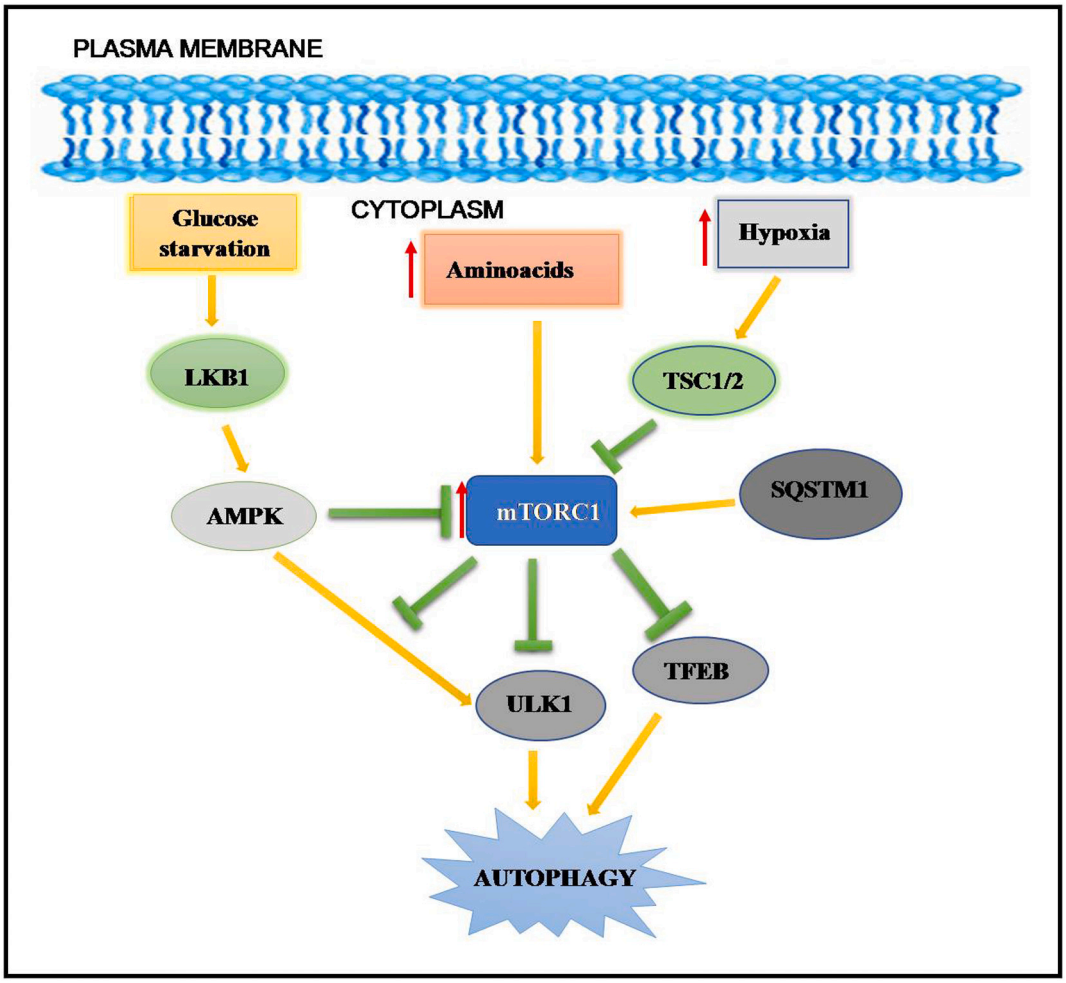

Fig. 4. Overview of the mechanism of mTORC1 regulation in CRC. The availability of nutrients and hypoxic condition together regulate the activation of mTORC and downstream autophagy machinery in CRC. Under starvation and hypoxia state, which is most prominently found in CRC, mTORC is inhibited which subsequently increases autophagic flux through a number of pathways including TFEB, ULK1 and AMPK thus causing cancer progression. Basal autophagy levels are also increased independent of mTORC through ULK1 phosphorylation as a consequence of AMPK activation.

availability of nutrients in the surrounding microenvironment. This nutrient deprived state activates several intracellular nutrient sensing pathways which further contribute to cell proliferation and tumor progression. mTORC1 is known to be activated in about 50% of CRC tumors. The cross-talk between mTORC1 and autophagy are essential in maintaining cell growth and proliferation [233]. As previously discussed, under normal conditions when essential nutrients are available, mTORC1 is activated which phosphorylates ULK1 complex and inhibit ULK1-AMPK interaction to block autophagy (Fig. 4) [234]. However, under starvation and hypoxic conditions, activation of AMPK by LKB1 and subsequent phosphorylation of tuberous sclerosis complex 1 (TSC1) and tuberous sclerosis complex 2 (TSC2) causes Tsc1/Tsc2-mediated inhibition of mTORC1 [235]. Furthermore, independent of mTORC1 pathway, AMPK activates the ULK1 complex under nutrient starvation [208]. In addition to this, autophagy is also regulated by availability of amino acids via TFEB, ULK1 and AMPK pathways in CRCs [236]. Apart from this, glucose availability plays a major role in proliferation of many cancer types, including CRC. Nutrient restriction of glucose or serum induced stress in colon cancer spheroids subsequently induced autophagy [237]. Furthermore, downregulation of autophagy-associated genes in glucose free conditions decreased cell viability of human colon carcinoma cell line (HCT 116) [238]. Similarly, under starvation conditions mutations in KRAS supports tumorigenesis by inducing autophagy for maintaining oxidative metabolism [239,240]. Autophagy-mediated upregulation of Claudin 1 is also associated with colon cancer progression by degrading SQSTM1/p62 components under starvation [241]. Thus, extensive analysis of autophagic pathways that are associated with nutrient availability is essential in understanding their role in CRC tumors.

Apart from nutritional status, hypoxia also plays a crucial role in mediating CRC progression and development. In CRC, activation of HIF-1α does not increase tumor progression whereas, HIF-2α is found to be important for CRC growth and development [242]. Moreover, the connection between hypoxia and mitophagy is well addressed where the expression of BNIP3 is upregulated via hypoxia in colon cancer. In patient derived human colorectal cancer cells, inhibition of autophagy with 3-methyladenin increased hypoxia-mediated apoptosis and cell death [243]. Furthermore, the cross-talk between hypoxia and mitophagy and the role of HIF-2a should be extensively elucidated to understand the underlying mechanism that regulates autophagy in CRC.

Autophagy inhibitors chloroquine (CQ) and hydroxychloroquine (HCQ) disrupts lysosomal function and subsequently impairs autophagic degradation. The anticancer properties of these autophagy inhibitors have been clinically assessed and the efficiency of combined administration of HCQ and Capecitabine/Oxaliplatin/Bevacizumab in CRC patients is in phase I and phase II clinical trials [244]. Additionally, a phase I clinical trial with combined treatment of HCQ and vorinostat, a histone deacetylase inhibitor, has been found to improve the anti-tumor immunity in metastatic CRC patients [245]. Based on the available evidence discussed above, combined use of autophagy inhibitor may overcome chemotherapy resistance and sensitize the CRC cells to chemotherapy.

10. Autophagy signalling in lymphomas

Lymphoproliferative disorders consist of a heterogenous group of T, B and NK-cell neoplasm with an extraordinary ability to resist cytotoxic or proapoptotic cells. Non-Hodgkin's lymphoma (NHL) accounts for more than 90% of all lymphomas whereas, the remaining 10% are referred to as Hodgkin's lymphoma (HL) [246]. NHL encompasses a wide range of cancers, of which approximately 90% arise from B lymphocytes and the rest from T or NK cells. These cancers usually develop in the lymph nodes, but can also be found in almost any tissues and the severity of cancer can also range from the more benign follicular lymphoma (FL) to the more aggressive Burkitt's lymphoma and diffuse, large B-cell lymphoma (DLBCL) [247]. HL involves malignancies in the peripheral lymph nodes and can also affect other tissues and organs including lung, liver and bone marrow. Because of the heterogenous nature of the lymphoma, the treatment response is very different and the overall survival rate of the patients has drastically improved over the past few years. Of particular interests, autophagy pathways-targeting agents have been widely studied and are emerging as a promising tool for lymphoma treatment [216].

Moreover, the molecular mechanisms of autophagy involved in the initiation and progression of lymphoid malignancies have been greatly elucidated over the past few years. The autophagy-related lymphoma signalling network mainly involves autophagy-associated pathways including PI3K/Akt/mTOR pathway, the beclin-1 protein and p53 signalling pathway (Fig. 5) [248]. Moreover, several studies suggest that the defective autophagy machinery can promote lymphoma tumorigenesis. In particular, beclin-1 heterozygous in mice showed altered autophagy response and increased lymphoma cell proliferation [40]. Absence of beclin-1 associated protein Bif-1 failed to generate autophagosome in starvation state and contributed to significantly higher incidence of lymphoma those wild-type mice [43]. Furthermore, haploinsufficiency of ATG5, which is known to induce autophagosome elongation, is involved in promoting lymphoid malignancies [249]. As stated earlier, activation of PI3K/Akt/mTOR signalling pathway promotes lymphoid tumorigenesis by stimulating mTOR which subsequently results in negative regulation of autophagy. Furthermore, mTOR pathway is found to be activated in several lymphoid cancers, including HL, DLBCL, mantle cell lymphoma (MCL), FL, chronic lymphocytic leukemia (CLL) and anaplastic large-cell lymphoma [250]. Moreover, downregulation of PTEN results in reduced inhibition of PI3K is commonly observed in HL and in MCL [251,252]. In several B-cell lymphomas, mTOR pathway is also activated by antigen-independent BCR activation [253]. In particular, spleen tyrosine kinase (Syk) is rapidly phosphorylated after BCR activation and is found to be upregulated and contributes to PI3K-independent mTOR activation in several lymphoid tumor types. Inhibition of Syk by using small interfering RNA or chemical inhibitors caused inhibition of mTOR activity in B-cell lymphomas [254]. Additionally, protein kinase Cζ/ERK/mTOR pathway is also known to regulate mTOR activation in FL cells [255]. PKCζ, an atypical form of PKC is upregulated in FL cells and contributes to abnormal mTOR regulation via ERK-dependent pathway. Recently it was found that the upregulation of the mTOR signalling pathway completely inactivates AMPK activity in both T and B-cell lymphoma cells [256]. In this regard, administration of an oral hypoglycemic agent and AMPK activator, metformin, modulates AMPK/mTOR pathway by inducing AMPK activation and subsequently inhibiting mTOR signalling [257]. This AMPK activator-mediated modulation of mTOR activity resulted in lymphoma cell growth inhibition and drug sensitization. The involvement of microRNA (miRNA), an intracellular non-coding RNA in regulating autophagy-associated machinery is recently being evaluated in lymphomas [258]. For example, miRNA-15a/16-1, a negative regulator of Bcl-2 is downregulated or deleted in several lymphomas including CLL [259]. Whereas, in aggressive B-cell lymphoma, miRNA-17-92 downregulates the expression of PTEN and results in subsequent mTOR activation [260]. Altogether, these defective autophagy machineries contribute to the pathogenesis and progression of lymphoproliferative disorders.

Several anticancer agents that induce autophagy in lymphoid cancers have already been tested and are in phase I/II clinical trials. For example, in preclinical studies using CLL cell lines, a selective inhibitor of the PI3K isoform p110δ, GS-1101, blocked PI3K signalling which subsequently inhibited the activation of mTOR resulting in decreased cell viability [240]. Similar results have also been obtained in other B-cell malignancies including DLBCL, MCL and FL [261]. GS-1101 inhibited tumor progression by causing cell cycle arrest and apoptosis in HL cell lines [262]. Additionally, IPI-145, an inhibitor of p110δ and p110γ isoforms of PI3K showed effective tolerability and rapid clinical responses in both B and T-cell lymphomas including NHL, CLL, MCL, HL

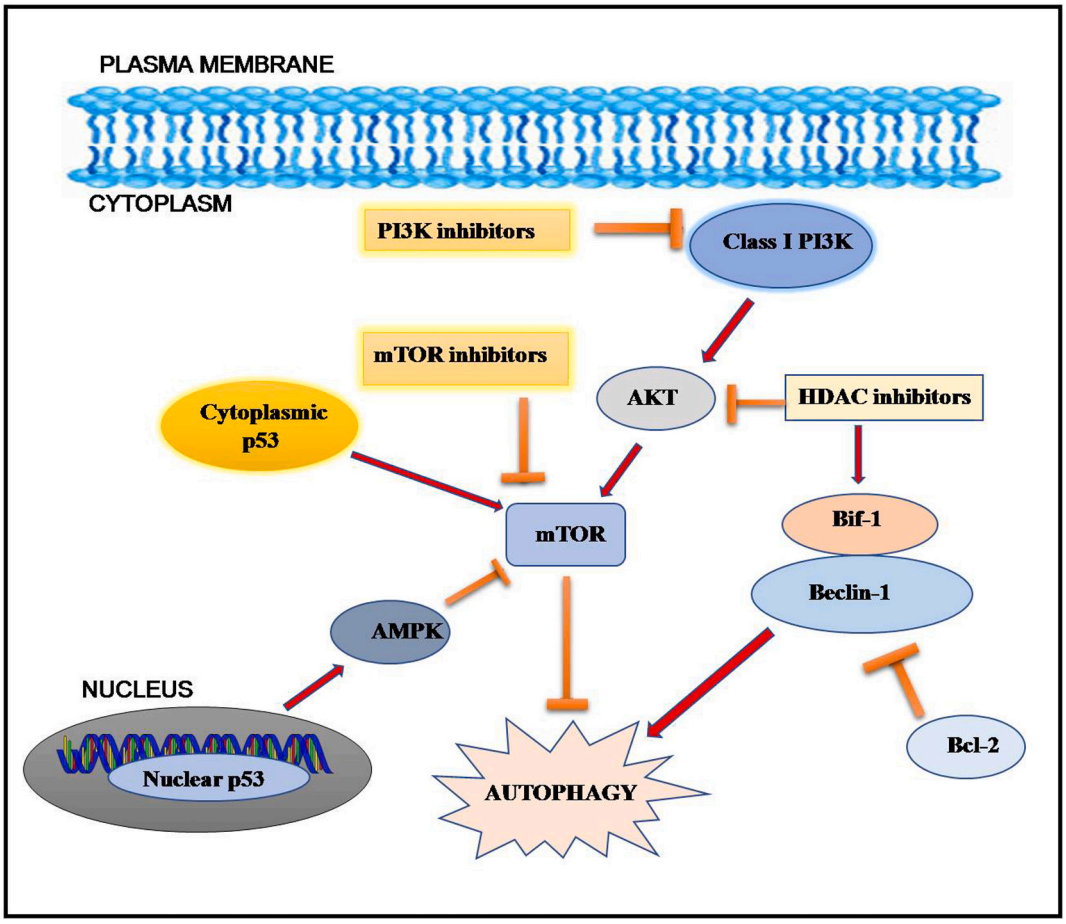

Fig. 5. Schematic representation of the autophagy signalling pathways involved in lymphoid malignancies. mTOR is the major pathway this is found to be associated with several lymphoid cancers. PI3K/Akt acts as a crucial upstream activator of mTOR. Activation of PI3K/Akt signalling network stimulates mTOR activation leading to decreased autophagic flux thereby promoting lymphoid tumorigenesis. Moreover, during starvation state, loss of Bif-1 accelerates lymphoma due to defect in generating autophagosome complex. In addition to this, activation of functional p53 pathway enables autophagy by downregulating AKT/mTOR pathway through the activation of AMPK. These autophagy related lymphoma networks can be exploited as probable drug targets for lymphoma treatment.

or T-cell lymphomas [263]. Furthermore, Rapamycin in association with other mTOR inhibitors including RTX, doxorubicin, vincristine, and bortezomib exerted a potent anti-tumor effect in vitro against several lymphoma cell lines [264]. Moreover, vorinostat, a member of histone deacetylase inhibitor (HDI), induces autophagy by upregulating the expression of ATG7 and Beclin-1 promoting the formation of ATG5-ATG12 complex and subsequently downregulating Akt/mTOR signalling pathway [265]. Furthermore, sorafenib, a multikinase inhibitor showed modest anti-tumor activity by inhibiting mTOR signalling in several lymphomas [266]. Also, CQ and HCQ are being applied in multiple tumor types [267]. However, the efficacy of these autophagic inhibitors in lymphoma malignancies is still under study.

11. Autophagy signalling in breast cancer

Breast cancer (BC) is the second major cause of death among women in United States and in the recent years, collaborative efforts have been taken for developing therapies for different types of breast cancers in an effective manner [268]. Radiation therapy, surgery and other therapeutic agents are the standard treatment regimen for patients with BC. Recent studies witnessed that the mortality rate of BC has been slowly declined due to the early diagnosis of the disease. It was also suggested that effective treatment options, novel target regimens and potent molecules are needed to eradicate BC [269]. Experimental evidences showed that autophagy has a considerable play in the growth, progression and BC response to chemotherapy [270]. Therefore, understanding the specific functions of autophagy in BC can revolutionize the field of research.

Beclin 1 is a tumor suppressor gene playing major role in breast cancer. The deletion of this gene at 17q21 chromosome for up to 40–75% causes sporadic human breast cancer while it was found in high levels in normal breast cells [271]. *Beclin 1* is co-deleted with BRCA1 which is being a primary mutation in breast cancer witnessing that *beclin 1* by itself is not a tumor suppressor gene [272]. *Beclin 1* overexpression in MCF7 breast cancer cell lines decline cell proliferation, in vitro clonogenicity and tumorigenesis [273]. *Beclin 1* interacts with Bcl-2 expression is major in BC tumorigenesis and low levels of *beclin 1* increase free Bcl-2 and an antiapoptotic response. This interaction of *beclin 1* with Bcl-2, on phosphorylation of *beclin 1* releases Bcl-2 and its proteins inducing autophagy [274].

Experimental evidences stated that downstream target of AKT, mTOR plays an important role in breast cancer stem cells (BCSC) wherein mTOR being the main key control point in autophagy and PI3K/AKT signalling also important in autophagic regulation [275]. Other pathways namely TGF-β, Wnt signalling, Notch signalling, hedgehog pathway and β-catenin are important regulators of autophagy. SMAD2/SMAD3 enhances the expression of TGF-β, eventually leading to autophagy regulation. Inhibition of Wnt signalling induces autophagy and even Notch and hedgehog pathway inhibition exerts the same function as Wnt signalling (Fig. 6) [276]. B-catenin suppresses the formation of autophagic vacuoles and expression of p62/SQSTM1 [277].

Fibrous sheath interacting protein 1 (FSIP1) is a cancer antigen

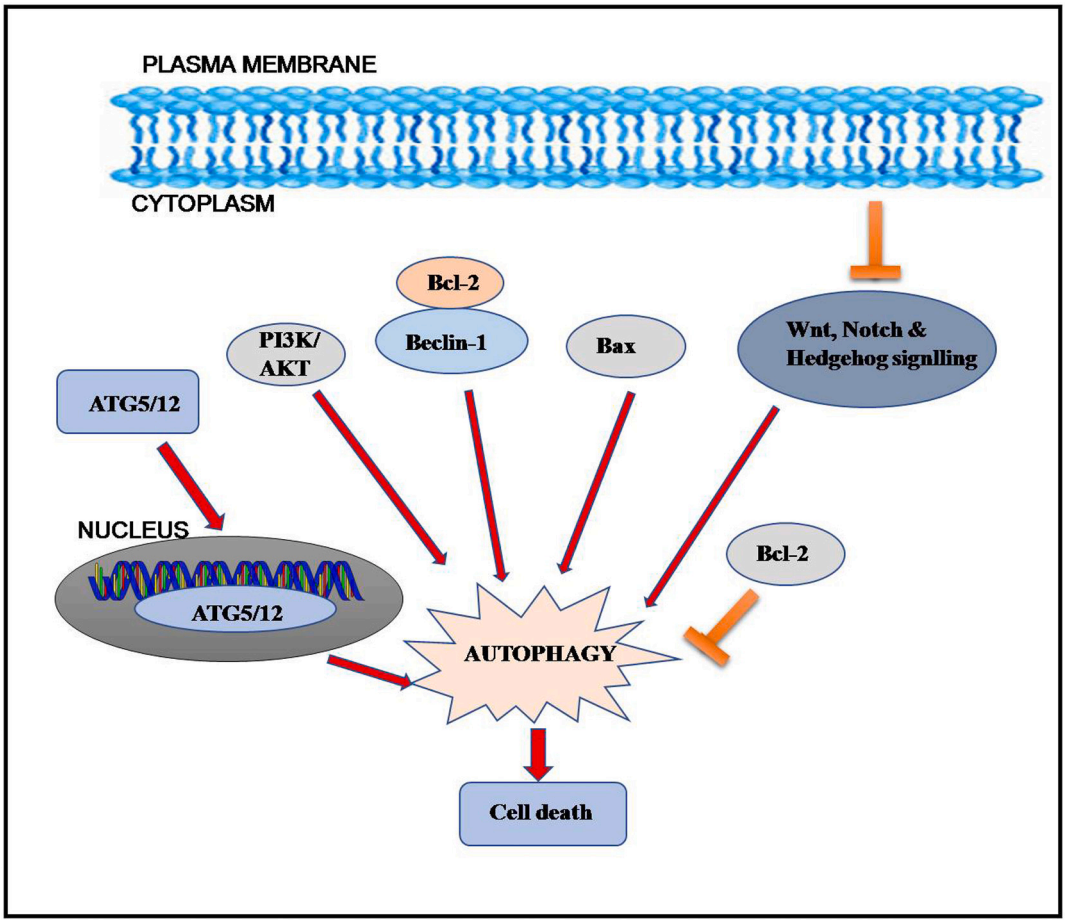

Fig. 6. Schematic representation of the autophagy signalling pathways involved in breast cancer. Autophagy in breast cancer is initiated by various signalling pathways namely PI3K/AKT, ATG5/12, Bax apoptotic proteins, Inhibition of three major pathways such as Wnt, notch and hedgehog signalling pathways induces autophagy. Beclin 1 interacts with Bcl-2 and activates autophagy. Phosphorylated form of beclin1 will not interact with Bcl-2, releases Bcl-2 inhibiting autophagy. Simultaneous activation of autophagy leads to cell death.

expressed in various cancer types namely breast cancers, non-small cell lung cancers and bladder cancers [278]. FSIP 1 expression is linked with higher invasiveness and poor prognosis in BC. FSIP1 interacts with HER2 which silences FSIP1 inhibiting proliferation and invasiveness in ER^+ and $HER2^+$ BC. Studies about FSIP1 can be an effective therapeutic target for ER^+ and $HER2^+$ BC. It is also expressed in triple-negative breast cancer but its role is not clear [279].

Chloroquine is an autophagy inhibitor, disrupts cancer stem cells through epigenetic regulation by modifying DNA methylation. It causes excessive DNA damage by enhancing oxidation in mitochondria and subsequently leads to cell death in triple-negative breast cancer stem cells [280].

12. Future perspectives

The divergent role of autophagy both in tumor progression and tumor suppression should be extensively uncovered to develop effective interventional strategies for cancer prevention and therapy. Since the contribution of autophagy in tumor is stage dependent, i.e., acting as tumor suppressor during initial stage and tumor promotor in advanced stage in cancer development, therapeutic approach should also be modified on the basis of cell context and stage of cancer [281]. Several questions needed to be answered to uncover mysteries associated with the paradoxical role of autophagy. Whether autophagic mechanism always promote tumorigenesis by providing energy and nutrients or it is only restricted to few cancer types is still needed to be known. So far it is identified that in several cancer types, autophagy assists the developing cancer by supplying metabolic demands and maintaining homeostatic microenvironment to sustain tumor growth [282]. However, several interventional approaches and autophagy inhibitor-based therapies are not effective enough in most of the cases (Table 1). Therefore, more detailed research is required for unravelling the autophagy regulation and its influence on different tissues, tumors and genes at the molecular level.

Available reports form preclinical and clinical trials indicates the possible utilization of autophagy as an anticancer therapy. In this context, optimal combination of autophagy inhibitor or inducer with chemotherapy or anti-cancer reagents can be an even more successful therapeutic strategy. Currently, several CQ and HCQ based autophagic inhibitors to suppress tumor progression are in clinical trials [299]. For example, in KRAS mutated cell lines, suppression of autophagy by CQ and 3-MA (3-Methyladenine) in trans-farnesylthiosalicylic acid (FTS)-treated cancer cells showed enhanced growth inhibition and apoptosis [300]. Combined administration of 3-Methyladenine (3-MA) and 2-(4-morpholinyl)-8-phenyl chromone (LY294002) provide inhibition of autophagy by suppressing the activity of PI3K, involved in the production of phosphatidylinositol (3,4,5)-triphosphate along with nucleation and extension of the phagophore [301]. Researchers have reported that pterostilbene in combination with 3-MA or BafA1 will enhance the efficacy of chemotherapeutic approaches in both chemo-sensitive and resistant lung cancer cells and in triple-negative breast cancer cells [302,303]. However, compelling evidences clearly indicates that inhibiting autophagy within the same cell population can differently affect the viability of cancer cells [304] (Table 2). Therefore, to better

Table 1
Autophagy inhibitors and their mechanism in targeting different cancer types.

Autophagy inhibitors	Mechanism	Targeting cancer cells	Inhibition stage	References
Chloroquine	Prevents autophagosomal fusion and degradation by increasing lysosomal pH	Breast cancer, NSCLC, PDAC, colorectal cancer, lymphomas	Late	[283–287]
Hydroxychloroquine	Disrupts lysosomal function and prevents autophagosome-lysosome fusion	Breast cancer, NSCLC, PDAC, colorectal cancer, lymphomas	Late	[288–290]
3-Methyladenine (3-MA)	Blocks autophagosome formation via the inhibition of PI3K	Breast cancer, colorectal cancer	Early	[291,292]
Bafilomycin A1	Acts as V-ATPase inhibitor and prevents autolysosome formation	Pancreatic cancer, human hepatocellular carcinoma, gastric cancer	Late	[293–295]
LY294002	PI3K inhibitor	Melanoma	Early	[296]
SBI-0206965	ULK1 inhibitor	Human glioblastoma and NSCLC	–	[297,298]

Table 2
Some of the autophagy inhibitors for lung, colon, pancreas, lymphoma and breast cancer in clinical trials.

Compound name[a]	Condition	Type	Institute/company/ brand name	Target(s)	FDA approved/ phase of development
Hydroxychloroquine and abemaciclib	Breast cancer (solid & advanced tumor)	Hydroxychloroquine-Autophagy inhibitor Abemaciclib-CDK4/6 inhibitor	Abramson Cancer Center of the University of Pennsylvania	Both are given in combination orally to target bone marrow disseminated tumor cells	Phase II trail
Abemaciclib and hydroxychloroquine	Hormone receptor positive (HR^+)/ Her2 negative breast cancer	Autophagy inhibitor	Medical College of Wisconsin	Abemaciclib synergizes with autophagy inhibitor hydroxychloroquine (HCQ/ Plaquenil), inducing apoptosis leading to tumor regression.	Phase I trail
Paricalcitol and hydroxychloroquine with gemcitabine and Nab-Paclitaxel	Advanced pancreatic cancer	Autophagy inhibitor	Emory University with National Cancer Institute	Paricalcitol blocks the signal in cancer cells and inhibits the growth and spreading of tumor. Hydroxycloroquine enhances standard chemotherapy activity on cancer cells and prevent its growth. Gemcitabine and nab-paclitaxel stop the growth of cancer cells by stopping them from dividing and growth	Phase II trail
Hydroxychloroquine and vorinostat [309]	Malignant solid tumors in colorectal cancer	Hydroxychloroquine-Autophagy inhibitor Vorinostat-histone deacetylase inhibitor	The University of Texas Health Science Center at San Antonio by Sukeshi Patel	Inhibits histone deacetylase in advanced solid tumors	Phase I trial

[a] Inhibitor clinical development information current as of Sep 2021from the United States National Institutes of health registry clinical trials and National Institute of health (available from: http://www.clinicaltrails.gov).

understand the role of autophagy in cancer progression and development, large-scale research is inevitable in the field of biochemistry, molecular biology and molecular oncology.

It is now clinically evident that the tumor-promoting role of autophagy supports cancer cell survival by providing nutrients, managing ROS and offering therapeutic resistance. However, the molecular mechanism that tumor cell employs to switch on high basal level expression of autophagy is still need to be elucidated. Also, few proteomic studies are concentrated in figuring out whether particular cargos that are selectively degraded are responsible for tumor growth. Therefore, major focus should be directed towards understanding the role of cargo receptors and selective autophagy. Furthermore, the dependence of tumor on autophagy for their survival should be clearly investigated by analysing the complexity of tumor-microenvironment interactions. In this context, cancer cell responds to hypoxic microenvironment by adapting their metabolic functions through several hypoxia-associated pathways including HIFs, UPR, mTOR and autophagy [305]. Part of the research are directed towards developing novel biomarkers of the basal autophagy level in tumors in order to discover new autophagy inhibition associated-anti-cancer therapeutic strategies [306,307]. Moreover, several studies now suggest that targeting selective autophagy would be a better therapeutic approach instead of concentrating in general autophagy components [308]. This is because, targeting general autophagy has been proven to be inadequate and risky, considering severity of the side effects observed in patients. However, it is necessary to mention that even targeting selective autophagy can elicit differential response on tumor progression, depending on the cell type and tumor stage.

Over the past few years, several researchers have elucidated multiple molecular mechanisms that interconnect autophagy and apoptosis and the crosstalk between them enabling coordinated regulation of degradation of cellular components in several cancer types. For example, BNIP3, BNIP3L/NIX, p53, ATG5, ATG3 and UVRAG are found to be involved in both autophagy and apoptotic cell death [32]. So far, conjectures have been made suggesting that their role may vary depending on the cancer cell type and future studies are required to confirm these speculations. However, unlike apoptosis, the role of autophagy appears to be diversified in cancer. Therefore, to address all the issues, more in vitro and in vivo clinical studies on detecting the role of autophagy in tumor initiation and progression is critical and immediately required for the development of anti-cancer drugs in current clinical research.

13. Conclusion

Autophagy is a dynamic cell survival pathway regulated by complex intracellular processes under conditions including nutrient starvation and the presence of damaged intracellular organelles and proteins. Although few intricate processes that regulate autophagy still remain a puzzle, the overall mechanism of macroautophagy has been extensively elucidated over the past few years. Moreover, the role of autophagy in cancer has been controversial in cell survival in the context of tumor initiation and progression. In addition, several in vitro and in vivo

studies conclude autophagy as a tumor suppressor during cancer initiation and tumor promoter in the advanced stage of cancer. However, preclinical studies conducted on defective RAS-induced malignant tumor clearly indicated that in most cases autophagy could function as a cell protective mechanism in numerous tumor types and can lead to its further development and metastasis depending on the cancer type. In particular, oncogenic KRAS-induced JNK activation upregulated the expression of ATG5 and ATG7 causing autophagy induction and subsequent cancer development. Therefore, approaches in inhibiting KRAS induced inhibition of cellular growth and increased apoptosis mediated cancer cell death.

Furthermore, several stress response mechanisms activated by hypoxia-tumor microenvironment converge on autophagy. The expression of key proteins including HIF-1, BNIP3 and BNIP3L are responsible for hypoxia-induced autophagy which plays a tumor protective role by reducing ROS production and maintain homeostasis. Therefore, manipulation of hypoxia-induced autophagy by using specific inhibitors could be a better therapeutic approach for cancer treatment. However, exact mechanism involved in regulating hypoxia-mediated selective autophagy is still need to elucidate. Apart from this, the role of selective autophagy components including mitophagy, pexophagy and ER-phagy and their tight regulation in cancer metabolism is emphasized in several studies. Selective autophagy, orchestrated by specific receptor molecules ensures tumor cell survival and mediates cancer homeostasis and development. Therefore, inhibition of selective autophagy in advanced tumors could lead to accumulation of misfolded proteins and oxidative stress which could result in cancer cell death via apoptosis and necrosis.

Finally, understanding the relationship between autophagy and cancer type specific autophagy inhibitors could produce promising effects on individual cancer types including lung, pancreas, colorectal, lymphomas, breast cancer and so on. However, the clinical data on autophagy inhibition in cancer patients is limited and future studies are needed to consider particular carcinomas individually in the aim to develop personalized anticancer therapies. Currently, only limited clinical trials on lung, pancreatic, melanoma, breast and prostate cancer are tested with CQ as a monotherapy. This is due to the fact that currently autophagy-specific modifiers that target multiple cellular pathways are scarce. Therefore, it is essential to design and synthesis novel autophagy modulators that are highly specific and selectively target particular tumor type. Although our knowledge on autophagy in the area of cancer have expanded rapidly in the last few decades, there are still several questions to be answered in the current research of autophagy. Overall, a wide range of studies concentrating on the role of autophagy in cancer is essential to fully elucidate the possibilities of autophagic modulation as anti-cancer therapy.

Declaration of competing interest

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.

Acknowledgement

The authors would like to acknowledge Department of Health Research for providing financial assistance to Dr. R.R. Rasmi under DHR-Young Scientist Scheme (Funding No: 12014/11/2018-HR/E-office:3151264). The authors are thankful to Dr. D. Brindha, Principal, PSG College of Arts & Science, Coimbatore for providing valuable support.

References

[1] D. Glick, S. Barth, K.F. Macleod, Autophagy: cellular and molecular mechanisms, J. Pathol. 221 (1) (2010) 3–12.
[2] Z. Yang, D.J. Klionsky, An overview of the molecular mechanism of autophagy, Curr. Top. Microbiol. Immunol. 335 (2009) 1–32.
[3] S. Jung, H. Jeong, S.W. Yu, Autophagy as a decisive process for cell death, Exp. Mol. Med. 52 (6) (2020) 921–930.
[4] M. Tsukada, Y. Ohsumi, Isolation and characterization of autophagy-defective mutants of Saccharomyces cerevisiae, FEBS Lett. 333 (1–2) (1993) 169–174.
[5] K. Abounit, T.M. Scarabelli, R.B. McCauley, Autophagy in mammalian cells, World J. Biol. Chem. 3 (1) (2012) 1–6.
[6] Z. Yang, D.J. Klionsky, Mammalian autophagy: core molecular machinery and signaling regulation, Curr. Opin. Cell Biol. 22 (2) (2010) 124–131.
[7] M. Thumm, R. Egner, B. Koch, M. Schlumpberger, M. Straub, M. Veenhuis, D. H. Wolf, Isolation of autophagocytosis mutants of Saccharomyces cerevisiae, FEBS Lett. 349 (2) (1994) 275–280.
[8] P.O. Seglen, P.B. Gordon, I. Holen, Non-selective autophagy, Semin. Cell Biol. 1 (6) (1990) 441–448.
[9] W. Li, P. He, Y. Huang, Y.-F. Li, J. Lu, M. Li, H. Kurihara, Z. Luo, T. Meng, M. Onishi, C. Ma, L. Jiang, Y. Hu, Q. Gong, D. Zhu, Y. Xu, R. Liu, L. Liu, C. Yi, Y. Zhu, N. Ma, K. Okamoto, Z. Xie, J. Liu, R.-R. He, D. Feng, Selective autophagy of intracellular organelles: recent research advances, Theranostics 11 (1) (2021) 222–256.
[10] S. Schuck, Microautophagy - distinct molecular mechanisms handle cargoes of many sizes, J. Cell Sci. 133 (17) (2020).
[11] Y. Feng, D. He, Z. Yao, D.J. Klionsky, The machinery of macroautophagy, Cell Res. 24 (1) (2014) 24–41.
[12] W. Li, M. Chen, E. Wang, L. Hu, M.J. Hawkesford, L. Zhong, Z. Chen, Z. Xu, L. Li, Y. Zhou, C. Guo, Y. Ma, Genome-wide analysis of autophagy-associated genes in foxtail millet (Setaria italica L.) and characterization of the function of SiATG8a in conferring tolerance to nitrogen starvation in rice, BMC Genomics 17 (1) (2016) 797.
[13] N. Mizushima, The role of the Atg1/ULK1 complex in autophagy regulation, Curr. Opin. Cell Biol. 22 (2) (2010) 132–139.
[14] D. Papinski, C. Kraft, Regulation of autophagy by signaling through the Atg1/ULK1 complex, J. Mol. Biol. 428 (9, Part A) (2016) 1725–1741.
[15] N. Hosokawa, T. Hara, T. Kaizuka, C. Kishi, A. Takamura, Y. Miura, S. Iemura, T. Natsume, K. Takehana, N. Yamada, J.L. Guan, N. Oshiro, N. Mizushima, Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy, Mol. Biol. Cell 20 (7) (2009) 1981–1991.
[16] A. Carrière, M. Cargnello, L.-A. Julien, H. Gao, É. Bonneil, P. Thibault, P.P. Roux, Oncogenic MAPK signaling stimulates mTORC1 activity by promoting RSK-mediated raptor phosphorylation, Curr. Biol. 18 (17) (2008) 1269–1277.
[17] F. Xu, L. Na, Y. Li, L. Chen, RETRACTED ARTICLE: roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours, Cell Biosci. 10 (1) (2020) 54.
[18] N. Mizushima, T. Noda, Y. Ohsumi, Apg16p is required for the function of the Apg12p-Apg5p conjugate in the yeast autophagy pathway, EMBO J. 18 (14) (1999) 3888–3896.
[19] Z. Xie, D.J. Klionsky, Autophagosome formation: core machinery and adaptations, Nat. Cell Biol. 9 (10) (2007) 1102–1109.
[20] M. Sakoh-Nakatogawa, K. Matoba, E. Asai, H. Kirisako, J. Ishii, N.N. Noda, F. Inagaki, H. Nakatogawa, Y. Ohsumi, Atg12–Atg5 conjugate enhances E2 activity of Atg3 by rearranging its catalytic site, Nat. Struct. Mol. Biol. 20 (4) (2013) 433–439.
[21] Y. Ichimura, T. Kirisako, T. Takao, Y. Satomi, Y. Shimonishi, N. Ishihara, N. Mizushima, I. Tanida, E. Kominami, M. Ohsumi, T. Noda, Y. Ohsumi, A ubiquitin-like system mediates protein lipidation, Nature 408 (6811) (2000) 488–492.
[22] Y. Kabeya, N. Mizushima, T. Ueno, A. Yamamoto, T. Kirisako, T. Noda, E. Kominami, Y. Ohsumi, T. Yoshimori, LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing, EMBO J. 19 (21) (2000) 5720–5728.
[23] N. Mizushima, D.J. Klionsky, Protein turnover via autophagy: implications for metabolism, Annu. Rev. Nutr. 27 (2007) 19–40.
[24] T. Yorimitsu, D.J. Klionsky, Autophagy: molecular machinery for self-eating, Cell Death Differ. 12 (Suppl 2) (2005) 1542–1552.
[25] A. Massey, R. Kiffin, A.M. Cuervo, Pathophysiology of chaperone-mediated autophagy, Int. J. Biochem. Cell Biol. 36 (12) (2004) 2420–2434.
[26] U. Bandyopadhyay, S. Kaushik, L. Varticovski, A.M. Cuervo, The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane, Mol. Cell. Biol. 28 (18) (2008) 5747–5763.
[27] J.F. Dice, Peptide sequences that target cytosolic proteins for lysosomal proteolysis, Trends Biochem. Sci. 15 (8) (1990) 305–309.
[28] B. Levine, G. Kroemer, Autophagy in the pathogenesis of disease, Cell 132 (1) (2008) 27–42.
[29] Z.J. Yang, C.E. Chee, S. Huang, F.A. Sinicrope, The role of autophagy in cancer: therapeutic implications, Mol. Cancer Ther. 10 (9) (2011) 1533–1541.
[30] B. Levine, D.J. Klionsky, Development by self-digestion: molecular mechanisms and biological functions of autophagy, Dev. Cell 6 (4) (2004) 463–477.
[31] D. Denton, S. Nicolson, S. Kumar, Cell death by autophagy: facts and apparent artefacts, Cell Death Differ. 19 (1) (2012) 87–95.
[32] M. Su, Y. Mei, S. Sinha, Role of the crosstalk between autophagy and apoptosis in cancer, J. Oncol. 2013 (2013), 102735.
[33] Y. Xi, J.S. Dhaliwal, M. Ceizar, M. Vaculik, K.L. Kumar, D.C. Lagace, Knockout of Atg5 delays the maturation and reduces the survival of adult-generated neurons in the hippocampus, Cell Death Dis. 7 (3) (2016), e2127.
[34] M. Condello, E. Pellegrini, M. Caraglia, S. Meschini, Targeting autophagy to overcome human diseases, Int. J. Mol. Sci. 20 (3) (2019) 725.
[35] E. White, R.S. DiPaola, The double-edged sword of autophagy modulation in cancer, Clin. Cancer Res. 15 (17) (2009) 5308–5316.

[36] B.J. Altman, J.C. Rathmell, Metabolic stress in autophagy and cell death pathways, Cold Spring Harb. Perspect. Biol. 4 (9) (2012), a008763.
[37] R. Mathew, C.M. Karp, B. Beaudoin, N. Vuong, G. Chen, H.Y. Chen, K. Bray, A. Reddy, G. Bhanot, C. Gelinas, R.S. Dipaola, V. Karantza-Wadsworth, E. White, Autophagy suppresses tumorigenesis through elimination of p62, Cell 137 (6) (2009) 1062–1075.
[38] S. Choudhury, V.K. Kolukula, A. Preet, C. Albanese, M.L. Avantaggiati, Dissecting the pathways that destabilize mutant p53: the proteasome or autophagy? Cell Cycl. (Georgetown, Tex.) 12 (7) (2013) 1022–1029.
[39] M. Athar, C.A. Elmets, L. Kopelovich, Pharmacological activation of p53 in cancer cells, Curr. Pharm. Des. 17 (6) (2011) 631–639.
[40] X. Qu, J. Yu, G. Bhagat, N. Furuya, H. Hibshoosh, A. Troxel, J. Rosen, E. L. Eskelinen, N. Mizushima, Y. Ohsumi, G. Cattoretti, B. Levine, Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene, J. Clin. Invest. 112 (12) (2003) 1809–1820.
[41] A. Takamura, M. Komatsu, T. Hara, A. Sakamoto, C. Kishi, S. Waguri, Y. Eishi, O. Hino, K. Tanaka, N. Mizushima, Autophagy-deficient mice develop multiple liver tumors, Genes Dev. 25 (8) (2011) 795–800.
[42] S. He, Z. Zhao, Y. Yang, D. O'Connell, X. Zhang, S. Oh, B. Ma, J.H. Lee, T. Zhang, B. Varghese, J. Yip, S. Dolatshahi Pirooz, M. Li, Y. Zhang, G.M. Li, S. Ellen Martin, K. Machida, C. Liang, Truncating mutation in the autophagy gene UVRAG confers oncogenic properties and chemosensitivity in colorectal cancers, Nat. Commun. 6 (2015) 7839.
[43] Y. Takahashi, D. Coppola, N. Matsushita, H.D. Cualing, M. Sun, Y. Sato, C. Liang, J.U. Jung, J.Q. Cheng, J.J. Mulé, W.J. Pledger, H.-G. Wang, Bif-1 interacts with beclin 1 through UVRAG and regulates autophagy and tumorigenesis, Nat. Cell Biol. 9 (10) (2007) 1142–1151.
[44] G.Y. Liou, P. Storz, Reactive oxygen species in cancer, Free Radic. Res. 44 (5) (2010) 479–496.
[45] L. Poillet-Perez, G. Despouy, R. Delage-Mourroux, M. Boyer-Guittaut, Interplay between ROS and autophagy in cancer cells, from tumor initiation to cancer therapy, Redox Biol. 4 (2015) 184–192.
[46] Y. Avalos, J. Canales, R. Bravo-Sagua, A. Criollo, S. Lavandero, A.F.G. Quest, Tumor suppression and promotion by autophagy, Biomed. Res. Int. 2014 (2014), 603980.
[47] S.K. Bhutia, S. Mukhopadhyay, N. Sinha, D.N. Das, P.K. Panda, S.K. Patra, T. K. Maiti, M. Mandal, P. Dent, X.-Y. Wang, S.K. Das, D. Sarkar, P.B. Fisher, Autophagy: cancer's friend or foe? Adv. Cancer Res. 118 (2013) 61–95.
[48] K. Degenhardt, R. Mathew, B. Beaudoin, K. Bray, D. Anderson, G. Chen, C. Mukherjee, Y. Shi, C. Gélinas, Y. Fan, D.A. Nelson, S. Jin, E. White, Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis, Cancer Cell. 10 (1) (2006) 51–64.
[49] J.D. Rabinowitz, E. White, Autophagy and metabolism, Science (New York, N.Y.) 330 (6009) (2010) 1344–1348.
[50] Z. Lu, R.Z. Luo, Y. Lu, X. Zhang, Q. Yu, S. Khare, R.C. Bast, The tumor suppressor gene ARHI regulates autophagy and tumor dormancy in human ovarian cancer cells, J. Clin. Invest. 118 (12) (2008) 3917–3929.
[51] L. Galluzzi, E.H. Baehrecke, A. Ballabio, P. Boya, J.M.Bravo-San Pedro, F. Cecconi, Molecular definitions of autophagy and related processes, EMBO J 36 (13) (2017) 1811–1836.
[52] H. Guo, M. Chitiprolu, L. Roncevic, C. Javalet, F.J. Hemming, M.T. Trung, Atg5 disassociates the V, Dev. Cell 43 (6) (2017) 716–730.
[53] J. Colicelli, Human RAS superfamily proteins and related GTPases 2004 (250) (2004), RE13.
[54] I.M. Ahearn, K. Haigis, D. Bar-Sagi, M.R. Philips, Regulating the regulator: post-translational modification of RAS, Nat. Rev. Mol. Cell Biol. 13 (1) (2011) 39–51.
[55] B. Margolis, E.Y. Skolnik, Activation of Ras by receptor tyrosine kinases, J. Am. Soc. Nephrol. 5 (6) (1994) 1288–1299.
[56] M.M. McKay, D.K. Morrison, Integrating signals from RTKs to ERK/MAPK, Oncogene 26 (22) (2007) 3113–3121.
[57] L.A. Quilliam, R. Khosravi-Far, S.Y. Huff, C.J. Der, Guanine nucleotide exchange factors: activators of the Ras superfamily of proteins, Bioessays 17 (5) (1995) 395–404.
[58] C. Herrmann, Ras–effector interactions: after one decade, Curr. Opin. Struct. Biol. 13 (1) (2003) 122–129.
[59] J. Cherfils, M. Zeghouf, Regulation of small GTPases by GEFs, GAPs, and GDIs, Physiol. Rev. 93 (1) (2013) 269–309.
[60] J.J. Harvey, An unidentified virus which causes the rapid production of tumours in mice, Nature 204 (1964) 1104–1105.
[61] A. Fernandez-Medarde, E. Santos, Ras in cancer and developmental diseases, Genes Cancer 2 (3) (2011) 344–358.
[62] M.P. Quinlan, J. Settleman, Isoform-specific ras functions in development and cancer, Future Oncol. 5 (1) (2009) 105–116.
[63] J. Downward, Targeting RAS signalling pathways in cancer therapy, Nat. Rev. Cancer 3 (1) (2003) 11–22.
[64] S.Y. Wu, S.-H. Lan, D.-E. Cheng, W.-K. Chen, C.-H. Shen, Y.-R. Lee, R. Zuchini, H.-S. Liu, Ras-related tumorigenesis is suppressed by BNIP3-mediated autophagy through inhibition of cell proliferation, Neoplasia (New York, N.Y.) 13 (12) (2011) 1171–1182.
[65] S. Erlich, L. Mizrachy, O. Segev, L. Lindenboim, O. Zmira, S. Adi-Harel, J. A. Hirsch, R. Stein, R. Pinkas-Kramarski, Differential interactions between beclin 1 and Bcl-2 family members, Autophagy 3 (6) (2007) 561–568.
[66] Z. Jiang, F. Yu, M. Li, Upregulation of BCL2 19 kD protein-interacting protein 3 (BNIP3) is predictive of unfavorable prognosis in uveal melanoma, medical science monitor, Int. J. Clin. Exp. Med. 24 (2018) 4711–4717.
[67] L. Sun, T. Li, Q. Wei, Y. Zhang, X. Jia, Z. Wan, L. Han, Upregulation of BNIP3 mediated by ERK/HIF-1α pathway induces autophagy and contributes to anoikis resistance of hepatocellular carcinoma cells, Future Oncol. 10 (8) (2014) 1387–1398.
[68] J.Y. Byun, C.H. Yoon, S. An, I.C. Park, C.M. Kang, M.J. Kim, S.J. Lee, The Rac1/MKK7/JNK pathway signals upregulation of Atg5 and subsequent autophagic cell death in response to oncogenic ras, Carcinogenesis 30 (11) (2009) 1880–1888.
[69] Y.Y. Zhou, Y. Li, W.-Q. Jiang, L.-F. Zhou, MAPK/JNK signaling: a potential autophagy regulation pathway, Biosci. Rep. 35 (2015).
[70] S. Furuta, E. Hidaka, A. Ogata, S. Yokota, T. Kamata, Ras is involved in the negative control of autophagy through the class I PI3-kinase, Oncogene 23 (22) (2004) 3898–3904.
[71] E. Schmukler, Y. Kloog, R. Pinkas-Kramarski, Ras and autophagy in cancer development and therapy, Oncotarget 5 (3) (2014) 577.
[72] M.J. Kim, S.J. Woo, C.H. Yoon, J.S. Lee, S. An, Y.H. Choi, S.G. Hwang, G. Yoon, S. J. Lee, Involvement of autophagy in oncogenic K-ras-induced malignant cell transformation, J. Biol. Chem. 286 (15) (2011) 12924–12932.
[73] Y. Wang, X.D. Wang, E. Lapi, A. Sullivan, W. Jia, Y.W. He, I. Ratnayaka, S. Zhong, R.D. Goldin, C.G. Goemans, A.M. Tolkovsky, X. Lu, Autophagic activity dictates the cellular response to oncogenic RAS, Proc. Natl. Acad. Sci. U. S. A. 109 (33) (2012) 13325–13330.
[74] S. Yang, X. Wang, G. Contino, M. Liesa, E. Sahin, H. Ying, A. Bause, Y. Li, J. M. Stommel, G. Dell'antonio, J. Mautner, G. Tonon, M. Haigis, O.S. Shirihai, C. Doglioni, N. Bardeesy, A.C. Kimmelman, Pancreatic cancers require autophagy for tumor growth, Genes Dev. 25 (7) (2011) 717–729.
[75] J.Y. Guo, E. White, Autophagy is required for mitochondrial function, lipid metabolism, growth, and fate of KRAS(G12D)-driven lung tumors, Autophagy 9 (10) (2013) 1636–1638.
[76] P.S. Chen, W.-T. Chiu, P.-L. Hsu, S.-C. Lin, I.C. Peng, C.-Y. Wang, S.-J. Tsai, Pathophysiological implications of hypoxia in human diseases, J. Biomed. Sci. 27 (1) (2020) 63.
[77] G.L. Semenza, Hypoxia, clonal selection, and the role of HIF-1 in tumor progression, Crit. Rev. Biochem. Mol. Biol. 35 (2) (2000) 71–103.
[78] R.G. Rampling, A.D. Cruickshank, S.A. Lewis, P.Workman Fitzsimmons, Direct measurement of pO2 distribution and bioreductive enzymes in human malignant brain tumors, Int. J. Radiat. Oncol. Biol. Phys. 29 (3) (1994) 427–431.
[79] A.C. Koong, E.Y. Chen, A.J. Giaccia, Hypoxia causes the activation of nuclear factor kappa B through the phosphorylation of I kappa B alpha on tyrosine residues, Cancer Res. 54 (6) (1994) 1425–1430.
[80] E. Minet, T. Arnould, G. Michel, I. Roland, D. Mottet, M. Raes, J. Remacle, C. Michiels, ERK activation upon hypoxia: involvement in HIF-1 activation, FEBS Lett. 468 (1) (2000) 53–58.
[81] F. Agani, B.H. Jiang, Oxygen-independent regulation of HIF-1: novel involvement of PI3K/AKT/mTOR pathway in cancer, Curr. Cancer Drug Targets 13 (3) (2013) 245–251.
[82] B. Muz, P. de la Puente, F. Azab, A.K. Azab, The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy, Hypoxia (Auckland, N.Z.) 3 (2015) 83–92.
[83] M. Quintero, N. Mackenzie, P.A. Brennan, Hypoxia-inducible factor 1 (HIF-1) in cancer, Eur. J. Surg. Oncol. 30 (5) (2004) 465–468.
[84] R.K. Bruick, S.L. McKnight, A conserved family of prolyl-4-hydroxylases that modify HIF, Science 294 (5545) (2001) 1337–1340.
[85] P.H. Maxwell, M.S. Wiesener, G.W. Chang, S.C. Clifford, E.C. Vaux, M. E. Cockman, C.C. Wykoff, C.W. Pugh, E.R. Maher, P.J. Ratcliffe, The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis, Nature 399 (6733) (1999) 271–275.
[86] D.A. Chan, P.D. Sutphin, N.C. Denko, A.J. Giaccia, Role of prolyl hydroxylation in oncogenically stabilized hypoxia-inducible factor-1alpha, J. Biol. Chem. 277 (42) (2002) 40112–40117.
[87] V.L. Dengler, M. Galbraith, J.M. Espinosa, Transcriptional regulation by hypoxia inducible factors, Crit. Rev. Biochem. Mol. Biol. 49 (1) (2014) 1–15.
[88] E.M. Conway, D. Collen, P. Carmeliet, Molecular mechanisms of blood vessel growth, Cardiovasc. Res. 49 (3) (2001) 507–521.
[89] B.L. Krock, N. Skuli, M.C. Simon, Hypoxia-induced angiogenesis: good and evil, Genes Cancer 2 (12) (2011) 1117–1133.
[90] P. Carmeliet, R.K. Jain, Molecular mechanisms and clinical applications of angiogenesis, Nature 473 (7347) (2011) 298–307.
[91] Y. Fang, J. Tan, Q. Zhang, Signaling pathways and mechanisms of hypoxia-induced autophagy in the animal cells, Cell Biol. Int. 39 (8) (2015) 891–898.
[92] J. Zhang, P.A. Ney, Role of BNIP3 and NIX in cell death, autophagy, and mitophagy, Cell Death Differ. 16 (7) (2009) 939–946.
[93] J. Zhou, C. Li, W. Yao, M.C. Alsiddig, L. Huo, H. Liu, Y.L. Miao, Hypoxia-inducible factor-1α-dependent autophagy plays a role in glycolysis switch in mouse granulosa cells, Biol. Reprod. 99 (2) (2018) 308–318.
[94] A.R. Schneider, H. Younis, J.S. Gutkind, Hypoxia-induced energy stress inhibits the mTOR pathway by activating an AMPK/REDD1 signaling axis in head and neck squamous cell carcinoma, Neoplasia 10 (11) (2008) 1295–1302.
[95] X. Qian, X. Li, Z. Lu, Protein kinase activity of the glycolytic enzyme PGK1 regulates autophagy to promote tumorigenesis, Autophagy 13 (2017).
[96] L. Qin, Y. Tian, Z. Yu, D. Shi, J. Wang, C. Zhang, R. Peng, X. Chen, C. Liu, Y. Chen, W. Huang, W. Deng, Targeting PDK1 with dichloroacetophenone to inhibit acute myeloid leukemia (AML) cell growth, Oncotarget 7 (2) (2015).
[97] J. Cosin-Roger, S. Simmen, H. Melhem, K. Atrott, I. Frey-Wagner, M. Hausmann, C. de Vallière, M.R. Spalinger, P. Spielmann, R.H. Wenger, J. Zeitz, S.R. Vavricka, G. Rogler, P.A. Ruiz, Hypoxia ameliorates intestinal inflammation through

NLRP3/mTOR downregulation and autophagy activation, Nat. Commun. 8 (1) (2017) 98.
[98] S. Chipurupalli, E. Kannan, V. Tergaonkar, R. D'Andrea, N. Robinson, Hypoxia induced ER stress response as an adaptive mechanism in cancer, Int. J. Mol. Sci. 20 (3) (2019) 749.
[99] X. Li, K. Zhang, Z. Li, Unfolded protein response in cancer: the physician's perspective, J. Hematol. Oncol. 4 (2011) 8.
[100] M. Wang, R.J. Kaufman, The impact of the endoplasmic reticulum protein-folding environment on cancer development, Nat. Rev. Cancer 14 (9) (2014) 581–597.
[101] H.P. Harding, Y. Zhang, A. Bertolotti, H. Zeng, D. Ron, Perk is essential for translational regulation and cell survival during the unfolded protein response, Mol. Cell 5 (5) (2000) 897–904.
[102] K.M. Rouschop, T. van den Beucken, L. Dubois, H. Niessen, J. Bussink, K. Savelkouls, T. Keulers, H. Mujcic, W. Landuyt, J.W. Voncken, P. Lambin, A. J. van der Kogel, M. Koritzinsky, B.G. Wouters, The unfolded protein response protects human tumor cells during hypoxia through regulation of the autophagy genes MAP1LC3B and ATG5, J. Clin. Invest. 120 (1) (2010) 127–141.
[103] R. Wu, Q.H. Zhang, Y.J. Lu, K. Ren, G.H. Yi, Involvement of the IRE1α-XBP1 pathway and XBP1s-dependent transcriptional reprogramming in metabolic diseases, DNA Cell Biol. 34 (1) (2015) 6–18.
[104] X. Chen, D. Iliopoulos, Q. Zhang, Q. Tang, M.B. Greenblatt, M. Hatziapostolou, E. Lim, W.L. Tam, M. Ni, Y. Chen, J. Mai, H. Shen, D.Z. Hu, S. Adoro, B. Hu, M. Song, C. Tan, M.D. Landis, M. Ferrari, S.J. Shin, M. Brown, J.C. Chang, X. S. Liu, L.H. Glimcher, XBP1 promotes triple-negative breast cancer by controlling the HIF1α pathway, Nature 508 (7494) (2014) 103–107.
[105] W.W. Wheaton, N.S. Chandel, Hypoxia. 2. Hypoxia regulates cellular metabolism, Am. J. Physiol. Cell Physiol. 300 (3) (2011) C385–C393.
[106] S. Wilkinson, ER-phagy: shaping up and destressing the endoplasmic reticulum, FEBS J. 286 (14) (2019) 2645–2663.
[107] K.S. Nakahira, M. Cloonan, K. Mizumura, A.M.K. Choi, S.W. Ryter, Autophagy: a crucial moderator of redox balance, inflammation, and apoptosis in lung disease, Antioxid. Redox Signal. 20 (3) (2014) 474–494.
[108] H. Weidberg, E. Shvets, T. Shpilka, F. Shimron, V. Shinder, Z. Elazar, LC3 and GATE-16/GABARAP subfamilies are both essential yet act differently in autophagosome biogenesis, EMBO J. 29 (11) (2010) 1792–1802.
[109] W.X. Ding, X.M. Yin, Mitophagy: mechanisms, pathophysiological roles, and analysis, Biol. Chem. 393 (7) (2012) 547–564.
[110] D.B. Zorov, M. Juhaszova, S.J. Sollott, Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release, Physiol. Rev. 94 (3) (2014) 909–950.
[111] I.E. Clark, M.W. Dodson, C. Jiang, J.H. Cao, J.R. Huh, J.H. Seol, S.J. Yoo, B. A. Hay, M. Guo, Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin, Nature 441 (7097) (2006) 1162–1166.
[112] C. Meissner, H. Lorenz, A. Weihofen, D. Selkoe, M. Lemberg, The mitochondrial intramembrane protease PARL cleaves human PINK1 to regulate PINK1 trafficking, J. Neurochem. 117 (2011) 856–867.
[113] G. Shi, G.A. McQuibban, "The mitochondrial rhomboid protease PARL is regulated by PDK2 to integrate mitochondrial quality control and metabolism, Cell Rep. 18 (6) (2017) 1458–1472.
[114] M.E. Gegg, ME, J.M. Cooper, K.-Y. Chau, M. Rojo, A.H.V. Schapira, J.-W. Taanman, Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy, Hum. Mol. Genet. 19 (24) (2010) 4861–4870.
[115] G.E. Choi, H.J. Lee, C.W. Chae, J.H. Cho, Y.H. Jung, J.S. Kim, S.Y. Kim, J.R. Lim, H.J. Han, BNIP3L/NIX-mediated mitophagy protects against glucocorticoid-induced synapse defects, Nat. Commun. 12 (1) (2021) 487.
[116] L.P. Poole, K.F. Macleod, Mitophagy in tumorigenesis and metastasis, Cell Mol. Life Sci. 78 (8) (2021) 3817–3851.
[117] M. Fujiwara, H. Marusawa, H.Q. Wang, A. Iwai, K. Ikeuchi, Y. Imai, A. Kataoka, N. Nukina, R. Takahashi, T. Chiba, Parkin as a tumor suppressor gene for hepatocellular carcinoma, Oncogene 27 (46) (2008) 6002–6011.
[118] J.Y. Chang, H.S. Yi, H.W. Kim, M. Shong, Dysregulation of mitophagy in carcinogenesis and tumor progression, Biochim. Biophys. Acta Bioenerg. 1858 (8) (2017) 633–640.
[119] H. Zhang, M. Bosch-Marce, L.A. Shimoda, Y.S. Tan, J.H. Baek, J.B. Wesley, F. J. Gonzalez, G.L. Semenza, Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia, J. Biol. Chem. 283 (16) (2008) 10892–10903.
[120] M. Vara-Perez, B. Felipe-Abrio, P. Agostinis, Mitophagy in cancer: a tale of adaptation, Cells 8 (5) (2019) 493.
[121] G.L. Semenza, Hypoxia-inducible factor 1: regulator of mitochondrial metabolism and mediator of ischemic preconditioning, Biochim. Biophys. Acta 1813 (7) (2011) 1263–1268.
[122] D.F. Wallace, The regulation of iron absorption and homeostasis, Clin. Biochem. Rev. 37 (2) (2016) 51–62.
[123] C. Li, Y. Zhang, X. Cheng, H. Yuan, S. Zhu, J. Liu, Q. Wen, Y. Xie, J. Liu, G. Kroemer, D.J. Klionsky, M.T. Lotze, H.J. Zeh, R. Kang, D. Tang, PINK1 and PARK2 suppress pancreatic tumorigenesis through control of mitochondrial iron-mediated immunometabolism, Dev. Cell 46 (4) (2018) 441–455, e448.
[124] H. Hou, P. Er, J. Cheng, X. Chen, X. Ding, Y. Wang, X. Chen, Z. Yuan, Q. Pang, P. Wang, D. Qian, High expression of FUNDC1 predicts poor prognostic outcomes and is a promising target to improve chemoradiotherapy effects in patients with cervical cancer, Cancer Med. 6 (8) (2017) 1871–1881.
[125] J. Liu, Z. Chen, J. Guo, L. Wang, X. Liu, Ambra1 induces autophagy and desensitizes human prostate cancer cells to cisplatin, Biosci. Rep. 39 (8) (2019), BSR20170770.
[126] R. Cristofani, M. Montagnani Marelli, M.E. Cicardi, F. Fontana, M. Marzagalli, P. Limonta, A. Poletti, R.M. Moretti, Dual role of autophagy on docetaxel-sensitivity in prostate cancer cells, Cell Death Differ. 9 (9) (2018) 889.
[127] T.W. Kim, S.J. Lee, Y.J. Park, S.Y. Park, B.M. Oh, Y.S. Park, B.Y. Kim, Y.H. Lee, H. J. Cho, S.R. Yoon, Y.K. Cho, H.G. Lee, Opa-interacting protein 5 modulates docetaxel-induced cell death via regulation of mitophagy in gastric cancer, Tumour Biol. 39 (10) (2017), 1010428317733985.
[128] H.K. Delille, N.A. Bonekamp, M. Schrader, Peroxisomes and disease - an overview, Int. J. Biomed. Sci. 2 (4) (2006) 308–314.
[129] H. Zhang, Z. Wang, J. Huang, J. Cao, Y. Zhou, J. Zhou, A novel thioredoxin-dependent peroxiredoxin (TPx-Q) plays an important role in defense against oxidative stress and is a possible drug target in babesia microti, Frontiers in veterinaryScience 7 (76) (2020).
[130] K. Germain, P.K. Kim, Pexophagy: a model for selective autophagy, Int. J. Mol. Sci. 21 (2) (2020) 578.
[131] R. Vasko, B.B. Ratliff, S. Bohr, E. Nadel, J. Chen, S. Xavier, P. Chander, M. S. Goligorsky, Endothelial peroxisomal dysfunction and impaired pexophagy promotes oxidative damage in lipopolysaccharide-induced acute kidney injury, Antioxid. Redox Signal. 19 (3) (2013) 211–230.
[132] W.H. Kunau, A. Hartig, Peroxisome biogenesis in Saccharomyces cerevisiae, Antonie Van Leeuwenhoek 62 (1–2) (1992) 63–78.
[133] J.C. Farré, R. Manjithaya, R.D. Mathewson, S. Subramani, PpAtg30 tags peroxisomes for turnover by selective autophagy, Dev. Cell 14 (3) (2008) 365–376.
[134] A.M. Motley, J.M. Nuttall, E.H. Hettema, Atg36: the Saccharomyces cerevisiae receptor for pexophagy, Autophagy 8 (11) (2021) 1680–1681.
[135] S. Meguro, X. Zhuang, H. Kirisako, H. Nakatogawa, Pex3 confines pexophagy receptor activity of Atg36 to peroxisomes by regulating Hrr25-mediated phosphorylation and proteasomal degradation, J. Biol. Chem. 295 (48) (2020) 16292–16298.
[136] D.S. Jo, N.Y. Park, D.H. Cho, Peroxisome quality control and dysregulated lipid metabolism in neurodegenerative diseases, Exp. Mol. Med. 52 (9) (2020) 1486–1495.
[137] P.K. Kim, D.W. Hailey, R.T. Mullen, J. Lippincott-Schwartz, Ubiquitin signals autophagic degradation of cytosolic proteins and peroxisomes, Proc. Natl. Acad. Sci. U. S. A. 105 (52) (2008) 20567–20574.
[138] W. Wang, S. Subramani, Role of PEX5 ubiquitination in maintaining peroxisome dynamics and homeostasis, Cell Cycle(Georgetown, Tex.) 16 (21) (2017) 2037–2045.
[139] B.H. Chi, S. Jin, Y.M. Whang, S.H. Ahn, J.D. Choi, S.Y. Lee, I.H. Chang, MP44-16 NBR1 and KIF14 are the mTOR pathway downstream to prdedict the recurrence in non-muscle invasive low grade urothelil carcinom of the bladder, Urol. J. 197 (4S) (2017) e570.
[140] H. Ruan, X. Li, H. Yang, Z. Song, J. Tong, Q. Cao, K. Wang, W. Xiao, H. Xiao, X. Chen, G. Xu, L. Bao, Z. Xiong, C. Yuan, L. Liu, Y. Qu, W. Hu, Y. Gao, Z. Ru, K. Chen, X. Zhang, Enhanced expression of caveolin-1 possesses diagnostic and prognostic value and promotes cell migration, invasion and sunitinib resistance in the clear cell renal cell carcinoma, Exp. Cell Res. 358 (2) (2017) 269–278.
[141] M. Cai, X. Sun, W. Wang, Z. Lian, P. Wu, S. Han, H. Chen, P. Zhang, Disruption of peroxisome function leads to metabolic stress, mTOR inhibition, and lethality in liver cancer cells, Cancer Lett. 421 (2018) 82–93.
[142] M.S. Dahabieh, Z. Ha, E. Di Pietro, J.N. Nichol, A.M. Bolt, C. Goncalves, D. Dupéré-Richer, F. Pettersson, K.K. Mann, N.E. Braverman, S.V. Del Rincón, W. H. Miller Jr., Peroxisomes protect lymphoma cells from HDAC inhibitor-mediated apoptosis, Cell Death Differ. 24 (11) (2017) 1912–1924.
[143] A.M. Weber, A.J. Ryan, ATM and ATR as therapeutic targets in cancer, Pharmacol. Ther. 149 (2015) 124–138.
[144] M. Antonelli, F. Strappazzon, I. Arisi, R. Brandi, M. D'Onofrio, M. Sambucci, G. Manic, I. Vitale, D. Barilà, V. Stagni, ATM kinase sustains breast cancer stem-like cells by promoting ATG4C expression and autophagy, Oncotarget 8 (13) (2017) 21692–21709.
[145] M.H. Haque, V. Gopalan, K.W. Chan, M.J. Shiddiky, R.A. Smith, A.K. Lam, Identification of novel FAM134B (JK1) mutations in oesophageal squamous cell carcinoma, Sci. Rep. 6 (2016) 29173.
[146] M. Cai, X. Sun, W. Wang, Z. Lian, P. Wu, S. Han, H. Chen, P. Zhang, Disruption of peroxisome function leads to metabolic stress, mTOR inhibition, and lethality in liver cancer cells, Cancer Lett. 421 (2018) 82–93.
[147] I. Daskalaki, I. Gkikas, N. Tavernarakis, Hypoxia and selective autophagy in cancer development and therapy, Front. Cell Dev. Biol. 6 (2018) 104.
[148] M.J. Phillips, G.K. Voeltz, Structure and function of ER membrane contact sites with other organelles, Nat. Rev. Mol. Cell Biol. 17 (2) (2016) 69–82.
[149] J.H. Lin, P. Walter, T.S.B. Yen, Endoplasmic reticulum stress in disease pathogenesis, Ann. Rev. Pathol. 3 (2008) 399–425.
[150] M. Hamasaki, T. Noda, M. Baba, Y. Ohsumi, Starvation triggers the delivery of the endoplasmic reticulum to the vacuole via autophagy in yeast, Traffic 6 (1) (2005) 56–65.
[151] A. Khaminets, T. Heinrich, M. Mari, P. Grumati, A.K. Huebner, M. Akutsu, L. Liebmann, A. Stolz, S. Nietzsche, N. Koch, M. Mauthe, I. Katona, B. Qualmann, J. Weis, F. Reggiori, I. Kurth, C.A. Hübner, I. Dikic, Regulation of endoplasmic reticulum turnover by selective autophagy, Nature 522 (7556) (2015) 354–358.
[152] P. Grumati, G. Morozzi, S. Hölper, M. Mari, M.-L.I. Harwardt, R. Yan, S. Müller, F. Reggiori, M. Heilemann, I. Dikic, Full length RTN3 regulates turnover of tubular endoplasmic reticulum via selective autophagy, eLife 6 (2017), e25555.
[153] J.E. Wu, Z. Zhang, Z. Teng, S.W. Abdullah, S. Sun, H. Guo, Sec62 regulates endoplasmic reticulum stress and autophagy balance to affect foot-and-mouth disease virus replication, Front. Cell. Infect. Microbiol. 11 (796) (2021).

[154] I. Dikic, Open questions: why should we care about ER-phagy and ER remodelling? BMC Biol. 16 (1) (2018) 131.
[155] M.D. Smith, M.E. Harley, A.J. Kemp, J. Wills, M. Lee, M. Arends, A. von Kriegsheim, C. Behrends, S. Wilkinson, CCPG1 is a non-canonical autophagy cargo receptor essential for ER-phagy and pancreatic ER proteostasis, Dev. Cell. 44 (2) (2018) 217–232, e211.
[156] Q. Chen, Y. Xiao, P. Chai, P. Zheng, J. Teng, J. Chen, ATL3 is a tubular ER-phagy receptor for GABARAP-mediated selective autophagy, Curr. Biol. 29 (5) (2019) 846–855, e846.
[157] S. Wilkinson, Emerging principles of selective ER autophagy, J. Mol. Biol. 432 (1) (2020) 185–205.
[158] M.H. Haque, V. Gopalan, K.W. Chan, M.J. Shiddiky, R.A. Smith, A.K. Lam, Identification of novel FAM134B (JK1) mutations in oesophageal squamous cell carcinoma, Sci. Rep. 6 (2016) 29173.
[159] F. Islam, V. Gopalan, J. Vider, R. Wahab, F. Ebrahimi, C.T. Lu, K. Kasem, A.K. Y. Lam, MicroRNA-186-5p overexpression modulates colon cancer growth by repressing the expression of the FAM134B tumour inhibitor, Exp. Cell Res. 357 (2) (2017) 260–270.
[160] K.P. Ng, A. Manjeri, K.L. Lee, W. Huang, S.Y. Tan, C.T. Chuah, L. Poellinger, S. T. Ong, Physiologic hypoxia promotes maintenance of CML stem cells despite effective BCR-ABL1 inhibition, Blood 123 (21) (2014) 3316–3326.
[161] M. Greiner, B. Kreutzer, V. Jung, R. Grobholz, A. Hasenfus, R.F. Stöhr, L. Tornillo, J. Dudek, M. Stöckle, G. Unteregger, J. Kamradt, B. Wullich, R. Zimmermann, Silencing of the SEC62 gene inhibits migratory and invasive potential of various tumor cells, Int. J. Cancer 128 (10) (2011) 2284–2295.
[162] M. Linxweiler, F. Bochen, B. Schick, S. Wemmert, B. Al Kadah, M. Greiner, A. Hasenfus, R.M. Bohle, I. Juhasz-Böss, E.F. Solomayer, Z.F. Takacs, Identification of SEC62 as a potential marker for 3q amplification and cellular migration in dysplastic cervical lesions, BMC Cancer 16 (1) (2016) 676.
[163] A.E. Rizzardi, N.K. Rosener, J.S. Koopmeiners, R. Isaksson Vogel, G.J. Metzger, C. L. Forster, L.O. Marston, J.R. Tiffany, J.B. McCarthy, E.A. Turley, C.A. Warlick, J. C. Henriksen, S.C. Schmechel, Evaluation of protein biomarkers of prostate cancer aggressiveness, BMC Cancer 14 (2014) 244.
[164] N. Gavert, A. Shvab, M. Sheffer, A. Ben-Shmuel, G. Haase, E. Bakos, E. Domany, A. Ben-Ze'ev, C-kit is suppressed in human colon cancer tissue and contributes to L1-mediated metastasis, Cancer Res. 73 (18) (2013) 5754–5763.
[165] L. Yang, N. Wei, L. Wang, X. Wang, Q.H. Liu, miR-498 promotes cell proliferation and inhibits cell apoptosis in retinoblastoma by directly targeting CCPG1, Childs Nerv. Syst. 34 (3) (2018) 417–422.
[166] B. Li, W. Feng, O. Luo, T. Xu, Y. Cao, H. Wu, D. Yu, Y. Ding, Development and validation of a three-gene prognostic signature for patients with hepatocellular carcinoma, Sci. Rep. 7 (1) (2017) 5517.
[167] X. Huang, H. Yang, Y. Zhou, J. Liu, B. Yin, X. Peng, B. Qiang, J. Yuan, Overexpression of human reticulon 3 (hRTN3) in astrocytoma, Clin. Neuropathol. 23 (1) (2004) 1–7.
[168] J. Malhotra, S.K. Jabbour, J. Aisner, Current state of immunotherapy for non-small cell lung cancer, Transl. Lung Cancer Res. 6 (2) (2017) 196–211.
[169] G. Liu, F. Pei, F. Yang, L. Li, A.D. Amin, S. Liu, J.R. Buchan, W.C. Cho, Role of autophagy and apoptosis in non-small-cell lung cancer, Int. J. Mol. Sci. 18 (2) (2017).
[170] E. Tasdemir, M. Chiara Maiuri, E. Morselli, A. Criollo, M. D'Amelio, M. Djavaheri-Mergny, F. Cecconi, N. Tavernarakis, G. Kroemer, A dual role of p53 in the control of autophagy, Autophagy 4 (6) (2008) 810–814.
[171] M. Wang, Y. Xu, J. Liu, J. Ye, W. Yuan, H. Jiang, Z. Wang, H. Jiang, J. Wan, Recent insights into the biological functions of sestrins in health and disease, Cell. Physiol. Biochem. 43 (5) (2017) 1731–1741.
[172] E. Morselli, S. Shen, C. Ruckenstuhl, M.A. Bauer, G. Mariño, L. Galluzzi, A. Criollo, M. Michaud, M.C. Maiuri, T. Chano, F. Madeo, G. Kroemer, p53 inhibits autophagy by interacting with the human ortholog of yeast Atg17, RB1CC1/FIP200, Cell Cycle 10 (16) (2011) 2763–2769.
[173] M. Mrakovcic, L.F. Fröhlich, "p53-mediated molecular control of autophagy in tumor cells, Biomolecules 8 (2) (2018) 14.
[174] S.A. Ahrendt, Y. Hu, M. Buta, M.P. McDermott, N. Benoit, S.C. Yang, L. Wu, D. Sidransky, p53 mutations and survival in stage I non-small-cell lung cancer: results of a prospective study, JNCI 95 (13) (2003) 961–970.
[175] H. Shen, C.G. Maki, Pharmacologic activation of p53 by small-molecule MDM2 antagonists, Curr. Pharm. Des. 17 (6) (2011) 560–568.
[176] D.L. Gibbons, L.A. Byers, J.M. Kurie, Smoking, p53 mutation, and lung cancer, Mol. Cancer Res. 12 (1) (2014) 3–13.
[177] M. Robles-Flores, A.P. Moreno-Londoño, M.C. Castañeda-Patlán, Signaling pathways involved in nutrient sensing control in cancer stem cells: an overview, Front. Endocrinol. 12 (2021).
[178] J. Kim, M. Kundu, B. Viollet, K.L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, Nat. Cell Biol. 13 (2) (2011) 132–141.
[179] Y.Y. Zhou, Y. Li, W.Q. Jiang, L.F. Zhou, MAPK/JNK signalling: a potential autophagy regulation pathway, Biosci. Rep. 35 (3) (2015).
[180] B. Jonchère, A. Bélanger, C. Guette, B. Barré, O. Coqueret, STAT3 as a new autophagy regulator, Jakstat 2 (3) (2013), e24353.
[181] R.A. Saxton, D.M. Sabatini, mTOR signaling in growth, metabolism, and disease, Cell 168 (6) (2017) 960–976.
[182] M. Paquette, L. El-Houjeiri, A. Pause, mTOR pathways in cancer and autophagy, Cancers (Basel) 10 (1) (2018).
[183] M. Jhanwar-Uniyal, A.G. Amin, J.B. Cooper, K. Das, M.H. Schmidt, R. Murali, Discrete signaling mechanisms of mTORC1 and mTORC2: connected yet apart in cellular and molecular aspects, Adv. Biol. Regul. 64 (2017) 39–48.
[184] M. Laplante, David M. Sabatini, mTOR signaling in growth control and disease, Cell 149 (2) (2012) 274–293.
[185] S. Alers, A.S. Löffler, S. Wesselborg, B. Stork, Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks, Mol. Cell. Biol. 32 (1) (2012) 2–11.
[186] The cancer genome atlas network, Comprehensive genomic characterization of squamous cell lung cancers, Nature 489 (7417) (2012) 519–525.
[187] A. Plotnikov, E. Zehorai, S. Procaccia, R. Seger, The MAPK cascades: signaling components, nuclear roles and mechanisms of nuclear translocation, Biochim. Biophys. Acta, Mol. Cell Res. 1813 (9) (2011) 1619–1633.
[188] Y.-Y. Zhou, Y. Li, W.-Q. Jiang, L.-F. Zhou, MAPK/JNK signalling: a potential autophagy regulation pathway, Biosci. Rep. 35 (3) (2015).
[189] H. Kiu, S.E. Nicholson, Biology and significance of the JAK/STAT signalling pathways, Growth Factors 30 (2) (2012) 88–106.
[190] L. You, Z. Wang, H. Li, J. Shou, Z. Jing, J. Xie, X. Sui, H. Pan, W. Han, The role of STAT3 in autophagy, Autophagy 11 (5) (2015) 729–739.
[191] S. Herzig, R.J. Shaw, AMPK: guardian of metabolism and mitochondrial homeostasis, Nat. Rev. Mol. Cell Biol. 19 (2) (2018) 121–135.
[192] J.W. Lee, S. Park, Y. Takahashi, H.G. Wang, The association of AMPK with ULK1 regulates autophagy, PLoS One 5 (11) (2010), e15394.
[193] C. He, D.J. Klionsky, Regulation mechanisms and signaling pathways of autophagy, Annu. Rev. Genet. 43 (2009) 67–93.
[194] A.B. Singh, EGFR-signaling and autophagy: how they fit in the cancer landscape, J. Adenocarcinoma 1 (2) (2016).
[195] Y. Wei, Z. Zou, N. Becker, M. Anderson, R. Sumpter, G. Xiao, L. Kinch, P. Koduru, C.S. Christudass, R.W. Veltri, N.V. Grishin, M. Peyton, J. Minna, G. Bhagat, B. Levine, EGFR-mediated beclin 1 phosphorylation in autophagy suppression, tumor progression, and tumor chemoresistance, Cell 154 (6) (2013) 1269–1284.
[196] J.P. Decuypere, J.B. Parys, G. Bultynck, Regulation of the autophagic bcl-2/beclin 1 interaction, Cells 1 (3) (2012) 284–312.
[197] T.C. Liu, X. Jin, Y. Wang, K. Wang, Role of epidermal growth factor receptor in lung cancer and targeted therapies, Am. J. Cancer Res. 7 (2) (2017) 187–202.
[198] S.Y. Ha, S.-J. Choi, J.H. Cho, H.J. Choi, J. Lee, K. Jung, D. Irwin, X. Liu, M.E. Lira, M. Mao, H.K. Kim, Y.S. Choi, Y.M. Shim, W.Y. Park, Y.-L. Choi, J. Kim, Lung cancer in never-smoker asian females is driven by oncogenic mutations, most often involving EGFR, Oncotarget 6 (7) (2005) 5465–5474.
[199] Y. Yarden, The EGFR family and its ligands in human cancer. Signalling mechanisms and therapeutic opportunities, Eur. J. Cancer 37 (Suppl 4) (2001) S3–S8.
[200] E.S. Henson, S.B. Gibson, Surviving cell death through epidermal growth factor (EGF) signal transduction pathways: implications for cancer therapy, Cell. Signal. 18 (12) (2006) 2089–2097.
[201] J. Yan, H. Yang, G. Wang, L. Sun, Y. Zhou, Y. Guo, Z. Xi, X. Jiang, Autophagy augmented by troglitazone is independent of EGFR transactivation and correlated with AMP-activated protein kinase signaling, Autophagy 6 (1) (2010) 67–73.
[202] X. Sui, N. Kong, M. Zhu, X. Wang, F. Lou, W. Han, H. Pan, Cotargeting EGFR and autophagy signaling: a novel therapeutic strategy for non-small-cell lung cancer, Mol. Clin. Oncol. 2 (1) (2014) 8–12.
[203] Y. Yu, S.M. Fan, Y.C. Ye, S. Tashiro, S. Onodera, T. Ikejima, The tyrphostin AG1478 augments oridonin-induced A431 cell apoptosis by blockage of JNK MAPK and enhancement of oxidative stress, Free Radic. Res. 46 (11) (2012) 1393–1405.
[204] L. Regales, M.N. Balak, Y. Gong, K. Politi, A. Sawai, C. Le, J.A. Koutcher, D. B. Solit, N. Rosen, M.F. Zakowski, W. Pao, Development of new mouse lung tumor models expressing EGFR T790M mutants associated with clinical resistance to kinase inhibitors, PLoS One 2 (8) (2007), e810.
[205] F.F. Moreira-Leite, L.R. Harrison, A. Mironov, R.A. Roberts, C. Dive, Inducible EGFR T790M-mediated gefitinib resistance in non-small cell lung cancer cells does not modulate sensitivity to PI103 provoked autophagy, J. Thorac. Oncol. 5 (6) (2010) 765–777.
[206] W. Han, H. Pan, Y. Chen, J. Sun, Y. Wang, J. Li, W. Ge, L. Feng, X. Lin, X. Wang, X. Wang, H. Jin, EGFR tyrosine kinase inhibitors activate autophagy as a cytoprotective response in human lung cancer cells, PLoS One 6 (6) (2011), e18691.
[207] M. Orth, P. Metzger, S. Gerum, J. Mayerle, G. Schneider, C. Belka, M. Schnurr, K. Lauber, Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches, Radiat. Oncol. 14 (1) (2019) 141.
[208] K. Barrera, A. Stanek, K. Okochi, Z. Niewiadomska, C. Mueller, P. Ou, D. John, A. E. Alfonso, S. Tenner, C. Huan, Acinar cell injury induced by inadequate unfolded protein response in acute pancreatitis, World J. Gastrointest. Pathophysiol. 9 (2) (2018) 37–46.
[209] L. Antonucci, J.B. Fagman, J.Y. Kim, J. Todoric, I. Gukovsky, M. Mackey, M. H. Ellisman, M. Karin, Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress, Proc. Natl. Acad. Sci. U. S. A. 112 (45) (2015) E6166–E6174.
[210] A. Ropolo, D. Grasso, R. Pardo, M.L. Sacchetti, C. Archange, A. Lo Re, M. Seux, J. Nowak, C.D. Gonzalez, J.L. Iovanna, M.I. Vaccaro, The pancreatitis-induced vacuole membrane protein 1 triggers autophagy in mammalian cells, J. Biol. Chem. 282 (51) (2007) 37124–37133.
[211] M.I. Molejon, A. Ropolo, M.I. Vaccaro, VMP1 is a new player in the regulation of the autophagy-specific phosphatidylinositol 3-kinase complex activation, Autophagy 9 (6) (2013) 933–935.
[212] A.E. Lo Ré, M.G. Fernández-Barrena, L.L. Almada, L.D. Mills, S.F. Elsawa, G. Lund, A. Ropolo, M.I. Molejon, M.I. Vaccaro, M.E. Fernandez-Zapico, Novel AKT1-GLI3-

VMP1 pathway mediates KRAS oncogene-induced autophagy in cancer cells, J. Biol. Chem. 287 (30) (2012) 25325–25334.
[213] H. Solomon, R. Brosh, Y. Buganim, V. Rotter, Inactivation of the p53 tumor suppressor gene and activation of the ras oncogene: cooperative events in tumorigenesis, Discov. Med. 9 (48) (2010) 448–454.
[214] S. Weissmueller, E. Manchado, M. Saborowski, E. Wagenblast, C.A. Davis, S. H. Moon, N.T. Pfister, D.F. Tschaharganeh, T. Kitzing, D. Aust, E.K. Markert, J. Wu, S.M. Grimmond, C. Pilarsky, C. Prives, A.V. Biankin, S.W. Lowe, J.P. t. Morris, Mutant p53 drives pancreatic cancer metastasis through cell-autonomous PDGF receptor β signaling, Cell 157 (2) (2014) 382–394.
[215] A.C. Hoffmann, R. Mori, D. Vallbohmer, J. Brabender, E. Klein, U. Drebber, S. E. Baldus, J. Cooc, M. Azuma, R. Metzger, A.H. Hoelscher, K.D. Danenberg, K. L. Prenzel, P.V. Danenberg, High expression of HIF1a is a predictor of clinical outcome in patients with pancreatic ductal adenocarcinomas and correlated to PDGFA, VEGF, and bFGF, Neoplasia 10 (7) (2008) 674–679.
[216] G. Bellot, R. Garcia-Medina, P. Gounon, J. Chiche, D. Roux, J. Pouysségur, N. M. Mazure, Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains, Mol. Cell. Biol. 29 (10) (2009) 2570–2581.
[217] H. Wu, S. Huang, Z. Chen, W. Liu, X. Zhou, D. Zhang, Hypoxia-induced autophagy contributes to the invasion of salivary adenoid cystic carcinoma through the HIF-1α/BNIP3 signaling pathway, Mol. Med. Rep. 12 (5) (2015) 6467–6474.
[218] S. Fujii, S. Mitsunaga, M. Yamazaki, T. Hasebe, G. Ishii, M. Kojima, T. Kinoshita, T. Ueno, H. Esumi, A. Ochiai, Autophagy is activated in pancreatic cancer cells and correlates with poor patient outcome, Cancer Sci. 99 (9) (2008) 1813–1819.
[219] S. Joshi, S. Kumar, M.P. Ponnusamy, S.K. Batra, Hypoxia-induced oxidative stress promotes MUC4 degradation via autophagy to enhance pancreatic cancer cells survival, Oncogene 35 (45) (2016) 5882–5892.
[220] R.M. Perera, S. Stoykova, B.N. Nicolay, K.N. Ross, J. Fitamant, M. Boukhali, J. Lengrand, V. Deshpande, M.K. Selig, C.R. Ferrone, J. Settleman, G. Stephanopoulos, N.J. Dyson, R. Zoncu, S. Ramaswamy, W. Haas, N. Bardeesy, Transcriptional control of autophagy-lysosome function drives pancreatic cancer metabolism, Nature 524 (7565) (2015) 361–365.
[221] A. Roczniak-Ferguson, C.S. Petit, F. Froehlich, S. Qian, J. Ky, B. Angarola, T. C. Walther, S.M. Ferguson, The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis, Sci. Signal. 5 (228) (2012) ra42.
[222] B.M. Wolpin, D.A. Rubinson, X. Wang, J.A. Chan, J.M. Cleary, P.C. Enzinger, C. S. Fuchs, N.J. McCleary, J.A. Meyerhardt, K. Ng, D. Schrag, A.L. Sikora, B. A. Spicer, L. Killion, H. Mamon, A.C. Kimmelman, Phase II and pharmacodynamic study of autophagy inhibition using hydroxychloroquine in patients with metastatic pancreatic adenocarcinoma, Oncologist 19 (6) (2014) 637–638.
[223] M.C. Yang, H.C. Wang, Y.C. Hou, H.L. Tung, T.J. Chiu, Y.S. Shan, Blockade of autophagy reduces pancreatic cancer stem cell activity and potentiates the tumoricidal effect of gemcitabine, Mol. Cancer 14 (2015) 179.
[224] D.L. Papademetrio, S.L. Lompardía, T. Simunovich, S. Costantino, C.Y. Mihalez, V. Cavaliere, É. Álvarez, Inhibition of survival pathways MAPK and NF-kB triggers apoptosis in pancreatic ductal adenocarcinoma cells via suppression of autophagy, Target. Oncol. 11 (2) (2016) 183–195.
[225] R.L. Siegel, K.D. Miller, S.A. Fedewa, D.J. Ahnen, R.G.S. Meester, A. Barzi, A. Jemal, Colorectal cancer statistics, 2017, CA Cancer J. Clin. 67 (3) (2017) 177–193.
[226] E.R. Fearon, Molecular genetics of colorectal cancer, Annu. Rev. Pathol. 6 (2011) 479–507.
[227] D.H. Cho, Y.K. Jo, S.C. Kim, I.J. Park, J.C. Kim, Down-regulated expression of ATG5 in colorectal cancer, Anticancer Res. 32 (9) (2012) 4091–4096.
[228] M. Niklaus, O. Adams, S. Berezowska, I. Zlobec, F. Graber, J. Slotta-Huspenina, U. Nitsche, R. Rosenberg, M.P. Tschan, R. Langer, Expression analysis of LC3B and p62 indicates intact activated autophagy is associated with an unfavorable prognosis in colon cancer, Oncotarget 8 (33) (2017) 54604–54615.
[229] T. Xiao, W. Zhu, W. Huang, S.S. Lu, X.H. Li, Z.Q. Xiao, H. Yi, RACK1 promotes tumorigenicity of colon cancer by inducing cell autophagy, Cell Death Dis. 9 (12) (2018) 1148.
[230] C.H. Ahn, E.G. Jeong, J.W. Lee, M.S. Kim, S.H. Kim, S.S. Kim, N.J. Yoo, S.H. Lee, Expression of beclin-1, an autophagy-related protein, in gastric and colorectal cancers, APMIS 115 (12) (2007) 1344–1349.
[231] S. Alves, L. Castro, M.S. Fernandes, R. Francisco, P. Castro, M. Priault, S. R. Chaves, M.P. Moyer, C. Oliveira, R. Seruca, M. Côrte-Real, M.J. Sousa, A. Preto, Colorectal cancer-related mutant KRAS alleles function as positive regulators of autophagy, Oncotarget 6 (31) (2015) 30787–30802.
[232] R. Scherz-Shouval, H. Weidberg, C. Gonen, S. Wilder, Z. Elazar, M. Oren, p53-dependent regulation of autophagy protein LC3 supports cancer cell survival under prolonged starvation, Proc. Natl. Acad. Sci. U. S. A. 107 (43) (2010) 18511–18516.
[233] M.G. Francipane, E. Lagasse, mTOR pathway in colorectal cancer: an update, Oncotarget 5 (1) (2014) 49–66.
[234] J. Kim, M. Kundu, B. Viollet, K.L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, Nat. Cell Biol. 13 (2) (2011) 132–141.
[235] J. Brugarolas, K. Lei, R.L. Hurley, B.D. Manning, J.H. Reiling, E. Hafen, L. A. Witters, L.W. Ellisen, W.G. Kaelin Jr., Regulation of mTOR function in response to hypoxia by REDD1 and the TSC1/TSC2 tumor suppressor complex, Genes Dev. 18 (23) (2004) 2893–2904.
[236] A.J. Meijer, S. Lorin, E.F. Blommaart, P. Codogno, Regulation of autophagy by amino acids and MTOR-dependent signal transduction, Amino Acids 47 (10) (2015) 2037–2063.
[237] M.M. Schroll, X. Liu, S.K. Herzog, S.B. Skube, A.B. Hummon, Nutrient restriction of glucose or serum results in similar proteomic expression changes in 3D colon cancer cell cultures, Nutr. Res. 36 (10) (2016) 1068–1080.
[238] M.M. Schroll, G.J. LaBonia, K.R. Ludwig, A.B. Hummon, Glucose restriction combined with autophagy inhibition and chemotherapy in HCT 116 spheroids decreases cell clonogenicity and viability regulated by tumor suppressor genes, J. Proteome Res. 16 (8) (2017) 3009–3018.
[239] J.Y. Guo, H. Y. Chen, R. Mathew, J. Fan, A. M. Strohecker, G. Karsli-Uzunbas, J. J. Kamphorst, G. Chen, J. M. Lemons, V. Karantza, H. A. Coller, R. S. Dipaola, C. Gelinas, J. D.
[240] J. Hoellenriegel, S.A. Meadows, M. Sivina, W.G. Wierda, H. Kantarjian, M. J. Keating, N. Giese, S. O'Brien, A. Yu, L.L. Miller, B.J. Lannutti, J.A. Burger, The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia, Blood 118 (13) (2011) 3603–3612.
[241] J. Kim, S. Choi, J.O. Kim, K.K. Kim, Autophagy-mediated upregulation of cytoplasmic claudin 1 stimulates the degradation of SQSTM1/p62 under starvation, Biochem. Biophys. Res. Commun. 496 (1) (2018) 159–166.
[242] X. Xue, S.K. Ramakrishnan, Y.M. Shah, Activation of HIF-1α does not increase intestinal tumorigenesis, Am. J. Physiol. Gastrointest. Liver Physiol. 307 (2) (2014) G187–G195.
[243] Y. Dong, Y. Wu, G.L. Zhao, Z.Y. Ye, C.G. Xing, X.D. Yang, Inhibition of autophagy by 3-MA promotes hypoxia-induced apoptosis in human colorectal cancer cells, Eur. Rev. Med. Pharmacol. Sci. 23 (3) (2019) 1047–1054.
[244] J.C. Landry, Y. Feng, R.S. Prabhu, S.J. Cohen, C.A. Staley, R. Whittington, E. R. Sigurdson, H. Nimeiri, U. Verma, A.B. Benson, Phase II trial of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: 5-year clinical outcomes ECOG-ACRIN cancer research group E3204, Oncologist 20 (6) (2015) 615–616.
[245] S. Patel, V. Hurez, S.T. Nawrocki, M. Goros, J. Michalek, J. Sarantopoulos, T. Curiel, D. Mahalingam, Vorinostat and hydroxychloroquine improve immunity and inhibit autophagy in metastatic colorectal cancer, Oncotarget 7 (37) (2016) 59087–59097.
[246] M. Pierdominici, C. Barbati, M. Vomero, S.L. Locatelli, C. Carlo-Stella, E. Ortona, W. Malorni, Autophagy as a pathogenic mechanism and drug target in lymphoproliferative disorders, FASEB J. 28 (2) (2014) 524–535.
[247] E.S. Jaffe, The 2008 WHO classification of lymphomas: implications for clinical practice and translational research, Hematol. Am. Soc. Hematol. Educ. Program (2009) 523–531.
[248] S. Zada, J.S. Hwang, M. Ahmed, T.H. Lai, T.M. Pham, O. Elashkar, D.R. Kim, Cross talk between autophagy and oncogenic signaling pathways and implications for cancer therapy, Biochim. Biophys. Acta Rev. Cancer 1876 (1) (2021), 188565.
[249] J. Iqbal, C. Kucuk, R.J. Deleeuw, G. Srivastava, W. Tam, H. Geng, D. Klinkebiel, J. K. Christman, K. Patel, K. Cao, L. Shen, K. Dybkaer, I.F. Tsui, H. Ali, N. Shimizu, W.Y. Au, W.L. Lam, W.C. Chan, Genomic analyses reveal global functional alterations that promote tumor growth and novel tumor suppressor genes in natural killer-cell malignancies, Leukemia 23 (6) (2009) 1139–1151.
[250] J.G. Foster, M.D. Blunt, E. Carter, S.G. Ward, Inhibition of PI3K signaling spurs new therapeutic opportunities in inflammatory/autoimmune diseases and hematological malignancies, Pharmacol. Rev. 64 (4) (2012) 1027–1054.
[251] G.V. Georgakis, Y. Li, G.Z. Rassidakis, L.J. Medeiros, G.B. Mills, A. Younes, Inhibition of the phosphatidylinositol-3 kinase/Akt promotes G1 cell cycle arrest and apoptosis in hodgkin lymphoma, Br. J. Haematol. 132 (4) (2006) 503–511.
[252] L.A. Leslie, A. Younes, Targeting oncogenic and epigenetic survival pathways in lymphoma, Leuk. Lymphoma 54 (11) (2013) 2365–2376.
[253] J. Dal Col, P. Zancai, L. Terrin, M. Guidoboni, M. Ponzoni, A. Pavan, M. Spina, S. Bergamin, S. Rizzo, U. Tirelli, A. De Rossi, C. Doglioni, R. Dolcetti, Distinct functional significance of akt and mTOR constitutive activation in mantle cell lymphoma, Blood 111 (10) (2008) 5142–5151.
[254] L. Leseux, S.M. Hamdi, T. Al Saati, F. Capilla, C. Recher, G. Laurent, C. Bezombes, Syk-dependent mTOR activation in follicular lymphoma cells, Blood 108 (13) (2006) 4156–4162.
[255] L. Leseux, G. Laurent, C. Laurent, M. Rigo, A. Blanc, D. Olive, C. Bezombes, PKC zeta mTOR pathway: a new target for rituximab therapy in follicular lymphoma, Blood 111 (1) (2008) 285–291.
[256] W.Y. Shi, D. Xiao, L. Wang, L.H. Dong, Z.X. Yan, Z.X. Shen, S.J. Chen, Y. Chen, W. L. Zhao, Therapeutic metformin/AMPK activation blocked lymphoma cell growth via inhibition of mTOR pathway and induction of autophagy, Cell Death Dis. 3 (3) (2012), e275.
[257] J. Kim, G. Yang, Y. Kim, J. Kim, J. Ha, AMPK activators: mechanisms of action and physiological activities, Exp. Mol. Med. 48 (4) (2016) e224.
[258] H. Tagawa, S. Ikeda, K. Sawada, Role of microRNA in the pathogenesis of malignant lymphoma, Cancer Sci. 104 (7) (2013) 801–809.
[259] A. Cimmino, G.A. Calin, M. Fabbri, M.V. Iorio, M. Ferracin, M. Shimizu, S. E. Wojcik, R.I. Aqeilan, S. Zupo, M. Dono, L. Rassenti, H. Alder, S. Volinia, C. G. Liu, T.J. Kipps, M. Negrini, C.M. Croce, miR-15 and miR-16 induce apoptosis by targeting BCL2, Proc. Natl. Acad. Sci. U. S. A. 102 (39) (2005) 13944–13949.
[260] V. Olive, M.J. Bennett, J.C. Walker, C. Ma, I. Jiang, C. Cordon-Cardo, Q.J. Li, S. W. Lowe, G.J. Hannon, L. He, miR-19 is a key oncogenic component of mir-17-92, Genes Dev. 23 (24) (2009) 2839–2849.
[261] B.J. Lannutti, S.A. Meadows, S.E. Herman, A. Kashishian, B. Steiner, A.J. Johnson, J.C. Byrd, J.W. Tyner, M.M. Loriaux, M. Deininger, B.J. Druker, K.D. Puri, R. G. Ulrich, N.A. Giese, CAL-101, a p110delta selective phosphatidylinositol-3-

kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability, Blood 117 (2) (2011) 591–594.
[262] S.A. Meadows, F. Vega, A. Kashishian, D. Johnson, V. Diehl, L.L. Miller, A. Younes, B.J. Lannutti, PI3Kδ inhibitor, GS-1101 (CAL-101), attenuates pathway signaling, induces apoptosis, and overcomes signals from the microenvironment in cellular models of Hodgkin lymphoma, Blood 119 (8) (2012) 1897–1900.
[263] L. So, D.A. Fruman, PI3K signalling in B- and T-lymphocytes: new developments and therapeutic advances, Biochem. J. 442 (3) (2012) 465–481.
[264] D.T. Teachey, S.A. Grupp, V.I. Brown, Mammalian target of rapamycin inhibitors and their potential role in therapy in leukaemia and other haematological malignancies, Br. J. Haematol. 145 (5) (2009) 569–580.
[265] Q. Cao, C. Yu, R. Xue, W. Hsueh, P. Pan, Z. Chen, S. Wang, M. McNutt, J. Gu, Autophagy induced by suberoylanilide hydroxamic acid in hela S3 cells involves inhibition of protein kinase B and up-regulation of beclin 1, Int. J. Biochem. Cell Biol. 40 (2) (2008) 272–283.
[266] A. Guidetti, C. Carlo-Stella, S.L. Locatelli, W. Malorni, M. Pierdominici, C. Barbati, R. Mortarini, L. Devizzi, P. Matteucci, A. Marchianò, R. Lanocita, L. Farina, A. Dodero, C. Tarella, M. Di Nicola, P. Corradini, A. Anichini, A.M. Gianni, Phase II study of sorafenib in patients with relapsed or refractory lymphoma, Br. J. Haematol. 158 (1) (2012) 108–119.
[267] M.L. Bristol, S.M. Emery, P. Maycotte, A. Thorburn, S. Chakradeo, D.A. Gewirtz, Autophagy inhibition for chemosensitization and radiosensitization in cancer: do the preclinical data support this therapeutic strategy? J. Pharmacol. Exp. Ther. 344 (3) (2013) 544–552.
[268] K. Jain, K.S. Paranandi, S. Sridharan, A. Basu, Autophagy in breast cancer and its implications for therapy, Am. J. Cancer Res. 3 (3) (2013) 251–265.
[269] S. Suman, T.P. Das, R. Reddy, A.M. Nyakeriga, J.E. Luevano, D. Kumar, P. Pahari, C. Damodaran, The pro-apoptotic role of autophagy in breast cancer, Br.J. Cancer 111 (2014) 309–317.
[270] J. Debanth, The multifaceted roles of autophagy in tumors-implicated for breast cancer, J. Mammary Gland Biol. Neoplasia 16 (3) (2011) 173–187.
[271] T. Negri, E. Tarantino, M. Orsenigo, J.F. Reid, M. Garibaldi, M. Zambetti, M. A. Pierotti, S. Pilotti, Chromosome band 17q21 in breast cancer: significant association between beclin 1 loss and HER2/NEU amplification, Genes Chromosome Cancer 49 (10) (2010) 901–909.
[272] S.V. Laddha, S. Ganesan, C.S. Chan, E. White, Mutational landscape of the essential autophagy gene BECN1 in human cancers, Mol. Cancer Res. 12 (4) (2014) 485–490.
[273] S. Oh, E. Xiaofei, D. Ni, S.D. Pirooz, J.Y. Lee, D. Lee, Z. Zhao, S. Lee, H. Lee, B. Ku, T. Kowalik, S.E. Martin, B.H. Oh, J.U. Jung, C. Liang, Downregulation of autophagy by Bcl-2 promotes MCF7 breast cancer cell growth independent of its inhibition of apoptosis, Cell Death Differ. 18 (3) (2011) 452–464.
[274] C. Bincoletto, A. Bechara, G.J.S. Pereira, C.P. Santos, F. Autunes, M. Muler, R. D. Gigli, P.T. Monteforte, H. Hirata, A. Jurkiewicz, S.S. Smaili, J. Peixoto de-Silva, Interplay between apoptosis and autophagy, a challenging puzzle: new perspectives on antitumor chemotherapies, Chemo-Biol. Interact. 206 (2) (2013) 279–288.
[275] R.L. Carpenter, S. Sirkisoon, D. Zhu, T. Rimkus, A. Harrison, A. Anderson, I. Paw, S. Qasem, F. Xing, Y. Liu, M. Chan, L. Metheny-Barlow, B.C. Psche, W. Debinski, K. Watabe, H. Lo, Combined inhibition of AKT and HSF1 suppresses breast cancer stem cells and tumor growth, Oncotarget 8 (43) (2017) 73947–73963.
[276] K.J. Petherick, A.C. Williams, J.D. Lane, P. Ordonez-Moran, J. Huelsken, T. J. Collard, H.J. Smartt, J. Batson, K. Malik, C. Paraskeva, A. Greenhough, Autolysosomal β-catenin degradation regulates wnt-autophagy- p62 crosstalk, EMBO J. 32 (2013) 1903–1906.
[277] Y. Wang, C. Han, L. Lu, S. Magliato, T. Wu, Hedgehog signalling pathway regulates autophagy in human hepatocellular carcinoma cells, Hepatology 58 (2013) 995–1010.
[278] K.M. Cappell, R. Sinnott, P. Taus, K. Maxfield, M. Sacrbrough, A.W. Whitehurst, Mutliple cancer testis antigens function to support tumor cell mitotic fidelity, Mol. Cell. Biol. 32 (20) (2012) 4131–4140.
[279] H. Zhang, M. Luo, Z. Jin, D. Wang, M. Sun, X. Zhao, Z. Zhao, H. Lei, M. Li, C. Liu, Expression and clinicopathological significance of FSIP1 in breast cancer, Oncotarget 6 (12) (2015) 10650–10666.
[280] D.H. Liang, D.S. Choi, J.E. Ensor, B.A. Kaipparettu, B.L. Bass, J.C. Chang, The autophagy inhibitor chloroquine targets cancer stem cells in triple negative breast cancer by inducing mitochondrial damage and impairing DNA break repair, Cancer Lett. 376 (2016) 249–258.
[281] A. Thorburn, D.H. Thamm, D.L. Gustafson, Autophagy and cancer therapy, Mol. Parmacol. 85 (6) (2014) 830–838.
[282] S.O. Bustos, F. Antunes, M.C. Rangel, R. Chammas, Emerging autophagy functions shape the tumor microenvironment and play a role in cancer progression - implications for cancer therapy, Front. Oncol. 10 (2549) (2020).
[283] A. Balic, M.D. Sørensen, S.M. Trabulo, B. Sainz Jr., M. Cioffi, C.R. Vieira, I. Miranda-Lorenzo, M. Hidalgo, J. Kleeff, M. Erkan, C. Heeschen, Chloroquine targets pancreatic cancer stem cells via inhibition of CXCR4 and hedgehog signaling, Mol. Cancer Ther. 13 (7) (2014) 1758–1771.
[284] F. Liu, Y. Shang, S.Z. Chen, Chloroquine potentiates the anti-cancer effect of lidamycin on non-small cell lung cancer cells in vitro, Acta Pharmacol. Sin. 35 (5) (2014) 645–652.
[285] D. Park, Y. Lee, Biphasic activity of chloroquine in human colorectal cancer cells, Dev. Reprod. 18 (4) (2014) 225–231.
[286] D.H. Liang, D.S. Choi, J.E. Ensor, B.A. Kaipparettu, B.L. Bass, J.C. Chang, The autophagy inhibitor chloroquine targets cancer stem cells in triple negative breast cancer by inducing mitochondrial damage and impairing DNA break repair, Cancer Lett. 376 (2) (2016) 249–258.
[287] C.I. Chude, R.K. Amaravadi, Targeting autophagy in cancer: update on clinical trials and novel inhibitors, Int. J. Mol. Sci. 18 (6) (2017) 1279.
[288] K.L. Cook, A. Wärri, D.R. Soto-Pantoja, P.A. Clarke, M.I. Cruz, A. Zwart, R. Clarke, Hydroxychloroquine inhibits autophagy to potentiate antiestrogen responsiveness in ER+ breast cancer, Clin. Cancer. Res. 20 (12) (2014) 3222–3232.
[289] R. Xu, Z. Ji, C. Xu, J. Zhu, The clinical value of using chloroquine or hydroxychloroquine as autophagy inhibitors in the treatment of cancers: a systematic review and meta-analysis, Medicine 97 (46) (2018) e12912.
[290] M. Piffoux, E. Eriau, P.A. Cassier, "Autophagy as a therapeutic target in pancreatic cancer, Br. J. Cancer 124 (2) (2021) 333–344.
[291] J. Li, N. Hou, A. Faried, S. Tsutsumi, T. Takeuchi, H. Kuwano, Inhibition of autophagy by 3-MA enhances the effect of 5-FU-induced apoptosis in colon cancer cells, Ann. Surg. Oncol. 16 (3) (2009) 761–771.
[292] P. Maycotte, A. Thorburn, Targeting autophagy in breast cancer, World J. Clin. Pathol. 5 (3) (2014) 224–240.
[293] T. Ohta, H. Arakawa, F. Futagami, S. Fushida, H. Kitagawa, M. Kayahara, T. Nagakawa, K. Miwa, K. Kurashima, M. Numata, Y. Kitamura, T. Terada, S. Ohkuma, Bafilomycin A1 induces apoptosis in the human pancreatic cancer cell line Capan-1, J. Pathol. 185 (3) (1998) 324–330.
[294] L.Q. Li, W.J. Xie, D. Pan, H. Chen, L. Zhang, Inhibition of autophagy by bafilomycin A1 promotes chemosensitivity of gastric cancer cells, Tumour Biol. 37 (1) (2016) 653–659.
[295] Y. Yan, K. Jiang, P. Liu, X. Zhang, X. Dong, J. Gao, Q. Liu, M.P. Barr, Q. Zhang, X. Hou, S. Meng, P. Gong, Bafilomycin A1 induces caspase-independent cell death in hepatocellular carcinoma cells via targeting of autophagy and MAPK pathways, Sci. Rep. 6 (1) (2016) 37052.
[296] O.O. Ryabaya, A.N. Inshakov, A.V. Egorova, M.A. Emelyanova, T.V. Nasedkina, A. S. Zasedatelev, D.A. Khochenkov, E.V. Stepanova, Autophagy inhibitors chloroquine and LY294002 enhance temozolomide cytotoxicity on cutaneous melanoma cell lines in vitro, Anti-Cancer Drugs 28 (3) (2017) 307–315.
[297] F. Tang, P. Hu, Z. Yang, C. Xue, J. Gong, S. Sun, L. Shi, S. Zhang, Z. Li, C. Yang, J. Zhang, C. Xie, SBI0206965, a novel inhibitor of Ulk1, suppresses non-small cell lung cancer cell growth by modulating both autophagy and apoptosis pathways, Oncol. Rep. 37 (6) (2017) 3449–3458.
[298] Y. Zheng, L. Liu, Y. Wang, S. Xiao, R. Mai, Z. Zhu, Y. Cao, Glioblastoma stem cell (GSC)-derived PD-L1-containing exosomes activates AMPK/ULK1 pathway mediated autophagy to increase temozolomide-resistance in glioblastoma, Cell Biosci. 11 (1) (2021) 63.
[299] J.M.M. Levy, C.G. Towers, A. Thorburn, Targeting autophagy in cancer, Nat. Rev. Cancer 17 (9) (2017) 528–542.
[300] E. Wolfson, E. Schmukler, S.T. Schokoroy, Y. Kloog, R. Pinkas-Kramarski, Enhancing FTS (Salirasib) efficiency via combinatorial treatment, Biol. Cell. 107 (5) (2015) 130–143.
[301] Y.P. Yang, L.F. Hu, H.F. Zheng, C.J. Mao, W.D. Hu, K.P. Xiong, F. Wang, C.F. Liu, Application and interpretation of current autophagy inhibitors and activators, Acta Pharmacol. Sin. 34 (2013) 625–635.
[302] M.J. Hsieh, C.W. Lin, S.F. Yang, G.T. Sheu, Y.Y. Yu, M.K. Chen, A combination of pterostilbene with autophagy inhibitors exerts efficient apoptotic characteristics in both chemosensitive and chemoresistant lung cancer cells, Toxicol. Sci. 137 (1) (2013) 65–75.
[303] K.Y.H. Wei-Chih Chen, C.M. Hung, Y.C. Lin, C.T.H. Ning-Sun Yang, S.C. Kuog, T. D. Way, The anti-tumor efficiency of pterostilbene is promoted with a combined treatment of Fas signaling or autophagy inhibitors in triple negative breast cancer cells, Food Funct. 5 (2014) 1856.
[304] S.M. Lim, E.A. Mohamad Hanif, S.F. Chin, Is targeting autophagy mechanism in cancer a good approach? The possible double-edge sword effect, Cell Biosci. 11 (1) (2021) 56.
[305] I. Daskalaki, I. Gkikas, N. Tavernarakis, Hypoxia and selective autophagy in cancer development and therapy, Front. CellDev. Biol. 6 (104) (2018).
[306] W.H. Kirsten, V. Schauf, J. McCoy, Properties of a murine sarcoma virus, Bibl. Haematol. 36 (1970) 246–249.
[307] L.M.O. Barbeau, T.G.H. Keulers, K.M.A. Rouschop, Tumors responsive to autophagy-inhibition: identification and biomarkers, Cancers 12 (9) (2020) 2463.
[308] A. Scrivo, M. Bourdenx, O. Pampliega, A.M. Cuervo, Selective autophagy as a potential therapeutic target for neurodegenerative disorders, Lancet Neurol. 17 (9) (2018) 802–815.
[309] D. Mahalingam, M. Mita, J. Sarantopoulos, L. Wood, R.K. Amaravadi, L.E. Davis, A.C. Mita, T.J. Curiel, C.M. Espitia, S.T. Nawrocki, F.J. Glies, J.S. Carew, Combined autophagy and HDAC inhibition: a phase I safety, tolerability, pharmacokinetic, and pharmacodynamic analysis of hydroxychloroquine in combination with the HDAC inhibitor vorinostat in patients with advanced solid tumors, Autophagy 10 (8) (2014) 1403–1414.