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Apoptosis and Autophagy: Therapeutic Implications in Cancer

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Abstract: Despite the advances in the medical field so far, cancer remains a global health priority even now. Considering the drug resistance and the failure of cancer therapies to achieve complete eradication of cancer cells in certain populations, developing molecules that induce programmed cell death or apoptosis has been the focus of cancer research for several decades. Apoptosis evasion is one of the hallmarks of cancer cells, and efforts continue to achieve complete annihilation of cancer cells through selective killing. On the other hand, autophagy, a mode of cell degradation, is considered a double-edged sword. Recent studies show that autophagy also can be manipulated to selectively target cancer cells based on the tumor microenvironment and cellular context. Studies show that autophagy is an evolutionarily conserved process initiated during stress response and has enormous importance in maintaining physiological balance. Most importantly, the dynamic equilibrium between apoptosis and autophagy is crucial in maintaining cellular homeostasis. Although a 'cell eating' process, the fate of autophagic cells depends entirely on the nature of stress and the extent of crosstalk between autophagy. This understanding is of immense significance when designing therapeutic interventions targeting apoptosis and autophagy. Currently, several studies are ongoing to gain insights into the role of autophagy in cancer initiation, invasion, progression, angiogenesis, and metastasis. This review focuses on the two major cell death mechanisms, apoptosis and autophagy, in the context of cancer, their crosstalk, and the therapeutic interventions targeting both modes of cell death.

Introduction

Cell death is a natural process occurring during the lifetime of an organism to maintain growth and development along with cellular homeostasis. However, it can also happen during a pathological condition, injury, or organ dysfunction (Green and Llambi, 2015; Tong et al., 2022; Kesavan et al., 2023; Saha and Yadav, 2023). Morphologically, cell death may be categorized into three types: Apoptosis (Type I), autophagy (Type II), and necrosis (Type III). Apoptosis or programmed cell death (Type I cell death) can happen either by extrinsic pathway triggered by death receptors such as Fas or intrinsic pathway triggered by mitochondrial outer membrane permeabilization (MOMP) by the Bcl-2 family of proteins (Carneiro and El-Deiry, 2020). Caspases, the cysteine-aspartic proteases, play a fundamental role in apoptosis (Hounsell and Fan, 2021). Apoptosis is an active process with distinct morphological changes such as cell shrinkage, membrane blebbing, pyknosis or chromatin condensation, and phosphatidyl serine flipping (D'Arcy, 2019). Autophagy (originated from the Greek for "self-eating") is a specialized form of cell death (Type II cell death) that is characterized by engulfment of the membrane and degradation of the cellular contents orchestrated by autophagy machinery (Liu et al., 2023). It is differentiated from other forms of cell death by forming intracellular vesicles (Solvik et al., 2021; Das et al., 2021; Boga and Bisgin, 2022;). Unlike a cell death process, autophagic cell death (ACD) is sometimes considered as a failed survival attempt initiated during metabolic stress (unavailability of ATP and/or amino acids) and/or for removing damaged cellular organelles

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(Chang et al., 2022; Peker and Gozuacik, 2020; White et al., 2021). Three categories of autophagy are identified: microautophagy, macroautophagy, and chaperone-mediated autophagy. Microautophagy is the non-selective degradation of cytoplasmic components and subcellular organelles in lysosomes (Wang et al., 2023; Mehta et al., 2023; Kulkarni et al., 2023). Macroautophagy is differentiated from other forms of autophagy by the formation of double-membrane vesicles that engulf and degrade cytoplasmic contents and subcellular organelles by fusing with lysosomes to form autolysosomes (Odle and Cook, 2020). Chaperone-mediated autophagy selectively degrades certain proteins in lysosomes with the help of chaperone proteins (Tedesco et al., 2023). Necrosis or Type III cell death occurs when there is irreparable damage (D'Arcy, 2019). Necrotic cells are characterized by distinct changes in the cellular morphology such as swelling, loss of membrane integrity and rupture, and degradation of subcellular organelles. However, unlike apoptosis, necrosis is not an active process (no ATP consumption) and chromatin condensation is also absent. However, a modified form of necrosis called necroptosis is an active process and involves the activation of RIP3/receptor-interacting protein kinase 3 by Toll-like receptors (TLRs), death receptors (DRs), and T-cell receptors (TCR). Studies have shown that the presence of double-stranded viral DNA in the cytosol can activate RIP3 triggering necroptosis (Ketelut-Carneiro and Fitzgerald, 2022).

Therapeutic modalities and their effectivity largely depend on cell death mechanisms in diseases such as cancer, cardiovascular diseases, and neurodegenerative disorders (Kist and Vucic, 2021; Rami et al., 2023). The regulatory mechanisms of cell death are complex and crucial for maintaining homeostasis. This review focuses on the mechanism and interplay between apoptosis and autophagy, their role in oncogenesis, the mechanism and targets of their inhibition, and how the crosstalk can be successfully used for cancer therapy for better therapeutic outcomes.

Apoptosis and Cancer

Among the different hallmarks of cancer progression, evasion of apoptosis is one of the early identified ones (Hanahan, 2022). Studies have shown that loss of apoptotic control is implicated in almost all cancers regardless of the site of origin or stage. This enables the cells to live longer and accumulate mutations responsible for their survival, invasiveness, angiogenesis, metastasis, etc (Tong et al., 2022).

Molecular Mechanism and Signalling Pathways

Role of caspases: Caspases are activated by death receptors (extrinsic pathway) or mitochondria (intrinsic pathway). The "c" of "caspase" indicates cysteine protease, whereas the "aspase" indicates the ability of the molecule to cleave the protein at a location after aspartic acid residues. Upstream caspases (caspases 2, 8, 9, and 10) are activated by pro-apoptotic signals that induce activation of the effector caspases (caspases 3, 6, and 7), which are in turn responsible for the subcellular degradation and subsequent morphological changes(Shalini et al., 2015).

Role of Bcl-2 family of proteins

The Bcl-2 family of proteins consists of both pro- and anti-apoptotic molecules. Bcl-2 and Bcl-XL are anti-apoptotic in nature, sequestering caspases and preventing the release of apoptosis-inducing factor/AIF and cyt c from mitochondria, whereas pro-apoptotic proteins such as Bak and Bax induce the release of caspases and apoptosis-inducing factors (Kale et al., 2018).

Extrinsic pathway of apoptosis via death receptors

Here, ligand binding activates death receptors (TNFR1, TRAIL-R1/2, or Fas). Fas/CD95 and TRAIL-Rs form a death-inducting signalling complex (DISC) upon binding by FasL and TRAIL, respectively, that recruits caspase 8 and activates it through the Fas-associated death domain (FADD). The cleavage of caspase 8 releases p10 and p18 subunits that activate caspase-3 and caspase-7, inducing type I apoptosis (Kashyap et al., 2021).

Intrinsic/mitochondrial pathway of apoptosis

During the intrinsic apoptosis pathway, cellular stress activates Bcl2 family of proteins which induces MOMP. The proapoptotic factors sequestered in the intermembrane space of mitochondria (Smac, cytochrome c, and Omi) are released to the cytosol. Cytochrome c initiates APAF1 oligomerization and activates caspase 9. Activated caspase 9 subsequently activates the executioner caspases, caspases-3 and -7 (Kashyap et al., 2021).

The common pathway of apoptosis

The intrinsic and extrinsic pathways of apoptosis merge at caspase 3. Caspase 3 cleaves the caspase-activated deoxyribonuclease inhibitor, causing apoptotic changes in the nucleus and other subcellular compartments.

The intrinsic endoplasmic reticulum pathway of apoptosis

Studies show that caspase 12 is the key player in this pathway and acts independently of mitochondria. Nutrient deprivation, the presence of free radicals, or

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hypoxia induce stress on the ER, causing protein unfolding and reduction in protein synthesis. This causes the dissociation of TRAF2/ TNF receptor-associated factor 2 from procaspase 12, causing the activation of caspase 12(Iurlaro & Muñoz-Pinedo, 2016).

Regulation of apoptosis

Bcl-2 family of proteins are crucial for the regulation of apoptosis, and the family has both pro- and anti-apoptotic molecules. They control the apoptosis machinery by controlling the mitochondrial outer membrane potential (Kale et al., 2018; Singh et al., 2019). The relative expression of anti-apoptotic and pro-apoptotic proteins decides the cell's fate. The ubiquitin-proteasome system (UPS) regulates the levels of E3 ligases via positive and negative feedback loops, thereby affecting the stability of the Bcl-2 proteins and inhibitors of apoptosis proteins, also known as IAPs (Abbas and Larisch, 2021). Epigenetics also plays a substantial role in the regulation of apoptosis. Besides the methylation or demethylation of DNA and histones, Bromodomain-containing protein 4, also known as Brd4, has emerged as a novel target since the inhibition of Brd4 can induce apoptosis (Hu et al., 2022; Ozyerli-Goknar and Bagci-Onder, 2021). Another major regulator of apoptosis is the intracellular calcium levels. Calcium (Ca^{2}+) is a second messenger and has immense roles in regulating various physiological functions (Patergnani et al., 2020). Under stress conditions, Ca^{2}+ influx to mitochondria destabilizes them by altering mitochondrial membrane potential, releasing cytochrome c. This event marks the onset of apoptosis (Matuz-Mares et al., 2022).

Biochemical and Morphological Changes

Apoptosis is distinct from other modes of cell death since the process does not generate inflammation(Saraste & Pulkki, 2000). During apoptosis, cells shrink, the cytoplasm becomes dense and eosinophilic, and the subcellular organelles undergo tight packaging (Kari et al., 2022). Chromatin condensation or pyknosis is one of the characteristic features of apoptosis. Blebbing of the plasma membrane is followed by progressive condensation and fragmentation of the nuclear membrane, also known as karyorrhexis. The formation of ‘apoptotic bodies’ from cell fragments is visible under a microscope, called ‘budding’. The nuclear membrane may be present or absent at this stage. Caspase-induced activation of DNases results in the formation of short stretches of double-stranded DNA fragments (180-200 bp) with blunt ends and single base 3′ ends detectable as ladder pattern in gel electrophoresis (Di Filippo and Bernardi, 2009). Nuclear lamins A and B undergo degradation by the action of caspases and disrupt the nuclear membrane integrity(Lindenboim et al., 2020). Cleavage of nuclear mitosis-associated protein (NuMa) disrupts the chromatin structure (Lin et al., 2007). The action of caspases also causes membrane flipping, exposing phosphatidylserine to macrophages. Parenchymal cells, macrophages, or neoplastic cells phagocytose the apoptotic bodies (Segawa and Nagata, 2015).

Apoptosis in Oncogenesis

Deregulation of apoptosis is observed during several pathological conditions, especially cancer(Ucker & Levine, 2018). Some of the recent studies shed light on the pro-apoptotic and pro-survival regulation of apoptosis in tumor cells. The general mechanism of apoptotic evasion is outlined in Figure 1.

Pro-apoptotic Regulation in Tumor Cells

Cancer cells are generally ‘primed’ for apoptosis. Since both pro- and anti-apoptotic molecules are upregulated in the cancer cells. Hence, selective inhibition of anti-apoptotic signals can make them susceptible to apoptosis(Pfeffer & Singh, 2018). Moreover, tumor cells are under significant stress because of the diminished accessibility of nutrients and are hence susceptible to the extrinsic pathway of apoptosis (Wang et al., 2022).

Pro-survival Regulation in Tumor Cells

The prolonged survival of cancer cells causes accumulation of mutations, which happens by (i) loss of activity of caspases, (ii) loss of BAX and/or BAK (iii) upregulation or enhanced activity of antiapoptotic proteins (Ashe and Berry, 2003; Campbell and Tait, 2018; Cetraro et al., 2022; Pfeffer and Singh, 2018; Wong, 2011). Since the apoptosis pathways influence the immune system's overall function, deregulation of apoptosis leads to poor anti-tumor immune response (Liu et al., 2022). Furthermore, cancer cells find ways to prevent mitochondrial outer membrane permeability (MOMP)(Bao et al., 2020). Apoptosis in cancer stem cells is prevented by ‘Blebbishield formation’ characterized by shield-like formation by apoptotic blebs. Some of the key signalling pathways during blebbi shield formation are activated by caspases, BAD, K-ras, etc (Jinesh and Kamat, 2017).

Autophagy and Cancer

Autophagy is complexly associated with the pathobiology of several diseases and understanding the pathways involved in autophagy is critical in designing therapeutic interventions for targeting the same (Bustos et al., 2020; Zhang et al., 2023**)**. The molecular mechanism regulating the autophagy signalling is discussed below.

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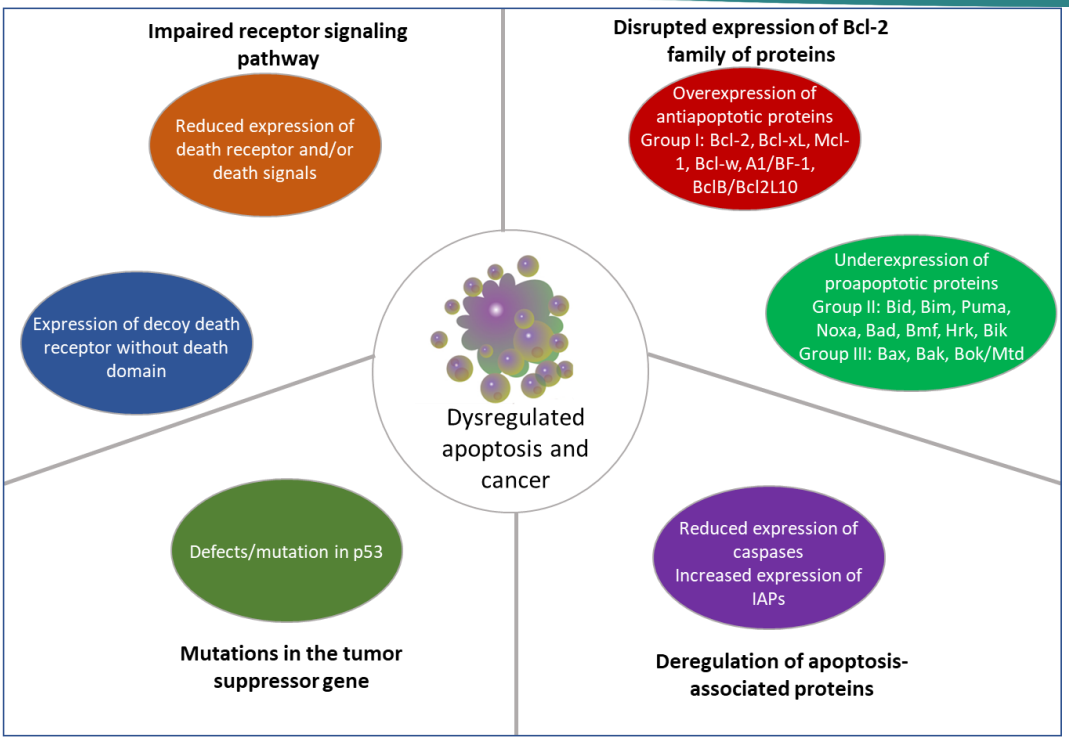

Figure 1. Mechanisms contributing to evasion of apoptosis.

Molecular Mechanism and Signalling Pathways

Autophagy has five stages: (1) initiation, (2) nucleation, (3) expansion and elongation, (4) closure and fusion, and (5) cargo degradation(Mulcahy Levy & Thorburn, 2020). AMP-activated protein kinase/AMPK is the cellular energy sensor, and under nutrient deprivation AMPK triggers autophagy(Filomeni et al., 2015; Rashid et al., 2015; Verfaillie et al., 2010). Cellular stress activates autophagy-related genes (ATGs). ATG/ULK complex inhibits mTORC1 and interacts with FIP200 to form a complex that involves Class III PI3K also known as Vps34, along with Atg6 and Beclin1. Further events leading to the complex formation by different partner proteins cause the autophagosome's membrane expansion (Lee & Lee, 2016). Autophagosome expansion is enabled by enzymes that activate ubiquitin (e.g., E1 and E2) (Chen et al., 2019). The autophagosome expansion involves Atg7 (E1 like), which activates Atg12 and is transferred to ATg5 via Atg10 (E2 like), which later binds to Atg6. Atg4 causes the conversion of LC3 precursor to LC3-I, which undergoes covalent bonding to PE by E1-like enzyme Atg7 and E3-like enzyme Atg3. to form LC3-II-PE responsible for forming autophagolysosome (Li et al., 2022). The fusion of autophagosome and lysosome is facilitated by the endosomal-sorting complex ESCRT and RabS, a monomeric GTPase (Lőrincz and Juhász, 2020). P62/SQSTM1 (an autophagy receptor protein) binds to the ubiquitin-associated (UBA) region via LIR, also known as LC3/Atg8 interaction region, and degrades the cellular components (Pankiv et al., 2007).

Regulation of Autophagy

Autophagy is regulated at different molecular levels during transcription, translation, post-translation, and epigenetic levels (Ma et al., 2022; Shu et al., 2023). The transcriptional regulation of autophagy is mainly controlled by Forkhead box transcription factor class O (FoxO), which regulates the transcription of Beclin1, LC3B, ATGs, etc (Di Malta et al., 2019). At the translational level, eIF4GI negatively affects autophagy, whereas eIF2α kinase signalling pathway and eukaryotic elongation factor-2 (eEF-2) positively affect autophagy (Sanchez et al., 2019). At the epigenetic level, HDACs regulate autophagy by affecting the transcription of LC3B, ATG, etc (Mrakovcic et al., 2018). At the post-translational level, ubiquitination of Atg8/LC3, Atg12 and phosphorylation of the Atg1/ULK kinase complex regulates autophagy (Chen et al., 2019; Wang et al., 2018). Ke et al. showed that hyperphosphorylation of JNK1 causes its dissociation from Beclin 1, which further kickstarts the autophagy process in osteoclasts (Ke et al., 2022). Similarly, phosphorylation of DAPK also triggers autophagy (Zalckvar et al., 2009). The acetylated and deacetylated status of ATG proteins also can regulate autophagy. ATG proteins are acetylated by p300 acetyltransferase when there are ample nutrients and undergo deacetylation during nutrient deprivation by Sirt, an NAD-dependent deacetylase (Xu and Wan, 2023). In addition to the transcriptional, translational, epigenetic,

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and post-translational regulation, autophagy is also regulated by various stresses which in turn act via signalling mechanisms such as Ras-cAMP-PKA and mTOR pathways (Grisan et al., 2021).

The Autophagy paradox: Oncogenic or anti-oncogenic?

The process of autophagy has been mentioned in several literature as a double-edged sword, and the cellular fate depends on the cell category, microenvironment, and stage of cancer(Ahmadi-Dehlaghi et al., 2023). The dual role of autophagy or 'autophagy paradox' is indicated in Fig. 2.

Role of autophagy in tumor suppression

Autophagy protects the cells against DNA damage and metabolic stress during the early phases of tumorigenesis. Autophagy can be induced by p53, DAPK, PTEN and TSC1/2, whereas Ras and Akt suppress autophagy (Aquila et al., 2020; Di Nardo et al., 2014; Mrakovcic and Fröhlich, 2018; Schmukler et al., 2014; Singh et al., 2016; Wang et al., 2012). Similarly, the down regulation of ATG or mutations that cause loss of function of ATG in certain cancers has tumor suppressive roles (Ariosa et al., 2021; Takamura et al., 2011). Autophagy reduces necrosis and subsequent inflammation, especially in cells with defective apoptotic pathways.

Contribution of autophagy in the progression of tumor

Autophagy helps the tumor cells to survive under severe metabolic stress and DNA damage. Tumor promoters such as Ras and Raf can enhance autophagy (Schmukler et al., 2014). Despite suppressing MAPK, prostate cancer cells survive by activating AMPK-dependent autophagy via STK11 protein (Grossi et al., 2015). In the later stages of cancer, metastasis can enhance the rate of autophagy for the uninterrupted supply of recycled cellular components and remove damaged organelles. Hypoxia-inducible factor-1 (HIF-1) increases the expression of BNIP3 which can trigger autophagy by interrupting interactions of Beclin-1 with Bcl2 or Bcl-XL (Guo et al., 2001). Similarly, canonical and non-canonical TGFβ signalling has been found to activate autophagy (Ding and Choi, 2014).

Autophagy and Apoptosis Crosstalk

The nature of crosstalk between apoptosis and autophagy varies depending on the cell type and the stage of maturation(El-Khattouti et al., 2013; Fairlie et al., 2020). The crosstalk between autophagy and apoptosis is indicated in Fig. 3, and the specific roles of each protein are discussed below.

Role of anti-apoptotic protein Bcl-2

Bcl-2 has a significant role in regulating the crosstalk

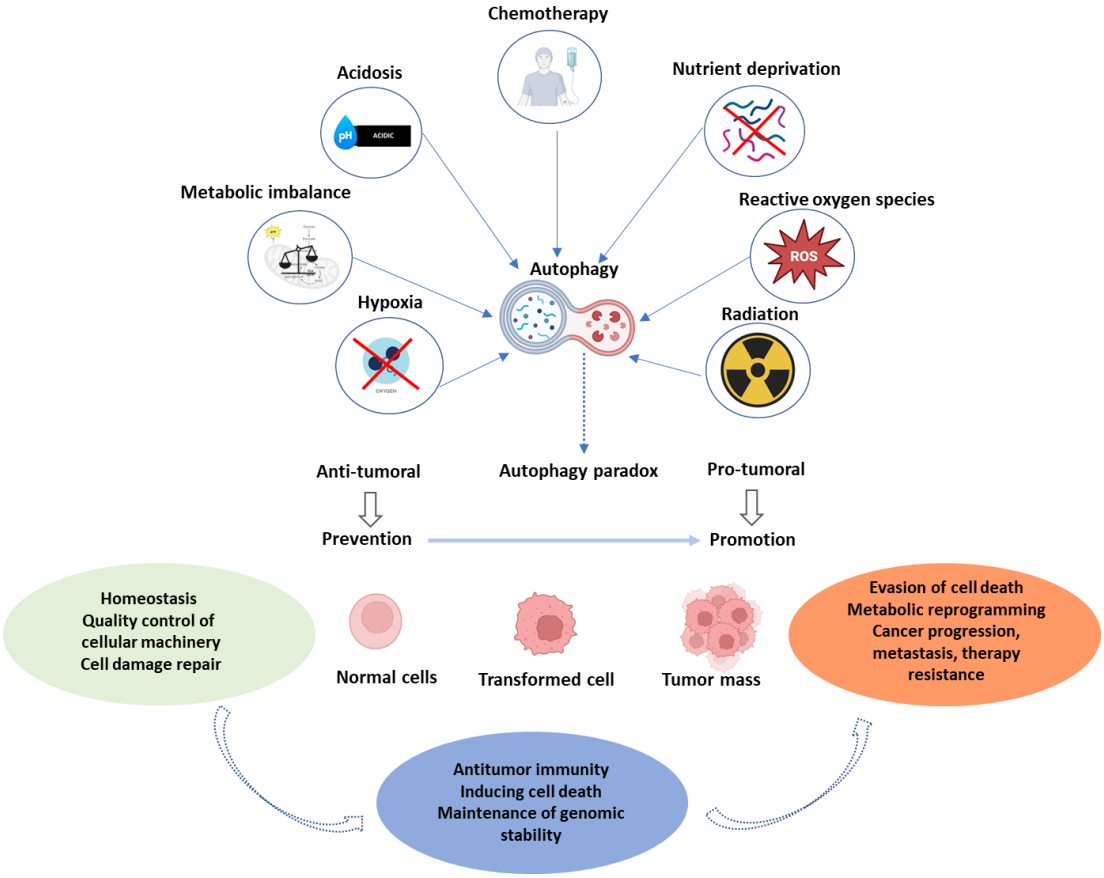

Figure 2. Factors inducing autophagy and its dual role in an organism.

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between apoptosis and autophagy. Bcl-2 mediates the binding of Beclin1 with the pro-apoptotic Bax, initiating apoptosis via mitochondria destabilization (Marquez and Xu, 2012). The extent of nutrient deprivation is a critical factor that determines the fate of the cell. The exhaustion of the nutrients initially releases Beclin1, which in turn activates PI3K, which marks autophagy (Menon and Dhamija, 2018). However, a high rate or extent of nutrient deficit can lead to the release of pro-apoptotic Bax from Bcl-2 and initiate apoptosis (Sa-nongdej et al., 2021).

Another important factor that regulates the autophagy-apoptosis switch is the subcellular localization of Bcl-2. Studies show that Bcl-2 localization to the ER regulates autophagy, whereas Bcl-2 in the mitochondria regulates apoptosis. Proteins such as ATG4D and PI3K are cleaved in addition to Beclin1 by caspases, promoting apoptosis (Marquez and Xu, 2012).

Role of ATG5: ATGs are autophagy regulating proteins and ATG5 is a key player in regulating apoptosis/autophagy crosstalk. During the onset of autophagy, ATG5 initiates the formation of autophagosomes. However, during cellular stress, ATG5 cleaved by calcium-activated protease calpain is translocated to the mitochondria and, undergoes binding with Bcl-XL and initiates apoptosis (Eisenberg-Lerner et al., 2009; Yousefi et al., 2006).

Role of Beclin1

Beclin1 is the mammalian orthologue of yeast Atg6 and is crucial in regulating autophagy. It interacts with several proteins such as VMP1, Ambra1, SLAM, PINK, HMGB1, Rubicon, UVRAG, Atg14L, surviving, IP3R, Bif-1, and nPIST during autophagy. Bcl-XL or Bcl-2 can inhibit BH3 domain of Beclin 1 by phosphorylation of Beclin 1 and Bcl-2 or Beclin1 ubiquitination. The complex formation between Beclin 1 and Bcl-2 is crucial in autophagy induction(Tran et al., 2021). Moreover, Beclin 1 can initiate autophagy by interacting with PI3K (McKnight & Zhenyu, 2013).

Role of NAF-1

Nutrient-deprivation autophagy factor-1/NAF-1 belongs to the iron-sulfur (FeS) protein family. Both ER and mitochondria have been identified as locations of NAF-1. It is crucial in stabilizing the Beclin-Bcl-2 complex to promote apoptosis (Chang et al., 2012).

Role of caspases and other apoptosis-mediating proteins

Caspase-mediated cleavage of autophagy-associated proteins and their translocation to mitochondria can prevent the onset of autophagy and initiate apoptosis by disrupting the mitochondrial membrane potential (Tsapras and Nezis, 2017). This is observed in the case of the pro-apoptotic role of N-terminal Atg5. Deficiency or inhibition of caspase 8 or mutations of FADD can enhance the formation of autophagosomes and thus switch to autophagy in myeloid cells (Wu et al., 2022). AMBRA1, the autophagy protein, undergoes irreversible degradation by the combination of caspases and calpains, preventing autophagy (Xi et al., 2022).

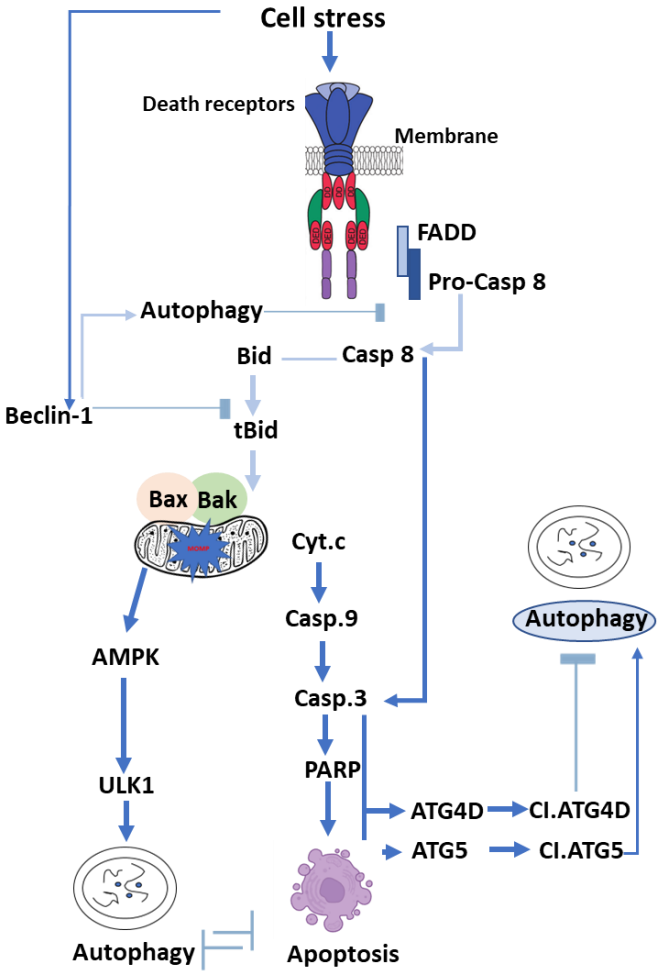

Figure 3. Schematic representation of the signalling pathways involved in crosstalk between autophagy and apoptosis.

Drugs targeting Apoptotic pathways

Several drugs have been investigated that selectively target specific molecules involved in the apoptosis pathway are listed in Table 1 and are as follows:

Targeting Caspases

Apoptin is a small molecule that activates caspases and selectively induces programmed cell death in cancer cells (Rohn and Noteborn, 2004). There are also peptide-based activators of caspases containing arginine-glycine-aspartate motifs that enhance the activity of caspases and induce apoptosis (Tamm et al., 2003). Capsase gene therapy and recombinant adenovirus carrying caspase 3 have also shown success in several experimental models (Pathak et al., 2023; Shinoura et al., 2000).

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Targeting Bcl family of proteins

BH3 mimetics are actively investigated for enhancing apoptosis in tumor cells of different origin. ABT-737 binds to the hydrophobic pocket of Bcl-Xl, Bcl-w, and Bcl-2 and inhibits them (Song et al., 2008). ABT-263/ navitoclax synergizes with MEK or tyrosine kinase inhibitors (Airiau et al., 2015). Carneiro et al. (2022) have shown efficacy of BCL-XL-based vaccine, and antibody–drug conjugate ABBV-155 inhibiting BCL-XL alone or in combination with taxanes (Carneiro et al., 2023). Stapled peptides (e.g., stabilized alpha-helix of BCL-2 domains/ SAHBA) are experimental molecules for targeting protein-protein interactions in the cell(Walensky & Bird, 2014). A small molecule named SMBA1-3 targets the regulatory site of Bax at S184 and prevents its phosphorylation, promoting the release of cytochrome c. BAM-7 and BTSA1 are Bax-activating molecules that have shown therapeutic efficacy in glioblastoma (Xin et al., 2014). Oblimersen sodium is an antisense oblimer against Bcl-2 that can sensitize cancer cells to conventional chemo drugs (Herbst and Frankel, 2004). NOXA, ATF3, and ATF4 are BH3 mimetics that bind to and inhibit Mcl-1. Some other BH3 mimetics are ABT-263, HA14-1, and GX15-070(Townsend et al., 2021). Other drugs that alter the expression of Bcl-2 family of proteins include depsipetide, sodium butyrate, flavopiridol, and fenretinide (Kang and Reynolds, 2009; Nelson et al., 2011).

Targeting IAPs and other pathways

LCL161 is an IAP antagonist that has shown therapeutic efficacy alone and is administered along with chemodrugs in several solid tumor models (Chesi et al., 2016). TL32711/ birinapant is an IAP inhibitor that has shown efficacy when used along with radiotherapy and anti-PD1 molecules such as pembrolizumab(Amaravadi et al., 2015; Medivir, 2020; National Cancer Institute (NCI), 2024; Noonan et al., 2016). Moreover, small molecules based on peptides and non-peptides (e.g., cyclopeptidic Smac mimetics) can serve as IAP antagonists by binding to XIAP and cIAP-1/2 and restoring the caspase functions. SM-164 is a non-peptidic IAP inhibitor that increases the activity of TRAIL by simultaneously targeting XIAP and cIAP1(Sun et al., 2010). In addition to this, several antisense strategies targeting IAPs are also under investigation (Schimmer and Dalili, 2005).

Recent studies have shown the success of epigenetic approaches targeting apoptosis in therapeutic interventions for cancer. ABBV-075 is a BET inhibitor that has shown efficacy when administered along with venetoclax in cutaneous T cell lymphoma(Sarnik et al., 2021). Panobinostat is an HDAC inhibitor that stimulates NOXA and suppresses Mcl-1 activity(C. Choi et al., 2021). Azacytidine is a hypomethylating agent that has shown significant activity in combination with venetoclax (Saliba et al., 2021). Among the chaperone-targeting apoptotic agents, Ganatespib, geldanamycin, XL888, onalespib, and TAS116 are hsp90 inhibitors that have exhibited enhanced apoptosis in cancer cells(Z.-N. Li & Luo, 2022). Small molecule inhibitors and antisense strategies are being investigated for inhibiting Survivin(Albadari & Li, 2023). AM-8621 is a Mcl-1 inhibitor, binds to its pocket with subsequent removal of BIM and induces apoptosis. AZD5991 and AMG 176 are Mcl-1 inhibitors that have shown synergistic toxicity effects with chemo drugs and venetoclax. S63845 and VU661013 are Mcl-1 inhibitors that can overcome resistance to venetoclax (Wei et al., 2020). Death receptor agonists have shown significant success in anticancer therapy. Recombinant Apo2L/TRAIL (e.g., Dulanermin) and agonist monoclonal antibodies (e.g., mapatumumab and lexatumumab) have been shown to stimulate death receptors DR4 and DR5. AMG655/ conatumumab, LBY135/tigatuzumab, and PRO95780/ drozitumab are DR5 agonists. ONC201 is a TRAIL-inducing small molecule that binds to CIpP/ mitochondrial caseinolytic protease P and dopamine receptors DRD2 and DRD3 and activates the stress response protein ATF4 and upregulates DR5 (Di Cristofano et al., 2023; Montinaro and Walczak, 2023, 2023; Soria et al., 2010).

Targeting p53

Retroviral vectors carrying wild-type p-53 injected into tumor cells have shown efficacy in solid tumors alone or in combination with other anticancer strategies. ONYX-015 is an oncolytic adenovirus, genetically engineered, that can eliminate p53 deficient tumor cells(Ries & Korn, 2002). Phikan083 is a carbazole derivative that can restore p53 activity in p53 mutant cells (Raghavan et al., 2019). CP-31398 also works similarly by intercalating with DNA and restoring p53 activity by destabilizing the core domain complex od DNA and p53 (Tanner & Barberis, 2004). Nutlins prevent the interactions between MDM2 and p53, being an analogue of cis-imidazoline, while MI-219 disrupts MDM2-p53 interaction, and tenovins are small molecules that activate p53 (Shen and Maki, 2011). Several viral vector-based vaccines and dendritic-cell-based vaccines carrying wild-type p53 are also under investigation. In addition to the above, other molecules target the tumor suppressor pathways. There are several MDM2 inhibitors under study, such as RG7388/idasanutlin, a nutlin-3a

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derivative, HDM201, DS-3032b, AMG-232, BI 907828, APG-115, ALRN-6924, HDM201, etc that work alone or in combination with other chemo drugs or inhibitors against BCL-2/BCL-XL, MEK 1/2, PI3K, BCL-2/BCL-XL, BRAF, etc (Alaseem, 2023). APR-246 restores p53 activity in tumors bearing p53 mutants(Xie et al., 2023). Palbociclib is a CDK4/6 inhibitor that sensitizes cancer cells to mediated apoptosis mediated by TRAIL(J. Zhang et al., 2017).

Drugs targeting Autophagy

As mentioned earlier, autophagy is a double-edged sword, and the consequences of using autophagy activators or inhibitors in treating cancer are purely contextual. Cell death can be induced either by inhibition or activation of autophagy and this is further regulated by crosstalk of autophagy pathways and other important signalling cascades. Recent evidence also shows that selective targeting of these pathways has cytotoxic effects on cancer stem cells (See Table 2).

Table 1. Treatment strategies that explore the mechanism of apoptosis.

Treatment strategy	Mechanism/agents	Reference
Targeting the Bcl-2 family of proteins		
Targeting Bcl-2 family proteins by different compounds	(i) Oblimersen sodium	(Herbst and Frankel, 2004)
	(ii) Small molecule inhibitors: ABT-737, sodium butyrate, ABT-263, depsipetide, HA14-1, fenretinide and flavipirodo, gossypol, and GX15-070	(Park et al., 2013)
	(iii) BH3 analogues: ABT-737 suppressing the functions of several anti-apoptotic proteins such as Bcl-2/xL/W, ATF3/4 etc	(Townsend et al., 2021)
Selective BCL-2 inhibitors	S55746 (BCL201) APG-2575 ABBV-155	(Ploumaki et al., 2023)
BCL-XL inhibitors	AMG 176	(Kargbo, 2023a)
Dual BCL-2 and BCL-XL inhibitors	Venetoclax	(Kargbo, 2023b)
MCL-1 inhibitors	MIK665 (S64315) AZD5991 S63845 UMI-77 A-1210477 VU661013 LCL161	(Bolomsky et al., 2020)
Bcl family proteins/gene silencing	(i) Bcl-2 siRNA and antisense nucleotides	(Gagliardi and Ashizawa, 2022; Meng et al., 2015)
	(ii) Bim-1 siRNA	(Schwulst et al., 2008; Wakabayashi et al., 2021)
Targeting p53		
p53-based gene therapy	(i) retroviral vector with wild type p53 gene	(Lane et al., 2010)
	(ii) ONYX-015	(Ries and Korn, 2002)

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p53-based drug therapy	(i) Phikan083 binds to mutant p53 (ii) CP-31398 intercalates with DNA (iii) Nutlins inhibiting MDM2-p53 interaction (iv) MI-219 disrupting MDM2-p53 interaction (v) Tenovins	(Alaseem, 2023; Levine, 2022; Tanner and Barberis, 2004; Xie et al., 2023)
p53-based immunotherapy	(i) human wildtype p53 carrying recombinant replication-defective adenoviral vector	(Hu et al., 2021)
	(ii) p53 peptide-pulsed dendritic cells	(Gu et al., 2020)
Targeting IAPS		
Targeting XIAP	(i) Antisense oligonucleotides	(Carter et al., 2011)
	(ii) siRNAs	(Gholizadeh et al., 2020)
Targeting Survivin	(i) siRNAs	(Eljack et al., 2022)
	(ii) antisense oligonucleotides	(Carrasco et al., 2011)
SMAC mimetic antagonists	Birinapant (TL32711)	(Sun et al., 2010)
Other IAP targeting agents	(i) Inhibitors of Cyclin-dependent kinase (ii) Inhibitors of Cyclin-dependent kinase (iii) Hsp90 inhibitors (iv) Gene therapy	(Chesi et al., 2016; Z.-N. Li & Luo, 2022; Schimmer and Dalili, 2005; Sun et al., 2010)
Targeting caspases		
Caspase-based therapy with different compounds	(i) Apoptin	(Rohn and Noteborn, 2004)
	(ii) Small molecules caspase activators	(Morgan et al., 2014)
Gene therapy	(i) Human caspase-3 gene (ii) Constitutively active caspse-3 gene transfer (iii) Recombinant adenovirus carrying caspase 3	(Pathak et al., 2023)
Targeting extrinsic pathway		
Death Receptor Agonists (DR4/5)	GEN1029 ABBV-621 MM-201 TLY012	(Di Cristofano et al., 2023)
Epigenetic modulators for inducing apoptosis		
Stimulating intrinsic pathway of apoptosis	Fimepinostat +venetoclax	(Thus et al., 2022)
	Azacytidine or decitabine + venetoclax	

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Targeting cancer stem cell (CSC)

Autophagy is important in CSCs for recycling intracellular components, maintaining the infinite survival of tumors, and hence selective targeting of relevant pathways can induce cell death either by their inhibition or activation in these cells (Wang et al., 2022). Chloroquine causes cell killing in breast CSCs and pancreatic CSCs by inhibiting autophagy via JAK2 and Hedgehog (Hh) signalling pathways, respectively. It is also found to inhibit metastasis of breast CSCs. (Balic et al., 2014; Choi et al., 2014; Liang et al., 2016). Salinomycin exerts inhibitory or proliferative effects in CSCs by increasing cellular ROS and inhibiting phagolysosome fusion (H. Wang et al., 2021). The dual PI3K and mTOR inhibitor NVP-BEZ235 has been shown to induce both types of cell deaths in glioma stem cells and sensitize the cells to ionizing radiation (W. Wang et al., 2013). Rottlerin, a small-molecule inhibitor of a protein kinase C-δ activates autophagy by regulating PI3k/Akt/mTOR pathway and promotes cell death in pancreatic CSCs and prostate CSCs (Kumar et al., 2014; Singh et al., 2012). Suberoylanilide hydroxamic acid (SAHA), the inhibitor of HDAC, has shown autophagic cell death in glioma stem cells (Chiao et al., 2013). Baicalein is a small molecule when bound to GTPase SAR1B protein, guanosine triphosphate inhibits autophagy and enhances the sensitivity of liver cancer stem-like cells to inhibitors of mTORC1(R. Wu et al., 2018). Quinacrine is an inhibitor of autophagy that can cross the blood-brain barrier and sensitizes the glioblastoma stem-like cells (GSCs) to temozolomide (Buccarelli et al., 2018; H. Kang et al., 2022). Moreover, phytochemicals (resveratrol and curcumin) have also shown inhibition on CSCs by inhibiting or activating autophagy pathways (Fu et al., 2014; Mao et al., 2021).

Targeting tumor cell

In myeloma and rat liver carcinoma, metformin induces autophagic cell death by regulating AMPK pathway (Park, 2015; Y. Wang et al., 2018). Cannabinoids induce autophagic cell death in pancreatic cancer cells (Dando et al., 2013). In colon cancer cells, safingol induces autophagy via PI3K/Akt/mTOR signalling (Coward et al., 2009). Similarly, HDAC inhibitors Panobinostat and SAHA induce autophagic cell death in colon cancer cells (Foggetti et al., 2019; Gandesiri et al., 2012). Lung cancer cells exhibit autophagy when treated with compound-6 and cabazitaxel via PI3K/Akt/mTOR pathway (Huo et al., 2016; Wang et al., 2018). *Ophiopogon japonicus* extract triggers autophagic cell death by regulating the same pathway (Chen et al., 2017). B-cell chronic lymphocytic leukemia cells undergo autophagic cell death when treated with MGCD0103, an HDAC inhibitor (El-Khoury et al., 2014). Itraconazole and GANT61 induce autophagic cell death in breast and liver cancer cells, respectively via Hh pathway (Wang et al., 2017; Wang et al., 2013). Similarly liver cancer cells undergo autophagic cell death when treated with Fangchinoline and PEITC via p53(N. Wang et al., 2011; Yeh et al., 2014). Breast cancer cells treated with CYT-Rx20 show an increase in autophagy(Hung et al., 2016). Melanoma cells exhibit autophagic cell death by AJ-5 via MAPK pathway when treated with DQ661 (Bleloch et al., 2019; Nicastri et al., 2018). When treated with arsenic trioxide, glioma cells undergo autophagic cell death (Chiu et al., 2010).

Targeting signalling

AMPK

The cellular energy demands regulate AMPK and since the tumor cells exhibit deregulated cellular metabolism, there are respective changes in AMPK activity which subsequently affect autophagy(S. Wang et al., 2022). In multiple myeloma, activation of AMPK/mTOR pathway by metformin induces autophagy causing proliferation inhibition (Wang et al., 2018). However, Park et al. (2013) showed that metformin inhibits autophagy and sensitizes the cells to apoptosis in H4IIE rat hepatocellular-carcinoma cells under glucose deprivation (Park, 2015). Cannabinoids induce autophagy and subsequent cell death in pancreatic tumor cells by activating AMPK pathway (Dando et al., 2013).

PI3K/Akt/mTOR

LY294002, 3-MA, and wortmannin inhibit PI3K/Akt/mTOR signalling, subsequently inhibiting autophagy and induce cell death (Ryabaya et al., 2017). Safingol is a sphingosine kinase and Protein kinase C inhibitor that prevents phosphorylation-inducing autophagic cell death (Coward et al., 2009). Cabazitaxel, a drug used for treating prostate cancer, exhibits antiproliferative effects in lung cancer by inducing autophagic cell death via PI3K/Akt/mTOR pathway (Huo et al., 2016). NVP-BEZ235 suppresses mTORC1 and induces autophagic cell death in multiple myeloma (Y. Ma et al., 2019). Apoptosis followed by autophagy is induced by certain compounds such as a hybrid of compound 6 also known as phenyl sulfonyl furoxan and 3-benzyl coumarin seco-B-ring derivative. This is achieved by inhibiting the phosphorylation of Akt, mTOR, p70S6K and 4EBP1(Q. Wang et al., 2018). Phytochemicals such as capsaicin and those derived from *Ophiopogon japonicus* cause antiproliferative effects in various tumor cells by regulating autophagy through PI3K/Akt/mTOR pathway. Arsenic trioxide and ionising

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radiation inhibit Akt/mTOR signalling and activate autophagic cell death (Chen et al., 2017; Chiu et al., 2010; Lin et al., 2017).

MAPK pathway

Autophagy is also regulated by MAPK pathway involving p38, JNK, and ERK(Zhou et al., 2015). Binuclear palladacycle complex, AJ-5 and CYT-Rx20, a β-nitrostyrene derivative, induce autophagic cell death in rhabdomyosarcoma and breast cancer cells, respectively by regulating the MAPK pathway (Bleloch et al., 2019; Hung et al., 2016).

p53

Tumor suppressor p53 affects autophagy based on its subcellular localization. Nuclear p53 enhances autophagy whereas p53 in the cytoplasm impedes autophagy (Rahman et al., 2022). Fangchinoline treatment causes p53 transport from the cytoplasm to the nucleus and activates autophagic cell death by activating sestrin 2 (Wang et al., 2011). Phenethyl isothiocyanate (PEITC), a phytochemical derived from cruciferous vegetables, inhibits the growth of tumor cells with mutant p53 by generating cell cycle arrest and sensitizing them to autophagic cell death (Yeh et al., 2014).

Epigenetic pathway

Inhibition of histone deacetylases induces autophagy in various tumors cells. Colon hepatic carcinoma cells undergo autophagic cell death when treated with SAHA induced via FoxO1-dependent pathway (Foggetti et al., 2019; Li et al., 2023). Panobinostat-treated colon cancer cells show proliferation reduction due to autophagy induction (Gandesiri et al., 2012). MGCD0103 impedes autophagy and sensitizes B-cell chronic lymphocytic leukemia (CLL) cells to apoptosis by activating caspases and PI3K/AKT/mTOR pathway (El-Khoury et al., 2014).

Autophagosome Fusion

A critical step in autophagy is the autophagosome-lysosome fusion to form autophago-lysosomes or simply autolysosomes. Chloroquine, quinine and their derivatives prevent the fusion of phagosome and lysosome and induce cell death by preventing the autophagic flux (Mauthe et al., 2018). Bafilomycin A1 inhibits vacuolar V-ATPases and enhances cell death (Yuan et al., 2015). DQ661 and lys05 also follow similar mechanisms of action (McAfee et al., 2012; Nicastri et al., 2018).

Small Molecule Inhibition of Autophagy related molecules

ULK1 inhibitor SBI-0206965 suppresses autophagy and cell proliferation in lung cancer cells (Tang et al., 2017). MRT68921 and MRT67307 inhibit autophagy by inhibiting both ULK1 and ULK2 (Petherick et al., 2015). In sharp contrast, LYN-1604 enhances autophagic flux and prevents cell proliferation in particular types of breast cancer (Zhang et al., 2017). SAR405 is a small molecule inhibitor of PI3K-III and PI3P that prevents autophagosome formation, and thus induces tumor cell death (Pasquier, 2015). Spautin-1 is a small-molecule that impedes the action of ubiquitin-specific peptidases USP13 and USP10 and inhibits autophagy (Pesce et al., 2018). S130, a small molecule inhibitor of Atg4B, causes delipidation of LC3-PE and inhibits autophagy (Fu et al., 2018). A similar mechanism is shown by another Atg4B inhibitor NSC185058 (Akin et al., 2014). GX15-070/Obatoclax is a Bcl-2 inhibitor that causes autophagic cell death (Cournoyer et al., 2019). Gossypol, a small-molecule inhibitor of Bcl-2 causes autophagic cell death by inhibiting Bcl-2 and Beclin1(Gao et al., 2010). p62 inhibitor verteporfin decreases the survival rate of breast cancer cells by preventing the binding of p62 to Atg8/LC3 (Wei and Li, 2020). In addition to the above molecules, miR-101 and miR-22 have also been shown to induce significant anti-proliferative effects in tumors by regulating autophagy (Frankel et al., 2011; C.-Y. Meng et al., 2020).

Challenges and Opportunities

Despite the promising advances, it is important to dig deeper into the non-canonical functions of molecules associated with apoptosis and autophagy to develop therapeutic interventions. The intricate signalling crosstalk of autophagy with apoptotic pathways is an important area of research. Since autophagy is critically involved in regulating several biological processes, deregulation has significant pathophysiological consequences. The role of autophagy in anti-tumor immunity and tumor microenvironment remodelling has massive implications in the era of cancer immunotherapy. However, autophagy research has several hurdles to overcome. Studying the consequences of post-translational and epigenetic changes in the expression and activity of autophagy-associated proteins is important. Since pan-autophagy inhibitors may have serious consequences on multiple organ systems, pursuing selective inhibition is the key. It is also critical to decide and target the most responsive patient population to therapeutic interventions exploiting autophagy, and this warrants extensive research on identifying the most relevant biomarkers, both predictive and pharmacodynamic. Recent advances indeed indicate a promising future for therapeutics targeting apoptosis and autophagy for successful clinical outcomes in cancer.

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Table 2. Drugs targeting autophagy.

Drug	Cancer Type	Mechanism	Reference
Targeting Stem cell			
Salinomycin	Breast	Increase in autophagy through ROS induction	(Wang et al., 2021)
	Breast	Inhibiting autophagy by triggering apoptosis	
	Colon	Increase in autophagy through ROS induction	(Klose et al., 2019)
Chloroquine	Breast	Inhibition of autophagy via JAK2, DNMT1	(Liang et al., 2016)
NVP-BEZ235	Glioma	Inducing autophagy via PI3K/AKT/mTOR pathway	(Wang et al., 2013)
SAHA	Glioblastoma	Inducing autophagy via HDAC	(Chiao et al., 2013)
Givinostat	Glioblastoma	Inhibiting autophagy via HDAC	(Nakagawa-Saito et al., 2023)
Quinacrine	Glioblastoma	Inhibiting autophagy via lipid peroxides	(Nicastri et al., 2018)
Baicalein	Mouse liver tumor	Inhibiting autophagy via GTPase SAR1B protein	(Wu et al., 2018)
Curcumin	Colon	Inducing autophagy via DCLK1	(Mao et al., 2021)
JQ1	Leukemia	Inducing autophagy via AMPK-ULK1 pathway	(Jang et al., 2017)
Resveratrol	Breast cancer	Inducing autophagy via Wnt/β-catenin pathway	(Fu et al., 2014)
Drug Targeting Cancer Cell			
Cannabinoids	Pancreatic cancer	Inducing autophagy via AMPK pathway	(Dando et al., 2013)
Compound 6	Lung	Inducing autophagy via PI3K/Akt/mTOR	(Wang et al., 2018)
Cabazitaxel	Lung	Inducing autophagy via PI3K/Akt/mTOR	(Huo et al., 2016)
Itraconazole	Hepato and Breast	Inducing autophagic cell death via Hh	(Wang et al., 2017)
lys05	Glioblastoma	Inhibits autophagy by inhibiting the autophagosome-lysosome fusion	(McAfee et al., 2012)
PEITC	Hepatic carcinoma	Induce autophagy via p53	(Yeh et al., 2014)
Bafilomycin A1	B-cell ALL	Inhibits autophagosome-lysosome fusion	(Yuan et al., 2015)
Metformin	Rat liver carcinoma	Inhibits autophagy via AMPK, p38/MAPK	(B. Park, 2015)
Safingol	Colon cancer	Induces autophagy via PI3K/Akt/mTOR	(Coward et al., 2009)

Arsenic-trioxide	Glioma	Induces autophagic cell death via PI3K/Akt, ERK1/2	(Chiu et al., 2010)
Capsaicin	Nasopharyngeal carcinoma	Induces autophagy via PI3K/Akt/mTOR	(Lin et al., 2017)
DQ661	Melanoma	Inhibits autophagy by inhibiting the autophagosome-lysosome fusion	(Nicastri et al., 2018)
AJ-5	Melanoma	Induces autophagic cell death via MAPK	(Bleloch et al., 2019)
CYT-Rx20	Breast cancer	Induces autophagy via MAPK	(Hung et al., 2016)
MGCD0103	B-cell CLL	Inhibits autophagy by inhibiting HDAC	(El-Khoury et al., 2014)
Drug/Small molecule Targeting Autophagy Related Molecules			
ABT-737	Colon cancer	Inhibition of autophagy via inhibiting Bcl-2	(Huo et al., 2016)
SBI-0206965	Lung cancer cell	Inhibits autophagy by inhibiting ULK1	(Cournoyer et al., 2019)
Verteporfin	Prostate cancer cell	Inhibits autophagy by inhibiting p62/SQSTM1	(Wei and Li, 2020)
Obatoclax	ALL	Inhibits Bcl-2 and induces autophagy	(Cournoyer et al., 2019)
Spautin-1	Cervical carcinoma	Inhibits autophagy by inhibiting Vps34	(Pesce et al., 2018)

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Conflict of Interest

The author declares that there is no conflict of interest.

References

Abbas, R., & Larisch, S. (2021). Killing by Degradation: Regulation of Apoptosis by the Ubiquitin-Proteasome-System. *Cells*, *10*(12), 3465. https://doi.org/10.3390/cells10123465

Ahmadi-Dehlaghi, F., Mohammadi, P., Valipour, E., Pournaghi, P., Kiani, S., & Mansouri, K. (2023). Autophagy: A challengeable paradox in cancer treatment. *Cancer Medicine*, *12*(10), 11542–11569. https://doi.org/10.1002/cam4.5577

Airiau, K., Prouzet-Mauléon, V., Rousseau, B., Pigneux, A., Jeanneteau, M., Giraudon, M., Allou, K., Dubus, P., Belloc, F., & Mahon, F.X. (2015). Synergistic cooperation between ABT-263 and MEK1/2 inhibitor: Effect on apoptosis and proliferation of acute myeloid leukemia cells. *Oncotarget*, *7*(1), 845–859.

Akin, D., Wang, S. K., Habibzadegah-Tari, P., Law, B., Ostrov, D., Li, M., Yin, X.M., Kim, J.-S., Horenstein, N., & Dunn, W. A. (2014). A novel ATG4B antagonist inhibits autophagy and has a negative impact on osteosarcoma tumors. *Autophagy*, *10*(11), 2021–2035. https://doi.org/10.4161/auto.32229

Alaseem, A. M. (2023). Advancements in MDM2 inhibition: Clinical and pre-clinical investigations of combination therapeutic regimens. *Saudi Pharmaceutical Journal : SPJ*, *31*(10). https://doi.org/10.1016/j.jsps.2023.101790

Albadari, N., & Li, W. (2023). Survivin Small Molecules Inhibitors: Recent Advances and Challenges. *Molecules*, *28*(3), 1376. https://doi.org/10.3390/molecules28031376

Amaravadi, R. K., Schilder, R. J., Martin, L. P., Levin, M., Graham, M. A., Weng, D. E., & Adjei, A. A. (2015). A Phase I Study of the SMAC-Mimetic Birinapant in Adults with Refractory Solid Tumors or Lymphoma. *Molecular Cancer Therapeutics*, *14*(11), 2569–2575. https://doi.org/10.1158/1535-7163.MCT-15-0475

Aquila, S., Santoro, M., Caputo, A., Panno, M. L., Pezzi, V., & De Amicis, F. (2020). The Tumor Suppressor PTEN as Molecular Switch Node Regulating Cell Metabolism and Autophagy: Implications in Immune System and Tumor Microenvironment. *Cells*, *9*(7), 1725. https://doi.org/10.3390/cells9071725

Ariosa, A. R., Lahiri, V., Lei, Y., Yang, Y., Yin, Z., Zhang, Z., & Klionsky, D. J. (2021). A perspective on the role of autophagy in cancer. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1867*(12), 166262. https://doi.org/10.1016/j.bbadis.2021.166262

Ashe, P. C., & Berry, M. D. (2003). Apoptotic signaling cascades. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *27*(2), 199–214. https://doi.org/10.1016/S0278-5846(03)00016-2

Balic, A., Sørensen, M. D., Trabulo, S. M., Sainz, B., Cioffi, M., Vieira, C. R., Miranda-Lorenzo, I., Hidalgo, M., Kleeff, J., Erkan, M., & Heeschen, C. (2014). Chloroquine Targets Pancreatic Cancer Stem Cells via Inhibition of CXCR4 and Hedgehog Signaling. *Molecular Cancer Therapeutics*, *13*(7), 1758–1771. https://doi.org/10.1158/1535-7163.MCT-13-0948

Bao, X., Liu, X., Li, F., & Li, C.-Y. (2020). Limited MOMP, ATM, and their roles in carcinogenesis and cancer treatment. *Cell & Bioscience*, *10*(1), 81. https://doi.org/10.1186/s13578-020-00442-y

Bleloch, J. S., du Toit, A., Gibhard, L., Kimani, S., Ballim, R. D., Lee, M., Blanckenberg, A., Mapolie, S., Wiesner, L., Loos, B., & Prince, S. (2019). The palladacycle complex AJ-5 induces apoptotic cell death while reducing autophagic flux in rhabdomyosarcoma cells. *Cell Death Discovery*, *5*, 60. https://doi.org/10.1038/s41420-019-0139-9

Boga, I., & Bisgin, A. (2022). Real-world applications of tumor mutation burden (TMB) analysis using ctDNA and FFPE samples in various cancer types of Turkish population. *Int. J. Exp. Res. Rev.*, *29*, 89-93. https://doi.org/10.52756/ijerr.2022.v29.010

Bolomsky, A., Vogler, M., Köse, M. C., Heckman, C. A., Ehx, G., Ludwig, H., & Caers, J. (2020). MCL-1 inhibitors, fast-lane development of a new class of anti-cancer agents. *Journal of Hematology & Oncology*, *13*(1), 173. https://doi.org/10.1186/s13045-020-01007-9

Buccarelli, M., Marconi, M., Pacioni, S., De Pascalis, I., D'Alessandris, Q. G., Martini, M., Ascione, B., Malorni, W., Larocca, L. M., Pallini, R., Ricci-Vitiani, L., & Matarrese, P. (2018). Inhibition of autophagy increases susceptibility of glioblastoma stem cells to temozolomide by igniting ferroptosis. *Cell Death & Disease*, *9*(8), 841. https://doi.org/10.1038/s41419-018-0864-7

Bustos, S. O., Antunes, F., Rangel, M. C., & Chammas, R. (2020). Emerging Autophagy Functions Shape the Tumor Microenvironment and Play a Role in Cancer Progression—Implications for Cancer Therapy. *Frontiers in Oncology*, *10*, 606436. https://doi.org/10.3389/fonc.2020.606436

Campbell, K. J., & Tait, S. W. G. (2018). Targeting BCL-2 regulated apoptosis in cancer. *Open Biology*, *8*(5), 180002. https://doi.org/10.1098/rsob.180002

Carneiro, B. A., & El-Deiry, W. S. (2020). Targeting apoptosis in cancer therapy. *Nature Reviews. Clinical Oncology*, *17*(7), 395–417. https://doi.org/10.1038/s41571-020-0341-y

Carneiro, B. A., Perets, R., Dowlati, A., LoRusso, P., Yonemori, K., He, L., Munasinghe, W., Noorani, B., Johnson, E. F., & Zugazagoitia, J. (2023). Mirzotamab clezutoclax as monotherapy and in combination with taxane therapy in relapsed/refractory solid tumors: Dose expansion results. *Journal of Clinical Oncology*, *41*(16_suppl), 3027–3027. https://doi.org/10.1200/JCO.2023.41.16_suppl.3027

Carrasco, R. A., Stamm, N. B., Marcusson, E., Sandusky, G., Iversen, P., & Patel, B. K. R. (2011). Antisense inhibition of survivin expression as a cancer therapeutic. *Molecular Cancer Therapeutics*, *10*(2), 221–232. https://doi.org/10.1158/1535-7163.MCT-10-0756

Carter, B. Z., Mak, D. H., Morris, S. J., Borthakur, G., Estey, E., Byrd, A. L., Konopleva, M., Kantarjian, H., & Andreeff, M. (2011). XIAP antisense oligonucleotide (AEG35156) achieves target knockdown and induces apoptosis preferentially in CD34+38- cells in a phase 1/2 study of patients with relapsed/refractory AML. *Apoptosis: An International Journal on Programmed Cell Death*,

16(1), 67–74. https://doi.org/10.1007/s10495-010-0545-1

Cetraro, P., Plaza-Diaz, J., MacKenzie, A., & Abadía-Molina, F. (2022). A Review of the Current Impact of Inhibitors of Apoptosis Proteins and Their Repression in Cancer. *Cancers*, *14*(7), Article 7. https://doi.org/10.3390/cancers14071671

Chang, K.-C., Liu, P.-F., Chang, C.-H., Lin, Y.-C., Chen, Y.J., & Shu, C.-W. (2022). The interplay of autophagy and oxidative stress in the pathogenesis and therapy of retinal degenerative diseases. *Cell & Bioscience*, *12*(1), 1. https://doi.org/10.1186/s13578-021-00736-9

Chang, N. C., Nguyen, M., Bourdon, J., Risse, P.-A., Martin, J., Danialou, G., Rizzuto, R., Petrof, B. J., & Shore, G. C. (2012). Bcl-2-associated autophagy regulator Naf-1 required for maintenance of skeletal muscle. *Human Molecular Genetics*, *21*(10), 2277–2287. https://doi.org/10.1093/hmg/dds048

Chen, J., Yuan, J., Zhou, L., Zhu, M., Shi, Z., Song, J., Xu, Q., Yin, G., Lv, Y., Luo, Y., Jia, X., & Feng, L. (2017). Regulation of different components from Ophiopogon japonicus on autophagy in human lung adenocarcinoma A549Cells through PI3K/Akt/mTOR signaling pathway. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *87*, 118–126. https://doi.org/10.1016/j.biopha.2016.12.093

Chen, R.-H., Chen, Y.-H., & Huang, T.-Y. (2019). Ubiquitin-mediated regulation of autophagy. *Journal of Biomedical Science*, *26*(1), 80. https://doi.org/10.1186/s12929-019-0569-y

Chesi, M., Mirza, N. N., Garbitt, V. M., Sharik, M. E., Dueck, A. C., Asmann, Y. W., Akhmetzyanova, I., Kosiorek, H. E., Calcinotto, A., Riggs, D. L., Keane, N., Ahmann, G. J., Morrison, K. M., Fonseca, R., Lacy, M. Q., Dingli, D., Kumar, S. K., Ailawadhi, S., Dispenzieri, A., … Bergsagel, P. L. (2016). IAP antagonists induce anti-tumor immunity in multiple myeloma. *Nature Medicine*, *22*(12), 1411–1420. https://doi.org/10.1038/nm.4229

Chiao, M.T., Cheng, W.Y., Yang, Y.C., Shen, C.C., & Ko, J.L. (2013). Suberoylanilide hydroxamic acid (SAHA) causes tumor growth slowdown and triggers autophagy in glioblastoma stem cells. *Autophagy*, *9*(10), 1509–1526. https://doi.org/10.4161/auto.25664

Chiu, H.W., Lin, J.H., Chen, Y.A., Ho, S.Y., & Wang, Y.J. (2010). Combination treatment with arsenic trioxide and irradiation enhances cell-killing effects in human fibrosarcoma cells in vitro and in vivo through induction of both autophagy and apoptosis. *Autophagy*, *6*(3), 353–365. https://doi.org/10.4161/auto.6.3.11229

Choi, C., Lee, G. H., Son, A., Yoo, G. S., Yu, J. I., & Park, H. C. (2021). Downregulation of Mcl-1 by Panobinostat Potentiates Proton Beam Therapy in Hepatocellular Carcinoma Cells. *Cells*, *10*(3), 554. https://doi.org/10.3390/cells10030554

Choi, D. S., Blanco, E., Kim, Y.S., Rodriguez, A. A., Zhao, H., Huang, T. H.M., Chen, C.L., Jin, G., Landis, M. D., Burey, L. A., Qian, W., Granados, S. M., Dave, B., Wong, H. H., Ferrari, M., Wong, S. T., & Chang, J. C. (2014). Chloroquine eliminates cancer stem cells through deregulation of Jak2 and DNMT1. *Stem Cells (Dayton, Ohio)*, *32*(9), 2309–2323. https://doi.org/10.1002/stem.1746

Cournoyer, S., Addioui, A., Belounis, A., Beaunoyer, M., Nyalendo, C., Le Gall, R., Teira, P., Haddad, E., Vassal, G., & Sartelet, H. (2019). GX15–070 (Obatoclax), a Bcl-2 family proteins inhibitor engenders apoptosis and pro-survival autophagy and increases Chemosensitivity in neuroblastoma. *BMC Cancer*, *19*(1), 1018. https://doi.org/10.1186/s12885-019-6195-y

Coward, J., Ambrosini, G., Musi, E., Truman, J.P., Haimovitz-Friedman, A., Allegood, J. C., Wang, E., Merrill, A. H., & Schwartz, G. K. (2009). Safingol (L-threo-sphinganine) induces autophagy in solid tumor cells through inhibition of PKC and the PI3-kinase pathway. *Autophagy*, *5*(2), 184–193. https://doi.org/10.4161/auto.5.2.7361

Dando, I., Donadelli, M., Costanzo, C., Pozza, E. D., D'Alessandro, A., Zolla, L., & Palmieri, M. (2013). Cannabinoids inhibit energetic metabolism and induce AMPK-dependent autophagy in pancreatic cancer cells. *Cell Death & Disease*, *4*(6), e664. https://doi.org/10.1038/cddis.2013.151

D'Arcy, M. S. (2019). Cell death: A review of the major forms of apoptosis, necrosis and autophagy. *Cell Biology International*, *43*(6), 582–592. https://doi.org/10.1002/cbin.11137

Das, J., Das, M., Doke, M., Wnuk, S., Stiffin, R., Ruiz, M., & Celli, J. (2021). A small molecule inhibits pancreatic cancer stem cells. *Int. J. Exp. Res. Rev.*, *26*, 1-15. https://doi.org/10.52756/ijerr.2021.v26.001

Di Cristofano, F., George, A., Tajiknia, V., Ghandali, M., Wu, L., Zhang, Y., Srinivasan, P., Strandberg, J., Hahn, M., Sanchez Sevilla Uruchurtu, A., Seyhan, A. A., Carneiro, B. A., Zhou, L., Huntington, K. E., & El-Deiry, W. S. (2023). Therapeutic targeting of

TRAIL death receptors. *Biochemical Society Transactions*, *51*(1), 57–70. https://doi.org/10.1042/BST20220098

Di Filippo, M., & Bernardi, G. (2009). The Early Apoptotic DNA Fragmentation Targets a Small Number of Specific Open Chromatin Regions. *PLoS ONE*, *4*(4), e5010. https://doi.org/10.1371/journal.pone.0005010

Di Malta, C., Cinque, L., & Settembre, C. (2019). Transcriptional Regulation of Autophagy: Mechanisms and Diseases. *Frontiers in Cell and Developmental Biology*, *7*. https://www.frontiersin.org/articles/10.3389/fcell.2019.00114

Di Nardo, A., Wertz, M. H., Kwiatkowski, E., Tsai, P. T., Leech, J. D., Greene-Colozzi, E., Goto, J., Dilsiz, P., Talos, D. M., Clish, C. B., Kwiatkowski, D. J., & Sahin, M. (2014). Neuronal Tsc1/2 complex controls autophagy through AMPK-dependent regulation of ULK1. *Human Molecular Genetics*, *23*(14), 3865–3874. https://doi.org/10.1093/hmg/ddu101

Ding, Y., & Choi, M. E. (2014). Regulation of Autophagy by TGF-β: Emerging Role in Kidney Fibrosis. *Seminars in Nephrology*, *34*(1), 62. https://doi.org/10.1016/j.semnephrol.2013.11.009

Eisenberg-Lerner, A., Bialik, S., Simon, H.-U., & Kimchi, A. (2009). Life and death partners: Apoptosis, autophagy and the cross-talk between them. *Cell Death & Differentiation*, *16*(7), Article 7. https://doi.org/10.1038/cdd.2009.33

Eljack, S., Allard-Vannier, E., Misericordia, Y., Hervé-Aubert, K., Aubrey, N., Chourpa, I., Faggad, A., & David, S. (2022). Combination of Nanovectorized siRNA Directed against Survivin with Doxorubicin for Efficient Anti-Cancer Activity in HER2+ Breast Cancer Cells. *Pharmaceutics*, *14*(11), 2537. https://doi.org/10.3390/pharmaceutics14112537

El-Khattouti, A., Selimovic, D., Haikel, Y., & Hassan, M. (2013). Crosstalk Between Apoptosis and Autophagy: Molecular Mechanisms and Therapeutic Strategies in Cancer. *Journal of Cell Death*, *6*, 37–55. https://doi.org/10.4137/JCD.S11034

El-Khoury, V., Pierson, S., Szwarcbart, E., Brons, N. H. C., Roland, O., Cherrier-De Wilde, S., Plawny, L., Van Dyck, E., & Berchem, G. (2014). Disruption of autophagy by the histone deacetylase inhibitor MGCD0103 and its therapeutic implication in B-cell chronic lymphocytic leukemia. *Leukemia*, *28*(8), 1636–1646. https://doi.org/10.1038/leu.2014.19

Fairlie, W. D., Tran, S., & Lee, E. F. (2020). Chapter Four—Crosstalk between apoptosis and autophagy signaling pathways. In J. K. E. Spetz & L. Galluzzi (Eds.), *International Review of Cell and Molecular Biology* (Vol. 352, pp. 115–158). Academic Press. https://doi.org/10.1016/bs.ircmb.2020.01.003

Filomeni, G., De Zio, D., & Cecconi, F. (2015). Oxidative stress and autophagy: The clash between damage and metabolic needs. *Cell Death & Differentiation*, *22*(3), Article 3. https://doi.org/10.1038/cdd.2014.150

Foggetti, G., Ottaggio, L., Russo, D., Mazzitelli, C., Monti, P., Degan, P., Miele, M., Fronza, G., & Menichini, P. (2019). Autophagy induced by SAHA affects mutant P53 degradation and cancer cell survival. *Bioscience Reports*, *39*(2), BSR20181345. https://doi.org/10.1042/BSR20181345

Frankel, L. B., Wen, J., Lees, M., Høyer-Hansen, M., Farkas, T., Krogh, A., Jäättelä, M., & Lund, A. H. (2011). microRNA-101 is a potent inhibitor of autophagy. *The EMBO Journal*, *30*(22), 4628–4641. https://doi.org/10.1038/emboj.2011.331

Fu, Y., Chang, H., Peng, X., Bai, Q., Yi, L., Zhou, Y., Zhu, J., & Mi, M. (2014). Resveratrol inhibits breast cancer stem-like cells and induces autophagy via suppressing Wnt/β-catenin signaling pathway. *PloS One*, *9*(7), e102535. https://doi.org/10.1371/journal.pone.0102535

Fu, Y., Hong, L., Xu, J., Zhong, G., Gu, Q., Gu, Q., Guan, Y., Zheng, X., Dai, Q., Luo, X., Liu, C., Huang, Z., Yin, X.-M., Liu, P., & Li, M. (2018). Discovery of a small molecule targeting autophagy via ATG4B inhibition and cell death of colorectal cancer cells in vitro and in vivo. *Autophagy*, *15*(2), 295–311. https://doi.org/10.1080/15548627.2018.1517073

Gagliardi, M., & Ashizawa, A. T. (2022). Making Sense of Antisense Oligonucleotide Therapeutics Targeting Bcl-2. *Pharmaceutics*, *14*(1), 97. https://doi.org/10.3390/pharmaceutics14010097

Gandesiri, M., Chakilam, S., Ivanovska, J., Benderska, N., Ocker, M., Di Fazio, P., Feoktistova, M., Gali-Muhtasib, H., Rave-Fränk, M., Prante, O., Christiansen, H., Leverkus, M., Hartmann, A., & Schneider-Stock, R. (2012). DAPK plays an important role in panobinostat-induced autophagy and commits cells to apoptosis under autophagy deficient conditions. *Apoptosis*, *17*(12), 1300–1315. https://doi.org/10.1007/s10495-012-0757-7

Gao, P., Bauvy, C., Souquère, S., Tonelli, G., Liu, L., Zhu, Y., Qiao, Z., Bakula, D., Proikas-Cezanne, T., Pierron, G., Codogno, P., Chen, Q., & Mehrpour, M. (2010). The Bcl-2 Homology Domain 3 Mimetic Gossypol Induces Both Beclin 1-dependent and

Beclin 1-independent Cytoprotective Autophagy in Cancer Cells. *The Journal of Biological Chemistry*, *285*(33), 25570–25581. https://doi.org/10.1074/jbc.M110.118125

Gholizadeh, M. A., Shamsabadi, F. T., Yamchi, A., Golalipour, M., Jhingan, G. D., & Shahbazi, M. (2020). Identification of hub genes associated with RNAi-induced silencing of XIAP through targeted proteomics approach in MCF7 cells. *Cell & Bioscience*, *10*(1), 78. https://doi.org/10.1186/s13578-020-00437-9

Green, D. R., & Llambi, F. (2015). Cell Death Signaling. *Cold Spring Harbor Perspectives in Biology*, *7*(12), a006080. https://doi.org/10.1101/cshperspect.a006080

Grisan, F., Iannucci, L. F., Surdo, N. C., Gerbino, A., Zanin, S., Di Benedetto, G., Pozzan, T., & Lefkimmiatis, K. (2021). PKA compartmentalization links cAMP signaling and autophagy. *Cell Death & Differentiation*, *28*(8), Article 8. https://doi.org/10.1038/s41418-021-00761-8

Grossi, V., Lucarelli, G., Forte, G., Peserico, A., Matrone, A., Germani, A., Rutigliano, M., Stella, A., Bagnulo, R., Loconte, D., Galleggiante, V., Sanguedolce, F., Cagiano, S., Bufo, P., Trabucco, S., Maiorano, E., Ditonno, P., Battaglia, M., Resta, N., & Simone, C. (2015). Loss of STK11 expression is an early event in prostate carcinogenesis and predicts therapeutic response to targeted therapy against MAPK/p38. *Autophagy*, *11*(11), 2102–2113. https://doi.org/10.1080/15548627.2015.1091910

Gu, Y., Zhao, X., & Song, X. (2020). Ex vivo pulsed dendritic cell vaccination against cancer. *Acta Pharmacologica Sinica*, *41*(7), Article 7. https://doi.org/10.1038/s41401-020-0415-5

Guo, K., Searfoss, G., Krolikowski, D., Pagnoni, M., Franks, C., Clark, K., Yu, K. T., Jaye, M., & Ivashchenko, Y. (2001). Hypoxia induces the expression of the pro-apoptotic gene BNIP3. *Cell Death & Differentiation*, *8*(4), Article 4. https://doi.org/10.1038/sj.cdd.4400810

Hanahan, D. (2022). Hallmarks of Cancer: New Dimensions. *Cancer Discovery*, *12*(1), 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059

Herbst, R. S., & Frankel, S. R. (2004). Oblimersen sodium (Genasense bcl-2 antisense oligonucleotide): A rational therapeutic to enhance apoptosis in therapy of lung cancer. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *10*(12 Pt 2), 4245s–4248s. https://doi.org/10.1158/1078-0432.CCR-040018

Hounsell, C., & Fan, Y. (2021). The Duality of Caspases in Cancer, as Told through the Fly. *International Journal of Molecular Sciences*, *22*(16), 8927. https://doi.org/10.3390/ijms22168927

Hu, J., Cao, J., Topatana, W., Juengpanich, S., Li, S., Zhang, B., Shen, J., Cai, L., Cai, X., & Chen, M. (2021). Targeting mutant p53 for cancer therapy: Direct and indirect strategies. *Journal of Hematology & Oncology*, *14*(1), 157. https://doi.org/10.1186/s13045-021-01169-0

Hu, J., Pan, D., Li, G., Chen, K., & Hu, X. (2022). Regulation of programmed cell death by Brd4. *Cell Death & Disease*, *13*(12), 1059. https://doi.org/10.1038/s41419-022-05505-1

Hung, A. C., Tsai, C.-H., Hou, M.-F., Chang, W.-L., Wang, C.H., Lee, Y.-C., Ko, A., Hu, S. C.-S., Chang, F.R., Hsieh, P.W., & Yuan, S.S. F. (2016). The synthetic β-nitrostyrene derivative CYT-Rx20 induces breast cancer cell death and autophagy via ROS-mediated MEK/ERK pathway. *Cancer Letters*, *371*(2), 251–261. https://doi.org/10.1016/j.canlet.2015.11.035

Huo, R., Wang, L., Liu, P., Zhao, Y., Zhang, C., Bai, B., Liu, X., Shi, C., Wei, S., & Zhang, H. (2016). Cabazitaxel-induced autophagy via the PI3K/Akt/mTOR pathway contributes to A549 cell death. *Molecular Medicine Reports*, *14*(4), 3013. https://doi.org/10.3892/mmr.2016.5648

Iurlaro, R., & Muñoz-Pinedo, C. (2016). Cell death induced by endoplasmic reticulum stress. *The FEBS Journal*, *283*(14), 2640–2652. https://doi.org/10.1111/febs.13598

Jang, J. E., Eom, J.I., Jeung, H.-K., Cheong, J.W., Lee, J. Y., Kim, J. S., & Min, Y. H. (2017). AMPK-ULK1-Mediated Autophagy Confers Resistance to BET Inhibitor JQ1 in Acute Myeloid Leukemia Stem Cells. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *23*(11), 2781–2794. https://doi.org/10.1158/1078-0432.CCR-16-1903

Jinesh, G. G., & Kamat, A. M. (2017). The Blebbishield Emergency Program Overrides Chromosomal Instability and Phagocytosis Checkpoints in Cancer Stem Cells. *Cancer Research*, *77*(22), 6144–6156. https://doi.org/10.1158/0008-5472.CAN-17-0522

Kale, J., Osterlund, E. J., & Andrews, D. W. (2018). BCL-2 family proteins: Changing partners in the dance towards death. *Cell Death & Differentiation*, *25*(1), Article 1. https://doi.org/10.1038/cdd.2017.186

Kang, H., Lee, H., Kim, D., Kim, B., Kang, J., Kim, H. Y., Youn, H., & Youn, B. (2022). Targeting Glioblastoma Stem Cells to Overcome Chemoresistance: An Overview of Current Therapeutic Strategies. *Biomedicines*, *10*(6), 1308. https://doi.org/10.3390/biomedicines10061308

Kang, M. H., & Reynolds, C. P. (2009). Bcl-2 Inhibitors: Targeting Mitochondrial Apoptotic Pathways in Cancer Therapy. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*, *15*(4), 1126–1132. https://doi.org/10.1158/1078-0432.CCR-08-0144

Kargbo, R. B. (2023a). Potent and Selective BCL-XL Inhibitors and PROTAC Compounds as Potential Cancer Treatment and Immunotherapy. *ACS Medicinal Chemistry Letters*, *14*(6), 702–704. https://doi.org/10.1021/acsmedchemlett.3c00181

Kargbo, R. B. (2023b). Redefining Cancer Therapy: Toward BCL-XL/BCL-2 Dual Inhibitors with Diminished Platelet Toxicity. *ACS Medicinal Chemistry Letters*, *14*(9), 1156–1158. https://doi.org/10.1021/acsmedchemlett.3c00357

Kari, S., Subramanian, K., Altomonte, I. A., Murugesan, A., Yli-Harja, O., & Kandhavelu, M. (2022). Programmed cell death detection methods: A systematic review and a categorical comparison. *Apoptosis*, *27*(7), 482–508. https://doi.org/10.1007/s10495-022-01735-y

Kashyap, D., Garg, V. K., & Goel, N. (2021). Intrinsic and extrinsic pathways of apoptosis: Role in cancer development and prognosis. *Advances in Protein Chemistry and Structural Biology*, *125*, 73–120. https://doi.org/10.1016/bs.apcsb.2021.01.003

Ke, D., Yu, Y., Li, C., Han, J., & Xu, J. (2022). Phosphorylation of BCL2 at the Ser70 site mediates RANKL-induced osteoclast precursor autophagy and osteoclastogenesis. *Molecular Medicine*, *28*(1), 22. https://doi.org/10.1186/s10020-022-00449-w

Kesavan, Y., Sahabudeen, S., & Ramalingam, S. (2023). Exosomes Derived from Metastatic Colon Cancer Cells Induced Oncogenic Transformation and Migratory Potential of Immortalized Human Cells. *Int. J. Exp. Res. Rev.*, *36*, 37-46. https://doi.org/10.52756/ijerr.2023.v36.003

Ketelut-Carneiro, N., & Fitzgerald, K. A. (2022). Apoptosis, Pyroptosis, and Necroptosis-Oh My! The Many Ways a Cell Can Die. *Journal of Molecular Biology*, *434*(4), 167378. https://doi.org/10.1016/j.jmb.2021.167378

Kist, M., & Vucic, D. (2021). Cell death pathways: Intricate connections and disease implications. *The EMBO Journal*, *40*(5), e106700. https://doi.org/10.15252/embj.2020106700

Klose, J., Trefz, S., Wagner, T., Steffen, L., Preißendörfer Charrier, A., Radhakrishnan, P., Volz, C., Schmidt, T., Ulrich, A., Dieter, S. M., Ball, C., Glimm, H., & Schneider, M. (2019). Salinomycin: Anti-tumor activity in a pre-clinical colorectal cancer model. *PLoS ONE*, *14*(2), e0211916. https://doi.org/10.1371/journal.pone.0211916

Kulkarni, N., Tank, S., Korlekar, P., Shidhaye, S., & Barve, P. (2023). A review of gene mutations, conventional testing and novel approaches to cancer screening. *Int. J. Exp. Res. Rev.*, *30*, 134-162. https://doi.org/10.52756/ijerr.2023.v30.015

Kumar, D., Shankar, S., & Srivastava, R. K. (2014). Rottlerin induces autophagy and apoptosis in prostate cancer stem cells via PI3K/Akt/mTOR signaling pathway. *Cancer Letters*, *343*(2), 179–189. https://doi.org/10.1016/j.canlet.2013.10.003

Lane, D. P., Cheok, C. F., & Lain, S. (2010). P53-based Cancer Therapy. *Cold Spring Harbor Perspectives in Biology*, *2*(9), a001222. https://doi.org/10.1101/cshperspect.a001222

Lee, Y.K., & Lee, J.A. (2016). Role of the mammalian ATG8/LC3 family in autophagy: Differential and compensatory roles in the spatiotemporal regulation of autophagy. *BMB Reports*, *49*(8), 424–430. https://doi.org/10.5483/BMBRep.2016.49.8.081

Levine, A. J. (2022). Targeting the P53 Protein for Cancer Therapies: The Translational Impact of P53 Research. *Cancer Research*, *82*(3), 362–364. https://doi.org/10.1158/0008-5472.CAN-21-2709

Li, J.Y., Tian, T., Han, B., Yang, T., Guo, Y.X., Wu, J.Y., Chen, Y.S., Yang, Q., & Xie, R.J. (2023). Suberoylanilide hydroxamic acid upregulates reticulophagy receptor expression and promotes cell death in hepatocellular carcinoma cells. *World Journal of Gastroenterology*, *29*(34), 5038–5053. https://doi.org/10.3748/wjg.v29.i34.5038

Li, W., Luo, L.X., Zhou, Q.Q., Gong, H.B., Fu, Y.Y., Yan, C.Y., Li, E., Sun, J., Luo, Z., Ding, Z.J., Zhang, Q.Y., Mu, H.L., Cao, Y.F., Ouyang, S.H., Kurihara, H., Li, Y.F., Sun, W.Y., Li, M., & He, R.R. (2022). Phospholipid peroxidation inhibits autophagy via stimulating the delipidation of oxidized LC3-PE. *Redox Biology*, *55*, 102421. https://doi.org/10.1016/j.redox.2022.102421

Li, Z.N., & Luo, Y. (2022). HSP90 inhibitors and cancer: Prospects for use in targeted therapies (Review). *Oncology Reports*, *49*(1), 6. https://doi.org/10.3892/or.2022.8443

Liang, D. H., Choi, D. S., Ensor, J. E., Kaipparettu, B. A., Bass, B. L., & Chang, J. C. (2016). The autophagy inhibitor chloroquine targets cancer stem cells in triple negative breast cancer by inducing mitochondrial damage and impairing DNA break repair. *Cancer Letters*, *376*(2), 249–258. https://doi.org/10.1016/j.canlet.2016.04.002

Lin, H.H., Hsu, H.L., & Yeh, N.H. (2007). Apoptotic cleavage of NuMA at the C-terminal end is related to nuclear disruption and death amplification. *Journal of Biomedical Science*, *14*(5), 681–694. https://doi.org/10.1007/s11373-007-9165-3

Lin, Y.-T., Wang, H.C., Hsu, Y.C., Cho, C.L., Yang, M.Y., & Chien, C.Y. (2017). Capsaicin Induces Autophagy and Apoptosis in Human Nasopharyngeal Carcinoma Cells by Downregulating the PI3K/AKT/mTOR Pathway. *International Journal of Molecular Sciences*, *18*(7), 1343. https://doi.org/10.3390/ijms18071343

Lindenboim, L., Zohar, H., Worman, H. J., & Stein, R. (2020). The nuclear envelope: Target and mediator of the apoptotic process. *Cell Death Discovery*, *6*(1), Article 1. https://doi.org/10.1038/s41420-020-0256-5

Liu, J., Hong, M., Li, Y., Chen, D., Wu, Y., & Hu, Y. (2022). Programmed Cell Death Tunes Tumor Immunity. *Frontiers in Immunology*, *13*, 847345. https://doi.org/10.3389/fimmu.2022.847345

Liu, S., Yao, S., Yang, H., Liu, S., & Wang, Y. (2023). Autophagy: Regulator of cell death. *Cell Death & Disease*, *14*(10), 648. https://doi.org/10.1038/s41419-023-06154-8

Lőrincz, P., & Juhász, G. (2020). Autophagosome-Lysosome Fusion. *Journal of Molecular Biology*, *432*(8), 2462–2482. https://doi.org/10.1016/j.jmb.2019.10.028

Ma, Q., Long, S., Gan, Z., Tettamanti, G., Li, K., & Tian, L. (2022). Transcriptional and Post-Transcriptional Regulation of Autophagy. *Cells*, *11*(3), 441. https://doi.org/10.3390/cells11030441

Ma, Y., Jin, Z., Yu, K., & Liu, Q. (2019). NVP-BEZ235-induced autophagy as a potential therapeutic approach for multiple myeloma. *American Journal of Translational Research*, *11*(1), 87–105.

Mao, X., Zhang, X., Zheng, X., Chen, Y., Xuan, Z., & Huang, P. (2021). Curcumin suppresses LGR5(+) colorectal cancer stem cells by inducing autophagy and via repressing TFAP2A-mediated ECM pathway. *Journal of Natural Medicines*, *75*(3), 590–601. https://doi.org/10.1007/s11418-021-01505-1

Marquez, R. T., & Xu, L. (2012). Bcl-2: Beclin 1 complex: Multiple, mechanisms regulating autophagy/apoptosis toggle switch. *American Journal of Cancer Research*, *2*(2), 214.

Matuz-Mares, D., González-Andrade, M., Araiza-Villanueva, M. G., Vilchis-Landeros, M. M., & Vázquez-Meza, H. (2022). Mitochondrial Calcium: Effects of Its Imbalance in Disease. *Antioxidants*, *11*(5), 801. https://doi.org/10.3390/antiox11050801

Mauthe, M., Orhon, I., Rocchi, C., Zhou, X., Luhr, M., Hijlkema, K.-J., Coppes, R. P., Engedal, N., Mari, M., & Reggiori, F. (2018). Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. *Autophagy*, *14*(8), 1435–1455. https://doi.org/10.1080/15548627.2018.1474314

McAfee, Q., Zhang, Z., Samanta, A., Levi, S. M., Ma, X.-H., Piao, S., Lynch, J. P., Uehara, T., Sepulveda, A. R., Davis, L. E., Winkler, J. D., & Amaravadi, R. K. (2012). Autophagy inhibitor Lys05 has single-agent antitumor activity and reproduces the phenotype of a genetic autophagy deficiency. *Proceedings of the National Academy of Sciences*, *109*(21), 8253–8258. https://doi.org/10.1073/pnas.1118193109

McKnight, N. C., & Zhenyu, Y. (2013). Beclin 1, an Essential Component and Master Regulator of PI3K-III in Health and Disease. *Current Pathobiology Reports*, *1*(4), 231–238. https://doi.org/10.1007/s40139-013-0028-5

Medivir. (2020). *A Phase 1/2 Multicenter, Single-Arm, Open-Label, Dose-Escalation Study of Birinapant in Combination With Pembrolizumab (KEYTRUDA®) in Patients With Relapsed or Refractory Solid Tumors* (Clinical Trial Registration NCT02587962). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02587962

Mehta, V., Dey, A., Thakkar, N., Prabhakar, K., Jothimani, G., & Banerjee, A. (2023). Anti-cancer Properties of Dietary Supplement CELNORM against Colon and Lung Cancer: An in vitro preliminary study. *Int. J. Exp. Res. Rev.*, *32*, 1-14. https://doi.org/10.52756/ijerr.2023.v32.001

Meng, C.Y., Zhao, Z.Q., Bai, R., Zhao, W., Wang, Y.X., Sun, L., Sun, C., Feng, W., & Guo, S.B. (2020). MicroRNA-22 regulates autophagy and apoptosis in cisplatin resistance of osteosarcoma. *Molecular Medicine Reports*, *22*(5), 3911–3921. https://doi.org/10.3892/mmr.2020.11447

Meng, W. B., Liu, J. P., Wang, X. W., & E, L. H. (2015). Effect of Bcl-2-siRNA on proliferation and apoptosis of pediatric acute B lymphoblastic leukemia (A-

BLL) cells. *Genetics and Molecular Research: GMR*, *14*(4), 12427–12436. https://doi.org/10.4238/2015.October.16.9

Menon, M. B., & Dhamija, S. (2018). Beclin 1 Phosphorylation – at the Center of Autophagy Regulation. *Frontiers in Cell and Developmental Biology*,*6*. https://www.frontiersin.org/articles/10.3389/fcell.2018.00137

Montinaro, A., & Walczak, H. (2023). Harnessing TRAIL-induced cell death for cancer therapy: A long walk with thrilling discoveries. *Cell Death & Differentiation*, *30*(2), Article 2. https://doi.org/10.1038/s41418-022-01059-z

Morgan, C. W., Julien, O., Unger, E. K., Shah, N. M., & Wells, J. A. (2014). Turning ON Caspases with Genetics and Small Molecules. *Methods in Enzymology*, *544*, 179. https://doi.org/10.1016/B978-0-12-417158-9.00008-X

Mrakovcic, M., Bohner, L., Hanisch, M., & Fröhlich, L. F. (2018). Epigenetic Targeting of Autophagy via HDAC Inhibition in Tumor Cells: Role of p53. *International Journal of Molecular Sciences*, *19*(12), 3952. https://doi.org/10.3390/ijms19123952

Mrakovcic, M., & Fröhlich, L. F. (2018). P53-Mediated Molecular Control of Autophagy in Tumor Cells. *Biomolecules*, *8*(2), 14. https://doi.org/10.3390/biom8020014

Mulcahy Levy, J. M., & Thorburn, A. (2020). Autophagy in cancer: Moving from understanding mechanism to improving therapy responses in patients. *Cell Death and Differentiation*, *27*(3), 843–857. https://doi.org/10.1038/s41418-019-0474-7

Nakagawa-Saito, Y., Mitobe, Y., Togashi, K., Suzuki, S., Sugai, A., Kitanaka, C., & Okada, M. (2023). Givinostat Inhibition of Sp1-dependent MGMT Expression Sensitizes Glioma Stem Cells to Temozolomide. *Anticancer Research*, *43*(3), 1131–1138. https://doi.org/10.21873/anticanres.16258

National Cancer Institute (NCI). (2024). *Birinapant and Intensity Modulated Re-Irradiation Therapy (IMRRT) for Locoregionally Recurrent Head and Neck Squamous Cell Carcinoma (HNSCC)* (Clinical Trial Registration NCT03803774). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03803774

Nelson, D. M., Joseph, B., Hillion, J., Segal, J., Karp, J. E., & Resar, L. M. S. (2011). Flavopiridol induces BCL-2 expression and represses oncogenic transcription factors in leukemic blasts from adults with refractory acute myeloid leukemia. *Leukemia & Lymphoma*, *52*(10), 1999–2006. https://doi.org/10.3109/10428194.2011.591012

Nicastri, M. C., Rebecca, V. W., Amaravadi, R. K., & Winkler, J. D. (2018). Dimeric quinacrines as chemical tools to identify PPT1, a new regulator of autophagy in cancer cells. *Molecular & Cellular Oncology*, *5*(1). https://doi.org/10.1080/23723556.2017.1395504

Noonan, A. M., Bunch, K. P., Chen, J.Q., Herrmann, M. A., Lee, J., Kohn, E. C., O'Sullivan, C. C., Jordan, E., Houston, N., Takebe, N., Kinders, R. J., Cao, L., Peer, C. J., Figg, W. D., & Annunziata, C. M. (2016). Pharmacodynamic markers and clinical results from the Phase II Study of the SMAC-Mimetic Birinapant in Women with Relapsed Platinum-Resistant or Refractory Epithelial Ovarian Cancer. *Cancer*, *122*(4), 588–597. https://doi.org/10.1002/cncr.29783

Odle, R. I., & Cook, S. J. (2020). Macroautophagy is repressed during mitosis—Seeing is believing. *Autophagy*, *16*(4), 775–776. https://doi.org/10.1080/15548627.2020.1725405

Ozyerli-Goknar, E., & Bagci-Onder, T. (2021). Epigenetic Deregulation of Apoptosis in Cancers. *Cancers*, *13*(13), 3210. https://doi.org/10.3390/cancers13133210

Pankiv, S., Clausen, T. H., Lamark, T., Brech, A., Bruun, J.-A., Outzen, H., Øvervatn, A., Bjørkøy, G., & Johansen, T. (2007). P62/SQSTM1 Binds Directly to Atg8/LC3 to Facilitate Degradation of Ubiquitinated Protein Aggregates by Autophagy*. *Journal of Biological Chemistry*, *282*(33), 24131–24145. https://doi.org/10.1074/jbc.M702824200

Park, D. B. (2015). Metformin Promotes Apoptosis but Suppresses Autophagy in Glucose-Deprived H4IIE Hepatocellular Carcinoma Cells. *Diabetes & Metabolism Journal*, *39*(6), 518–527. https://doi.org/10.4093/dmj.2015.39.6.518

Park, D., Magis, A. T., Li, R., Owonikoko, T. K., Sica, G. L., Sun, S.-Y., Ramalingam, S. S., Khuri, F. R., Curran, W. J., & Deng, X. (2013). Novel Small-Molecule Inhibitors of Bcl-XL to Treat Lung Cancer. *Cancer Research*, *73*(17), 5485–5496. https://doi.org/10.1158/0008-5472.CAN-12-2272

Pasquier, B. (2015). SAR405, a PIK3C3/Vps34 inhibitor that prevents autophagy and synergizes with MTOR inhibition in tumor cells. *Autophagy*, *11*(4), 725–726. https://doi.org/10.1080/15548627.2015.1033601

Patergnani, S., Danese, A., Bouhamida, E., Aguiari, G., Previati, M., Pinton, P., & Giorgi, C. (2020). Various Aspects of Calcium Signaling in the Regulation of

Apoptosis, Autophagy, Cell Proliferation, and Cancer. *International Journal of Molecular Sciences*, *21*(21), 8323. https://doi.org/10.3390/ijms21218323

Pathak, S., Singh, V., Kumar, N., & Jayandharan, G. R. (2023). Inducible caspase 9-mediated suicide gene therapy using AAV6 vectors in a murine model of breast cancer. *Molecular Therapy Methods & Clinical Development*, *31*. https://doi.org/10.1016/j.omtm.2023.101166

Peker, N., & Gozuacik, D. (2020). Autophagy as a Cellular Stress Response Mechanism in the Nervous System. *Journal of Molecular Biology*, *432*(8), 2560–2588. https://doi.org/10.1016/j.jmb.2020.01.017

Pesce, E., Sondo, E., Ferrera, L., Tomati, V., Caci, E., Scudieri, P., Musante, I., Renda, M., Baatallah, N., Servel, N., Hinzpeter, A., di Bernardo, D., Pedemonte, N., & Galietta, L. J. V. (2018). The Autophagy Inhibitor Spautin-1 Antagonizes Rescue of Mutant CFTR Through an Autophagy-Independent and USP13-Mediated Mechanism. *Frontiers in Pharmacology*, *9*. https://www.frontiersin.org/articles/10.3389/fphar.2018.01464

Petherick, K. J., Conway, O. J. L., Mpamhanga, C., Osborne, S. A., Kamal, A., Saxty, B., & Ganley, I. G. (2015). Pharmacological Inhibition of ULK1 Kinase Blocks Mammalian Target of Rapamycin (mTOR)-dependent Autophagy. *The Journal of Biological Chemistry*, *290*(18), 11376–11383. https://doi.org/10.1074/jbc.C114.627778

Pfeffer, C. M., & Singh, A. T. K. (2018). Apoptosis: A Target for Anticancer Therapy. *International Journal of Molecular Sciences*, *19*(2), 448. https://doi.org/10.3390/ijms19020448

Ploumaki, I., Triantafyllou, E., Koumprentziotis, I.A., Karampinos, K., Drougkas, K., Karavolias, I., Trontzas, I., & Kotteas, E. A. (2023). Bcl-2 pathway inhibition in solid tumors: A review of clinical trials. *Clinical and Translational Oncology*, *25*(6), 1554–1578. https://doi.org/10.1007/s12094-022-03070-9

Raghavan, V., Agrahari, M., & Gowda, D. K. (2019). Virtual screening of p53 mutants reveals Y220S as an additional rescue drug target for PhiKan083 with higher binding characteristics. *Computational Biology and Chemistry*, *80*, 398–408. https://doi.org/10.1016/j.compbiolchem.2019.05.005

Rahman, M. A., Park, M. N., Rahman, M. H., Rashid, M. M., Islam, R., Uddin, M. J., Hannan, M. A., & Kim, B. (2022). p53 Modulation of Autophagy Signaling in Cancer Therapies: Perspectives Mechanism and Therapeutic Targets. *Frontiers in Cell and Developmental Biology*, *10*. https://www.frontiersin.org/articles/10.3389/fcell.2022.761080

Rami, N., Kulkarni, B., Chibber, S., Jhala, D., Parmar, N., & Trivedi, K. (2023). In vitro antioxidant and anticancer potential of *Annona squamosa* L. Extracts against breast cancer. *Int. J. Exp. Res. Rev.*, *30*, 264-275. https://doi.org/10.52756/ijerr.2023.v30.024

Rashid, H.O., Yadav, R. K., Kim, H.R., & Chae, H.J. (2015). ER stress: Autophagy induction, inhibition and selection. *Autophagy*, *11*(11), 1956–1977. https://doi.org/10.1080/15548627.2015.1091141

Ries, S., & Korn, W. M. (2002). ONYX-015: Mechanisms of action and clinical potential of a replication-selective adenovirus. *British Journal of Cancer*, *86*(1), 5–11. https://doi.org/10.1038/sj.bjc.6600006

Rohn, J. L., & Noteborn, M. H. M. (2004). The viral death effector Apoptin reveals tumor-specific processes. *Apoptosis: An International Journal on Programmed Cell Death*, *9*(3), 315–322. https://doi.org/10.1023/b:appt.0000025808.48885.9c

Ryabaya, O. O., Inshakov, A. N., Egorova, A. V., Emelyanova, M. A., Nasedkina, T. V., Zasedatelev, A. S., Khochenkov, D. A., & Stepanova, E. V. (2017). Autophagy inhibitors chloroquine and LY294002 enhance temozolomide cytotoxicity on cutaneous melanoma cell lines in vitro. *Anti-Cancer Drugs*, *28*(3), 307–315. https://doi.org/10.1097/CAD.0000000000000463

Saha, A., & Yadav, R. (2023). Study on segmentation and prediction of lung cancer based on machine learning approaches. *Int. J. Exp. Res. Rev.*, *30*, 1-14. https://doi.org/10.52756/ijerr.2023.v30.001

Saliba, A. N., John, A. J., & Kaufmann, S. H. (2021). Resistance to venetoclax and hypomethylating agents in acute myeloid leukemia. *Cancer Drug Resistance*, *4*(1), 125–142. https://doi.org/10.20517/cdr.2020.95

Sanchez, M., Lin, Y., Yang, C.C., McQuary, P., Campos, A. R., Blanc, P. A., & Wolf, D. A. (2019). Cross Talk between eIF2α and eEF2 Phosphorylation Pathways Optimizes Translational Arrest in Response to Oxidative Stress. *iScience*, *20*, 466. https://doi.org/10.1016/j.isci.2019.09.031

Sa-nongdej, W., Chongthammakun, S., & Songthaveesin, C. (2021). Nutrient starvation induces apoptosis and autophagy in C6 glioma stem-like cells. *Heliyon*, *7*(2), e06352.

https://doi.org/10.1016/j.heliyon.2021.e06352

Saraste, A., & Pulkki, K. (2000). Morphologic and biochemical hallmarks of apoptosis. *Cardiovascular Research*, *45*(3), 528–537. https://doi.org/10.1016/s0008-6363(99)00384-3

Sarnik, J., Popławski, T., & Tokarz, P. (2021). BET Proteins as Attractive Targets for Cancer Therapeutics. *International Journal of Molecular Sciences*, *22*(20), 11102. https://doi.org/10.3390/ijms222011102

Schimmer, A. D., & Dalili, S. (2005). Targeting the IAP family of caspase inhibitors as an emerging therapeutic strategy. *Hematology. American Society of Hematology. Education Program*, 215–219. https://doi.org/10.1182/asheducation-2005.1.215

Schmukler, E., Kloog, Y., & Pinkas-Kramarski, R. (2014). Ras and autophagy in cancer development and therapy. *Oncotarget*, *5*(3), 577–586.

Schwulst, S. J., Muenzer, J. T., Peck-Palmer, O. M., Chang, K. C., Davis, C. G., McDonough, J. S., Osborne, D. F., Walton, A. H., Unsinger, J., McDunn, J. E., & Hotchkiss, R. S. (2008). Bim siRNA decreases lymphocyte apoptosis and improves survival in sepsis. *Shock (Augusta, Ga.)*, *30*(2), 127–134. https://doi.org/10.1097/shk.0b013e318162cf17

Segawa, K., & Nagata, S. (2015). An Apoptotic 'Eat Me' Signal: Phosphatidylserine Exposure. *Trends in Cell Biology*, *25*(11), 639–650. https://doi.org/10.1016/j.tcb.2015.08.003

Shalini, S., Dorstyn, L., Dawar, S., & Kumar, S. (2015). Old, new and emerging functions of caspases. *Cell Death & Differentiation*, *22*(4), Article 4. https://doi.org/10.1038/cdd.2014.216

Shen, H., & Maki, C. G. (2011). Pharmacologic activation of p53 by small-molecule MDM2 antagonists. *Current Pharmaceutical Design*, *17*(6), 560–568.

Shinoura, N., Muramatsu, Y., Yoshida, Y., Asai, A., Kirino, T., & Hamada, H. (2000). Adenovirus-mediated transfer of caspase-3 with Fas ligand induces drastic apoptosis in U-373MG glioma cells. *Experimental Cell Research*, *256*(2), 423–433. https://doi.org/10.1006/excr.2000.4848

Shu, F., Xiao, H., Li, Q.N., Ren, X.S., Liu, Z.G., Hu, B.W., Wang, H.S., Wang, H., & Jiang, G.M. (2023). Epigenetic and post-translational modifications in autophagy: Biological functions and therapeutic targets. *Signal Transduction and Targeted Therapy*, *8*(1), Article 1. https://doi.org/10.1038/s41392-022-01300-8

Singh, B. N., Kumar, D., Shankar, S., & Srivastava, R. K. (2012). Rottlerin induces autophagy which leads to apoptotic cell death through inhibition of PI3K/Akt/mTOR pathway in human pancreatic cancer stem cells. *Biochemical Pharmacology*, *84*(9), 1154–1163. https://doi.org/10.1016/j.bcp.2012.08.007

Singh, P., Ravanan, P., & Talwar, P. (2016). Death Associated Protein Kinase 1 (DAPK1): A Regulator of Apoptosis and Autophagy. *Frontiers in Molecular Neuroscience*, *9*. https://www.frontiersin.org/articles/10.3389/fnmol.2016.00046

Singh, R., Letai, A., & Sarosiek, K. (2019). Regulation of apoptosis in health and disease: The balancing act of BCL-2 family proteins. *Nature Reviews. Molecular Cell Biology*, *20*(3), 175–193. https://doi.org/10.1038/s41580-018-0089-8

Solvik, T. A., Nguyen, T. A., Lin, Y.-H. T., Marsh, T., Huang, E. J., Wiita, A. P., Debnath, J., & Leidal, A. M. (2021). *Autophagy cargo receptors are secreted via extracellular vesicles and particles in response to endolysosomal inhibition or impaired autophagosome maturation* (p. 2021.08.12.456045). bioRxiv. https://doi.org/10.1101/2021.08.12.456045

Song, J. H., Kandasamy, K., & Kraft, A. S. (2008). ABT-737 Induces Expression of the Death Receptor 5 and Sensitizes Human Cancer Cells to TRAIL-induced Apoptosis. *The Journal of Biological Chemistry*, *283*(36), 25003–25013. https://doi.org/10.1074/jbc.M802511200

Soria, J.C., Smit, E., Khayat, D., Besse, B., Yang, X., Hsu, C.-P., Reese, D., Wiezorek, J., & Blackhall, F. (2010). Phase 1b study of dulanermin (recombinant human Apo2L/TRAIL) in combination with paclitaxel, carboplatin, and bevacizumab in patients with advanced non-squamous non-small-cell lung cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *28*(9), 1527–1533. https://doi.org/10.1200/JCO.2009.25.4847

Sun, H., Liu, L., Lu, J., Qiu, S., Yang, C.-Y., Yi, H., & Wang, S. (2010). Cyclopeptide Smac mimetics as antagonists of IAP proteins. *Bioorganic & Medicinal Chemistry Letters*, *20*(10), 3043–3046.

Takamura, A., Komatsu, M., Hara, T., Sakamoto, A., Kishi, C., Waguri, S., Eishi, Y., Hino, O., Tanaka, K., & Mizushima, N. (2011). Autophagy-deficient mice develop multiple liver tumors. *Genes & Development*, *25*(8), 795–800. https://doi.org/10.1101/gad.2016211

Tamm, I., Trepel, M., Cardó-Vila, M., Sun, Y., Welsh, K., Cabezas, E., Swatterthwait, A., Arap, W., Reed, J. C., & Pasqualini, R. (2003). Peptides Targeting Caspase Inhibitors*. *Journal of Biological Chemistry*, *278*(16), 14401–14405. https://doi.org/10.1074/jbc.M210133200

Tang, F., Hu, P., Yang, Z., Xue, C., Gong, J., Sun, S., Shi, L., Zhang, S., Li, Z., Yang, C., Zhang, J., & Xie, C. (2017). SBI0206965, a novel inhibitor of Ulk1, suppresses non-small cell lung cancer cell growth by modulating both autophagy and apoptosis pathways. *Oncology Reports*, *37*(6), 3449–3458. https://doi.org/10.3892/or.2017.5635

Tanner, S., & Barberis, A. (2004). CP-31398, a putative p53-stabilizing molecule tested in mammalian cells and in yeast for its effects on p53 transcriptional activity. *Journal of Negative Results in Biomedicine*, *3*, 5. https://doi.org/10.1186/1477-5751-3-5

Tedesco, B., Vendredy, L., Timmerman, V., & Poletti, A. (2023). The chaperone-assisted selective autophagy complex dynamics and dysfunctions. *Autophagy*, *19*(6), 1619–1641. https://doi.org/10.1080/15548627.2022.2160564

Thus, Y. J., Eldering, E., Kater, A. P., & Spaargaren, M. (2022). Tipping the balance: Toward rational combination therapies to overcome venetoclax resistance in mantle cell lymphoma. *Leukemia*, *36*(9), 2165–2176. https://doi.org/10.1038/s41375-022-01627-9

Tong, X., Tang, R., Xiao, M., Xu, J., Wang, W., Zhang, B., Liu, J., Yu, X., & Shi, S. (2022). Targeting cell death pathways for cancer therapy: Recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. *Journal of Hematology & Oncology*, *15*(1), 174. https://doi.org/10.1186/s13045-022-01392-3

Townsend, P. A., Kozhevnikova, M. V., Cexus, O. N. F., Zamyatnin, A. A., & Soond, S. M. (2021). BH3-mimetics: Recent developments in cancer therapy. *Journal of Experimental & Clinical Cancer Research*, *40*(1), 355. https://doi.org/10.1186/s13046-021-02157-5

Tran, S., Fairlie, W. D., & Lee, E. F. (2021). BECLIN1: Protein Structure, Function and Regulation. *Cells*, *10*(6), 1522. https://doi.org/10.3390/cells10061522

Tsapras, P., & Nezis, I. P. (2017). Caspase involvement in autophagy. *Cell Death and Differentiation*, *24*(8), 1369–1379. https://doi.org/10.1038/cdd.2017.43

Ucker, D. S., & Levine, J. S. (2018). Exploitation of Apoptotic Regulation in Cancer. *Frontiers in Immunology*, *9*. https://www.frontiersin.org/articles/10.3389/fimmu.2018.00241

Verfaillie, T., Salazar, M., Velasco, G., & Agostinis, P. (2010). Linking ER Stress to Autophagy: Potential Implications for Cancer Therapy. *International Journal of Cell Biology*, *2010*, e930509. https://doi.org/10.1155/2010/930509

Wakabayashi, Y., Masuda, T., Fujitaka, K., Nakashima, T., Okumoto, J., Shimoji, K., Nishimura, Y., Yamaguchi, K., Sakamoto, S., Horimasu, Y., Miyamoto, S., Iwamoto, H., Ohshimo, S., Hamada, H., & Hattori, N. (2021). Clinical significance of BIM deletion polymorphism in chemoradiotherapy for non-small cell lung cancer. *Cancer Science*, *112*(1), 369–379. https://doi.org/10.1111/cas.14711

Walensky, L. D., & Bird, G. H. (2014). Hydrocarbon-Stapled Peptides: Principles, Practice, and Progress. *Journal of Medicinal Chemistry*, *57*(15), 6275–6288. https://doi.org/10.1021/jm4011675

Wang, C., Wang, H., Zhang, D., Luo, W., Liu, R., Xu, D., Diao, L., Liao, L., & Liu, Z. (2018). Phosphorylation of ULK1 affects autophagosome fusion and links chaperone-mediated autophagy to macroautophagy. *Nature Communications*, *9*(1), Article 1. https://doi.org/10.1038/s41467-018-05449-1

Wang, H., Zhang, H., Zhu, Y., Wu, Z., Cui, C., & Cai, F. (2021). Anticancer Mechanisms of Salinomycin in Breast Cancer and Its Clinical Applications. *Frontiers in Oncology*, *11*. https://www.frontiersin.org/articles/10.3389/fonc.2021.654428

Wang, L., Klionsky, D. J., & Shen, H.-M. (2023). The emerging mechanisms and functions of microautophagy. *Nature Reviews Molecular Cell Biology*, *24*(3), Article 3. https://doi.org/10.1038/s41580-022-00529-z

Wang, N., Pan, W., Zhu, M., Zhang, M., Hao, X., Liang, G., & Feng, Y. (2011). Fangchinoline induces autophagic cell death via p53/sestrin2/AMPK signalling in human hepatocellular carcinoma cells. *British Journal of Pharmacology*, *164*(2b), 731. https://doi.org/10.1111/j.1476-5381.2011.01349.x

Wang, Q., Guo, Y., Jiang, S., Dong, M., Kuerban, K., Li, J., Feng, M., Chen, Y., & Ye, L. (2018). A hybrid of coumarin and phenylsulfonylfuroxan induces caspase-dependent apoptosis and cytoprotective autophagy in lung adenocarcinoma cells. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, *39*, 160–167. https://doi.org/10.1016/j.phymed.2017.12.029

Wang, R. C., Wei, Y., An, Z., Zou, Z., Xiao, G., Bhagat, G., White, M., Reichelt, J., & Levine, B. (2012). Akt-Mediated Regulation of Autophagy and Tumorigenesis Through Beclin 1 Phosphorylation. *Science (New York, N.Y.)*, *338*(6109), 956. https://doi.org/10.1126/science.1225967

Wang, S., Li, H., Yuan, M., Fan, H., & Cai, Z. (2022). Role of AMPK in autophagy. *Frontiers in Physiology*, *13*.
https://www.frontiersin.org/articles/10.3389/fphys.2022.1015500

Wang, W., Long, L., Yang, N., Zhang, Q., Ji, W., Zhao, J., Qin, Z., Wang, Z., Chen, G., & Liang, Z. (2013). NVP-BEZ235, a novel dual PI3K/mTOR inhibitor, enhances the radiosensitivity of human glioma stem cells in vitro. *Acta Pharmacologica Sinica*, *34*(5), Article 5. https://doi.org/10.1038/aps.2013.22

Wang, X., Lee, J., & Xie, C. (2022). Autophagy Regulation on Cancer Stem Cell Maintenance, Metastasis, and Therapy Resistance. *Cancers*, *14*(2), 381. https://doi.org/10.3390/cancers14020381

Wang, X., Wei, S., Zhao, Y., Shi, C., Liu, P., Zhang, C., Lei, Y., Zhang, B., Bai, B., Huang, Y., & Zhang, H. (2017). Anti-proliferation of breast cancer cells with itraconazole: Hedgehog pathway inhibition induces apoptosis and autophagic cell death. *Cancer Letters*, *385*, 128–136. https://doi.org/10.1016/j.canlet.2016.10.034

Wang, Y., Han, C., Lu, L., Magliato, S., & Wu, T. (2013). Hedgehog Signaling Pathway Regulates Autophagy in Human Hepatocellular Carcinoma Cells. *Hepatology (Baltimore, Md.)*, *58*(3), 995–1010. https://doi.org/10.1002/hep.26394

Wang, Y., Xu, W., Yan, Z., Zhao, W., Mi, J., Li, J., & Yan, H. (2018). Metformin induces autophagy and G0/G1 phase cell cycle arrest in myeloma by targeting the AMPK/mTORC1 and mTORC2 pathways. *Journal of Experimental & Clinical Cancer Research*, *37*(1), 63. https://doi.org/10.1186/s13046-018-0731-5

Wang, Y.C., Wang, L.T., Hung, T. I., Hong, Y.-R., Chen, C.H., Ho, C.J., & Wang, C. (2022). Severe cellular stress drives apoptosis through a dual control mechanism independently of p53. *Cell Death Discovery*, *8*(1), Article 1. https://doi.org/10.1038/s41420-022-01078-2

Wei, A. H., Roberts, A. W., Spencer, A., Rosenberg, A. S., Siegel, D., Walter, R. B., Caenepeel, S., Hughes, P., McIver, Z., Mezzi, K., Morrow, P. K., & Stein, A. (2020). Targeting MCL-1 in Hematologic Malignancies: Rationale and Progress. *Blood Reviews*, *44*, 100672. https://doi.org/10.1016/j.blre.2020.100672

Wei, C., & Li, X. (2020). Verteporfin inhibits cell proliferation and induces apoptosis in different subtypes of breast cancer cell lines without light activation. *BMC Cancer*, *20*(1), 1042. https://doi.org/10.1186/s12885-020-07555-0

White, E., Lattime, E. C., & Guo, J. Y. (2021). Autophagy Regulates Stress Responses, Metabolism, and Anticancer Immunity. *Trends in Cancer*, *7*(8), 778–789. https://doi.org/10.1016/j.trecan.2021.05.003

Wong, R. S. (2011). Apoptosis in cancer: From pathogenesis to treatment. *Journal of Experimental & Clinical Cancer Research*, *30*(1), 87. https://doi.org/10.1186/1756-9966-30-87

Wu, R., Murali, R., Kabe, Y., French, S. W., Chiang, Y.-M., Liu, S., Sher, L., Wang, C. C., Louie, S., & Tsukamoto, H. (2018). Baicalein Targets GTPase-Mediated Autophagy to Eliminate Liver Tumor-Initiating Stem Cell-Like Cells Resistant to mTORC1 Inhibition. *Hepatology (Baltimore, Md.)*, *68*(5), 1726–1740. https://doi.org/10.1002/hep.30071

Wu, Y.-H., Mo, S.-T., Chen, I.-T., Hsieh, F.-Y., Hsieh, S.-L., Zhang, J., & Lai, M.-Z. (2022). Caspase-8 inactivation drives autophagy-dependent inflammasome activation in myeloid cells. *Science Advances*, *8*(45), eabn9912. https://doi.org/10.1126/sciadv.abn9912

Xi, H., Wang, S., Wang, B., Hong, X., Liu, X., Li, M., Shen, R., & Dong, Q. (2022). The role of interaction between autophagy and apoptosis in tumorigenesis (Review). *Oncology Reports*, *48*(6), 208. https://doi.org/10.3892/or.2022.8423

Xie, X., Fan, C., Luo, B., Zhang, J., Jensen, L. D., Burman, J., Jönsson, C., Ljusberg, A., Larsson, P., Zhao, Z., & Sun, X.-F. (2023). APR-246 Enhances Colorectal Cancer Sensitivity to Radiotherapy. *Molecular Cancer Therapeutics*, *22*(8), 947–961. https://doi.org/10.1158/1535-7163.MCT-22-0275

Xin, M., Li, R., Xie, M., Park, D., Owonikoko, T. K., Sica, G. L., Corsino, P. E., Zhou, J., Ding, C., White, M. A., Magis, A. T., Ramalingam, S. S., Curran, W. J., Khuri, F. R., & Deng, X. (2014). Small Molecule Bax Agonists for Cancer Therapy. *Nature Communications*, *5*, 4935. https://doi.org/10.1038/ncomms5935

Xu, Y., & Wan, W. (2023). Acetylation in the regulation of autophagy. *Autophagy*, *19*(2), 379. https://doi.org/10.1080/15548627.2022.2062112

Yeh, Y.T., Yeh, H., Su, S.H., Lin, J.S., Lee, K.J., Shyu, HW., Chen, Z.F., Huang, S.Y., & Su, S.J. (2014). Phenethyl isothiocyanate induces DNA damage-

associated G2/M arrest and subsequent apoptosis in oral cancer cells with varying p53 mutations. *Free Radical Biology & Medicine*, *74*, 1–13. https://doi.org/10.1016/j.freeradbiomed.2014.06.008

Yousefi, S., Perozzo, R., Schmid, I., Ziemiecki, A., Schaffner, T., Scapozza, L., Brunner, T., & Simon, H.-U. (2006). Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis. *Nature Cell Biology*, *8*(10), Article 10. https://doi.org/10.1038/ncb1482

Yuan, N., Song, L., Zhang, S., Lin, W., Cao, Y., Xu, F., Fang, Y., Wang, Z., Zhang, H., Li, X., Wang, Z., Cai, J., Wang, J., Zhang, Y., Mao, X., Zhao, W., Hu, S., Chen, S., & Wang, J. (2015). Bafilomycin A1 targets both autophagy and apoptosis pathways in pediatric B-cell acute lymphoblastic leukemia. *Haematologica*, *100*(3), 345–356. https://doi.org/10.3324/haematol.2014.113324

Zalckvar, E., Berissi, H., Mizrachy, L., Idelchuk, Y., Koren, I., Eisenstein, M., Sabanay, H., Pinkas-Kramarski, R., & Kimchi, A. (2009). DAP-kinase-mediated phosphorylation on the BH3 domain of beclin 1 promotes dissociation of beclin 1 from Bcl-XL and induction of autophagy. *EMBO Reports*, *10*(3), 285–292. https://doi.org/10.1038/embor.2008.246

Zhang, J., Zhou, L., Zhao, S., Dicker, D. T., & El-Deiry, W. S. (2017). The CDK4/6 inhibitor palbociclib synergizes with irinotecan to promote colorectal cancer cell death under hypoxia. *Cell Cycle*, *16*(12), 1193–1200. https://doi.org/10.1080/15384101.2017.1320005

Zhang, L., Fu, L., Zhang, S., Zhang, J., Zhao, Y., Zheng, Y., He, G., Yang, S., Ouyang, L., & Liu, B. (2017). Discovery of a small molecule targeting ULK1-modulated cell death of triple negative breast cancer in vitro and in vivo. *Chemical Science*, *8*(4), 2687–2701. https://doi.org/10.1039/c6sc05368h

Zhang, P., Cheng, S., Sheng, X., Dai, H., He, K., & Du, Y. (2023). The role of autophagy in regulating metabolism in the tumor microenvironment. *Genes & Diseases*, *10*(2), 447–456. https://doi.org/10.1016/j.gendis.2021.10.010

Zhou, Y.Y., Li, Y., Jiang, W.Q., & Zhou, L.F. (2015). MAPK/JNK signalling: A potential autophagy regulation pathway. *Bioscience Reports*, *35*(3), e00199. https://doi.org/10.1042/BSR20140141

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