Plant natural compounds: targeting pathways of autophagy as anti-cancer therapeutic agents

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Abstract

Natural compounds derived from plant sources are well characterized as possessing a wide variety of remarkable anti-tumour properties, for example modulating programmed cell death, primarily referring to apoptosis, and autophagy. Distinct from apoptosis, autophagy (an evolutionarily conserved, multi-step lysosomal degradation process in which a cell destroys long-lived proteins and damaged organelles) may play crucial regulatory roles in many pathological processes, most notably in cancer. In this review, we focus on highlighting several representative plant natural compounds such as curcumin, resveratrol, paclitaxel, oridonin, quercetin and plant lectin – that may lead to cancer cell death – for regulation of some core autophagic pathways, involved in Ras-Raf signalling, Beclin-1 interactome, BCR-ABL, PI3KCl/Akt/mTOR, FOXO1 signalling and p53. Taken together, these findings would provide a new perspective for exploiting more plant natural compounds as potential novel anti-tumour drugs, by targeting the pathways of autophagy, for future cancer therapeutics.

Introduction

Natural compounds originally derived from plants, have historically been regarded as an invaluable source of potential therapeutic agents, and are also are well known to play essential roles in a variety of human disease treatments, such as in cancer (1). Also, they have held (and still hold) important positions in primary health care in China, and have been recently recognized by Western countries as revealing more novel molecules for potential current cancer drug discovery (1). Cancer is a complex genetic disease with ten hallmark traits, acquired during their multistep development into human tumours, including: sustaining cell proliferative signalling, evading activity of cell population growth suppressors, enabling replicative immortality, inducing angiogenesis, activating cell invasion and metastasis, exhibiting genetic diversity, inflammation, re-programming of energy metabolism, evading immune destruction and resisting programmed cell death (PCD) (2,3).

Apoptosis, or type I PCD, is characterized by specific morphological and biochemical changes exhibited by dying cells, including: cell shrinkage, nuclear condensation and fragmentation, dynamic membrane blebbing and loss of cell-cell adhesion. Biochemical changes include chromosomal DNA cleavage into inter-nucleosomal fragments, phosphatidylserine (PS) externalization, and a number of intracellular substrate cleavages by proteolysis. As phagocytic cells can recognize and remove the apoptotic bodies, the inflammatory response is not stimulated by apoptotic cell death (4). Differing from apoptosis, autophagy, or type II PCD is an evolutionarily conserved catabolic process, which occurs when cells deliver their own cytoplasmic materials and organelles to lysosomes for degradation. In general, autophagy plays a crucial pro-survival role in cell and tissue homeostasis, required during starvation or growth factor deprivation stress. However, accumulating evidence has revealed that autophagic cells may commit suicide by undergoing cell death and coping with excessive stress, which differs from apoptosis (5).

Hitherto, several natural compounds have been reported to modulate some autophagic signalling pathways (such as Ras/Raf/MAPK, Beclin-1 complex,

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PI3KCI/Akt/mTOR, BCR-ABL, FOXO1 signalling and p53), thus ultimately cumulating in cancer cell death (6). Here, we focus on summarizing about some selected plant natural compounds that can target autophagy in the 'decisions' of cancer cell death, which may provide more new clues towards exploiting them as potential anti-tumour agents.

## The autophagic process and monitoring methods

To initiate autophagy, intact organelles and/or cytoplasmic components enclosed in double-membrane vacuoles, so-called autophagosomes (6) mature by fusing with lysosomes, leading to the formation of autophagolysosomes (7). This process includes progressive steps for autophagic vacuole production and turnover, including autophagic induction, vesicle nucleation, vesicle elongation and completion, docking and fusion, followed by degradation and recycling (Fig. 1).

To date, some methods have been developed for monitoring autophagy in higher eukaryotes, of which observation by electron microscopy is the most dependable approach, by directly detecting cytoplasmic accumulation of autophagosomes (8,9). In addition, some members of the Atg family have become general biomarkers for autophagy. Amongst them, LC3 is the mammalian homologue of Atg8, which undergoes ubiquitin-like post-translational modification that can target it to the isolation plasmamembrane. Localization of LC3 can easily be examined by generating chimaeric proteins fused to green fluorescent protein (GFP), and examination of GFP-LC3 localization is simple, as it requires no more than high-resolution fluorescence microscope (9). Moreover, the C-terminal fragment of LC3 can be cleaved with synthesis following, to yield a cytosolic form called LC3-I and later, a subpopulation of LC3-I can be converted into an autophagosome-associating form, LC3-II (10). With immunoblotting of both LC3-I and LC3-II, activity of autophagy can be detected easily in mammalian cells. Beclin-1, an orthologue of yeast Atg6, can play an important role in regulating autophagy. Levels of Beclin-1 in mammalian cells can help determination of autophagic activity by western blotting (11) although some chemical compounds, such as 3-MA, Wortmannin and LY294002 are found to inhibit autophagy (12).

Core pathways of autophagy in cancer

Under low-oxygen and low-nutrient conditions, autophagy promotes tumour progression, by contributing to cancer cell survival (13), while in contrast under normal conditions, autophagy may function as a tumour suppressor, playing a cell death-promoting role as a *bona fide* tumour cell death mechanism (14). These paradoxical investigation results, however, can seem to be confused, dependent on different types of tissue-specific cancer cells, thereby regulating either pro-survival or pro-death
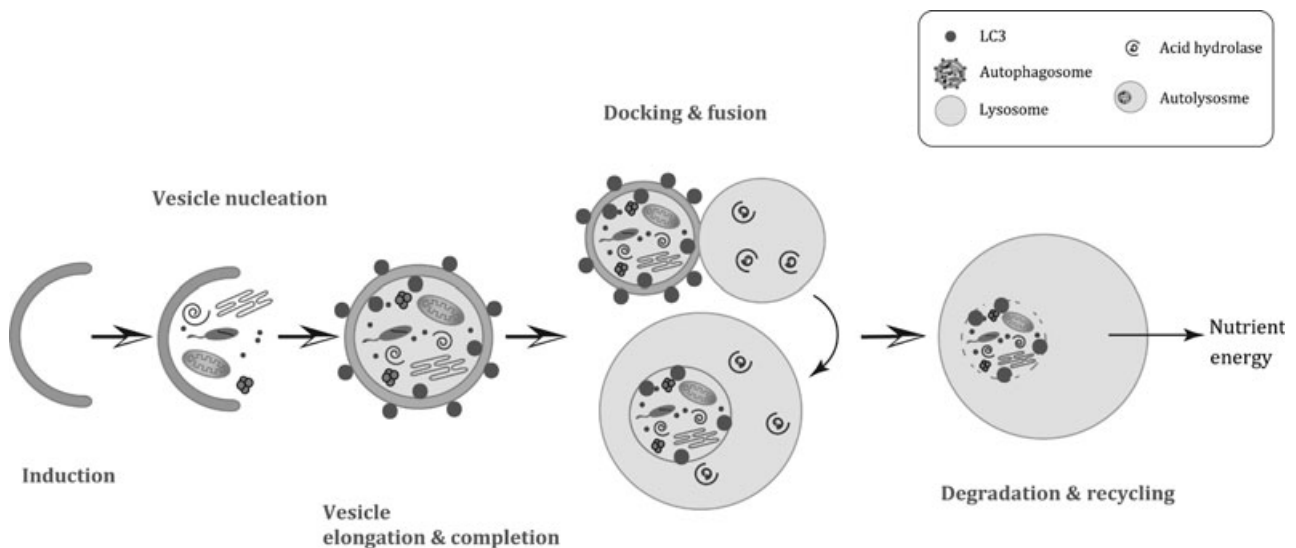
Figure 1. Stages of the process of autophagy. Autophagy can be stimulated by nutrient deprivation, hypoxia, cytokine activity, hormone activity and DNA damage. (a) Induction requires Atg 1 and Atg13, which in turn can be inhibited by mTOR. (b) Vesicle nucleation depends on Beclin-1-class III PI3K-Vps15 core complexes and other proteins. (c) Vesicle elongation and completion mediated by Atg16L complex and LC3. (d) Docking and fusion refer to maturation of autolysosomes promoted by Rab7, LAMP1, LAMP2, SKD1, Vtil 1b and ESCRT complex. (e) In the final stage of degradation and recycling of components, autophagosomal cargoes are digested, and nutrients and inherent energy are recycled.

signalling pathways (15,16). At the molecular level, autophagy plays a 'Janus role', by regulation of oncogenes and/or tumour suppressors (Fig. 2).

Oncogenic autophagic pathways

On the one hand, oncogenic pathways involved in PI3KCI, Akt, mTOR, Ras, BCR-ABL, Bcl-2 and Bcl-X_L can play important roles in 'deciding' cancer cell survival. Amongst them, the mammalian target of rapamycin (mTOR) may serve as a main negative regulator of autophagy in cancer cells. mTOR exists in two functionally different complexes in mammalian cells; of these, only mammalian target of rapamycin complex 1 (mTORC1) is sensitive to rapamycin (13). PI3KCI-Akt, Ras-Raf-1-MEK1/2-ERK1/2 signalling pathways can activate mTORC1 yet on the contrary, the liver kinase B1 (LKB1)-AMP-activated protein kinase (AMPK) pathway can inhibit mTORC1 (13). In addition, mTORC1 can negatively regulate autophagy when competed with ULK1 (Atg1) and mAtg13 that can be positively regulated by its upstream PI3KCI-Akt-1 pathway, suggesting that oncogenic action of constitutively active PI3KCI-Akt-mTORC1 may lead to inhibition of autophagy (17). Additionally, constitutively active Akt can inhibit induction of autophagy (15) and Ras can converge on activating mTOR for stimulating cell proliferation and inhibiting autophagy. Sustained Ras-Raf-MAPK may be required for tumour survival by autophagy and additionally, BCR-ABL (product of a further oncogene), can serve as the key factor for stimulating transcription of mTOR *via* PI3KCI-Akt-FOXO signalling, in chronic myeloid leukaemia (CML), suggesting an inhibitory role of the autophagy process (18). Bcl-2 and Bcl-X_L can play key roles by mediating autophagic signalling pathways (19) (Fig. 2).

Tumour suppressive autophagic pathways

Tumour suppressive pathways include various regulators, such as Beclin-1 and p53 which can exert ambiguous functions for regulation of autophagy, acting as haploin-
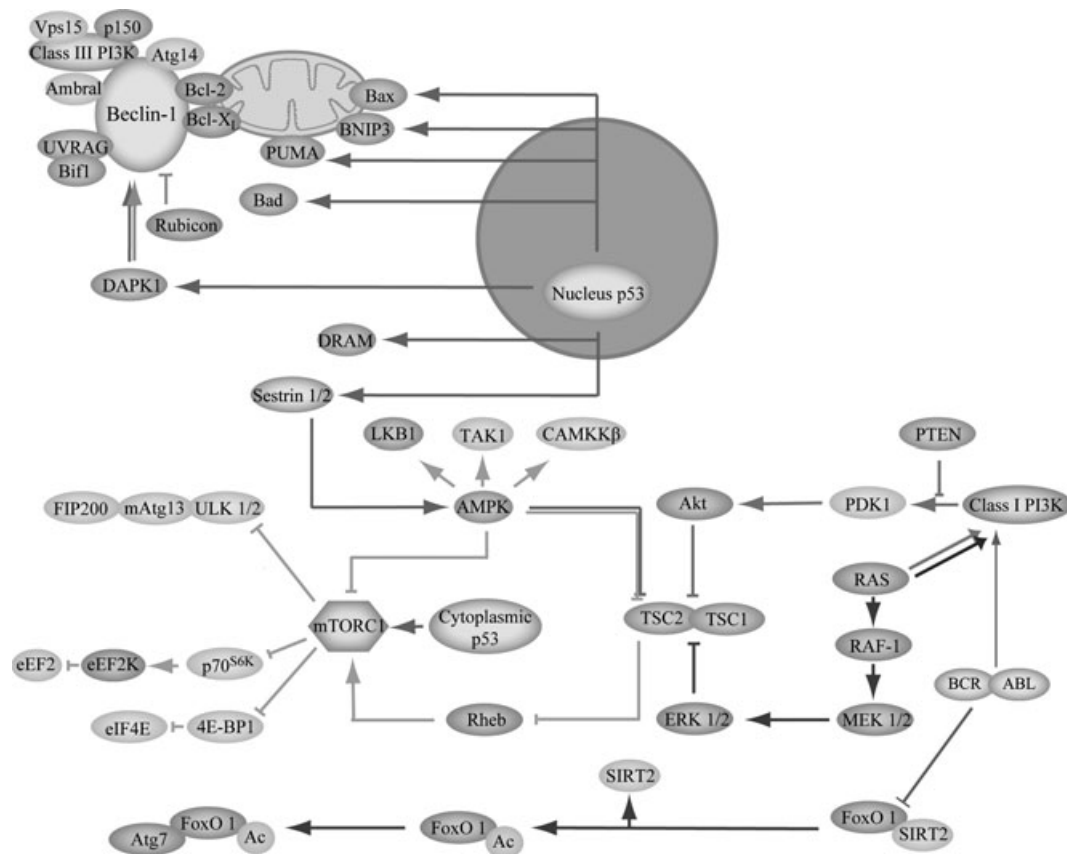
Figure 2. Core autophagic signalling pathways in cancer cells. Autophagy may decide the ultimate fate of cancer cells for regulation of key survival or death signalling pathways, such as Beclin-1 complex, PI3K/Akt/mTOR, Ras/Raf/MAPK, BCR-ABL, p53 and FOXO1 signalling in many types of cancer cells.

sufficient tumour suppressor proteins (20,21). Beclin-1 can cooperate with Ambra-1, Bif-1 and UVRAG to activate lipid kinase Vps34, thereby inducing autophagy (17). However, it can suppress tumour function in the lysosomal degradation pathway of autophagy. p53, interacting with Bad, Noxa and PUMA, plays a distinct role in autophagy, depending on its different subcellular localizations (21). Nuclear p53 can promote autophagy through interacting with its targets, DRAM and sestrin1/2, whereas, cytoplasmic p53 can inhibit autophagy by activating Bax, and/or inhibiting Bcl-2/Bcl-X_L (Fig. 2).

Cytosolic FOXO1, a fork-head O family protein, is a mediator of autophagy. Under conditions of stress, FOXO1 dissociates from a complex with sirtuin-2 (SIRT2) followed by its acetylation; acetylation status of FOXO1 is balanced by histone acetylases and HDAC. While SIRT1 is located in the nucleus, SIRT2 is primarily located in the cytosol and is the main deacetylase of cytosolic FOXO1 (22). Then, acetylated FOXO1 binds to E1-like Atg7 (Atg7 plays an important role in ubiquitin-like conjugation (Ublc) systems for autophagosome expansion). The FOXO1-Atg7 complex influences the autophagic process, which ultimately culminates in cell death, and FOXO1-modulated cell death may be associated with tumour suppressor activity (22,23) (Fig. 2). Accordingly, below we discuss in more detail, some representative natural compounds of plant origin that can result in cancer cell death by targeting the aforementioned autophagic signalling pathways, in cancer pathology and therapy.

## Plant natural compound-induced autophagy in cancer

Curcumin

Curcumin, derived from turmeric (*Curcumin longa*), chemically is known as diferuloylmethane (C21H20O6) (24) (Fig. 3a). As an active ingredient from the rhizome in the plant, curcumin has been shown to demonstrate activity in a wide range of biological functions, particularly against cancer (25–30). Moreover, curcumin has been reported to regulate autophagy, resulting in inhibition of several types of cancer cell proliferation (for example, in chronic myeloid leukaemia, malignant glioma and oesophageal cancer cells) (30–32). After treatment with curcumin, levels of LC3-II and Beclin-1 have been detected to be elevated in K562 cells, indicating that this compound may affect autophagosome formation (30). In U87-MG and U373-MG cells, curcumin has been found to inhibit the Akt/p70^{S6} kinase pathway, as well as to activate ERK1/2, resulting in autophagic induction, whereas PI3K activity was not affected (33).

Intriguingly, reactive oxygen species (ROS), upregulating Beclin-1 and p53, have been found to be induced by curcumin in activation of autophagy, thereby culminating in concomitant cell death of HCT 116 human colon cancer cells (34). Additionally, serine/threonine protein phosphatases type-1 (PP1) and type-2A (PP2A) are key players in phosphorylation and dephosphorylation and curcumin can downregulate PP1, which might stimulate phosphorylation of ERK (31). Besides these autophagy-inducing activities, curcumin has been observed to inhibit viability of K562 cells in a dose- and time-dependent manner. Curcumin-induced cell death has been found to be associated with formation of the apoptosome complex, collapse of the mitochondrial membrane potential (MMP) and caspase-3 activation. Also, curcumin treatment has induced Bid cleavage and downregulated expression of Bcl-2 protein in K562 cells (30). In addition, curcumin has been shown to enhance adriamycin-induced human liver-derived hepatoma G_2 cell death through activation of mitochondria-mediated apoptosis and autophagy (35).

Resveratrol

Resveratrol (Res), a phytoalexin found in grapes and root extracts of *Polygonum cuspidatum*, has been demonstrated to result in a wide range of biological effects including anti-proliferative activity (36) (Fig. 3b). In a murine investigation in 1997, topical application of Res was reported to reduce numbers of skin tumours *per* mouse by up to 98%, which triggered research on Res (37). It is notable that Res can inhibit initiation and growth of tumours in a wide range of cancer models, such as cell population growth in leukaemias as well as in prostate, breast and further epithelial cancers (35). When treated with Res, Bcl-2 and Bcl-X_L were found to be involved in autophagy, thus mediating a response to this agent, in ovarian A2780 cancer cells (35). Beclin-1 promotes autophagy when overexpressed in MCF-7 cells, and levels of typical autophagic protein Atg7 (Beclin-1) remain unchanged after Res treatment. It has been suggested that Res, unlike many kinds of natural compound that rely on activation of Beclin-1 for regulating autophagy, can induce Beclin-1-independent autophagy in breast cancer cells (38). Res-induced autophagy has been reported to inhibit Akt/protein kinase B (PKB) phosphorylation and mTOR signalling by phosphorylation of p70^{S6K}, a direct mTOR substrate, indicating that Res-induced autophagy is dependent on mTOR inhibition. Moreover, N-acetyl-sphingosine (C2-Cer)-induced autophagy is characterized by inhibition of Akt/mTOR signalling in MCF-7^{casp-3} and MCF-7^{vc} cells (39). As mTOR can upregulate Akt and AMPK,
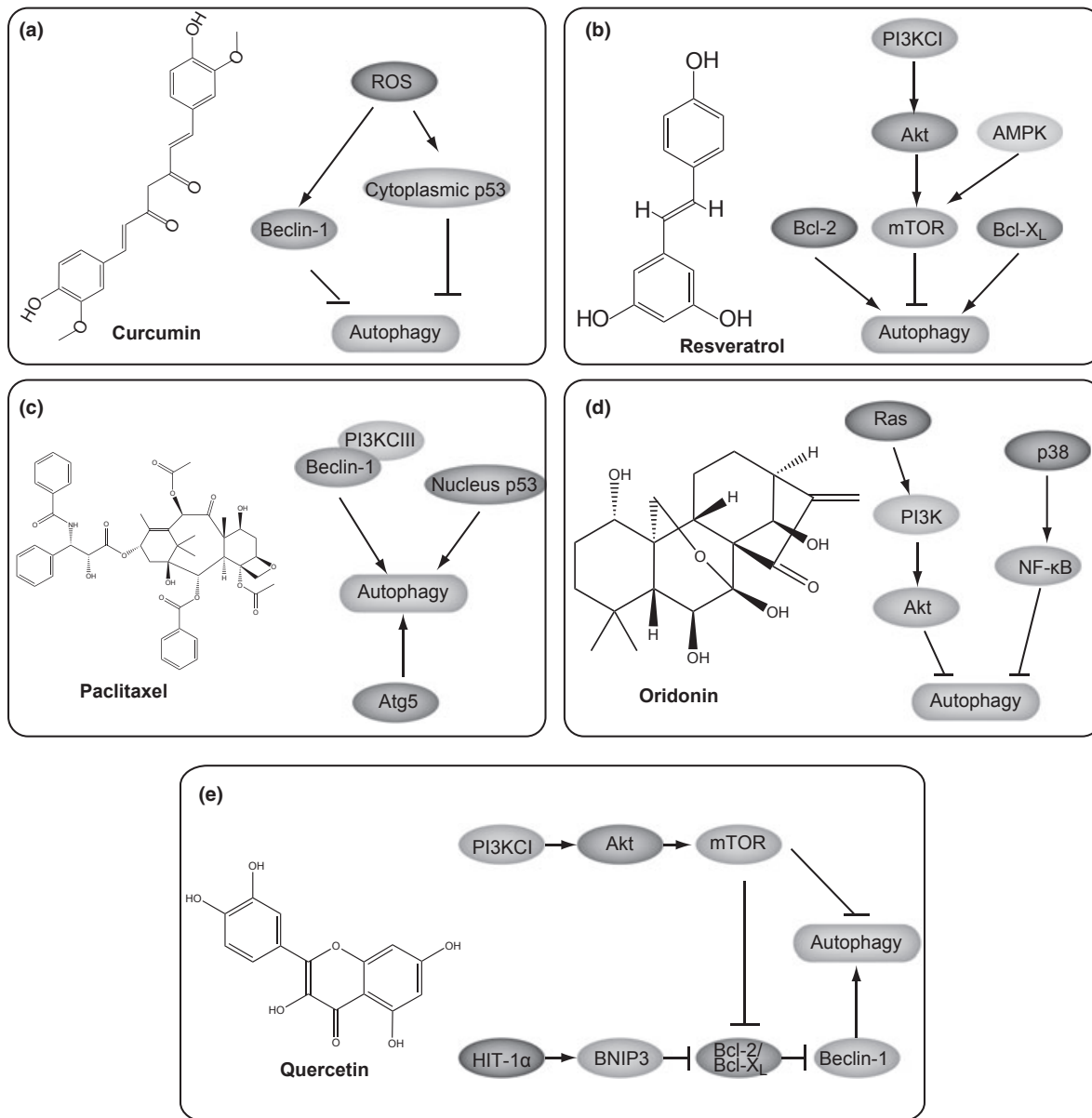
Figure 3. Representative natural small molecules targeting autophagic pathways. (a) Curcumin; (b) Resveratrol; (c) Paclitaxe; (d) Oridonin; (e) Quercetin.

the latter can play their key roles in Res-induced autophagy; thus Res can induce autophagy by modulating activities of Akt and AMPK in autophagy (31,40). Res can induce autophagy in gastric cancer cells after increase in dihydroceramides, the immediate ceramide metabolic precursor in *de novo* sphingolipid synthesis (41). However, some studies have also suggested that resveratrol may potentially be useful in cancer chemotherapy, when used in combination with other drugs, in hepatocellular carcinoma and leukaemia cell lines, mainly due to its effect on apoptosis (42).

Paclitaxel

Paclitaxel, originally isolated from the bark of the Pacific yew tree, is a widely used agent for treatments of lung, ovarian, breast and head and neck cancers (43) (Fig. 3c). Due to its notable effects, paclitaxel-based combination therapies have been noted as standard treatments for many patients diagnosed with non-small cell lung carcinoma (44). As paclitaxel may generate unacceptable levels of toxicity to normal cells in clinical settings, more experiments need to be focused on how to

enhance its effectiveness, as well as to reduce toxicity. During this process, paclitaxel has been found to induce autophagy (45). LC3-II, an ingredient of the autophagosome, has been shown to be elevated in paclitaxel-treated A549 cancer cells, suggesting a role for it in autophagy (46,47). Atg5 and Beclin-1 are also required for autophagosome formation, and paclitaxel treatment can lead to increase in expression levels of Atg5 and Beclin-1 in a dose-dependent manner in the A549 cells (46). Beclin-1, combining with PI3KCIII, can induce autophagy at the initiation stage, suggesting the positive role of Beclin-1 in autophagy, to inhibit tumourigenesis (48). Additionally, paclitaxel treatment has been found to induce autophagy by detection of GFP-LC3 punctate formation in human U87 glioma cells, human PC-3 prostate cancer and colon HT-29 cancer cells, transfected with an expression plasmid containing GFP-LC3 (49). Moreover, paclitaxel can increase p53 expression before regulation of LC3B, thus regulating induction of autophagy (50). Paclitaxel-caused autophagy has also been shown to play a critical role in mediating caspase-independent cancer cell death (51,52). Interestingly, paclitaxel resistance has been shown to be associated with profound changes in the cell death response, with deletion of multiple apoptotic factors balanced by upregulation of the autophagic pathway, and collateral sensitivity to platinum (53).

Oridonin

Oridonin (7, 20-epoxy-ent-kauranes), a diterpenoid isolated from the medicinal herb *Rabdosia rubescens,* was discovered in 1967 – and subsequently synthesized in 1973 (54–56). Oridonin has been found to exhibit remarkable anti-proliferative activity, particularly inhibiting tumour growth, thus leading to cancer cell death of melanoma and cervical carcinoma cells (54,57) (Fig. 3d). Some transcriptional factors in apoptosis and autophagy can be regulated by oridonin, which inhibit tumour cell proliferation, indicating that oridonin can have both apoptosis- and autophagy-inducing activities maybe in many types of cancer cell (57). The PI3KCI/Akt signalling pathway is found to switch between apoptosis and autophagy, which is frequently found to be implicated in cancer cells. In oridonin-induced HeLa cell death, PI3KCI/Akt signalling has been found to be augmented in autophagy, as well as to suppress apoptosis, and in this context, autophagy might serve as a survival mechanism to protect cells from apoptotic death (58). When treated with oridonin, autophagy can be significantly upregulated with manumycin A, a Ras-specific inhibitor. Treatment with a combination of oridonin and manumycin A can downregulate phosphorylation

of downstream PI3KCI, and Akt (58). Thus, associated with activation of PI3KCI and Akt, Ras can negatively regulate autophagy in oridonin-treated cancer cells, suggesting that oridonin may induce autophagy *via* negatively regulating Ras/PI3KCI/Akt (59). In addition, NF-κB can function as a molecular switch in a similar way to PI3KCI/Akt, by which autophagy can protect cancer cells from death, by upregulating the p38-NFκB survival pathway, or facilitating autophagy in oridonin-treated human HT1080 sarcoma cells by p53 activation (60). However, under oridonin treatment, expression of Beclin-1 (which leads to autophagy-inducing activity), remained at the same level, suggesting that Beclin-1 does not participate in oridonin-induced autophagy (58).

Oridonin also has been well characterized to induce apoptosis in many types of cancer cell. In oridonin-induced HeLa cell death, PI3K/Akt signalling has been found to be augmented in autophagy, but suppressed in apoptosis; thus autophagy may serve as a survival mechanism to protect cells from apoptotic death. In a further scenario, NF-κB has been found to function as a molecular switch in a similar way, by which autophagy could protect cells from apoptosis through upregulating the p38-NF-κB survival pathway (56). A further study has demonstrated that NF-κB facilitated both apoptosis and autophagy in oridonin-treated human HT1080 fibrosarcoma cells by activating p53. In oridonin-treated MCF-7 cells, autophagy contributed to cell death by its synergic effects on apoptosis, and ERK was found to be inhibited, whereas JNK and p38 were provoked into action (56).

Quercetin

Quercetin represents the most abundant dietary flavonoid found in a broad range of fruits, vegetables and beverages, whose antioxidant and anti-inflammatory properties have been associated with prevention of, and therapy for, cancer. It has been known to be a promising cancer chemopreventive agent that inhibits tumour promotion by inducing cell cycle arrest and promoting apoptotic cell death (61). Quercetin triggers accumulation of HIF-1α, which represses mTOR signalling and induces expression of BNIP3/BNIP3L, to disrupt the Beclin-1/Bcl-2 (Bcl-X_L) complex, leading to activation of Atg7, Atg12-Atg5 conjugate and LC3 turnover, in gastric cancer (62) (Fig. 3e). In addition, quercetin has been reported to inhibit cell viability as well as cancer cell properties such as anchorage-independent cell population growth. It can mediate preferential degradation of oncogenic Ras, thus causing autophagy in Ha-RAS-transformed human colon cells (63) (Fig. 3e).

Interestingly, quercetin has been reported to bypass death receptor resistance through multiple mechanisms, in HPB-ALL, a human acute lymphocytic leukaemia cell line. Quercetin however, can induce apoptosis only when present in combination with a CD95 agonist antibody. At the molecular level, quercetin can reduce intracellular ROS, the reduced MMP, thereby leading to expression of the CD95 receptor remaining unchanged (64).

Plant lectins

Plant lectins, a class of highly diverse non-immune-origin proteins, containing at least one non-catalytic domain, can selectively recognize and reversibly bind to specific free sugars or glycans present on glycoproteins and glycolipids (8,65). *Galanthus nivalis* agglutinin (GNA)-related lectins and legume lectins have been widely reported to induce cancer cell death by targeting autophagy and apoptosis (65). *Polygonatum cyrtonema* lectin (PCL), a mannose/sialic acid plant lectin belonging to the GNA-related lectin family, was first isolated from the rhizomes of *Polygonatum cyrtonema* Hua, a traditional Chinese medicinal herb, in 1996 (66) (Fig. 4a). After its isolation, more physiological and biochemical characteristics of PCL have been revealed with respect to cancer, including breast and cervical carcinomas (67–69). Recently, PCL has been reported to induce

autophagic death *via* a mitochondria-mediated pathway, in human A375 melanoma cells, and such PCL-induced autophagic death was further confirmed to be a mitochondrial-mediated ROS–p38–p53 pathway (69). In addition, inhibition of Ras could promote L929 cell death, suggesting that the Ras–Raf signalling pathway may play the role of a key negative regulator of PCL-induced autophagy (23). Moreover, the PI3KCI–Akt signalling pathway has been shown to play the role of a negative regulator in PCL-induced autophagy (1). Thus, the aforementioned evidence has demonstrated that PCL can induce cancer cell autophagy by promoting the ROS–p38–p53 pathway, as well as by blocking Ras–Raf and PI3K–Akt signalling pathways, in different types of cancer cells (70). Moreover, PCL has also been reported to induce cancer cell apoptosis of HeLa, MCF-7, A375 and L929 cells, but with concomitant low toxicity to melanocytes cells. Further studies demonstrate that PCL induces cancer cell apoptosis by activating the caspase-dependent pathway and mitochondrial ROS-p38-p53 pathway, as well as through blocking Ras-Raf and PI3K-Akt pathways (68).

Concanavalin A (ConA) from the jack bean, was in 1936, the first legume lectin to be purified and crystallized; it is the most well-known representative of the legume lectin family (71–73) (Fig. 4b). After associating with the mannose moiety residing on cell membrane
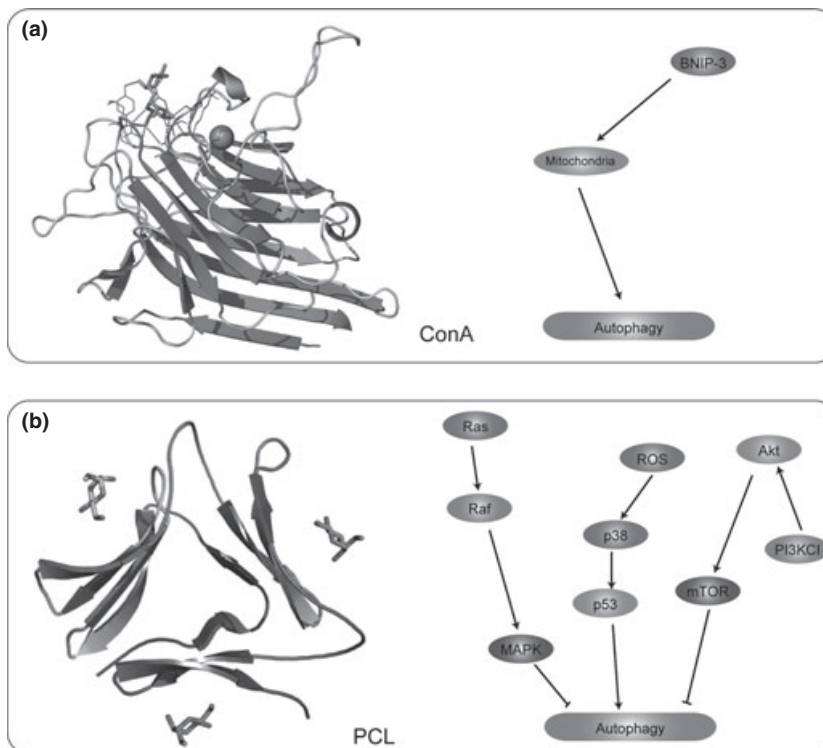
Figure 4. Representative natural macromolecules targeting autophagic pathways. (a) Concanavalin A (ConA); (b) *Polygonatum cyrtonema* lectin (PCL).

glycoprotein, ConA is preferentially internalized and initially transported to mitochondria *via* clathrin-mediated endocytosis, before autophagic cell death is initiated (74), with the observation of marked morphological changes after ConA intervention (75). ConA has been treated into Chang MHCC97-H liver cells (75) and also, experimental data have shown that it can induce autophagic cell death in hepatoma cells using the adenovirus Bcl2/adenovirus E1B 19kDa-interacting protein 3 (BNIP-3)-mediated pathway (76). In addition to its autophagy-inducing activities, ConA has been reported to induce different types of cancer cell death by mitochondria-mediated pathways, p73-FOXO1a-Bim apoptotic pathways, as well as IKK-NF-κB-COX-2, SHP-2-MEK-1-ERK and SHP-2-Ras-ERK anti-angiogenic pathways (76).

Other plant natural compounds

Recently, other natural compounds from plants have been found to induce cancer cell death by regulation of autophagy. Spermidine, a ubiquitous polycation synthesized from putrescine, has been widely accepted as a potential drug to promote cell longevity (77). Recent reports have demonstrated its crucial role for regulating autophagy as it can enhance transactivation of autophagy-related genes such as *Atg7*, *Atg8*, *Atg11* and *Atg15*, in various types of cancer cells (78). Genistein, a natural isoflavenoid found in soybean products, has been reported to have therapeutic potential in multiple tumour types, including prostate, breast, colon, gastric, lung and pancreatic adenocarcinomas, and in lymphoma. Genistein exerts its anti-tumour effect by inhibition of Akt activation, suggesting that it can help cause cancer cell death through autophagocytosis (79) and chloroquine (CQ), traditionally used as an anti-malarial medication, has been reported to induce autophagy, resulting in glioma cell death through a p53-independent pathway (80,81).

Concluding remarks

Cancer, the leading cause of death nowadays worldwide, attracts a great deal of attention. Accumulating lines of evidence have recently revealed that targeting autophagic signalling pathways may be a promising avenue for potential therapeutic purposes. These aforementioned oncogenic/tumour suppressive signalling pathways implicated in Beclin-1 complex, PI3KCI/Akt/mTOR, BCR-ABL, Ras/Raf/MAPK, FOXO1 signalling and p53 may play crucial roles in autophagy-related cancer cell death networks. Interestingly, some natural compounds of plant origin, such as curcumin, resveratrol, paclitaxe, oridonin, quercetin and plant lectins, can induce these autophagic pathways as potential therapeutic agents to deal with carcinogenesis (Table S1).

With the accumulating exploration of molecular mechanisms of plant natural compound activity, they have been widely used as candidate anti-tumour agents; more importantly, some have been further applied to pre-clinical and clinical cancer therapies by using apoptotic pathways. Even though apoptosis and autophagy bear distinct morphological characteristics and physiological processes, there still exist some intricate interrelationships between them. Under some circumstances, apoptosis and autophagy can exert synergistic effects, while other times autophagy can be triggered only when apoptosis is suppressed. Moreover, recent studies have pointed out that apoptosis and autophagy may be interconnected and even simultaneously regulated by the same triggers in cancer.

Due to the complex two-faced nature of autophagy, establishing its dual role in tumour cell survival versus death may help in determining cancer therapeutic potential. Inhibiting autophagy may enhance efficacy of currently used anti-cancer drugs in chemo- and radiotherapy-induced activation of autophagic signalling pathways, which may augment anti-tumour activity, and thus efficacy of radiation and/or anti-cancer drugs. On the other hand, promoting autophagy may induce autophagy-inducing cancer cell death with high thresholds to apoptosis.

Intriguingly, there is a novel emerging viewpoint concerning disruption of protein–protein interactions (PPIs), and with increasing alacrity, more plant natural compounds that inhibit or promote the PPIs can be further screened as novel candidate anti-cancer drugs. Thus, the best hope for cancer therapeutics may lie in the discovery of more novel natural compounds, targeting the physiological effects of core autophagy pathways, and even autophagic networks in cancer cells, rather than their individual gene or protein components. In summary, both strategies have significant potential for translation into ongoing clinical trials that may provide more valuable information on whether and how these natural plant compounds target autophagy pathways to make better sense in cancer treatments.

Acknowledgements

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table. S1 Representative plant natural compounds targeting autophagy as anti-cancer agents

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