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ORIGINAL ARTICLE

Non-coding RNAs associated with autophagy and their regulatory role in cancer therapeutics

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Abstract

Cancer widely affects the world's health population and ranks second leading cause of death globally. Because of poor prognosis of various types of cancer such as sarcoma, lymphoma, adenomas etc., their high recurrence and metastasis rate and low early diagnosis rate have become concern lately. Role of autophagy in cancer progression is being studied since long. Autophagy is cell's self-degradative mechanism towards stress and has role in degradation of the cytoplasmic macromolecules which has potential to damage other cytosolic molecules. Autophagy can promote as well as inhibit tumorigenesis depending upon the associated protein combinations in cancer cells. Recent studies have shown that non-coding RNAs (ncRNAs) do not code for protein but play essential role in modulation of gene expression. At transcriptional level, different ncRNAs like lncRNAs, miRNAs and circRNAs directly or indirectly affect different stages of autophagy like autophagy-dependent and non-apoptotic cell death in cancer cells. This review focuses on the involvement of ncRNAs in autophagy and the modulation of several cancer signal transduction pathways in cancers such as lung, breast, prostate, pancreatic, thyroid, and kidney cancer.

Keywords ncRNA · Autophagy · Apoptosis · Cancer · Therapeutics

Abbreviations

Non-coding RNA	NcRNA
lncRNA	Long non coding RNA
miRNA	MicroRNA
circRNA	Circular RNA
ATG	Autophagy related gene
ATG16L1	Autophagy related 16 like 1 protein
mTOR	Mammalian target of rapamycin
ULK1	Unc-51 like autophagy activating kinase 1
FIP200	Focal adhesion kinase family-interacting protein of 200 kDa
PIP3 kinase III	Phosphatidylinositol 3 kinase III
LC3II	Microtubule-associated protein 1A/1B-light chain 3
piRNA	Piwi interacting RNA
siRNA	Small interfering RNA
snoRNA	Small nucleolar RNA
ceRNA	Competing endogenous RNA
TKI	Tyrosine kinase inhibitor
NSCLC	Non-small cell lung cancer
TIGAR	TP53-inducible glycolysis and apoptosis regulator
ROS	Reactive oxygen species
DDP	Dipeptidyl peptidase
EPG2	Ectopic P granules protein 2
MALAT1	Metastasis-Associated Lung Adenocarcinoma Transcript 1
HuR	Human antigen R
PI3K	Phosphoinositide 3-kinase
GAS5	Growth arrest specific 5 gene
BLACAT 1	Bladder cancer associated transcript 1
MRP1	Multidrug resistance associated protein 1
TSLNC8	Tumor-suppressive lncRNA on chromosome 8p12
STAT3	Signal transducer and activator of transcription 3
HIF-1α	Hypoxia inducible factor 1α
PIK3CB	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
SQSTM1	Sequestosome 1

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PRKAA/AMPK	Protein kinase AMP activated catalytic subunit alpha
TOR	Target of rapamycin
Wnt	Wingless-related integration site
BRCA1	Breast cancer gene 1
PTEN	Phosphatase and Tensin Homolog deleted on chromosome 10
ELK1	ETS like-1 protien
ELK3	ETS like-2 protien
SMAD4	SMAD family member 4
TGFβ	Transforming growth factor beta
MAPK	Mitogen activated protein kinase
XIAP	X-linked inhibitor of apoptosis protein
HMGB1	High mobility group box 1
PAX6	Paired box protein 6
MMPs	Matrix metalloproteinases
JNK	C-Jun N-terminal kinase 1
MAPT-AS1	MAPT Antisense RNA 1
ERK1/2	Extracellular signal regulated kinase 1/2
LAMP1	Lysosomal-associated membrane protein 1
RELN	Reclin
Nrf2	Nuclear factor erythroid related factor 2
SMC1A	Structural maintenance of chromosome protein 1A
TRIP13	Thyroid receptor-interacting protein 13
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
MAP1LC3B2	Microtubule associated protein 1 light chain 3 beta 2
H2AFY	H2A histone family, member Y
HnRNP-1	Heterogeneous nuclear ribonucleoprotein A1
EGR1	Early growth response 1 gene
KIF18A	Kinesin family member 18A
TUG1	Taurine up-regulated 1
LKB1	Liver kinase B1
AMPK	AMP activated protein kinase
TSPAN1	Tetraspanin 1
FAM83A	Family member with sequence similarity 83A
eIF5A2	Eukaryotic translation initiation factor 5A2
AGR2	Anterior gradient protein 2 homolog
STK4	Serine/threonine-protein kinase 4
FOXA1	Forkhead box protein A1
CHD6	Chromodomain helicase DNA binding protein 6
GAS8-AS1	GAS8-antisense RNA 1
LRRK2	Leucine rich repeat kinase 2
SLC7A11	Solute carrier family 7 member 11
FOXP3	Foxhead box P3
FOXE1	Foxhead box E1
ITGA3	Integrin subunit alpha 3
ITPR1	Inositol 1,4,5-trisphosphate receptor type 1
NOX4	NADPH oxidase 4
CCNB1	Cyclin B1

Introduction

Cancer remains one of the major mortalities causing disease globally [1]. Cancer cells alter many cellular mechanisms which include uncontrolled nutrient supply, anti-senescence signals, uncontrolled blood supply and thus, acquire infinite growth and development [2]. According to statistics, there were 1,898,160 new cases of cancer and 608,570 cancer-related deaths in 2021.In male, the incidence and mortality rate is high for lung and prostate cancer. In contrary to males, breast cancer is of great concern for female, while the rate of pancreatic, kidney and thyroid cancers has been found to be increased in both [1].

Non-coding RNAs (ncRNAs) do not code for any protein, rather they protect the genome and act as regulators of autophagy and may aid in disease progression or inhibition [5]. Based on the number of nucleotides, the ncRNAs are classified into long non-coding RNAs (lncRNA) (more than 200 bp nucleotides), small ncRNA (less than 200 bp nucleotides) and circular RNAs (circRNA) [5, 10]. Small ncRNAs are further classified into microRNA (miRNA) (18–25 nucleotides), piwi interacting RNA (piRNA), small interfering RNA (siRNA) and small nucleolar RNA (snoRNA) [5]. ncRNAs do not code for any protein [11]. The epigenetic regulatory role of ncRNAs has been studied thoroughly with lncRNAs and miRNAs [5, 12]. circRNAs are a long chain ncRNAs, which has a closed loop structure. Research has shown that lncRNAs epigenetically control cancer cells by regulating invasion, metastasis, apoptosis and autophagy [5] and also regulates expression of autophagy related mRNAs and sponges miRNAs [13]. Like lncRNAs, circRNAs also sponge miRNAs and regulate autophagy associated cancer metastasis, progression [10].

Autophagy is an evolutionary conserved cytoplasmic catabolic mechanism of cells, which is regulated by autophagy related genes (ATG) [3–5]. It aids in the removal of damaged cellular organelles, misfolded proteins, pathogens, and bulk cytoplasm from the cell, as well as the recycling of nutrients for cells. [2, 4]. Autophagy plays a crucial role in cancer metastasis and also helps in escaping tumor formation [4]. Autophagy can both kill cancer cells by degrading essential biological components, leading to apoptosis, and protect cancer cells by catabolic processes during conditions

like administration of drugs administered and nutrient deficiency [6, 7]. Studies have shown the regulatory potentials of autophagy on anticancer drug discovery too [8]. ATG also regulate ncRNA, that modulate DNA methylation and histone modification, which may often induce autophagy too. The core autophagy process can be divided into 4 major steps. The first step, induction is initiated by the mTOR pathway where autophagic proteins such as ULK1, ATG13, ATG101 and FIP200 are involved. The following second step is phagophore nucleation, which is formed by BECLIN1 associated PIP3 kinase III. Autophagosomal membrane elongation is the third step which is modulated by two ubiquitin-like conjugation systems and involve autophagic factors like ATG3, ATG4, ATG5, ATG7 and ATG12. Until the maturation stage, the cellular machinery is recycled except a portion of LC3II, which gets attached to the membrane. The fourth step, also known as the maturation step, is marked by fusion of the autophagosome with lysosome [9]. Early autophagosome formation is regulated by ATG6 or BECLIN 1 [3]. BECLIN1 is found to be overexpressed in lung, prostate, breast, pancreatic cancers and are found to be regulated by different miRNAs and lncRNAs [3, 4, 14, 15]. Drug resistance poses as serious problem in cancer therapeutics, and it is primarily related to many signalling pathways [16]. Drug resistance is also modulated by autophagy related genes and associated miRNAs [17] and have thus been discussed in the study. Recent research on ncRNA-targeted medicines has significant implications for cancer therapy. The present review focuses on autophagy related ncRNAs (lncRNAs, miRNAs and circRNAs) in detailed manner, which can be used in lung, breast, prostate, pancreatic, kidney and thyroid cancers in future.

Autophagy related ncRNAs in lung cancer

Autophagy related miRNAs in lung cancer

Autophagy can act as an inhibitor or promotor of tumorigenesis and cancer progression. In Src tyrosine kinase inhibitor (TKI) induced autophagy, it is found out that upregulation of ULK1 and downregulation of miR-106a resulted into significant cell death in non-small cell lung cancer (NSCLC) cell line [18]. Overexpressed miR-21 was potentially found to be an oncogene, which act by inducing autophagy by upregulating ULK1/LC3BII protein expressions, increasing autophagosome levels and downregulating p62, suggesting lymphatic metastasis in A549 cells [19]. In A549 and H460 lung cancer cell lines, miR-144 overexpression increased autophagy and apoptosis via LC3-II as well as BECLIN1 expression by targeting TIGAR protein, that functions to eliminate ROS from tumour cells, aiding suppression of tumour proliferation and metastasis inhibition [20]. miRNA also provides drug sensitivity towards NSCLC by downregulating autophagy related protein. miR-153-3p provide gefitinib-sensitivity in NSCLC cells by inhibiting ATG5 and upregulation of miR-1 is associated with DDP sensitivity by preventing ATG3-induced autophagy [21, 22]. Genetic inhibition of c-myc/miR-150 significantly repressed lung cancer by upregulating EPG2 concentration, which is autophagosome maturation-related protein [23].

Autophagy related lncRNAs in lung cancer

Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) is a lncRNA usually overexpressed in NSCLC. To activate autophagy, MALAT1 binds to RNA binding protein HuR [24]. Increased expression of lncRNA KTN1-AS1 in NSCLS acts as a prognostic marker for tumour progression and its knockdown results in increased apoptosis. miR-130a-5p acts as a negative regulator of KTN-AS1 and modulates autophagy targeting 3-phosphoinositide-dependent protein kinase 1 (PDPK1) [25]. Some lncRNAs like LCPAT1 can control the regulation of tumour suppressor miRNAs like miR-186-5p, miR-206, and miR-218-5p, which act on PI3K/AKT/mTOR pathway. This finding suggests that lncRNA can compete with miRNAs for activation of autophagy related proteins such as LC3, ATG and BECLIN2, resulting in tumour proliferation [26]. lncRNA *loc146880* is related to biogenesis of lung cancer, and ROS induction by particulate matter enhances the expression of this lnRNA. This leads to BECLIN1 regulated autophagy activation and subsequent tumour cell migration and invasion [27]. A lncRNA, GAS5 is found to repress autophagy in NSCLC which is known to enhance the cisplatin sensitivity via downregulating BECLIN1, ATG3, ATG5, ATG7, ATG12 and LC3B expression [28]. BLACAT1 induced cisplatin chemoresistance in NSCLC was found to be modulated by upregulation of ATG7, MRP1 LC3-II/LC3-I and BECLIN1. miR-17 was found out to be the potential target for BLACAT1 lncRNA and may induce cisplatin sensitivity in NSCLC via miR-17/ATG7 [29]. lncRNA-HOTAIR supress ULK1, which is vital in initiation of autophagosome formation and upon silencing induces Crizotinib drug sensitivity and apoptosis in NSCLC [30]. lncRNA PANDAR acts as tumour suppressor by upregulating expression of BECLIN1, hence inducing autophagic response and BECLIN1 activates pro-apoptotic protein BAX in mitochondria, and eventually triggers apoptotic signals, leading to apoptosis of NSCLC cells [31]. Tumor-suppressor lncRNA on chromosome 8p12 (TSLNC8) inhibits tumour growth and supresses proliferation, metastasis in lung cancer via IL-6/STAT3/HIF-1α signaling pathways and eventually hypoxia induced autophagy is initiated [32]. Recent studies suggest that lncRNA ADAMTS9-AS2 act on AKT, PIK3CB, mTOR and autophagy-related proteins light chain 3-I/II (LC3-I/II), BECLIN1, sequestosome 1 (SQSTM1)]

and apoptosis-related proteins (Bax and Bcl-2), contributing essential role in inhibition of tumour via modulating PI3K/AKT/mTOR signalling pathway [33].

Autophagy related circRNAs in lung cancer

Lately, circular RNAs are emerging as important controller of various cellular mechanisms and regulator of gene expression by acting as sponges of miRNA and lncRNA. One of the few circRNAs that play important role in cancer, circHIPK3 act as an oncogene in NSCLC. Silencing of circHIPK3 increases autophagy in tumour via activation of miR-124-3p, which is an activator of PRKAA/AMPK signalling pathway [34]. hsa_circ_0085131 circRNA activates autophagy related protein ATG7 by competing with miR-654-5p hence enhancing chemoresistance towards cisplatin in lung cancer cells [35]. In recent study by Fan and colleagues, it was found that six circRNAs are potentially intersecting miRNA-mRNA axes that regulate Chaperone-mediated autophagy, macroautophagy and regulatory protein of autophagy and act as potential modulatory mechanisms. This suggests that, in NSCLC, autophagy can be regulated by hsa_circ_0019709, hsa_circ_0040569, hsa_circ_0081983, hsa_circ_0098996, hsa_circ_0112354, hsa_circ_0135500 and these circRNAs can induce resistance to radiation therapy in NSCLC [36]. High expression of hsa_circ_0010235 in NSCLC downregulate expression of miR-433-3p. Downregulation of this circRNA and upregulation of miR-433-3p inhibited autophagy and initiated apoptosis in NSCLC via targeting mTOR signaling pathway regulator-like TIPRL protein that inhibit mTOR signaling [37].

Autophagy related ncRNAs in breast cancer

Autophagy related miRNAs in breast cancer

Breast cancer is one of the major cancers found in women. Many miRNAs provide drug resistance to cancer which is the main reason for invasion, metastasis and recurrence of breast cancer [38]. Oncogenic miR-638 acts on DACT3, the main modulator of Wnt/ β-catenin pathway and inhibits its activity. It was found that miR-638 activates mTOR induced autophagy and suppresses the expression of tumour suppressors such as BRCA1, PTEN and P53 [39], whereas tumour suppressive miR-135a inhibits proliferation of breast cancer MCF-7 and T47D cell lines via attenuating ELK1 and ELK3 oncogenes and decrease autophagy [40]. In a study, it was found that miR-224-5p inhibits autophagy via targeting SMAD4, which is a central mediator of transforming growth factor beta (TGFβ) and upon induction, it promotes proliferation and metastasis in MDA-MB-231 cells, a triple negative breast cancer cell line [41]. miRNA cluster analysis in breast cancer cell lines reveals that miR-106b, miR-93, and miR-25 modulate ULK1 (Unc-51 Like Autophagy Activating Kinase 1), TGFβ and promote invasiveness in breast cancer cells via AKT/MAPK signalling pathway [42]. In a study by Chen and colleagues, it was demonstrated that miR-23a increases breast cancer autophagic activity by XIAP and the mediated autophagic activation of LC3/p62 promotes metastasis and invasion of cancer cells [43]. In some breast cancer cases, it is reported that miRNA mediated loss of autophagy enhances the tumorigenesis via increasing intracellular reactive oxygen species (ROS) levels and DNA damage response (DDR) by targeting several key regulators of autophagy, including BECLIN 1, ATG16L1 and SQSTM1. A triple-negative breast cancer cell line and xenograft study demonstrates that miR-20a inhibits starvation induced autophagy and lysosomal activity through downregulating the expression of ATG16L1, BECLIN 1 and SQSTM1 [44]. In breast cancer, miR-489 and miR-567 reverse drug resistance of trastuzumab and doxorubicin by silencing autophagic flux [45, 46]. Taxol resistant breast cancer cell lines has been sensitized by upregulating miR-129-5p via supressing autophagy and enhancing apoptosis by inhibiting HMGB1, an autophagy-regulating protein that functions to displace Bcl-2 to bind to BECLIN1, in order to activate BECLIN1 for induction of autophagy [47].

Autophagy related lncRNAs in breast cancer

When lncRNAs were considered, DANCR-miR-758-3p-PAX6 axis was found to regulate autophagy and apoptosis as DANCR negatively regulates miR-758. Downregulation of DANCR was found to be beneficial in inhibiting malignant breast cancer [48]. HOTAIR, another lncRNA play important role in epigenetic gene silencing. HOTAIR cross talk with various ATGs and matrix metalloproteinases (MMPs) via various miRNAs, hence it has a pivotal role in breast cancer progression. When HOTAIR is downregulated, a decrease in migration and invasiveness in MCF-7 cells was observed with associated downregulation of MMP2, MMP9 and altered regulation of p53/Akt/JNK pathway, leading to arrest of cell cycle at G1 phase [49]. GAS5 as a lncRNA, was found to be overexpressed in MCF-7 cell line and BECLIN 1, ATG7, ATG12 and LC3B was found to be downregulated also, which affects ULK1 and ULK2 expression, resulting in upregulated apoptosis and supressed autophagy [50]. Upregulation of MAPT-AS1 was also correlated with better patient survival in breast cancer [51].

Autophagy related circRNAs in breast cancer

Autophagy associated circRNAs such as circCDYL act as sponge on miR-1275 and modulate expression of autophagy associated downstream genes ATG7 and ULK1[52].

Increased expression of circular RNA circ-DNMT11 in breast cancer was positively correlated with increased proliferation and survival of breast cancer cells and it also stimulated autophagic flux downregulating p53 expression [53]. Autophagy related ncRNAs which are found to be involved in breast cancer and their targets are given in Table 1 below.

Autophagy related ncRNAs in prostate cancer

Autophagy related miRNAs in prostate cancer

Prostate cancer (PTC) is one of the most common cancers in men. In a study by Liao and colleagues, miR-381 has been found to downregulate the reclin (RELN) and promote the autophagy of PTC cells [61]. In another study, it was revealed that upregulation of LC3II and BECLIN 1 by miR-139 and miR-381 was led to increase in autophagy [15, 18]. There was inhibition of the PI3K/AKT/mTOR signalling pathway due to reduced expression of RELN, which was found to be modulated by miR-139 [15, 18]. The formation of autophagic flux blockade by miR-139 resulted in apoptosis of PTC [15]. Usually, ULK2 is overexpressed in PTC cells by regulating mTOR signalling pathway and ATG protein upregulation. Another study found out that when miR-26b has been upregulated, it led to downregulation of ULK2 and resulted in inhibition of the autophagy process in PTC [62].

Autophagy related lncRNAs in prostate cancer

TUG1, a lncRNA, has been found to balance oxidative stress and regulate autophagy by regulating antioxidant signalling pathways and NRF2 expression and enhances the invasion and proliferation of PTC. Knockdown of TUG1 resulted in decrease in NRF2 level [63–65]. TUG1 sponges miR-139-5p and positively regulates SMC1a. Knockdown of TUG1 results in radiosensitization of PTC cell lines [64]. Upregulation of a lncRNA TINCR decreases the proliferation, invasion and migration of PTC cells via suppressing TRIP13 expression [66]. LINC01116 knockdown has shown the increased expression of GAPDH, MAP1LC3B2 or LC3II and H2AFY, which resulted in inhibition of PTC cell proliferation. The expression of LINC01116 has been altered by sulforaphane following a novel mechanism and can be used as therapeutic strategies [67]. Radiosensitivity of PTC cells has been increased when GAS5 was upregulated by sponging miR-18a [68]. HULC has been found to suppress the phosphorylation of BECLIN 1 and reduced autophagy via mTOR signalling pathway. Knockdown of HULC, a lncRNA, has been found to enhance the radiosensitivity of PTC cells [69].

Autophagy related circRNAs in prostate cancer

circCSPP1 is modulated by HnRNP-1 and sponges miR-520 h, which in turn upregulate EGRI. As a result, circCSPP1 induces autophagy and accelerates the proliferation of PTC cells through circCSPP1-miR-520 h-EGR1 axis [70]. circ_0001747 promotes autophagy and increases the proliferation of PTC cells [71]. circRNA_CCNB2 knockdown enhances expression of miR-30b-5p and inhibits autophagy, which increases the sensitivity of irradiation resistance PTC cells towards irradiation by suppressing the expression of KIF18A [72].

Table 1 Autophagy related ncRNAs in breast cancer and their target

Type of ncRNA	ncRNA	Target protein in Autophagy	Autophagy modulation	References
microRNA	miR-21	PTEN, BECLIN 1, LC3-II	Inhibit autophagy	[54]
	miR-375	ATG7	Inhibit autophagy	[55]
	miR-124-3p, miR-221	BECLIN 1	Inhibit autophagy	[56, 57]
	miR-224-5p	Smad4	Inhibit autophagy	[58]
	miR-567	ATG5	Inhibit autophagy	[45]
	miR-1275	ULK1	Inhibit autophagy	[59]
lncRNA	MALAT1	miR-216b, miR-101, miR-124, and miR-23b-3p	Induce autophagy	[11]
	ROR	Regulate miR-34a	Inhibit autophagy	[11]
	H19	ERK1/2 pathway	Induce autophagy	[11]
	MEG3	LC3, ATG3, and LAMP1	Inhibit autophagy	[11]
	PVT1	ATG7 and BECLIN 1, ULK1	Induce autophagy	[60]

Autophagy related ncRNAs in pancreatic cancer

Autophagy related miRNAs in pancreatic cancer

Pancreatic cancer (PC) is a common and important malignancy in the western world [73, 74]. ncRNAs are found to play a crucial role in metastasis, invasion, autophagy and apoptosis in PC [74]. Borchardt and colleagues have shown that expression of MYC is modulated by miR-24-3p, which induce apoptosis, modulate ROS generation and initiate autophagy in PC. The result showed the powerful effect of tumor inhibitory action of miR-24-3p in PC [73]. A study by Gu and colleagues depicted that miR-7 inhibits cell proliferation and metastasis of PC cells as miR-7 modulates the LKB1-AMPK-mTOR signaling pathway and decreases the autophagy. This process interferes with glycolysis to reduce the glucose levels in PC cells in *in-vivo* and *in-vitro* conditions [74]. Another study showed that miR-7 expression was found to be reduced in PC cells. Overexpression of miR-7 induced autophagy and reduced the glycolytic pathway, and also decreased the resistance of PC cells to gemcitabine [75]. Highly expressed miR-29c has inversely correlated with autophagy in PC [76]. Tetraspanin 1 (TSPAN1) is found to be actively participating in cell proliferation and enhances autophagy. FAM83A which is a positive regulator of TSPAN1 offers chemo-resistant to pancreatic cells. miR-454 targets both FAM83A and TSPAN1[77]. Overexpressed miR-137 directly targeted the ATG5 gene and downregulated autophagy in PC cells, and also increased the sensitivity to doxorubicin [78]. miR-9 downregulated eIF5A2 by directly acting upon 3'UTR of eIF5A2 and inhibited autophagy. PC cells with overexpressed miR-9 have shown more sensitivity to doxorubicin by repressing autophagy in PC cells [79].

Autophagy related lncRNAs in pancreatic cancer

In a study by Liu and colleagues, LINC01207 has been shown to interact with miR-143-5p which interacts with AGR2. Silencing of LINC01207 led to upregulation of miR-143-5p and downregulation of AGR2, which induced apoptosis and autophagy in PC cells [14]. PVT1, a lncRNA sponges miR-20a-5p in PC cells and modulate ULK1 expression [80].

Autophagy related circRNAs in pancreatic cancer

circRNA such as hsa_circ_0071922 act as miRNA sponge for miR-663a-5p by targeting the mTOR pathway in PC cells. This led to autophagy and inhibit cell proliferation in PC [10]. circRHOBTB3 acts as direct sponge to miR-600 and it enhances autophagy and proliferation of pancreatic ductal adenocarcinoma cells through inhibition of AKT/mTOR pathway [81]. Addition of chloroquine diphosphate causes autophagy suppression in pancreatic cancer and both miR-663a-5p and miR-154-3p were found to be under-expressed in chloroquine diphosphate treated cells [82]. These circRNAs can be exploited in pancreatic cancer therapeutics.

Autophagy related ncRNAs in thyroid cancer

Autophagy related miRNAs in thyroid cancer

miRNAs have been reported as prominent biomarkers and therapeutic targets in thyroid cancer (TC) [83–85]. Elevated expression of miR-183 and miR-375 were found in medullary thyroid cancer cells. Further study reported that knockdown of the elevated miR-183 resulted in increased expression of LC3B and autophagy in TC [84]. In another *in-vitro* study of medullary thyroid cancer cells, miR-9-3p transfection inhibited autophagy by targeting ATG5 and BECLIN 1 and resulted in decreased cell viability and increased apoptosis [85]. Binding of miR-30d to BECLIN 1 resulted to reduction of autophagy in anaplastic thyroid cancer cells and sensitivity of TC to cisplatin drug was increased [86]. In cisplatin treated anaplastic thyroid cells, miR-144 targets TGF-α and downregulates autophagy preventing TC progression [87]. Also, miR-30d and miR-144 enhance the sensitivity of anaplastic TC cells towards cisplatin, however, miR-30d reduces autophagy while miR-144 induces autophagy. Furthermore, overexpression of miR-125b negatively regulate FOXP3 expression which eventually modulate the expression of ATG7, BECLIN 1 and LC3II, and stimulate autophagy in thyroid cancer cells [88]. miR-524-5p directly downregulates ITGA3 and FOXE1 which leads to increase in the rate of apoptosis and autophagy and decline in proliferation and invasion of papillary TC cells. [89]. Therefore, expression of miR-183, miR-9-3p, miR-375, miR-524-5p, miR-125b, miR-144 and miR-30d have shown reduce TC cells proliferation by either downregulation or upregulation of autophagy associated gene expression.

Autophagy related lncRNAs in thyroid cancer

Altered lncRNAs expression have been reported in TC [90]. Yang and colleagues and Peng and colleagues have revealed that overexpression of a lncRNA TNRC6C-AS1 is associated with increased methylation of STK4 promoter gene which in turn induce TC proliferation. Silencing of TNRC6C-AS1 led to expression of STK4 which have been found to promote autophagy, apoptosis and proliferation of TC cells by activating Hippo signalling pathway. Suppression of

TNRC6C-AS1 was also found to serve as protection against TC by inducing autophagy and apoptosis. [90, 91]. An *in-vivo* study has shown that lncRNA MALAT1 regulate miR-200a-3p/FOXA1 axis by acting as ceRNA and modulate the proliferation of anaplastic TC cells. Suppression of MALAT1 led to upregulation of miR-220a-3p and inhibition of miR-220a-3p resulted in overexpression of FOXA1. It was reported that inhibition of MALAT1 expression and upregulation of miR-220a-3p led to increase in BECLIN1 expression and LC-3II/I ratio, leading to increased apoptosis and autophagy, and eventually suppressed anaplastic TC cells proliferation [83]. In papillary TC, a lncRNA namely Linc00941 was found to be involved in the regulation of CHD6 expression and TGFβ signalling in papillary TC and was associated in inhibiting autophagy [92]. Overexpressed lncRNA GAS8-AS1 was also found to upregulate ATG5, leading to induction of autophagy [6]. In another study, lncRNA RP11-476D10.1 was found to downregulate miR-138-5p and upregulate LRRK2 expression. Silencing of lncRNA RP11-476D10.1 reverse its regulation on miR-138-5p and LRRK2, and resulted in increased BECLIN1, LC3B, Bax expression and decreased BECLIN 2 expression, leading to induction of autophagy and apoptosis of papillary thyroid cancer cells [93].

Autophagy related circRNAs in thyroid cancer

circ_0067934 sponges and inhibits miR-545-3p to repress ferroptosis of TC cells by upregulation of negative regulator of ferroptosis, SLC7A11. Upon silencing of circ_0067934, ferroptosis is induced and its knockdown eventually increases ferroptosis, autophagy and apoptosis in TC cells [94]. Another study reveals that knockdown of circEIF6 along with cisplatin treatment reduces LC3 II/LC3 I ratio, autophagy and cell proliferation of TC cells in vivo by enhancing miR-144-3p expression and inhibiting TGF-α expression [95].

Some of the ncRNAs along with their target molecules have been listed in Table 2. The role of different miRNAs, lncRNAs and circRNAs in kidney cancer and their associated process of modulation of autophagy have been provided in Table 3. Modulation of PI3K/AKT/mTOR pathway in autophagy by various ncRNAs in different cancers have been explained in Fig. 1.

Role of autophagy-based ncRNAs in drug resistance and therapeutics

Drug resistance

Drug resistance is an inevitable impediment for an effective and lasting cancer treatment [16]. Cancer cells are found to be resistant to many chemotherapeutic drugs such as cisplatin, crizotinib, trastuzumab, gemcitabine, gefitinib, doxorubicin, temozolomide and capecitabine [21, 28–30, 35, 45, 46, 75, 78, 79, 86–88, 92, 95, 113]. Trastuzumab and doxorubicin are commonly used drugs but they fail to exert bioactivity due to chemoresistance. Studies have shown that regulating autophagic flux can retrieve cancer cells sensitivity towards trastuzumab and doxorubicin. ncRNAs have been found to play pivotal roles in breast cancer, TC, PTC, LC and PC drug resistance. In breast cancer, miR-567 reverses drug resistance of trastuzumab by inactivating autophagic flux [45]. Furthermore, in TC, ncRNAs have been found to increase the drug sensitivity by modulating autophagy associated genes. Introduction of miR-30d in the system increases the sensitivity of TC towards cisplatin by inhibiting BECLIN 1 mediated autophagy [86]. miR-144 is found to enhance the effects of cisplatin by inhibiting

Table 2 Autophagy related ncRNA*s* in thyroid cancer

Type of ncRNA	ncRNA	Target RNA/protein in autophagy	Autophagy modulation	References
miRNA	miR-30a-3p	ATG12	Inhibit autophagy	[102]
	miR-100	NOX4	Induce autophagy	[103]
	miR-30a	BECLIN 1	Inhibit autophagy	[104]
	miR-143	LC3B, MAPK/AKT and PI3K/ERK signaling pathways	Induce autophagy	[105]
	miR-204	LC3B	Inhibit autophagy	[106]
lncRNA	KIF9-AS1	miR-497-5p	Induce autophagy	[107]
	SCAMP1	miR-429 and ZEB1/JUN	Inhibit autophagy	[108]
	HOTAIR	miR-17-5p and BECLIN 1	Induce autophagy	[109]
	HOTTIP	PI3K/Akt/ATG13signaling pathway	Induce autophagy	[110]
	SPINT1-AS1, WDFY3-AS2	LC3-I/II	Induce autophagy	[111]
circRNA	circ_0035483	Target miR-335 and Cyclin B1 (CCNB1)	Induce autophagy	[4, 112]

Table 3 Autophagy related ncRNAs in Kidney cancer

Type of ncRNA	ncRNA	Target RNA/protein in Autophagy	Autophagy modulation	References
miRNA	miR-17-5p	Phosphatase and tensin homolog (PTEN)	Inhibit autophagy	[96]
	miR-125b	ATG7, FOXP3	Induce autophagy	[88]
	miR-9-3p	ATG5	Inhibit autophagy	[97]
	miR-524-5p	FOXE1 and ITGA3	Induce autophagy	[89]
	miR-138-5p	lncRNA RP11-476D10.1, Bax, LC3B, and BECLIN 1	Induce autophagy	[98]
	miR-144	TGF-α	Inhibit autophagy	[99]
lncRNA	GAS8-AS1	ATG5, ATG7, sponges miR-187-3p and miR-1343-3p	Induce autophagy	[6, 7]
	SNHG9	YBOX3 and P21 pathways	Inhibit autophagy	[100]
	TNRC6C-AS1	STK4	Induce autophagy	[91]
	SLC26A4-AS1	ITPR1	Induce autophagy	[101]

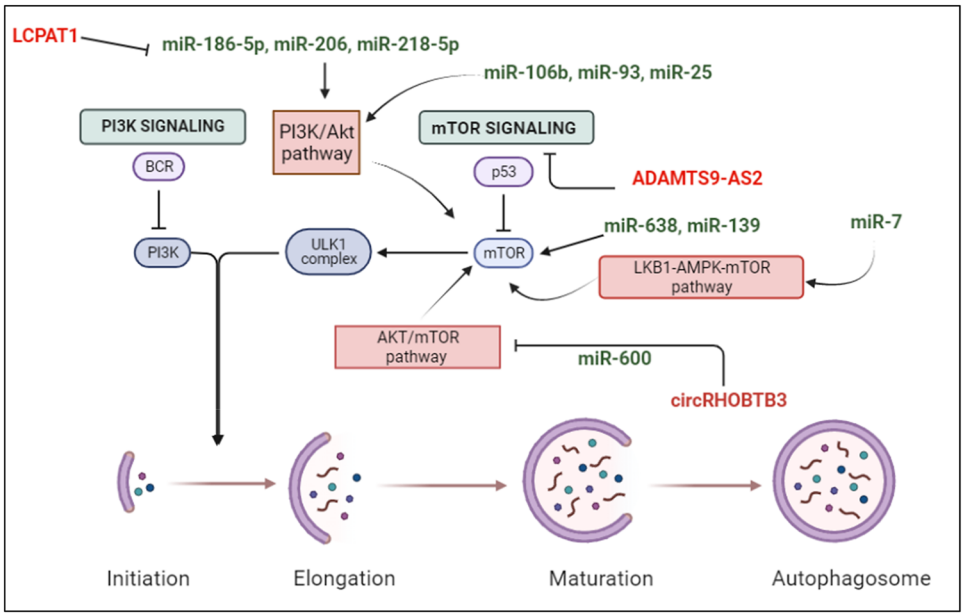

Fig. 1 Modulation of PI3K/AKT/mTOR pathway in Autophagy by various ncRNAs in lung, thyroid, prostate, breast, kidney and pancreatic cancers. ncRNAs shown in red inhibit the PI3K/AKT/mTOR pathway via sponging miRNA or directly inhibiting associated protein. ncRNA shown in green modulate PI3K/AKT/mTOR pathway promoting autophagy

cisplatin induced autophagy while miR-125b enhances cisplatin induced autophagy [87]. Moreover, overexpressed miR-125b improves the sensitivity of TC cells towards sorafenib and cisplatin [88]. circEIF6 improves cisplatin induced autophagy and increases its resistance in anaplastic and papillary TC cells by targeting miR-144-3p [95].

Therapeutic roles of autophagy associated ncRNAs in cancers

Autophagy related ncRNAs may be used in therapeutics to cure or get relieve from cancers [84]. Autophagy serves as either survival or destruction mechanism in cancers. Addition of some ncRNAs subsequently lead to significant decline in autophagy and some ncRNAs lead to overexpression of autophagy flux. Therefore, these ncRNAs can be therapeutically targeted to diminish cancer [85]. Several studies have been reported where ncRNAs acts as tumour suppressor. In a recent study, Qin and colleagues found that overexpression of lncRNA GAS8-AS1 lead to suppression of papillary TC through ATG5 regulated autophagy [6]. Another study by Zhang and colleagues suggests that miR-30d acts as critical regulator of cisplatin drug, so it can be exploited as therapeutic target of TC [86]. Cisplatin in combination with overexpressed miR-125b in TC cells have shown potential to reduce TC cells proliferation [88]. In another study Lu and colleagues have reported high expression of a circRNA, circCSP1, which significantly increases proliferation, migration and invasion of PTC cells via autophagy upregulation [70]. Yang and colleagues have found that a lncRNA, TNRC6C-AS1 enhance the proliferation of TC cells by promoting autophagy and apoptosis [90]. Therefore, these ncRNAs can be targeted accordingly in future for cancer therapeutics. Autophagy associated ncRNAs which can be targeted in different types of cancers have been depicted in Fig. 2.

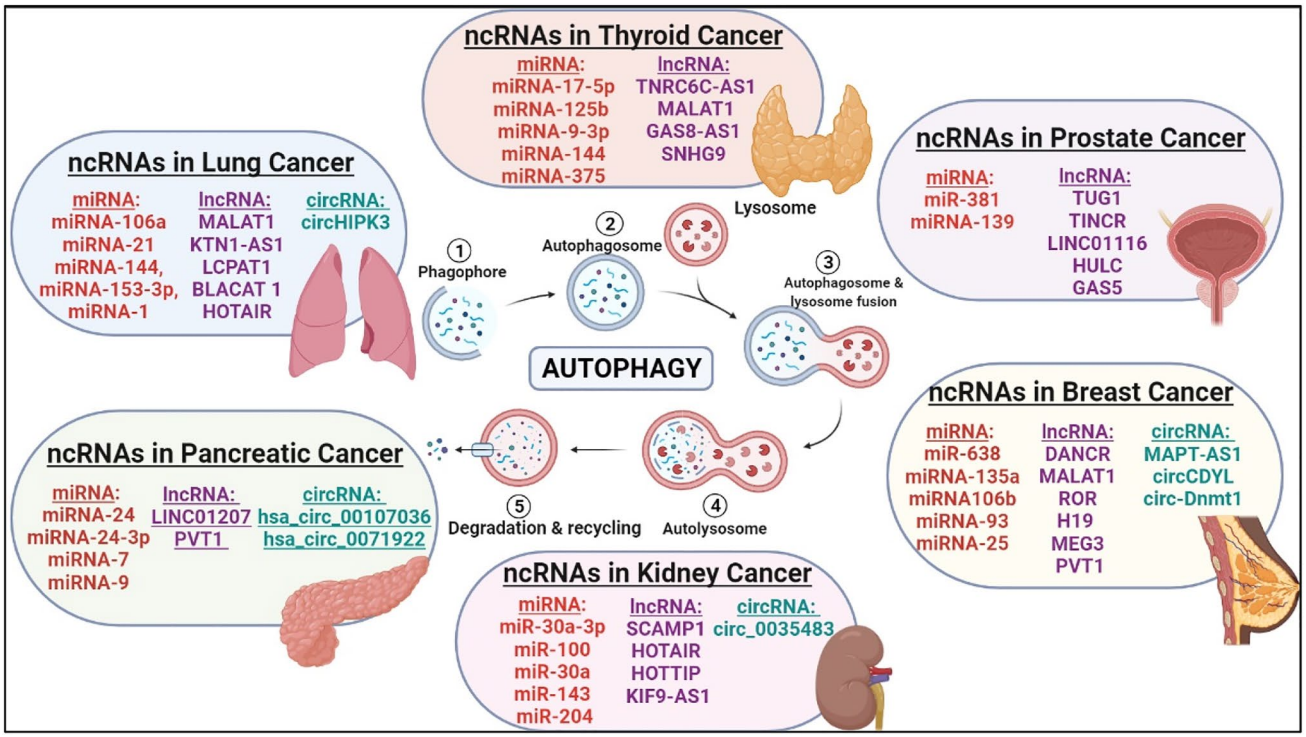

Fig. 2 Autophagy modulating ncRNAs in different types of cancer including lung, thyroid, prostate, breast, kidney and pancreatic cancer

Conclusion

In this review, the role of autophagy-related ncRNAs is highlighted which can be useful to devise newer therapeutic strategies for cancer in future. The ncRNAs either enhance or suppress the autophagy by modulating ATG genes, BECLIN1, PTEN, ULK, LC3-I/II etc. or pathways such as PIK3/AKT/ATG, MAPK/AKT, PI3K/ERK etc. Potential diagnostic and prognostic ncRNAs associated with six most lethal cancers (lung, breast, prostate, kidney, thyroid and pancreatic cancers) have been explained here. miRNA and lncRNAs interact with a mRNA which is directly or indirectly affects autophagy and cell proliferation of cancer cells. siRNA, circRNA, lncRNA and shRNA act as sponges for miRNA and these ncRNA either upregulate or downregulate the miRNA or related mRNA or other protein which either increases or decreases the incidence of autophagy of cancer cells. From various studies, it has been understood that not only upregulation of autophagy but downregulation of autophagy can also lead to inhibition of cancer cell proliferation, invasion and metastasis. For developing any new therapeutic strategies, it is very essential to understand of the mechanism of action of the therapeutic targets and its associated pathways in the disease. The mechanisms of action of all ncRNAs as autophagy inducers or inhibitors have been studied here and still demand more experiments to be conducted in this area. The ncRNAs mentioned in the study play important role in autophagy and can therefore can be explored as potential as well as promising therapeutic strategies for lung, breast, prostate, kidney, thyroid and pancreatic cancer treatment.

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Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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