

Review

Novel Insights into Epigenetic Control of Autophagy in Cancer

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Abstract

The autophagy mechanism recycles the damaged and long-standing macromolecular substrates and thus maintains cellular homeostatic and proteostatic conditions. Autophagy can be an unavoidable target in cancer therapy because its deregulation leads to cancer formation and progression. Cancer can be controlled by regulating autophagy at different genetic, epigenetic, and post-translational levels. Epigenetics refers to the heritable phenotypic changes that affect gene activity without changing the sequence. Modern biology employs epigenetic alterations as molecular tools to detect and treat a wide range of disorders, including cancer. However, modulating autophagy at the epigenetic level may inhibit cancer growth and progression. Epigenetics-targeting drugs involved in preclinical and clinical trials may trigger antitumor immunity. Here, we have reviewed some experimental evidence in which epigenetics have been used to control deregulated



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autophagy in cancerous diseases. Furthermore, we also reviewed some current clinical trials of epigenetic therapy against cancer. We hope that this information can be utilized in the near future to treat and overcome cancer.

Keywords

Autophagy; genetic; epigenetic; cancer therapy

1. Introduction

Despite breakthroughs in technology, research, and medication over the previous few decades, cancer remains a global challenge. Cancer is currently the world's largest cause of death, contributing to 10 million deaths by 2020 [1]. Traditional cancer treatments such as chemotherapy, surgery, radiotherapy, and immunotherapy are the mainstream therapeutic approaches for cancer. However, they come with a longer list of disadvantages, such as damage to normally growing healthy cells, long-term side effects, systemic toxicity, structural distortions, drug resistance by tumor cells, and psychological problems. Furthermore, side effects can limit the use of anticancer drugs, lowering a patient's quality of life [2, 3]. Thus, despite advances in cancer research, diagnosis, and treatment, searching for new therapeutic agents and therapies remains a hot topic in cancer research [4].

Over the last few years, discoveries in cancer biology have increased the knowledge of many significant biomarkers of cancer, including changes in cell physiological processes such as programmed cell death, control at cell cycle checkpoints, immunological modulation, and angiogenesis [5]. Cancer is known to be caused by genetic and epigenetic factors [6]. Changes at the epigenetic level regulate the expression of various genes by controlling the accessibility of promoter sites to transcriptional factors. Different epigenetic modifications like histone modifications, DNA methylation, and microRNA changes may modulate cell growth cycle, apoptosis, and autophagy [6, 7]. Abnormal gene silencing mediated by epigenetic changes is also a significant factor in tumorigenesis and development.

Autophagy is a catabolic process that is critical in the initiation and development of cancer [8]. Autophagy interacts with cell metabolic reactions, cell survival, and the turnover of proteins and organelles at multiple levels, implying that autophagy in cancer has paradoxical and complicated roles [5]. It has been suggested that the deregulation of autophagy is controlled by various signaling pathways, including epigenetic control. Although the role of epigenetic regulation in autophagy is larger unknown [6].

Cancer can be regarded as a disease controlled by multiple players. Hence, targeting the relationship between different cellular mechanisms may yield a better therapeutic response instead of targeting only one cellular mechanism. So in this study, we discuss the epigenetic modulation of autophagy in cancer.

2. Epigenetics and Cancer

The study of changes in gene expression that are heritable and occur without any changes in the gene sequence is known as epigenetics [9]. C. H. Waddington coined epigenetics in 1942 to

describe how heritable phenotypic expression alters gene expression and potentially reversible changes in chromatin structure and DNA methylation. An essential feature of epigenetic mechanisms is that they can change gene functions in response to exogenous stimuli. They also provide a means for steadily disseminating gene activity states between generations [9-11].

Epigenetic mechanisms have significant roles in maintaining gene expression patterns in specific tissues and normal mammalian development [12]. This reprogramming is a heritable trait but can be reversed [13] and affects cell growth, proliferation, differentiation, and migratory properties. Cancer emergence, progression, and treatment responsiveness are all linked to aberrant epigenetic profiles [14], so it's not surprising that these processes are involved. Despite the promise of epigenetic therapeutics, further investigation into the precise pathways involved is necessary for the safe and efficient development and application of epigenetic therapeutics, either alone or in combination with existing therapies [15]. DNA methylation, modification of histone tails, RNA-associated silencing, and genomic imprinting are the four types of epigenetics-mediated gene silencing [Figure 1]. Other factors, such as the environment and xenobiotics can also result in gene silencing. Still, DNA methylation and histone modification of chromatin are the two most important changes responsible for developing malignant diseases [16].

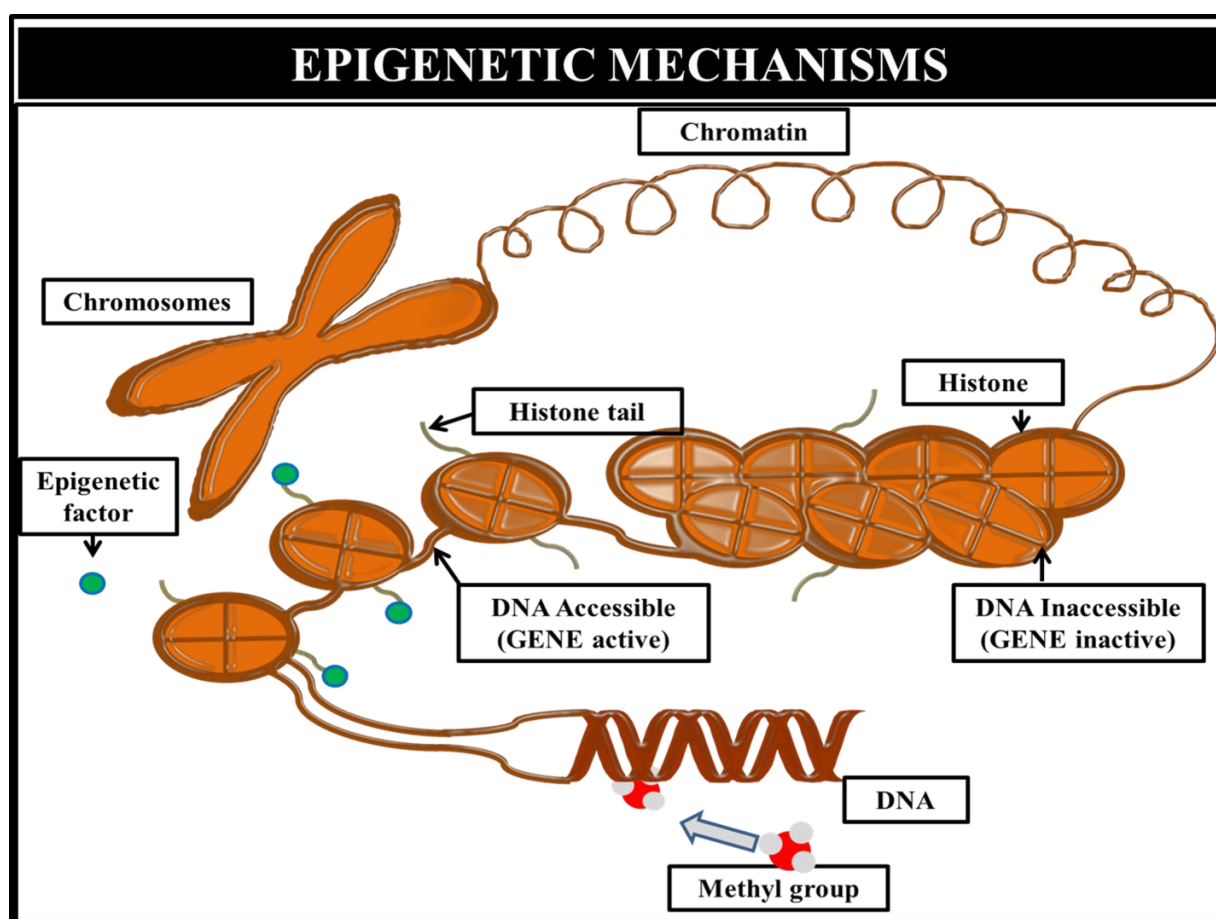


Figure 1 Epigenetic mechanisms. Epigenetic changes significantly direct the abnormal expression of oncogenes that drive cell malformation and cancer development. Changes in DNA methylation patterns were the first epigenetic hallmarks linked to carcinogenesis and changes in gene expression through the silencing of tumor suppressor genes (TSGs) [17].

2.1 DNA Methylation

Adding a methyl group to a cytosine-guanine dinucleotide (also called a “CpG site”) is the most common type of epigenetic modification [18]. CpG sites are usually found at the end of genes, occupying about 60% to 70% of gene promoters in vertebrates that remain unchanged over time [19]. This is because DNA methylation is affected by both genetic and environmental factors [18]. Various cellular processes are influenced by epigenetic changes in the genome or DNA methylation, which affects embryo growth, mRNA synthesis, chromatin structure, and stability of chromosomes and may also inactivate the X chromosome [20]. It also helps control gene expression by recruiting proteins that help stop cell growth or block transcription factors, which help control gene expression. Demethylation and methylation are processes that significantly control epigenetic changes. DNA methylation affects the binding of transcription factors and the accessibility of regulatory regions in DNA, affecting gene expression [21]. DNMTs i.e., DNA methyltransferases, commonly mark DNA by attaching a CH_3 group to the fifth carbon of a cytosine residue in a CpG dinucleotide, resulting in 5-methylcytosine [21, 22] (Figure 2a).

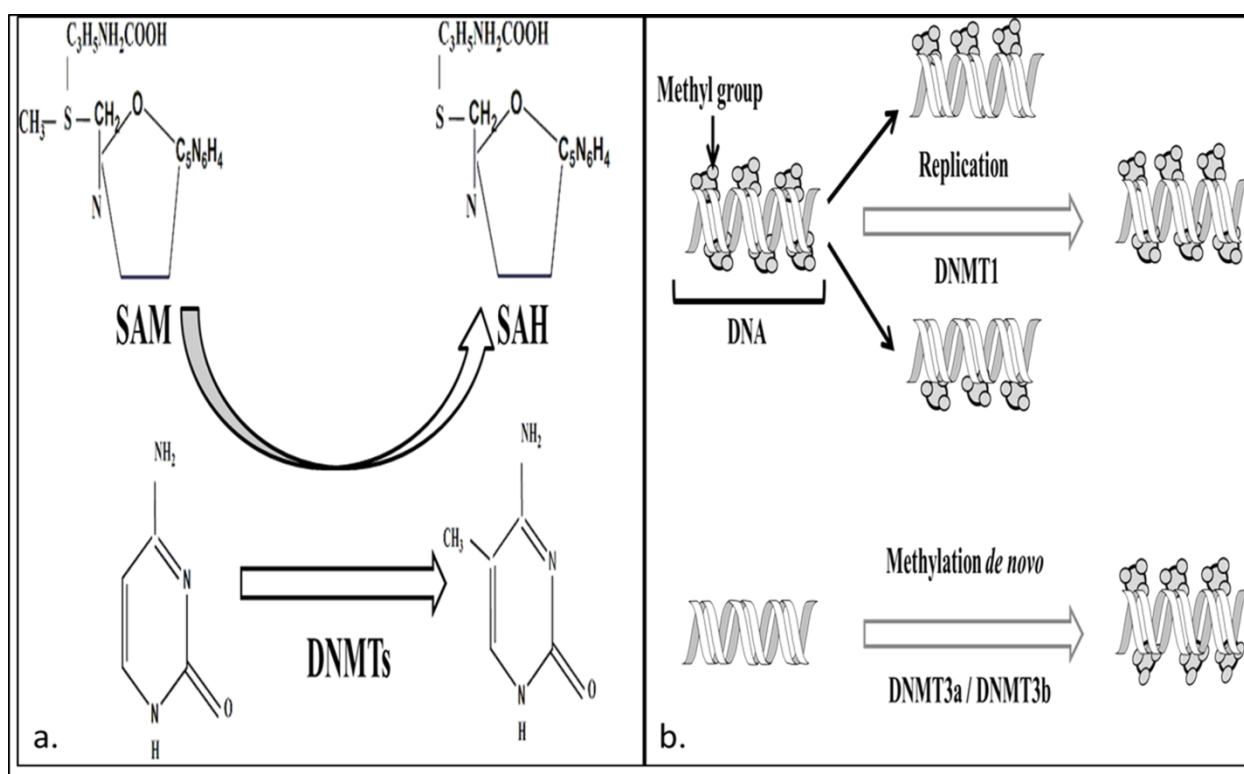


Figure 2 (a) CH_3 group from S-adenyl methionine (SAM) to the 5th carbon of a cytosine residue to make 5-methylcytosine; (b) Methylation through DNMT1 and de-novo methylation through DNMT 3a/3b.

2.1.1 DNA Methyltransferases (DNMTs)

Dnmt1, Dnmt2, Dnmt3A, and Dnmt3B are members of the mammalian DNMT family. This family is split into two groups: maintenance and de novo methyltransferases. CH_3 groups are added to the hemi-methylated DNA by the maintenance of DNMT1 during DNA synthesis, whereas CH_3 groups are added to the CpG dinucleotide sites of DNA molecule by de novo DNMT3A and

DNMT3B (Figure 2b) [23]. The conventional DNA methylation pattern in somatic cells is maintained during cell division by DNMT1 [24-26]. DNMT1 adds CH₃ group to the new DNA strand at the fifth position of the cytosine base within the CpG dinucleotides by being a component of the DNA replication complex thereby maintaining methylation of the newly formed DNA molecule [27]. Isoforms of DNA methyltransferases, associated with the DNMT1 gene, have been identified in somatic cells, oocytes, pachytene sperm cells, and preimplantation embryos. These isoforms are produced by another use of different first exons of the DNMT1 primary transcript, which can be found in the DNMT1 gene. The role of enzymes DNMT3A and DNMT3B in establishing an additional methylation style in genomic DNA has been identified [23, 24, 28].

Dnmt3a and Dnmt3b can make novel methylation patterns in unchanged DNA, which is why they are called de novo DNMT. When DNA is being made, Dnmt1 is used to reproduce the pattern of DNA methylation from the parent DNA template onto the new daughter strand [22].

DNMTs have an important function in the methylation of mammalian genomic DNA. The expression of the DNMTs is much higher in breast, colon, endometrium, prostate, stomach cancer, and uterine leiomyoma than in other types of cancers [29]. And the aberrant DNA methylation has been found in many cancers, like breast, oral, gastric, colon, liver, lung, and pancreatic cancers [30-36].

Hypermethylation, hypomethylation, and loss of imprinting are three types of changes that can happen to the DNA. Changes in the methylation pattern of promoter sequences, such as the hypermethylation or hypomethylation in TSGs and proto-oncogenes, respectively, are linked to cancer malignancy [34-37].

2.1.2 DNA Hypermethylation

In the last 10 years, a new way for tumor growth has been found: the hypermethylation of TSGs. Tumor series show that hypermethylation of TSGs may play a role in the oncogenesis in children. Thus, these epigenetic changes could be used to indicate the disease, and genes that control methylation should be considered as possible new therapeutic targets [38].

DNA hypermethylation is a term that primarily refers to the acquisition of methylation at places that aren't normally methylated. This kind of methylation happens mainly in the promoter region of CpG sites. A CpG island is a DNA sequence (more than 200 bp) with >50% GC content. Expected CpG ratio of more than 0.6 [39, 40], is called "abnormal promoter CpG island hypermethylation", which has been linked to the loss of gene function and the stabilization of transcriptional repression, which happens mostly in TSGs [41, 42]. Most of the changes affecting gene regulation due to DNA methylation are found at the non-promoter sites near CGIs (approx. 2 kb long with low GC density) [43]. Most tissue-specific DNA methylation is found near CGI sites instead of CpG islands [44]. This data supports the concept that epigenetic changes like DNA methylation have crucially important roles in cancer development because they affect the differentiation of specific tissues.

2.1.3 DNA Hypomethylation

The loss of DNA methylation in genome-wide areas is the most common cause of DNA hypomethylation. Feinberg and Vogelstein first found that in two different types of cancers, a significant number of genes were methylated compared to normal cells [45]. Many studies have

reported that DNA hypomethylation has been found in many different types of tumors, including skin, colorectal, and gastric cancers [46]. DNA hypomethylation takes place in several parts of the genome, like repetitive elements, retrotransposons, and introns which causes instability in the genome [42]. In repeat sequences, DNA hypomethylation occurs by an advanced rate of chromosomal reorganizations and by an increased chance of translocation in retrotransposons to other parts of the genome [47, 48]. The amount of DNA methylation increases with the growth of a tumor from benign to malignant and invasive phenotype [49].

2.1.4 Loss of Imprinting

Loss of imprinting occurs when one of the two parental alleles doesn't have the same amount of DNA methylation as the other. Susceptibility toward cancer, such as colorectal cancer, increases with the loss of IGF2 imprinting, which has also been observed in different cancers [50].

2.2 Chromatin Remodeling

The human genome contains chromatin, a complex of DNA and protein condensed into nucleoprotein form [51]. The nucleosome is the basic component of chromatin with an octamer of histones from packaging two molecules each of H2A, H2B, H3, and H4. 147 base pairs of DNA wound twice around this octamer of histones to form a nucleosome. ATP-dependent chromatin remodeling complexes transfer histone octamers among the DNA molecules and thus mediate the density and position of histone octamers along the molecule of DNA [52, 53]. Poly-ADP ribosylation, ubiquitination of histone amino termini and addition of acetyl, methyl, and phosphate groups regulate the affinity of histones for DNA and proteins associated with chromatin [54]. The availability of DNA for mRNA synthesis, DNA synthesis, DNA methylation, recombination, and repair is controlled by the positions of histones which shapes the genome into either open or condensed chromatin. These modifications, i.e., positioning of histones, form a histone code or epigenetic 'memory'. This memory is transferred to the daughter cells from the parent cells [55]. Cancer is caused by the mutable changes in genes affecting the functional characteristics of chromatin-remodeling complexes [56].

2.3 Histone Modification

Proteins of nucleosomes can also be changed by covalent bonds besides CpG methylation of DNA. Four pairs of histones form the core set of histones in nucleosomes i.e., H2A, H2B, H3, and H4 [57]. When DNA gets condensed in a nucleosome structure, it is called chromatin. Histones are alkaline proteins that help build chromatin. These parts of the cellular machinery control how genes are turned on and off [58, 59]. Histones are the main determinants of chromosome shape and stability, and they can be changed after they've been made. These modifications can change chromatin, leading to gene expression modifications. H3 lysine 4 trimethylation is a hallmark of active promoters, while H3 lysine 27 trimethylation and H3 lysine 9 trimethylation are signatures of histones flanking inactive promoters [57, 60]. Additionally, a tight association exists between enhancers and regions consisting of H3 lysine 4 monomethylation [61]. Cancer cells commonly have an excess of repressive histone marks compared to normal cells, which can lead to the suppression of some major TSGs [62]. Post-translational histone modifications modulate

chromatin conformation and accessibility and thus control gene expression. Extracellular signals can target specific residues at histone tails by the families of histone-modifying enzymes [63]. Structurally, histones have a C-terminal domain and an N-terminal tail. The N-terminal tail through various post-translational modifications (PTMs) that alter chromatin conformation like methyl, acetyl, phosphate, and small ubiquitin-related modifier protein (SUMO) group addition, ubiquitylation and ADP-ribosylation on specific residues [58, 59].

2.3.1 Acetylation

Acetylation refers to the reversible attachment of an acetyl group to the ϵ -amino group of lysine residues regulated by histone acetyltransferases and deacetylases, thereby leading to the activation of gene transcription. Acetyl group is added or removed by histone acetyltransferases and histone deacetylases respectively [64]. Acetylation or deacetylation has been reported to affect DNA damage repair and synthesis, mRNA synthesis and cancer cell invasiveness. In all these alterations, histone acetylation can be controlled dynamically by histone acetyltransferases and histone deacetylases. Histone deacetylases (HDACs) maintain transcriptional silencing by adding or removing acetyl groups at the lysine residues present at the N-terminal of histones, however, HATs activate gene transcription [65, 66].

2.3.2 Methylation

Histone methylation i.e. the attachment of methyl groups to lysine and/or arginine residues at histone terminal region/tail is a dynamic process with main roles in differentiation and development. Histone methyl transferases trigger this process, however, histone demethylases (HDMs) reverse this progress due to the removal of the added methyl groups. Methylation can be classified as activating or repressive depending on the modified residue [67].

2.3.3 Phosphorylation

Histone phosphorylation occurs primarily at serine, threonine, and tyrosine residues of histone tail, which is linked with transcription and an accessible chromatin conformation. Histone H3 phosphorylation at tyrosine 41 residue primarily occurs at active promoter sites flanking transcription initiation sites along with the H3 lysine 4 trimethylation mark [68].

Most current studies focus on acetylation, methylation, and phosphorylation of histones, however many other histone modifications have also been studied like ubiquitination, tyrosine hydroxylation, lysine crotonylation, propionylation, butyrylation, biotinylation, neddylation, O-GlcNAc, sumoylation, ADP ribosylation, proline isomerization, N-formylation, and citrullination [63].

2.4 Non-Coding RNA (NcRNA)-Associated Gene Silencing

NcRNAs are widely expressed in organisms and belong to a class of RNAs that do not express any protein. NcRNAs are categorized into 2 groups: housekeeping and regulatory NcRNAs. Regulatory NcRNAs can be subclassified according to their size into short NcRNAs (including small interfering RNAs (siRNAs), microRNAs (miRNAs), and Piwi-interacting RNAs (piRNAs)), mid-size

NcRNAs and long non-coding RNAs (lncRNAs) where short NcRNAs have <50 nucleotides, mid-size NcRNAs range between 50-200 nucleotides, and lncRNAs have >200 nucleotides [69, 70].

Most of the NcRNAs were thought to be “junk RNAs”. But recently the mutations in ncRNAs have been implicated in diseases like cancer [71]. NcRNAs account for ~90% of human genome-derived RNAs which include lncRNAs, pseudogene transcripts, and circular RNAs (circRNAs) whereas miRNAs, piRNAs and tRNA-derived small RNAs (tsRNAs), are NcRNAs of 200 bp in length [72]. Around 2,000 miRNAs have been discovered in humans which control physiological and developmental processes such as cell growth and differentiation, transcriptional regulation, autophagy and apoptosis, by binding to the 3' untranslated region of the mRNA and thus suppress the expression of genes at the post-transcriptional level [73-75]. For example, one study provided evidence that MiR-30a expression suppressed Beclin1 expression, leading to the inhibition of autophagy in the medulloblastoma [74]. As well as another study showed that miR-34a physically interacts with and functionally targets tRNA precursors and suppresses breast carcinogenesis, at least in part by lowering the levels of tRNAⁱ Met through Argonaute 2 (AGO2)-mediated repression, thereby inhibiting breast cancer cells proliferation and inducing cell cycle arrest and apoptosis [75]. In this way, miRNAs are involved in cancer regulation by controlling cellular differentiation and apoptosis, or by modulating the activity of oncogenes and/or TSGs [76]. Regulation of >50% of miRNA genes, present in genomic regions of cancer, can contribute to tumorigenesis, invasion, metastasis and drug-resistant phenotypes [77, 78]. So, different epigenetic modulations (DNA methylation, histone modifications, and miRNAs) may control cell cycle, apoptosis and autophagy.

3. Autophagy

Autophagy is fundamental (Greek for “self-eating”) [79] and a conserved trafficking pathway mainly regulated by environmental conditions. Autophagy is activated during starving conditions and also in response to specific hormones in mammalian cells [80]. During autophagy, some portion of cytoplasm is captured into a vesicle called autophagosome and directed for degradation to the lysosome. There are three types of autophagy processes, namely microautophagy, macroautophagy, and chaperone-mediated autophagy [81]. Among all the three types of autophagy, macroautophagy (hereafter referred to as autophagy) is the major pathway for energy and metabolites supply during nutrient-deprived conditions [82]. Dysfunctional autophagy has been reported may cause different types of mammalian diseases [79].

There are around 42 Atg genes that play a regulatory role in autophagy. The target of rapamycin (TOR) kinase is one of the important players which gets inactivated in response to different stress stimuli. Hypophosphorylated Atg13 formed as a result of TOR Kinase inactivation and forms a complex of Atg13-ATG1-ATG17. The crosstalk between Atg13-Atg1-Atg17 is required for the kinase activity of Atg1 in regulating Atg9, which in turn facilitates phagophore membrane assembly by extracting phospholipids from different organelles membrane. Interaction of class III PI (phosphoinositide) 3 kinases with Beclin-1 leads to the production of phosphatidylinositol-3-phosphate (PI3P) for the formation of autophagosome during elongation [83]. Atg7 and Atg10 are responsible for the conjugation of Atg12 to Atg5, followed by pairing with Atg16 to form the Atg5-Atg12-Atg16 complex, which in turn is required for the vesicle elongation of phagophore. Disassociation of the complex takes place when the phagophore develops into a double-

membrane ring known as “autophagosome”. Upon initiation of autophagy, LC3B (Atg8) is cleaved by an ubiquitin-like system i.e. cysteine protease Atg4 to produce LC3B-I, which is activated by conjugation with Atg7 in an ATP-dependent manner. Afterward, the cascade proceeds with Atg3, and Atg5-Atg12-Atg16 complex mediates the conjugation of LC3I to phosphatidylethanolamine (PE) and thus forms LC3II [84, 85]. LC3-II acts as a receptor for the selection of substrates, interacting with damaged mitochondria or protein aggregates and subsequently promoting their uptake and degradation by lysosomal hydrolases [86, 87] [Figure 3].

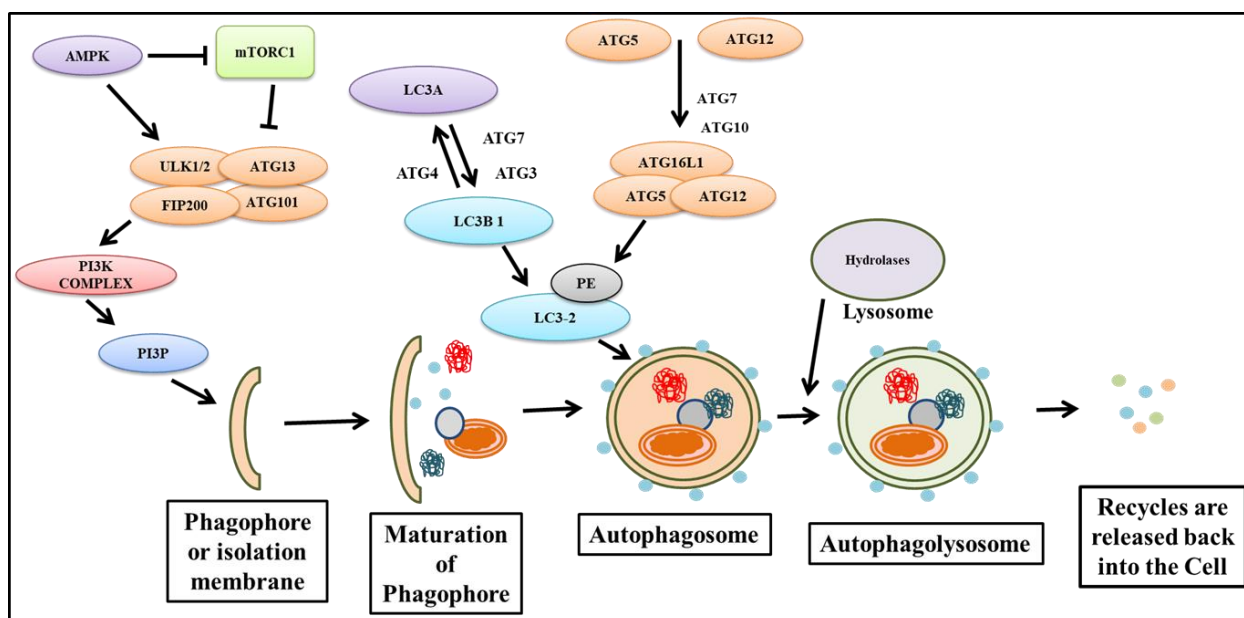


Figure 3 The macroautophagy process in mammalian cells. Autophagy contributes not only to the normal but also to the pathological processes, thus it may act as a major modulator of different facets of cancer biology. Since autophagy is activated during the nutrient crisis to provide metabolites for protein synthesis and can also degrade organelles (e.g., mitochondria), aggregated proteins, and infectious agents selectively [88]. Thus, the role of autophagy is complicated, and defects in autophagy can inhibit or promote cancer [5, 89].

3.1 Dual Effect of Autophagy in Cancer

A lot of studies have shown that autophagy has an important effect on several diseases. However, it is not clear whether autophagy has a pro or anti role in the diseased state [90]. In cancer, autophagy plays a dual role in promoting and stopping cancer growth. Autophagy removes damaged cells and organelles from the body in the initial and malignant phases of cancer [91]. During cancer development, autophagy acts as a protective mechanism by providing the required metabolites and energy supplies to the cells [92]. The protective roles of autophagy include the provision of nutrients during starving conditions, generation of resistance towards anticancer drugs, inhibition of various cell death mechanisms, remodeling of cellular metabolic reactions, maintaining genome integrity, etc. [93-97]. However, the tumor inhibitory roles of autophagy lead to cancer cell death due to increased ROS, protein aggregation and degradation of essential proteins [98, 99].

Thus, autophagy has both promoting and inhibitory roles for cancer cells, which can inhibit tumor formation in early stages while can cause tumor cell survival and malignant transformation in response to various stressful triggers in later cancer stages [93, 100, 101].

Autophagy not only maintains the growth of healthy cells but it is also responsible for the development of various diseased conditions like neurodegeneration [102], cancer [103], type II diabetes [104] and cardiovascular diseases [105] due to its deregulation.

3.2 Epigenetic Regulation Mechanisms of Autophagy in Cancer

Multiple studies have mentioned the significant contributions of epigenetic alterations in cancer. Studies have also demonstrated that the expression of autophagy genes is regulated by epigenetic modifications in cancer cells [Table 1].

3.2.1 DNA Methylation

DNA methylation of autophagy regulatory genes has an impact on the regulation of cancer.

Hypermethylation: Hypermethylation of Ulk2 (required for autophagy initiation) causes its downregulation and autophagy disruption during the development of glioblastoma [106]. Also, hypermethylation of ATG2B, responsible for the nucleation of vesicles during autophagy, induces the growth of invasive breast cancer and ductal carcinomas. Besides this, hypermethylation of ATG4D (which has a significant regulatory role in ATG8/LC3 system) and ATG9 orthologs, also occurs in invasive ductal carcinomas [107, 108]. Hypermethylation of the promoter region of ATG5 (which forms a complex with ATG12 and ATG16 during autophagy) causes its downregulation and the growth of melanoma [85, 107, 109]. Hypermethylation of promoter regions of autophagy regulatory elements, having tumor suppressive roles, lead to cancer promotion, for instance, hypermethylation of Beclin1 or Atg6 (which is involved in the initiation of isolation membrane formation) causes its downregulation in breast cancer cells [110, 111]. Apart from this, methylation of the LC3-encoding gene i.e. MAP1LC3A1 leads to its silencing, thereby inhibiting autophagy in normal and cancerous gastric mucosae [112]. In gastric cancer, methylation of promoter sites of the Klotho gene causes its activation which consequently leads to the enhancement of LC3-I/LC3-II expression and apoptosis in gastric cancer cells [113].

Protocadherin 17 (PCDH17), a tumor suppressor gene, increases starvation-induced autophagy and inhibits cellular proliferation in esophageal squamous cell carcinoma, colorectal cancer and gastric cancer [114, 115]. It can also be silenced by the methylation of its promoter and its restoration can cause enhancement in the formation of autophagic vacuoles and upregulation of Atg-5, Atg12, and LC3B II [114]. Overexpression of tumor suppressor candidate 3 (TUSC3) occurs due to its methylation in human non-small cell lung cancer (NSCLC) cells, which inhibits cell proliferation by the induction of autophagy and apoptosis [116]. Ap1as Ras homolog member 1 (ARHI), a maternally imprinted tumor suppressor gene, is overexpressed and associated with breast and ovarian tumor progression by autophagic induction due to its loss of function and hypermethylation of CpG promoter elements in ARHI [117]. Ankyrin repeat and death domain containing 1A is another tumor suppressor gene whose overexpression causes inhibition of hypoxia tolerance of glioblastoma cells by damaging glucose metabolism and autophagy and is hypermethylated at its promoter region, thus is downregulated in glioblastoma [118].

Promoter methylation of B-cell translocation genes (BTG1 and BTG3 in gastric cancer, BTG1 in colorectal cancer) causes aggressive and malignant cancer growth, however, BTGs have tumor-defeating roles due to their overexpression and cause inhibition of metastasis, angiogenesis, cellular proliferation and upregulation of autophagy and apoptosis [119-121]. BCLB (the most recently identified and the least studied Bcl-2 family member) modulates autophagy and apoptosis by acting as a starvation stress sensor. It is repressed in hepatocellular carcinoma (HCC) due to hypermethylation of the promoter region [122]. The aggressiveness and stage of cancer are associated with promoter methylation of transcription factor 21 (TCF21) due to the inhibition of autophagy in NSCLC [123].

Diminution of an enzyme nicotinamide n-methyl transferase (NNMT) causes liver carcinogenesis during metabolite depletion due to dephosphorylation of p-ULK1 activity and increased PP2A methylation leading to an increased pro-survival form of autophagy [124]. Regulation of autophagy and cancer can also occur due to the methylation of some enzymes like methylation at CpG islands of argininosuccinate synthetase (ASS1) and argininosuccinate lyase (ASL) in glioblastomas. Pro-survival autophagic response can be activated initially due to exposure to PEGylated arginine deiminase (ADI-PEG20) and inhibition by chloroquine exposure increased cytotoxicity [125].

Hypomethylation/demethylation: Tumor progression can also occur due to demethylation and hypomethylation of some regulatory regions of DNA. Pro-survival form of autophagy can be activated due to the abnormal DNA demethylation of LC3A in lung adenocarcinoma [126]. The poor prognosis of ovarian tumor-initiating cells (OTICs) is due to the hypomethylation of ATG4A and histone cluster 1 H2B family member N while their DNA methylation may lead to improved patient condition [127]. Hypomethylation of the promoter region of ELFN2 (extracellular leucine rich repeat and fibronectin type III domain containing 2) leads to the activation of its tumor-promoting role by the mediation of enhanced autophagy in glioblastoma [128].

However, DNA methylation may also lead to the suppression of the oncogenic role of regulatory regions of autophagy genes. The increased methylation of endothelial PAS domain protein 1 (EPAS1) and ATG16L1 and subsequent reduction of medulloblastoma proliferation occur due to the repression of oncogenic hypoxia-inducible factor 1- α in medulloblastomas [128]. Thus, it can be stated that the methylation of autophagy-regulated effector molecules may affect cancer regulation substantially.

3.2.2 Histone Modifications

In cancer, histone acetylation and deacetylation are regularly occurring mechanisms, which modulate autophagy. Some of the histone modifications suppress tumors, such as the disruption of HDAC1 can cause autophagic cell death in human hepatocellular carcinoma. And HDAC6 expression deficiency can cause HCC, however, its upregulation inhibits cancer proliferation by triggering autophagic cell death in HCC [129, 130]. HDAC7 is oncogenic in salivary mucoepidermoid carcinoma and thus can be used as an attractive target to overcome the problem. As reported in the literature, inhibition of HDAC7 suppressed cell growth due to the inhibition of c-Myc oncogene expression. HDAC7 inhibition also induces cell cycle arrest along with the induction of autophagy and apoptosis [131]. HDAC10 activates the pro-survival autophagy mechanism to

promote cancer cell growth and protect them from cytotoxic compounds in neuroblastoma. Thus HDAC isozyme could act as a druggable target of high-grade cancer [132].

Likewise, acetylated FoxO1 has been reported to activate autophagy by binding to Atg7, thereby inducing apoptosis in human colon cancer and xenograft mouse [133]. Normally, PCAF (P300/CBP-associated factor) is found to be in a suppressed form in HCC while its upregulation in HCC causes activation of autophagy, resulting in cancer inhibition in vitro and in vivo [134]. Prostatic intraepithelial neoplasia (PIN) is caused by the reduction in autophagy due to homozygous deletion of the SIRT1 gene. Expression of androgen-responsive gene suppression and autophagy activation caused by endogenous SIRT1 in the prostate provides evidence for its tumor suppressive and checkpoint activities in the prostate and the development of PIN respectively [135]. At times, histone acetylation-regulated autophagy modulation may result in tumorigenesis, for instance, HDAC8 is highly expressed in oral squamous cell carcinoma (OSCC) however its inhibition suppressed the cancer cell growth due to the activation of apoptosis. Therefore, combination therapy with autophagy inhibitors and HDAC8 inhibitors can be a good anticancer approach in OSSC [136]. Also, epithelial-to-mesenchymal transition is linked with p62-regulated autophagy repression by maintaining the level of HDAC6 in aggressive prostate cancer [137]. Cancer cell growth is promoted by the inhibition of autophagosome maturation due to the acetylation of Atg6 by p300 at lysine 430 and 437 residues [138]. Additional, histone modification can also activate organelle-specific autophagy in cancer, for example, SIRT3 protects glioma cells against apoptotic cell death by activating mitophagy due to the association between VDAC1 and parkin [139]. Autophagy-associated cancer modulation has also been reported to be linked with methylation or de-methylation of histone. Bladder cancer growth is promoted by the overexpression of SMYD3 (a histone methyltransferase), by inducing autophagy and activating BCL2-associated transcription factor 1 (BCLAF1) expression [140]. Autophagosome formation is inhibited by histone methyltransferase (HMT) G9a (highly expressed in a wide variety of cancers), by the transcription repression of LC3 and WIPI1 [141]. Down-regulation of lysine-specific demethylase 2B (a JHDM family member, commonly expressed in gastric cancer and acts as a histone lysine demethylase), inhibits cancer cell proliferation in vitro and gastric cancer xenograft model by the activation of autophagy [142]. However, inhibition of lysine-specific demethylase 4A may inhibit glioma cell survival by autophagy activation and thus, it can be used as a promising marker for combating aggressive gliomas [143]. Proliferation of neuroblastoma cells can be suppressed by the inhibition of G9a, an H3K9 methyltransferase, by autophagy activation due to the up-regulation of autophagy genes and LC3B expression [144]. Activation of Beclin-1 leads to autophagy activation due to the inhibition of euchromatic histone-lysine N-methyltransferase 2, which in turn prevents cancer cell growth in breast cancer [145]. Thus, histone modification levels in autophagy regulation may affect tumor regulation significantly.

3.2.3 Micro RNAs

A lot of miRNAs that modulate autophagy also have growth inhibitory effects in cancer cells, such as in breast cancer cells, the tumor-inhibition by miR-101 is due to the basal and rapamycin-induced autophagy repression by affecting RAB5A, STMN1, and ATG4D [146]. It has been reported that miR-30a inhibits Beclin-1 expression by binding to the 3'-UTR, which in turn leads to autophagy and tumor cell growth inhibition in medulloblastoma cells [74, 147]. miR-30d inhibits

autophagy by targeting pPI3-K, Beclin-1 and Atg5 in colon carcinoma which also abrogates growth and promotes apoptosis [148]. miR-372 has a tumor-suppressing role by lowering the expression of ULK1 and autophagy in human pancreatic adenocarcinomas [149]. miR-130a lowers the expression of ATG2B and DICER1 in chronic lymphocytic leukemia and also inhibits autophagy by suppressing autophagosomal formation and inducing apoptosis [150]. miR-204 (a von Hippel-Lindau (VHL)-regulated tumor suppressor) is known to suppress cancer cell proliferation by inhibiting LC3B-mediated autophagy in renal clear cell carcinoma [151]. miR-375 negatively affects the viability of hepatocellular carcinoma cells by inhibiting autophagy under hypoxic conditions due to the suppression of ATG7 [152]. In NSCLC, miR-143 inhibited cancer cell growth through the down-regulation of autophagy gene ATG2B at mRNA and protein levels [153]. Overexpression of a few tumor-inhibitory miRNAs which have less expression in cancers may inhibit cancer cell growth. Restoration of downregulated miR-340 in glioma cells can cause cell growth suppression and induces cell-cycle arrest, autophagy, and apoptosis [154]. In human glioblastoma, the overexpression of miR224-3p suppresses the precursor form of autophagy in hypoxic conditions by targeting ATG5 and FIP200 [155]. YY1 is found to promote SQSTM1 expression, which subsequently activates autophagy by the inhibition of miR-372 expression epigenetically, whereas high expression of miR-372 inhibits the protective effects of autophagy in breast cancer in vivo [156]. Colon cancer is suppressed by miR-18a through the induction of apoptosis via autophagic degradation of heterogeneous nuclear ribonucleoprotein A1 [157]. In the same way, miR-107 inhibits tumor growth, cellular proliferation and migration due to the regulation of high mobility group protein B1 (HMGB1) by autophagy repression in breast cancer [158]. In cervical and lung cancer, miR7-3HG/mir-7 lowers the expression of AMBRA1 at mRNA and protein levels by targeting the 3'UTR region of AMBRA1 and consequently affects oncogenesis by inhibiting autophagy [159]. The association of onco-miRNA with autophagy genes also has oncogenic properties. In NSCLC, overexpression of miR-18a-5p causes tumorigenesis by targeting interferon regulatory factor 2 (IRF2) and inhibiting cell proliferation through apoptosis and protective autophagy [160]. In esophageal squamous cell carcinoma and breast cancer, oncogenic miR-638 promotes malignant tumor growth by targeting tumor-suppressor DACT3 and promoting autophagy [161]. Similarly, miR-638 suppresses autophagy, promotes melanoma growth by increasing metastasis and expression of the transcriptional repressor TFAP2A/AP2 α [162]. miR-30e which inhibits autophagy by targeting 3'UTR of ATG5, is inhibited by DIM (3, 3'-diindolylmethane), an indole derivative, which in turn leads to the suppression of gastric cancer cell proliferation [163]. Likewise, UVRAG-induced autophagy and apoptosis are regulated by miR-183 in colorectal cancer, and inhibition of miR-183 suppresses in vivo cancer growth in the HT-29 xenograft model [164]. In laryngeal carcinoma, cancer cell growth is inhibited by autophagy induction due to suppression of miR-26b [165]. In glioma cells, overexpression of p72 promotes invasion and migration by inhibiting the Beclin-1 gene due to up-regulation of miR-5195-3p and miR-34-5p [166]. In melanoma, autophagic cell death (due to glucose deprivation through down-regulation Atg7 and ULK1) is inhibited by miR-290-295 cluster [167]. MiR-20a mediates breast oncogenesis by inhibiting autophagy and instability in target proteins, such as BECLIN-1, SQSTM1 and ATG16L1 [168]. Thus onco-miRNAs as well as tumor-suppressive miRNAs have regulatory effects on autophagy and may significantly affect tumor regulation.

Table 1 Role of epigenetic modifications in cancer-related autophagy and associated proteins.

Type of Epigenetic modification	Elements which regulates autophagy	Effect on autophagy	Roles	Cancers	References
DNA hypermethylation	ULK2	Autophagy suppressed	Tumor activated	Glioblastoma	[106]
		Not determined	Tumor activated	Gastric carcinoma	[108, 112]
	ATG2B, ATG4D, ATG9A, ATG9B	Autophagy suppressed	Tumor activated	Breast cancer	[108]
	ATG5	Autophagy suppressed	Tumor activated	Melanoma	[109]
	ATG5	Autophagy suppressed	Tumor activated	Melanoma	[109]
	MAP1LC3Av1	Autophagy suppressed	Tumor activated	Gastric cancer	[112]
	MAP1LC3Av1	Autophagy suppressed	Tumor activated	Lung cancer	[169]
	BECN1	Autophagy suppressed	Tumor activated	Childhood acute lymphatic leukemia	[170]
		Autophagy suppressed	Tumor activated	Breast cancer	[111]
	BECN1	Autophagy suppressed	Tumor activated	Breast cancer	[111]
	ATG16L1	Autophagy suppressed	Tumor suppressed	Medulloblastoma	[171]
	klotho gene	Autophagy suppressed	Tumor activated	Gastric cancer	[113]
	BTG1, BTG3	Autophagy suppressed	Tumor activated	Gastric cancer	[119, 120]
	BTG1, BTG3	Autophagy suppressed	Tumor activated	Gastric cancer	[119, 120]
	BTG1	Autophagy suppressed	Tumor activated	Colorectal cancer	[121]
	BTG1	Autophagy suppressed	Tumor activated	Colorectal cancer	[121]
	TUSC3	Autophagy suppressed	Tumor activated	Non-small cell lung cancer	[116]

TUSC3	Autophagy suppressed	Tumor activated	Non-small cell lung cancer	[116]
ARHI	suppressed	Tumor activated	Ovarian and breast cancer	[117]
ARHI	suppressed	Tumor activated	Ovarian and breast cancer	[117]
PCDH17	Autophagy suppressed	Tumor activated	Gastric and colorectal cancer	[114]
PCDH17	Autophagy suppressed	Tumor activated	Gastric and colorectal cancer	[114]
BCLB	Autophagy suppressed	Tumor activated	Hepatocellular carcinoma	[122]
BCLB	Autophagy suppressed	Tumor activated	Hepatocellular carcinoma	[122]
TCF21	Autophagy suppressed	Tumor activated	Non-small cell lung cancer	[123]
ANKDD1A	Autophagy suppressed	Tumor activated	Glioblastoma	[118]
ANKDD1A	Autophagy suppressed	Tumor activated	Glioblastoma	[118]
PP2A	Autophagy activated	Tumor activated	Liver cancer	[124]
PP2A	Autophagy activated	Tumor activated	Liver cancer	[124]
ASS1, ASL	Autophagy activated	Tumor activated	Glioblastoma	[125]
ASS1, ASL	Autophagy suppressed	Tumor activated	Glioblastoma	[125]
BNIP3	Autophagy suppressed	Tumor activated	Colorectal cancer	[172]
GL1	Autophagy suppressed	Tumor activated	Lung Cancer	[7]
LC3A	Autophagy activated	Tumor activated	Lung Cancer	[126]

DNA demethylation	LC3A	Autophagy activated	Tumor activated	Lung Cancer	[126]
	ATG4A	Autophagy activated	Tumor activated	Ovarian cancer	[127]
DNA hypomethylation	ATG4A	Autophagy activated	Tumor activated	Ovarian cancer	[127]
	ELFN2	Autophagy activated	Tumor activated	Glioblastoma	[128]
	ELFN2	Autophagy activated	Tumor activated	Glioblastoma	[128]
	FoxO1	Autophagy activated	Tumor suppressed	Colon tumors	[133]
Histone acetylation	FoxO1	Autophagy activated	Tumor suppressed	Colon tumors	[133]
	Beclin-1	Autophagy suppressed	Tumor activated	Breast cancer	[138]
	Beclin-1	Autophagy suppressed	Tumor activated	Breast cancer	[138]
	HDAC6	Autophagy activated	Tumor suppressed	Hepatocellular carcinoma	[129]
Histone deacetylation	HDAC6	Autophagy activated	Tumor suppressed	Hepatocellular carcinoma	[129]
	SIRT1	Autophagy activated	Tumor suppressed	Prostate cancer	[135]
	SIRT1	Autophagy activated	Tumor suppressed	Prostate cancer	[135]
	HDAC8	Autophagy activated	Tumor activated	Oral cancer	[136]
	HDAC8	Autophagy activated	Tumor activated	Oral cancer	[136]
	HDAC1	Autophagy activated	Tumor activated	Hepatocellular carcinoma	[130]

	HDAC1	Autophagy activated	Tumor activated	Hepatocellular carcinoma	[130]
	HDAC6	Autophagy suppressed	Tumor activated	Prostate cancer	[137]
	HDAC6	Autophagy suppressed	Tumor activated	Prostate cancer	[137]
	HDAC7	Autophagy activated	Tumor activated	Mucoepidermoid carcinoma	[131]
	HDAC7	Autophagy activated	Tumor activated	Mucoepidermoid carcinoma	[131]
	HDAC10	Autophagy activated	Tumor activated	Neuroblastoma	[132]
	HDAC10	Autophagy activated	Tumor activated	Neuroblastoma	[132]
	SIRT3	Autophagy activated	Tumor activated	Glioma	[139]
	SIRT3	Autophagy activated	Tumor activated	Glioma	[139]
	G9a	Autophagy suppressed	Tumor activated	Neuroblastoma	[144]
	G9a	Autophagy suppressed	Tumor activated	Neuroblastoma	[144]
	G9a	Autophagy activated	Tumor suppressed	Gastric cancer	[173]
	G9a	Autophagy activated	Tumor suppressed	Gastric cancer	[173]
	EHMT2	Autophagy suppressed	Tumor activated	Breast cancer	[145]
	EHMT2	Autophagy suppressed	Tumor activated	Breast cancer	[145]
	SMYD3	Autophagy activated	Tumor activated	Bladder cancer	[140]
	SMYD3	Autophagy activated	Tumor activated	Bladder cancer	[140]
Histone methylation					

	SMYD3	Autophagy activated	Tumor activated	Bladder cancer	[140]
	KDM2B	Autophagy suppressed	Tumor activated	Gastric cancer	[142]
Histone demethylation	KDM2B	Autophagy suppressed	Tumor activated	Gastric cancer	[142]
	KDM4A	Autophagy suppressed	Tumor activated	Glioma	[143]
	KDM4A	Autophagy suppressed	Tumor activated	Glioma	[143]
	miR7-3HG/mir-7	Autophagy suppressed	Tumor suppressed	Cervical and lung cancer	[159]
NcRNA	miR-18a	Autophagy activated	Tumor suppressed	Colon cancer	[157]
	miR-20a	Autophagy suppressed	Tumor activated	Breast cancer	[168]
	miR-26b	Autophagy suppressed	Tumor activated	Laryngeal carcinoma	[165]
	miR-30a	Autophagy suppressed	Tumor suppressed	Brain cancer	[74, 147]
	miR-30d	Autophagy suppressed	Tumor suppressed	Colon cancer	[148]
	miR-30e	Autophagy suppressed	Tumor activated	Gastric cancer	[163]
	miR-101	Autophagy suppressed	Tumor suppressed	Breast cancer & hepatocellular carcinoma	[146, 174]
	miR-107	Autophagy suppressed	Tumor suppressed	Breast cancer	[158]
	miR-130a	Autophagy suppressed	Tumor suppressed	Chronic lymphocytic leukemia	[150]
	miR-143	Autophagy suppressed	Tumor suppressed	Lung cancer	[153]
	miR-183	Autophagy suppressed	Tumor activated	Colorectal cancer	[164]
	miR-204	Autophagy suppressed	Tumor suppressed	Renal clear cell carcinoma	[175]
	miR224-3p	Autophagy suppressed	Tumor suppressed	Glioblastoma	[155]
	miR-340	Autophagy activated	Tumor suppressed	Glioma	[154]
	miR-372	Autophagy suppressed	Tumor suppressed	Pancreatic & Breast cancer	[149, 156]
	miR-375	Autophagy suppressed	Tumor suppressed	Hepatocellular carcinoma	[152]

	miR-18a-5p	Autophagy activated	Tumor activated	Non-small cell lung cancer	[160]
	miR-638	Autophagy activated	Tumor activated	Esophageal squamous cell carcinoma and breast cancer	[161]
	miR-34-5p, miR-5195-3p	Autophagy suppressed	Tumor activated	Glioma	[166]
	miR-290-295	Autophagy suppressed	Tumor activated	Melanoma	[167]
	miR-23a	Autophagy activated	Tumor suppressed	Lung cancer	[176]
	DRAIC	Autophagy activated	-	Breast cancer	[177]
lncRNA	NEAT1	Autophagy activated	-	Neuroglial cells	[178]

4. Epigenetic Modifications of Autophagy and Therapeutic Response

It is noteworthy that bioactive constituents of plants have the ability to inhibit cancer at all stages including initiation, promotion, and progression [179]. Many anticancer natural products have been reported to have the ability to regulate gene expression through epigenetic mechanisms [Table 2] [180]. A great range of plant-based compounds have gene expression modulation ability through epigenetic pathways [181] and thus can be used as therapeutics due to their potential to regulate autophagy pathways in cancer models in vitro or in vivo [182]. For instance, polyphenols are the most common naturally bioactive compounds found in fruits, seeds, vegetables, and nuts [183]. Several polyphenols (resveratrol, curcumin) can also affect numerous cell targets that can induce or inhibit autophagy. Autophagy modulation occurs due to epigenetic changes and thus can be profoundly investigated further.

Table 2 Bioactive dietary compounds and their sources.

S.no.	Dietary compounds	Family	Sources	Epigenetic modification	Role in autophagy	Cancer type/ Cells	References
1	All-trans retinoic acid	Derivative of Vitamin-A	Carrots, sweet potatoes, etc.	Upregulate miR-663	-	HL-60cells	[184]
2	Anthocyanin	Phenol	Illawarra plum	Upregulate class III HDAC Sirtuin 1	Upregulate autophagy	Colon cancer	[185]
3	Apigenin	Flavonoid	Parsley (Petroselinum)	Upregulate miR-520b	Downregulate ATG7	Hepatocellular carcinoma	[186]
4	Cinnamaldehyde	flavonoid	Cinnamomum cassia	G9a	Upregulate Autophagy	Gastric cancer	[187]
5	Curcumin	Polyphenol	Turmeric (Curcuma longa)	miR-143	Downregulate ATG2B	Prostate cancer	[188]
6	Celastrol	Triterpenoid	Tripterygium wilfordii	Downregulate miR-17-92a	ATG7	Prostate cancer	[189]
7	Diindolylmethane	Indoles	Cruciferous vegetables	Downregulate miR-30e	Upregulate ATG5	Gastric cancer	[163]
8	Epi-GalloCatechin-3-Gallate (EGCG)	polyphenol	Green tea (Camellia sinensis)	Upregulate miR-16	Downregulate BCL-2	Hepatocellular carcinoma	[190]
9	Genistein	Isoflavone	Soybean (Glycine max)	miR221/222	ARH-I/ DIRAS3	Prostate cancer	[191]
10	Isoliquiritigenin	Flavonoid	root of licorice	Downregulate miR-25	Upregulate LC3-II and ULK1	Breast cancer	[192]
11	Kaempferol	Flavonoid	fruits, vegetables, and traditional herbal	HDAC/G9a	IRE1-JNK-CHOP	Gastric cancer	[173]

			medicine				
12	pterostilbene	Resveratrol derivative	-	Upregulate lncRNA	Upregulate autophagy	Breast cancer	[193]
13	Resveratrol	Polyphenol	Red grapes, (Vitis vinifera)	miRNAs	ARH-I/DIRAS3	Ovarian cancer	[194]
14	Retinoic acid	Derivative of Vitamin-A	Carrots, sweet potatoes, etc.	Upregulate miR-10	-	Breast cancer, Acute myeloid leukemia	[184]
15	Sulphorophane	Sulfur-rich compound	Cruciferous vegetables (Brassicaceae)	Downregulate miR-23b, miR-92b, miR-381 and miR-382	Downregulate AKT signalling	Breast cancer	[195]

Scientists all over the world are becoming more and more interested in the biological and clinical effects of epigenetic changes in cancer autophagy. Most of the literature on epigenetic modifications of autophagy contributes to cancer diagnosis and treatment. Epigenetic modifications are potentially reversible and can be restored to normal state by therapeutic approaches, as such, these are considered hallmarks to study cancer and designing next-generation cancer therapies [196]. Besides natural products, some other therapeutic molecules that can modulate autophagy through epigenetic modification are listed in Table 3.

Table 3 Effects of some epigenetic drugs on autophagy in cancer cells.

Target	Epigenetic Drug	Autophagy	Cancer Origin	References
DNMT	Decitabine	Upregulate autophagy	Ovarian carcinoma and Chronic myeloid leukemia	[197, 198]
	Azacitidine	Increase ROS level	P53 mutant leukemic T cells	[199]
	Zebularine	Upregulate autophagy	Colorectal carcinoma	[200]
SETD7	Cyprohept	Decrease mTOR expression	Urothelial carcinoma	[201]
G9a	BIX01294	Increase of LC3B-II and vesicles	Bone carcinoma	[202]
BETi	JQ1	Increase ATG gene expression	Pancreas carcinoma	[203]
	DZNep	Increase of LC3B-II	Colorectal carcinoma	[204]
	GSK126	Increase of LC3B-II and decrease of phospo AKT/mTOR/ULK1	Gastric carcinoma	[205]
EZH2	GSK343	Increase of LCB-II, autophagic vesicles and decrease of P62/SQSTM1	Bone carcinoma, Colorectal carcinoma, Triple-negative breast cancer, pancreatic cancer	[206-208]
	1o	Increase of LCB-II	Myelogenous leukemia, Neuroblastoma	[209]
	UNC1999	Increase LC3B-II flux and autophagic vesicles, activation of ATG gene expression	Colon cancer, Colorectal carcinoma, Cervix carcinoma, Tongue squamous cell carcinoma, Neuroblastoma, Colorectal carcinoma, Bladder cancer	[202, 210-214]
HDAC	Apicidin	Increase of LC3B-II, ATG5, AVOs and decreased P62	Oral squamous carcinoma, Mucoepidermoid carcinoma	[215-217]
	Romidepsin	Increase LC3, MAPK and ROS	Gastric cancer	[218]

Trichostatin A	Decrease mTOR	Colon cancer	[219]
Tucidinost	Increase mTOR, downregulate autophagy	Lymphocytic leukemia	[220]
Psammaplin A	Downregulate p53, Upregulate autophagy	SCC-81, M87-MG, RKO cells	[221]
Panobinostat	Upregulate FOXO3 and FOXO4	Human pre-B ALL Nalm-6 cells	[222]
Givinostat	Downregulate ATG gene	Glioblastoma	[223]
Abexinost	Upregulate ROS	Diffuse Large B-Cell Lymphoma Cell (DLBCL)	[224]
Quisinostat	Upregulate ROS	Neuroblastoma	[225]
Entinostat	Downregulate mTOR and Upregulate ATG genes	Liver carcinoma	[226]
Mocetinostat	Upregulate mTOR, downregulate autophagy	Lymphocytic leukemia	[227]
Butyrate	Increase of vesicles and autophagic cell death	Cervix carcinoma	[228]
ITF2357 (givinostat)	Increase of LCB-II, ATG5, ATG7, BECLIN-1, autophagic cell death	Glioblastoma	[229]
MGCD0103	decrease of LCB-II, ATG5, ATG12, P62/SQSTM1, BECLIN-1 and of autophagic flux	B-cell chronic Lymphocytic leukemia	[230]
MHY218	Increase of LCB-II and BECLIN-1	Breast (LumA)	[230]
Panobinostat (LBH589)	Increase of LCB-II, BECLIN-1 and decrease of P62/SQSTM1	Hodgkin lymphoma, Hepatocarcinoma, Triple-negative breast cancer	[231-233]
OSU-HDAC42 SAHA	Increase of LCB-II and vesicles	Hepatocarcinoma	[234]
(Vorinostat)	Increase of LCB-II, ATG5, BECLIN-1, vesicles, AVOs, autophagic cell death and decrease of P62/SQSTM1	Cervix carcinoma, Chondrosarcoma, Hepatocarcinoma, Glioblastoma, Breast cancer, T-cell lymphoma, Cutaneous, melanoma, Colorectal	[227, 234-242]

			carcinoma, B-cell lymphoma	
	Sulforaphane	Increase of LCB-II, BECLIN-1 and vesicles and decrease of P62/SQSTM1	Triple-negative breast cancer	[243]
	ZW2-1	Increase of LCB-II, vesicles	Leukemia	[244]
HDAC (class I/II)	FK228	Increase of LC3B-II and vesicles, autophagic cell death	Malignant rhabdoid tumors	[245]
	Valproate	Increase of LCB-II, BECLIN-1, vesicles and decrease of P62/SQSTM1, P-mTOR	Melanoma, Burkitt leukemia/ lymphoma, Acute megakaryocytic Leukemia, T-lymphoma, B-lymphoma, Hepatocarcinoma, Cervix carcinoma	[240, 246-250]
JMJD2	ML324	Increase of LCB-II	Bone carcinoma	[205]
KDM5B	PBIT	Increase of LCB-II and P62/SQSTM1	Bone carcinoma	[205]
KDM6B/ JMJD3	GSKJ4	Increase of LCB-II, decrease of P62/SQSTM1]	Bone carcinoma	[205]
	GSK-LSD1	Increase of LCB-II, decrease of P62/SQSTM1	Bone carcinoma	[205]
	Tranylcypromine	Increase of LCB-II and vesicles	Neuroblastoma	[251]
LSD1	S2101	Increase of LCB-II, GFP-LC3B vesicles and decrease P62/SQSTM1	Ovarian carcinoma	[252]
	JL1037	Increase of LCB-II and vesicles	Acute myeloid leukemia	[253]

	NCL1	Increase of LCB-II flux, vesicles	Prostate carcinoma	[254]
	SP2509	Increase of LCB-II, ATG7 and P62/SQSTM1	Neuroblastoma and Ovarian carcinoma	[255, 256]
	TCP	Increase of LCB-II and GFP-LC3B vesicles	Neuroblastoma and Ovarian carcinoma	[255, 257]
	Sirtinol	Increase of LCB-II and AVOs	Breast (LumA)	[258]
	J11-C1	Increase of LCB-II and BECLIN-1	Ovarian carcinoma	[259]
	15dPGJ2	Increase of LCB-II	Ovarian carcinoma	[259]
SIRT1	J19	Increase of LCB-II, ATG3 and BECLIN-1	Ovarian carcinoma	[259]
	MHY2256	Increase of LCB-II, ATG5/7, BECLIN-1, AVOs	Endometric carcinoma, Breast (LumA), Ovarian carcinoma	[260, 261]
	NCO-90/NCO141	Increase of LCB-II	Leukemia/T-lymphoma	[262]
SIRT6	UBCS039	Increase of LCB-II, GFP-LC3B vesicles and autophagic flux	Non-small cell lung carcinoma, Cervix carcinoma	[263]
BRD4	JQ-1	Upregulate AMPK-ULK1 and autophagy	Acute Myeloid Leukemia (AML)	[264]
	FL-411	Upregulate ATG genes	Breast cancer	[265]

Clinical trials of epigenetic therapy in cancers: several epigenetic inhibitors are under development or in ongoing clinical trials. The present epigenetic therapy mainly involves agents of DNA methylation and histone modification. We summarize the current clinical trials of epigenetic therapy for different cancers [Table 4].

Table 4 Clinical trials of epigenetic therapy in cancer patients (clinicaltrials.gov).

Clinical trial identifier	Clinical trial phase	Epigenetic agent	Combined agent	Patients	Status
NCT01023737	Phase I	Vorinostat	Hydroxychloroquine	Malignant solid tumor	Active, not recruiting
NCT02034123	Phase I	GSK2879552	NA	Relapsed/refractory SCLC	Terminated
NCT01266057	Phase I	Sirolimus or vorinostat	Hydroxychloroquine	Advanced cancers	Active, not recruiting
NCT02446704	Phase I/II	Temozolomide	Olaparib	Small Cell Lung Carcinoma	Active, not recruiting
NCT01638546	Phase II	Temozolomide	Veliparib	Recurrent Small Cell Lung Carcinoma	Completed
NCT01222936	Phase II	Panobinostat (LBH589)	NA	Small Cell Lung Carcinoma	Completed
NCT02316340	phase II	Vorinostat	Hydroxychloroquine	Colorectal cancer	Active
NCT03243461	phase III	Temozolomide	Valproic Acid	Glioblastoma	Recruiting

Nevertheless, it has not been experimentally proven yet that the bioactive constituents with cancer-inhibitory properties can modulate autophagy via epigenetics. However, the experimental validation in this aspect may vary depending on the cell type and target proteins.

5. Conclusions

Epigenetic modifications like DNA methylation, histone modification, and miRNAs may directly or indirectly impact autophagy. In cancer, epigenetically regulated autophagy is majorly involved in tumorigenesis, metastasis, and drug resistance. Thus, potent biomarkers of cancer can be identified with the help of a deeper understanding of epigenetic modification of autophagy. However, the role of autophagy in human diseases is still difficult to understand while the mutations associated with epigenetics generate carcinogenic signals to promote cancer.

Finally, epigenetic regulation of autophagy is precise and depends widely on different stages and types of tumors. Various epigenetic modifications have been reported to affect and modulate the expression of autophagy genes. Some epigenetic regulators have been detected to be involved in autophagy and have also been confirmed as potential targets for antitumor therapy. Due to technological and pharmacochimistry progress in the past decade, different methods have been developed to identify selective, small molecule inhibitors of the enzymes associated with epigenetics modifications. Inhibition of these enzymes may trigger protective or lethal autophagy. Conclusively, the above information gives a new insight into the molecular mechanism of epigenetic modulation of autophagy in cancer.

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Author Contributions

SP: Conceptualization, Writing - original draft, Writing - review & editing; SFR: writing – Review & Editing; AH: writing – Review & Editing; UA: writing – Review & Editing; SSM: conceptualization, Supervision, Writing - original draft, Writing - review & editing, Critical revision of the article. All authors contributed to the article and approved the submitted version.

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Competing Interests

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