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Editorial Board Member of World Journal of Stem Cells, Carlo Cenciarelli, PhD, Research Scientist, Institute of Translational Pharmacology, the National Research Council of Italy, Via Fosso del Cavaliere, 100, Rome 00133, Italy. carlo cenciarelli@ift.cnr.it

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REVIEW

Epigenetic regulation of autophagy: A key modification in cancer cells and cancer stem cells

Harpreet K Mandhair, Urban Novak, Ramin Radpour

ORCID number: Harpreet K Mandhair 0000-0001-8753-7078; Urban Novak 0000-0001-7642-2101; Ramin Radpour 0000-0002-5632-7833.

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Harpreet K Mandhair, Urban Novak, Ramin Radpour, Department for BioMedical Research, University of Bern, Bern 3008, Switzerland

Harpreet K Mandhair, Urban Novak, Ramin Radpour, Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern 3008, Switzerland

Corresponding author: Ramin Radpour, MSc, PhD, Lecturer, Senior Scientist, Department for BioMedical Research, University of Bern, Murtenstrasse 35, Bern 3008, Switzerland. ramin.radpour@dbmr.unibe.ch

Abstract

Aberrant epigenetic alterations play a decisive role in cancer initiation and propagation via the regulation of key tumor suppressor genes and oncogenes or by modulation of essential signaling pathways. Autophagy is a highly regulated mechanism required for the recycling and degradation of surplus and damaged cytoplasmic constituents in a lysosome dependent manner. In cancer, autophagy has a divergent role. For instance, autophagy elicits tumor promoting functions by facilitating metabolic adaption and plasticity in cancer stem cells (CSCs) and cancer cells. Moreover, autophagy exerts pro-survival mechanisms to these cancerous cells by influencing survival, dormancy, immunosurveillance, invasion, metastasis, and resistance to anti-cancer therapies. In addition, recent studies have demonstrated that various tumor suppressor genes and oncogenes involved in autophagy, are tightly regulated *via* different epigenetic modifications, such as DNA methylation, histone modifications and non-coding RNAs. The impact of epigenetic regulation of autophagy in cancer cells and CSCs is not wellunderstood. Therefore, uncovering the complex mechanism of epigenetic regulation of autophagy provides an opportunity to improve and discover novel cancer therapeutics. Subsequently, this would aid in improving clinical outcome for cancer patients. In this review, we provide a comprehensive overview of the existing knowledge available on epigenetic regulation of autophagy and its importance in the maintenance and homeostasis of CSCs and cancer cells.

Key Words: Autophagy; Cancer stem cells; Cancer cells; Epigenetics; Histone remodeling; DNA methylation; Non-coding RNA

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Core Tip: Cancer stem cells are a distinct population in the tumor bulk with enhanced self-renewal capability. Autophagy primarily exerts oncogenic activity and adaptive signals during cancer progression. Similarly, epigenetic modifications display a crucial role in tumor initiation and cancer development through its regulation of tumor suppressor genes and oncogenes. Emerging studies report epigenetic modifications regulate autophagy and metabolic pathways promoting tumor growth, elicit immunosuppressive activity and contribute to therapy resistance. Therefore, understanding this complex signaling patterns can theoretically lead to a more efficient and targeted cancer treatment.

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INTRODUCTION

Autophagy has been described to be a "self-eating" function. Autophagy is a tightly regulated catabolic process involved in the degradation of damaged organelles and misfolded proteins. The generated intermediate metabolites, such as free fatty acids, serve as an energy supply for cellular components, thus, supporting cellular homeostasis and differentiation^[1]. Autophagy is activated by a multitude of environmental factors, including hypoxia, nutrient availability, DNA damage, oxidative stress, inflammation, and infections[2-6]. Defective autophagy has been associated to several pathological conditions, including inflammatory disease and cancer^[7]. In cancer, autophagy has a context dependent role in disease initiation and propagation[8].

The orchestrated events of autophagy lead to the lysosome fusion for degradation. Three distinct forms of autophagy exist: microautophagy, chaperone mediated autophagy (CMA), and macroautophagy. Microautophagy is a poorly understood process. In mammalian cells, microautophagy is involved in the direct internalization of the cytosolic substrates through indentation of the lysosomal membrane. This resembles the formation of the late endosomes multivesicular bodies[9]. CMA is a form of selective autophagy. CMA targets substrates encoded with a specific pentapeptide sequence (KFERQ-like motifs). Cytosolic chaperones recognize these proteins and bind to the sequence. This interaction promotes the translocation of the cargo protein to the lysosomal membrane and bind to lysosomal associated membrane protein 2A (LAMP2A). This interaction will eventually facilitate degradation[10]. In contrast, macroautophagy (herein referred to as autophagy) is involved in the clearance of bulk cargo. In this instance, double membraned vesicles called autophagosomes, sequester their cytoplasmic cargo and fuse with the lysosome for the breakdown of the intracellular components. The biogenesis of the autophagosomes is a hallmark of autophagy[11,12]. The formation of the autophagosomes proceeds in multiple stages: initiation, elongation, and maturation. Thereafter, the autophagosome fuses with the lysosomes (Figure 1).

THE FORMATION AND MECHANISM OF CANONICAL AUTOPHAGY

A consensus of studies indicate that the autophagosome membrane originates from the mitochondria and the endoplasmic reticulum (ER)[13]. However, emerging studies implicate additional cellular compartments that act as autophagy contact sites, such as the plasma membrane, Golgi and recycling endosomes[14-16]. These sites contribute to the expansion of the nascent autophagosome. The process of autophagy is governed by autophagy related genes (ATGs).

Nutrient sensing and amino acid availability are finely regulated by mammalian target of rapamycin (mTOR) and 5' adenosine monophosphate activated protein kinase (AMPK). It is generally assumed that under glucose deprivation, the mTOR pathway is inhibited; whereas, increased amino acid availability and the promotion of cellular anabolism inhibits autophagy by activating mTOR[17,18]. Both pathways





Figure 1 Role of autophagy in cancer cells and cancer stem cells. Autophagy is a multifaceted pro-survival mechanism that supports the proliferation, growth, and stemness of cancer stem cells (CSCs). Autophagy facilitates CSCs plasticity by promoting immunosuppression, therapy resistance, metastasis, and invasion of CSCs. Several autophagy-related genes (*ATGs*) aid in the development, maturation and closure of the autophagosome (the *ATG* related signaling has been exhaustively discussed in our previous review; this figure has been adapted accordingly)[8,12]. CC: Cancer cell; ER: Endoplasmic reticulum; PE: Phosphatidylethanolamine; PI3P: Phosphatidyl-inositol-3-phosphate; TIL: Tumor-infiltrating lymphocytes; TME: Tumor microenvironment; WIPI: WD-repeat domain phosphoinositide-interacting protein.

converge on unc-51-like kinase 1 (ULK1). Under nutrient rich conditions, the ULK1 complex is bound to mTOR and remains inactive[17,18].

The initiation of autophagy requires the activation of the ULK1 complex consisting of ULK2, FAK family kinase interacting protein of 200 kDa (FIP200), ATG13 and ATG101. This is followed by translocation to the ER and the phosphorylation of class III phosphatidylinositol-3-kinase vacuole protein sorting (VPS) 34 (VPS34/PI3KC3) complex, composed of VPS15, Beclin-1 (BECN1) and ATG14. This complex is also referred to as the BECN1 complex. The activation of these complexes generates a reservoir of phosphatidyl-inositol-3-phosphate (PI3P)[19]. ATG9 positive vesicles on ER contribute to the autophagosome nucleation. PI3P enriched membranes recruit effector proteins, such as WD-repeat domain phosphoinositide-interacting protein-2 (WIPI-2) and double FYVE-containing protein 1 (DFCP1)[20,21].

Furthermore, WIPI-2 promotes the expansion of the phagophore which assists in the recruitment of two conjugation systems[22]. The first conjugation complex is the covalent conjugation of ATG12-ATG5-ATG16L proteins by ATG7 and ATG10. The second conjugation system functions as an E3-like ligase, mediated by ATG12 and ATG5; assisting in the attachment of ATG8 family member microtubule associated proteins 1A/1B light chain (LC3) to phosphatidylethanolamine. The membrane bound LC3 matures and expands the autophagosome. Prior to the closure of the matured autophagosome, the ATG proteins dissociate from the autophagosome membrane, leaving the lipidated LC3 (LC3B protein, *MAP1LC3B* gene encoding) inside the autophagosome[23] (Figure 1).

Proteins comprising an LC3-interacting region interact with LC3 and serve as cargo receptors to target defined structures. Cargo receptors like sequestisome-1 (SQSTM1, also known as p62) and neighbor of BRCA1 facilitate the degradation of misfolded and ubiquitin-positive proteins[24]. LC3B and SQSTM1 are referred as the gold standard of measuring autophagy[25].

The formation of the autophagosome without the hierarchical activity of the core autophagy proteins is referred to as non-canonical autophagy. Limited information is currently available characterizing these alternative mechanisms[8].

TRANSCRIPTIONAL REGULATION OF AUTOPHAGY

Transcription factor EB (TFEB) plays a crucial role in lysosome biogenesis and autophagy by modulating the coordinated lysosomal expression and regulation (*CLEAR*) gene network^[26]. TFEB belongs to the microphthalmia family of basic helixloop-helix-leucine-zipper (bHLH-Zip) transcription factors (MiT family), including, transcription factor E3 (TFE3) and transcription factor EC[27]. These transcriptional factors are commonly dysregulated in cancer [27,28]. Nutrient sufficient conditions promote the phosphorylation at serine amino acids 142 and 211 in TFEB or at Serine 321 in TFE3 mediated by mTOR or extracellular signal regulated kinase-2 (ERK2). These proteins then translocate into the cytosol by 14-3-3 proteins and remain inactive [29-32]. In contrast, under starvation, lysosomal calcium is released, activating calcineurin, which triggers TFEB dephosphorylation, and nuclear translocation[33,34]. TFEB binding has been found to be enhanced under starved conditions as the promoters of autophagy core genes contain TFEB binding sites, including, UVRAG, WIPI, MAP1LC3B, SQSTM1, VPS11, VPS18 and ATG9B[35]. In contrast, zinc finger transcription factor (ZKSCAN3) has been identified as a master transcriptional repressor of autophagy[36]. Bladder cancer cells (UM-UC13) and colon cancer cells (RKO) transiently transfected with streptavidin flag tagged ZKSCAN3 vector was treated with Rapamycin (mTOR inhibitor) this downregulated LC3B protein expression. Thus, indicating the mTOR-TFEB/MiT family-ZKSCAN3 transcriptional axis is tightly regulating autophagy[37].

Nuclear factor kappa-B (NF-KB) is a crucial signaling pathway and exerts predominately pro-survival regulation of several biological functions, for example, immune responses, inflammation, cellular proliferation, differentiation, and anti-apoptotic functions. To the contrary, NF-κB activation facilitated apoptosis by upregulating BAX in breast cancer cells[38,39]. Indeed, this action required the nuclear translocation of RELA/p65 to initiate the relocalization of nucleophosmin to the cytoplasm. In consequence, this stimulated the mitochondrial localization of BAX, independent of NF-KB transcriptional activity[40]. These findings reveal a context dependent role for NF-KB

Emerging studies report a reciprocal crosstalk between NF-κB and autophagy. Notably, under nutrient deprived conditions, the expression of autophagic genes Lc3, Atg5 and Becn1 were found to be increased in an IKK dependent phosphorylation of the p85a regulatory subunit of PI3K[41,42], which led to Akt and mTOR inhibition [42]. In contrast, in PTEN null prostate cancer cells, IKKa mediated mTOR activation resulted in autophagy suppression[43]. Interestingly, prolonged starvation promoted the accumulation of non-canonical NF-KB p52. These findings suggest the IKK complex is an essential mediator of autophagy and participates in the regulation of *ATGs*[41].

Furthermore, loss of IKKa in pancreatic acinar cells resulted in the accumulation of ubiquitinated proteins aggregating SQSTM1, with subsequent autophagy impairment and ER stress[44]. Moreover, knockdown of SQSTM1 in IKKa deficient pancreatic acinar cells ameliorated pancreatitis, reduced oxidative stress and ER stress markers [44]. These findings demonstrate a crucial interaction between IKKa, autophagy and ER. Interestingly, RELA/p65 regulates BECN1 transcription as it can bind to BECN1 promotor in T cells and induce autophagy [45]. Indeed, human T cell leukemia virus type 1 (HTLV-1) transformed T cells expressing retroviral oncoprotein TAX required BECN1, ATG5 and PI3KC3 to maintain constitutive activation of IxB kinase (IKK)/NFκB and Stat3[46].

In mantle cell lymphoma (MCL), it has been reported that transglutaminase $TG2/NF-\kappa B$ activation stimulated interleukin 6 (IL-6) dependent autophagy for cytoprotection and tumorigenesis. $ATG5^{\kappa 0}$ in SP53 and JeKo cell lines proved to inhibit these signaling patterns, whilst demonstrating impaired autophagic structures, such as autophagosomes and autolysosomes, reduced proliferation rate, decreased chemoresistance, and increased apoptosis^[47]. As expected, increased TG2, p50 and p65 levels were observed in MCL patients and correlated with poor prognosis[47]. These findings suggest therapeutically targeting $TG2/NF-\kappa B/IL-6$ and autophagy may prove to be beneficial for MCL patients. Similar findings were reported in amino acid and serum deprived conditions in HeLa cells. Silencing BECN1 and ATG5 or BECN1 and VPS34 decreased STAT3 phosphorylation and *IL-6* as compared to the control[48].

NF-κB activation in mouse model of Ras induced lung adenocarcinoma requires SQSTM1. Sqstm1^{-/-} mice significantly reduced Ras transformed cells in colony formation assay and tumor burden. Furthermore, genetic ablation of Sqstm1 impaired NF-κB activation as Ras is necessary to stimulate IKK through the poly ubiquitination of tumor necrosis factor receptor associated factor 6[49]. As consequence, increased c-



Jun NH2-terminal kinase (JNK) phosphorylation in the knockdowns promoted the reduction of reactive oxygen species (ROS) scavenger FHC. This study identified SQSTM1 as a crucial mediator of Ras induced transformed cells. In squamous cell carcinoma and melanoma cells, Chloroquine (CQ; lysosomotropic agent) treatment induced NF-xB activation, and in turn, increased the expression of hypoxia inducible factor 1-alpha (HIF-1 α), and IL-8. Additionally, ATG5 and ATG7 knockdown in Mel624 melanoma cells decreased NF-kB activation and increased SQSTM1 protein, though decreased expression LC3B protein, indicating the loss of autophagosome formation. SQSTM1 or JNK knockdown impaired CQ induced IKK phosphorylation, NF-κB activation and SQSTM1[50]. It can be postulated that NF-κB signaling pathway regulates SQSTM1 levels via a positive feedback mechanism. However, SQSTM1 knockdown or NF-KB inhibition augmented CQ cytotoxicity leading to apoptosis in cancer cells[50]. To the contrary, NF- κ B inhibition in macrophages due to IKK β ablation or pharmacological IKK β inhibitors, can enhance IL-1 β secretion and mitochondrial damage by reducing SQSTM1 levels. NF-kB activation and SQSTM1 is capable of countering excessive inflammatory by suppressing NLR family pyrin domain containing 3 inflammasome activation[51]. In this instance, NF-KB activation mediates an anti-inflammatory response.

Of note, IKK complex is degraded by autophagy and inhibits NF-KB signaling. For instance, Bortezomib (proteasomal inhibitor) promoted the accumulation of poly ubiquitinated proteins in diffuse large b cell lymphoma (DLBCL) cell lines. This led to CHOP accumulation- an indicator of ER stress and LC3B dependent autophagy [52]. CQ treatment in DLBCL cell lines significantly reduced Bortezomib induced IkBa degradation and DNA binding activity of NF-KB/cREL and NF-KB nuclear translocation. Moreover, immunofluorescence data revealed accumulation of IkBa/SQSTM1 aggregation. Furthermore, the synergistic effect of CQ on Bortezomib promoted caspase 3 activation preceding apoptosis. These findings were confirmed in primary DLBCL and follicular lymphoma cells[52].

CANCER STEM CELLS

Tumorigenic potential in neoplasms is defined by phenotypical and functional heterogeneity. The intra-tumoral heterogeneity is a hallmark in cancer initiation, chemotherapeutic resistance and, in turn, negatively influences the clinical outcome for cancer patients^[53]. Multiple factors contribute to this diversity, including, genetic mutations, pathologic epigenetic alterations, tumor microenvironment (TME) and the presence of cancer stem cells (CSCs; also known as tumor initiating cells)[53-55]. CSCs exhibit stem cell-properties with enhanced capabilities to escape immune response, self-renew, proliferate and metastasize[53]. In CSCs, the acquisition of genetic mutations and atypical epigenetic modifications are key underlying mechanisms involved in immunosurveillance and therapeutic resistance[56]. Overall, these factors grant CSCs resilience to chemotherapeutics and radiation[56-58]. The presence of CSCs have been detected in hematological malignancies[59-61], as well as in multiple solid cancers, including, glioblastoma[62], pancreatic[63], breast[64], ovarian[65] and liver **[66]**.

The role of autophagy in CSCs

Autophagy is a bimodal process with a context dependent role in tumorigenesis (Figure 1). In the early stage of tumor formation, autophagy is regarded as a longevity and elicits tumor suppressive functions by fostering the clearance of damaged mitochondria, preserving cellular integrity by limiting genotoxic stress and tissue damage, and decreasing inflammation[67]. During advanced stages of tumorigenesis and neoplastic transformation, autophagy deserts the above role and executes oncogenic activity by providing adaptive responses towards extracellular stimuli, including oxidative stress, hypoxia, and nutrient deprivation. Autophagy provides CSCs with recycled bioenergetic substrates for growth, supports migration and invasion by modulating the focal adhesion molecules dependent on ATG5 and FIP200 [68]. In addition, autophagy stimulates the secretion of pro migratory cytokines through Rho family of small GTPases CDC42, for example, IL-6[69]. For further details, we would like to refer to our previous review deciphering the divergent roles of autophagy in CSCs and cancer cells[8].

Liu et al[66] reported, PIK3C3 governs the stemness and expansion of CD133⁺ liver CSCs independent of LC3B. Notably, PIK3C3 silencing reduced the protein expression of CD133 and NANOG. Overexpression of PIK3C3 increased the number of sphere



formation in xenograft model treated with VPS34-IN-1 (PI3KC3 inhibitor), while reducing the proportion of CD133⁺ CSCs, as wells as the tumor formation capability [66]. Lung CSC stemness is dependent on TP53 signaling. TP53 knockdown prevented autophagy inhibition when ATG5 is silenced, suggesting that autophagy requires TP53 to sustain lung stemness[70]. HIF genes are transcriptionally active under oxygen sensing, such as hypoxia. Hypoxia promotes the transcription of pluripotent stem cell inducing transcription factors NANOG, SOX2, OCT4, KLF4, MYC in numerous cancer models^[71,72]. In addition, primary prostate tumors expressing increased NANOG, OCT4 and HIF1a markers correlated with increased prostate tumor stage[71]. The leukemia stem cells (LSCs) in acute myeloid leukemia (AML) are dependent on ATG5 expression, an essential protein for basal autophagy. ATG5 knockdown or 3-Methyladenine (3-MA, autophagy inhibitor) demonstrated less proliferative capacity of LSCs and an increased proportion of cells in G0/G1 phase in comparison to G2[73]. Breast CSCs expressing CD44⁺/CD24⁻ exhibit stem cell like properties through amplified expression of OCT4, NANOG and SQSTM1 genes. Xenograft models with depleted SQSTM1, abolished CSCs frequency and tumor growth[74]. The role of autophagy in epithelial-mesenchymal transition (EMT) is complex. CD44⁺/CD24⁻ breast cancer stemlike phenotype is regulated by ATG5 gene. ATG5 knockdown and CQ treatment suppressed Vimentin (an invasion marker) in response to transforming growth factor1- β (TGF-1 β) and in parallel increased CD24 transcription, and disrupted invasion[75]. On the other hand, death-effector domain-containing DNA-binding protein (DEDD) abrogated EMT transcriptional factors (SNAIL and TWIST) by inducing autophagy through PI3KC3/BECN1 complex and resulted to their degradation. Additionally, DEDD acted as a tumor suppressor by inhibiting tumor development and metastasis in breast cancer[76].

The role of autophagy in differentiated cancer cells

Primary DLBCL tumors expressing high BECN1 with low B cell lymphoma-2 (Bcl-2) correlated with the presence of LC3. This association led to favorable clinical outcome of patients [77,78]. Conversely, in gastric cancer, BECN1, LC3 and SQSTM1 substantially correlated with lymph node and hepatic metastasis and invasion. Unlike the previous studies, these indicators correlated with poor clinical outcome for patients with early-stage disease^[79]. Similar findings were observed in patients with non-small cell lung cancer (NSCLC)[80]. Autophagy deficiency in triple negative breast cancer (TNBC) cells suppressing the trafficking of CD3⁺/CD28⁺ T cells within tumors in vivo. It can be speculated that autophagy deficiency results to T cell mediated immunosuppression. Furthermore, in TNBC patients, a negative correlation was identified with CD8⁺ T cell tumor infiltration and LC3B expression[81]. Moreover, downregulation of ATG7 has been reported in TNBC patients, and this correlated with a poor survival outcome. Corresponding in vitro findings demonstrated ATG7 overexpression impaired proliferation, migration and decreased EMT proteins (e.g., N-cadherin, SMA, Vimentin, SNAIL and SLUG) and upregulated E-cadherin, through abrogation of aerobic glycolysis metabolism[82].

Notably, autophagy repression improves antigen presentation by augmenting CD8⁺ T cell proliferation and function by attenuating tumor growth *in vivo*[83]. CQ treatment with dual immune-checkpoint therapy (anti-PD1 and anti-CTLA-4 antibodies) led to enhanced anti-tumoral activity by elevating the immune response. Therefore, it can be elucidated that pronounced autophagy degrades MHC-I to promote immune evasion[83].

Interestingly, autophagosomes containing cytoplasmic cargo and tumor specific antigens that fail to fuse with the lysosome are released into the extracellular milieu by cells under stressful conditions, including, hypoxia[84]; this is termed as tumor cellreleased autophagosomes (TRAPs)[85,86]. In colorectal cancer and invasive melanomas, abundance of autophagosomes were reported and were associated with tumor cell proliferation, malignancy, and poor clinical outcome[87,88]. TRAPs harvested from supernatant of tumor cells or malignant effusions or ascites of cancer patients expressed LC3B positive autophagosomes accompanied with HMGB1 expression[84,86]. HMGB1 is a pro autophagic protein that directly interacts with BECN1 by displacing Bcl-2[89]. TRAPs promoted B cell differentiation into IL-10 producing regulatory B cells (B regs)[86]. TRAPs were reported to polarize monocytes to M2- like phenotype and enhance programmed death ligand-1 (PD-L1), CD163 and IL-10 levels with poor HLA-DR (MHC-II cell surface receptor) expression[90]. TRAPs elicit further immunosuppressive functions by diminishing CD4⁺ and CD8⁺ T cell proliferation and suppress interferon-gamma secretion; thus, promoting tumor growth and metastasis[86,90-92].

EPIGENETIC REGULATION OF CSCS AND CANCER CELLS

Epigenetics is the chemical and physical modification of DNA and chromatin, and these changes result in the regulation of gene expression without altering DNA sequences. Epigenetics mediate the gene expression via DNA methylation, histone modifications and non-coding RNAs (ncRNAs) that modifies the accessibility of the chromatin or changes the expression of different genes[93]. Epigenetic modifications are stimulated by individual genetic background or environmental factors, and therefore, can influence the occurrence of pathological conditions, including, cancer [93]. As a consequence, detrimental alterations in the epigenome can be the cause, mediator or consequence of genomic instabilities and contribute to cancer initiation and progression[94,95]. The underlying epigenetic signature in cancer cells is also referred to as "epimutation", and similar to a gene mutation, can lead to uncontrollable cell growth resulting to multiple forms of resistance: growth-inhibiting signals, apoptotic, immortalization, angiogenesis, as well as invasion and metastasis [93].

DNA methylation

DNA methylation is the covalent binding of a methyl group to the 5'-position of cytosine, resulting to the formation of 5'-methylcytosine (5mC). It is catalyzed by DNA methyltransferase (DNMT) enzymes, which transfer the methyl groups from Sadenosyl methionine[93]. Methylation predominately affects cytosine nucleotide, as it is located next to the guanine on the 5'-side of the sequence, cytosine-p-guanine (CpG). DNA sections with high frequency sequences of CpG sites (so-called CpG islands) are found in the promoter region of several genes[96,97].

One of the epigenetic characteristics of cancer is genome-wide DNA hypomethylation, leading to the overexpression of oncogenes or causing genome instability, whereas, individual tumor suppressors or DNA repair genes are repressed by local hypermethylation[96,98,99]. In addition, 5-hydroxymethylcytosine (5hmC) is the second most important modification of DNA bases. 5hmC is formed by the oxidation of 5mC[100]. The 5hmC content appears to be tissue-specific and is associated with the regulation of stem cells pluripotency and carcinogenesis[100].

DNA methylation patterns are plastic. Depending on the degree of cell differentiation; type and age, they vary among individuals and cell types. DNA methylation analysis of tumors provides information concerning the transcriptional regulation and repression of gene expressions with tumor biological relevance[94,95,101]. Accumulating studies demonstrate that promoter hypermethylation of individual tumor entities assign as diagnostic, prognostic, or predictive biomarkers[94,95,98,99,102,103].

Histone remodeling and modifications

The second major mechanism of epigenetic regulation is histone modification, a process that controls gene expression patterns by changing the chromatin structure, making the DNA and the genes encoded on it accessible to the transcription apparatus [104,105]. Histones are nuclear proteins that associate with DNA in the nucleus and help condense it into chromatin structure. The smallest packaging unit of the compressed DNA is named a nucleosome, composed of two of each histone protein H2A, H2B, H3 and H4. The remaining histone H1 links the individual nucleosomes [105]. Histones consist of a globular center and flexible terminal arms ("histone tails"). In addition to the histone nuclei, the amino acids in these arms in particular can be chemically modified [105]. Beside methyl groups, other chemical tags, such as acetyl or phosphate residues or the addition of ubiquitin and similar smaller proteins are attached to histones. The result is variable patterns and a regular histone code that is interpreted differently by the cell's genetic apparatus[104].

The following modifications are frequently observed: H3K27ac (acetylation of H3 to lysine 27), H3K4me1, H3K4me3, H3K36me3, H3K27me3 and H3K9me3 (methyl group(s) to lysines)[106]. For instance, specific acetylation of histone H3 (H3K9ac) leads to accessibility of the chromatin and increased in the gene expression. In contrast, the methylation of the amino acid lysine in histone 3 (H3K27me2 or H3K27me3) results in compression of the chromatin with subsequently reduced transcription of the affected gene loci [106,107]. By determining these histone modifications, different chromatin states of region can be defined [107]. Histone modifications can be subjected to tightening or loose packaging under pathological conditions, including, cancer[108,109]. Histones are modified by specific enzymes. Therefore, chromatin-modifying enzymes are ideal targets for the development of specific inhibitors to modulate atypical histone modifications. Different histone deacetylase (HDAC) inhibitors (HDACis) have been approved and are currently effective drug



targets in oncology.

ncRNAs

ncRNAs are additional epigenetic regulators[93,110]. This group includes long ncRNAs (lncRNAs), comprising of at least 200 nucleotides and mainly regulate the expression of target genes. They do this by forming mRNA-riboprotein complexes with proteins. These complexes are bound to specific sites in the genome and modify those regions[110]. In comparison, short ncRNAs, such as microRNAs (miRNAs), consisting of 17-25 nucleotides regulate the expression at the post-transcriptional level [111]. They bind to the untranslated mRNA region of a target gene and suppress mRNA translation through degradation. Alternatively, gene expression is activated by an RNA interference mechanism (RNAi), using the RNA-induced silencing complex [102,111]. Therefore, lncRNAs and miRNAs effect a complex fine-tuning of the gene products on various molecular levels and play crucial role in carcinogenesis[112].

EPIGENETIC REGULATION OF AUTOPHAGY IN CSC AND CANCER CELLS

Autophagy has been implicated in cancer as an entity governing cancer progression, invasion, and metastasis. Additionally, multiple studies have recognized the contributory role of DNA methylation, histone modifications and ncRNAs in cancer. Recent accumulating reports have unveiled the convergence of autophagy and epigenetics in CSCs and cancer cells (Figure 2).

DNA METHYLATION REGULATING AUTOPHAGY

DNA hypomethylation

Autophagy associated genes display oncogenic function due to DNA hypomethylation, consequently leading to tumor progression. In ovarian CSCs, hypomethylation of ATG4A and histone cluster 1 H2B family member N (HIST1H2BN) were identified. Moreover, patients that harbor these genetic characteristics were found to have a poor clinical outcomes and survival[113]. Overexpression of ATG4A in SKOV3 and CP70 ovarian carcinoma cells demonstrated the tumorigenic functions of AT4A. For example, transcription factors associated to the regulation of human embryonic stem cells (ESCs) pluripotency, were found to be enhanced, such as, SOX2, NANOG, OCT4 and CD44[113]. These findings highlight the function of ATG4 promoter hypomethylation in ovarian cancer and a rational to target DNA methylation in these patients as a therapeutic opportunity[113]. Zhu et al[114] reported overexpression ATG7 promoted demethylation of ubiquitin specific peptidase (USP28) mediated through TET methylcytosine dioxygenase 1 (TET1), leading to increased USP28 expression; resulting to accumulation of CD44 protein that contributed to the invasion and lung metastasis of bladder CSCs.

Likewise, promoter hypomethylation of extracellular leucine rich repeat and fibronectin type III domain containing 2 (ELFEN2) was reported in patients with an astrocytoma, which correlated with increased ELFEN2 expression. Similar associations were found in glioma patients. ELFEN2 is a putative oncogene and elicits tumorigenic behavior by promoting autophagy via increasing the expressions of BECN1, ATG7, ATG3 and LC3B proteins[115]. In lung adenocarcinoma, the promoter of MAP1LC3A was found to be hypomethylated and contributed to resistance to epidermal growth factor receptor-tyrosine kinase inhibitors by promoting cytoprotective autophagy [116]. Aberrant DNA methylation has been described to modulate the TME. For example, hypomethylation of PIK3R5 was identified in inducible pluripotent stem cells conditioned with media of Lewis lung carcinoma[117].

Chen *et al*[118] reported the anti-tumoral role of autophagy in esophageal squamous cell carcinoma (ESCC). Hypomethylation of phospholipase C epsilon 1 (PLCE1) in primary ESCC tumors elicited poor clinical prognosis. PLCE1 triggers tumorigenesis through autophagy suppression and downregulation of P53 activity and MDM2 ubiquitination resulting in P53 degradation. PLCE1 silencing induced autophagy and subsequently attenuated tumor cell proliferation through P53[118]. Moreover, Caveolin-1 (CAV1) has been associated with glucose metabolism. In primary colorectal tumors and various corresponding cell lines, an abnormal overexpression of CAV1 due to promoter hypomethylation was demonstrated. CAV1 silencing led to the promotion





Figure 2 Epigenetic regulation of autophagy in cancer cells and cancer stem cells. Autophagy in cancer cells and cancer stem cells is tightly regulated by the dynamic interplay of different epigenetic modifications, such as DNA methylation, histone remodeling and non-coding RNAs. Pathological epigenetic changes in cancer can directly regulate autophagy by targeting the core genes or indirectly through the regulatory elements. ER: Endoplasmic reticulum; M: Methyl group; TF: Transcription factor.

of autophagy through AMPK and P53 dependent cell cycle arrest[119].

DNA hypermethylation

Promoter hypermethylation is an important causative factor in repressing tumor suppressor genes; for example, hypermethylation of *BECN1* gene. In primary sporadic breast tumors, monoallelic loss of BECN1 was found in 45% of tumors and this loss was accompanied with significant promoter hypermethylation[120]. Equally, ATG2B, ATG4D, ATG9A and ATG9B promoter hypermethylation was identified in specimens of invasive ductal carcinoma. In autophagy, these genes are relevant. For instance, ATG2 homologs act as peripheral membrane proteins and are associated to cellular nucleation. ATG4D is part of the ATG4 family and is associated in regulating the ATG8-LC3 conjugation system. ATG9 protein is a functional orthologue that interacts with the phagophore[121]. Genome-wide methylation analysis and bisulfite sequencing reported low levels of ULK2 transcripts due to hypermethylation in glioblastoma[122]. In NSCLC, promoter methylation of transcription factor 21 is associated with repressed autophagy; this negatively correlated with tumor stage, metastasis, and invasion[123]. Methylation analysis revealed silencing of MAP1LC3Av1 caused by Helicobacter pylori infection in non-cancerous and cancerous gastric mucosae cells, which led to impaired autophagy[124]. Equally, MAP1LC3Av1, not MAP1LC3B, was frequently inactivated in ESCC due to demethylation and overexpression of MAP1LC3Av1 in those cells and exhibited anti-tumoral activity, such as decreasing the tumor volume and weight *in vivo*[125].

In gastric cancer, promoter hypermethylation of tumor suppresser gene KLOTHE was identified. Overexpression of *KLOTHE* engaged in autophagy induction by increasing LC3-I/II ratio and decreased the protein phosphorylation of insulin growth factor-1 receptor, insulin receptor substrate-1, PI3K, Akt and mTOR signaling, as well as apoptosis in gastric cancer cells[126]. Hypermethylation of BCL2/Adenovirus E1B 19KDa Protein-Interacting Protein 3 (BNIP3) promoter has been reported in human colorectal cancer cells. Treatment with demethylating agents, such as 5-aza-2'deoxycytidine (DAC) is capable of restoring this BNIP3 via KRAS dependency and MAPK kinase activation[127]. GABARAP family members were differentially expressed in human breast cancer biopsies, suggesting global aberrant DNA methylation. Grade III lymph node-positive breast cancer tissues strongly correlated with the downregulation of GABARAPL1[128]. It was determined that nicotinamide

N-methyl transferase (NNMT) negatively regulates autophagy. NNMT knockdown enhanced liver tumor growth under nutrient deprived conditions through PP2A methylation and decreased the ULK1 activity augmenting protective autophagy[129]. ATG5 promoter was hypermethylated in melanoma and was associated with suppressed basal autophagy, hence, promoting oncogene induced cell proliferation in primary epidermal melanocytes[130].

HISTONE REMODELING AND MODIFICATION REGULATING AUTOPHAGY

Histone deacetylation/acetylation

Several findings report core autophagy-related genes could be silenced via histone deacetylations[131]. In human and mouse CSCs, HDAC enzyme activity has been suggested to function as a pluripotent factor. Pharmacological inhibition or knockdown of HDAC6, inhibited CSCs proliferation and reduced the protein levels of POU5F1, NANOG and SOX2 (pluripotent factors) in human NT2/D1 and murine P19 embryonic carcinoma CSCs[132]. HDAC6 silencing led to the activation of autophagy with increased proteins levels of ATG5, ATG7 and decreased SQSTM1. ATG7 and ATG12 knockdown NT2/D1 decreased HDAC6 protein levels and promoted differentiation. In comparison, HDAC6 silencing, downregulated autophagy and promoted apoptosis in differentiated breast cancer cells[132]. These findings are indicative of the discriminatory role of HDAC6 in the maintenance of CSCs, as well as differentiated cancer cells. Similarly, glioma CSCs expressing increased levels of HDAC6 contributed to their stemness [132,133]. Chemotherapy and radiotherapy resistance is often mediated by the stemness characteristic of CSCs and is an important prognostic factor in various tumors. Yang et al[133] indicated HDAC6 inhibition rendered the transcription of SHH signaling pathway, decreased glioma CSCs neurosphere formation and protein expression of SOX2 and BMIL1, suggesting the induction of cell differentiation. Subsequently, HDAC6 knockdown resulted to radiosensitivity in glioma CSCs[133]. HDAC6 silencing achieved radio sensitization through the activation of BECN1; however, autophagy inhibition through 3-MA countered this phenomenon[134]. It can be proposed that HDAC6 promotes radio resistance by suppressing BECN1.

A study on neuroblastoma cohort indicated that ATG4D positively correlated with HDAC10 expression. HDAC10^{high} expression was correlated with significantly poor survival outcome of patients. In addition, HDAC10 overexpression in neuroblastoma cells promoted Doxorubicin resistance in neuroblastoma cells through HSC70/HSP70 interaction via its deacetylation function [135]. SIRT6 (Sirtuin family member of NAD dependent deacetylase) was reported to be overexpressed in primary ESCC samples. SIRT6 initiated LC3B mediated autophagic flux in ESCC cells by interacting with ULK1 and inhibited mTOR. In parallel, SIRT6 promoted cellular proliferation and participated in regulating the G2M phase. These observations support the potential oncogenic role of SIRT6 and its role in activating autophagy[136]. HDAC1 suppression led to tumor growth regression by inciting mitotic defects and caspase-independent of autophagic cell death via LC3B in hepatocellular carcinoma (HCC)[137]. Similarly, overexpression of HDAC8 is prevalent in oral squamous cell carcinoma and HDAC8 silencing led to anti-proliferative effects and cell death mediated through caspase 9, 3 and 7. The administration of CQ with silenced HDAC8 substantially reduced cellular viability (as compared to HDAC8 knockdown without CQ)[138]. In salivary mucoepidermoid carcinoma cells, HDAC7 silencing attenuated cellular proliferation and c-MYC expression and triggered G2/M phase cell cycle arrest mediated through P27. This stimulated apoptosis and autophagy[139].

To the contrary, HDAC activity has been implicated in positive regulation of autophagy in differentiated cancer cells. It has been reported that HDAC6 dependent autophagy compensated for the impaired ubiquitin-proteosome pathway[140]. Ectopic overexpression of HDAC6 in hepatocellular carcinoma cell line Hep3B reduced cell growth and proliferation without inducing pro-apoptotic proteins. Notably, HDAC6 activated autophagic cell death. Xenograft mouse model demonstrated similar findings and determined that autophagy cell death required the activation of BECN1 and JNK[141].

The Bromodomain and extra-terminal domain (BET) family are epigenetic regulators that preferentially bind to acetylated histones. Proteomic analysis revealed binding of BET proteins caused them to localize by the chromosome recruiting positive transcription elongation factor b (P-TEFb). Transcriptional kinase cyclin dependent kinase-9 (CDK9) and regulatory subunits CyclinT1, T2 or K bind to BRD4



resulting in the phosphorylation of pol II (RNA polymerase II), which results in gene transcription[142]. The BET family is composed of four members: BRD2, BRD3, BRD4 and BRDT[143]. BRD4 has a prominent role in G1 phase in the cell cycle[144]. Colocalization of BRD4 and P-TEFB was identified in late mitotic to early G1 phase. This interaction promoted the recruitment of P-TEFb to mitotic chromosomes to stimulate gene transcription relating to growth and trigger progression to S phase[145].

Impairment of histone acetylation results in aberrant gene expression. For example, BRD4 overexpression has been attributed to enhanced transcription of MYC[146]. In colon cancer cell lines and primary tumors, BRD4 is frequently aberrantly hypermethylated, leading to BRD4 downregulation. Its re-expression in vivo impaired tumor growth indicating its role as a tumor suppressor [147]. Several studies have implicated BRD4 in multiple cancers, including, breast cancer, medulloblastoma, prostate cancer and hematological malignancies[143,148-151].

BET inhibitor JQ1 and genetic silencing of BRD4 in pancreatic ductal adenocarcinoma (PDAC) KP-4 cells led to an increase in LC3B and WIPI expression and autophagic flux, suggesting the formation of autophagosomes and upregulation of autophagosome-lysosome fusion protein[152]. BRD4 is a negative repressor of autophagy; its knockdown upregulated the autophagy genes BECN1, VMP1 (vacuole membrane protein-1), PIK3C3, ATG2A, ATG9B and MAP1LC3B, the autophagy cargo proteins SQSTM1 and OPTN (optineurin), as well as the autophagosome-lysosome fusion genes PLEKHM1 and TECPR1. Consistent findings were observed in overexpression studies, whilst the addition of JQ1 countered these findings. BRD4 knockdown promoted an upregulation in the lysosome biogenesis and function genes and at protein levels: LAMP1, LAMP2, acid sphingomyelinase (ASM), a-glucosidase (GAA), and heavy chain of mature cathepsin B (CTSB HC) and cathepsin D (CTSD HC). Furthermore, silencing studies confirmed that the BRD4-NUT axis is capable of transcriptionally regulating autophagy independently of the MiT family (TFEB, TFE3 and MITF)[152].

As discussed previously, starvation induced autophagy acquires the activation of AMPK and the direct phosphorylation of ULK1 and inhibition of mTOR. ATG7 is crucial in starvation induced autophagy for autophagosome formation, recycling of amino acids, mitochondria integrity and the clearance of ubiquitin-positive aggregates [153]. The role of AMPK, mTOR and ULK1 has gained much attention in numerous solid cancers[146,154-158]. Treatment of AML cell lines and primary CD34⁺ enriched LSCs with the Bet inhibitor JQ1 led to the downregulation of c-MYC protein[159]. Autophagy activation was preferentially observed in JQ1-resistant AML primary cells and in selected LSC cell lines KG1 and KG1a. AMPK (pThr172)/ULK1 (pSer555) pathway was found to induce autophagy independent of mTOR, thereby conferring resistance to JQ1 mediated apoptosis[160]. AMPK provides metabolic adaption in cancer cells in vitro and xenograft models through maintenance of ATP and NADH homeostasis[161]. AMPK deletion in MLL-AF9 (mixed lineage leukemia-AF-9 genes) suppressed disease propagation and depleted the LSCs in the hypoxic environment of the bone marrow[159]. Sakamaki et al[152] suggests AMPK and SIRT1 (Sirtuin-1) function as nutrient sensing mechanisms with the ability to directly interact with BRD4 to govern the transcription of autophagy genes. As such, nutrient deprivation would initiate the dissociation of BRD4 from the autophagy gene promoters, thus, inducing de-repression of autophagy gene transcription and cell survival[152].

Interestingly, the BR4 inhibitor 9f induced ATG5 dependent autophagy associated cell death in breast cancer cells by preventing the interaction between BRD4-AMPK. Furthermore, ATG5 silencing led to LC3B lipidation and accumulation of SQSTM1; however, this did not disrupt AMPK activation. These results indicate that 9f modulates autophagy through ATG5 by using the AMPK-mTOR-ULK1 pathway [155]. ATG5 silencing in bladder cancer cells diminished anti-proliferative ability of BRD4 inhibitor JQ1. In addition, AMPKa knockdown elicited similar results. Collectively, these findings suggest ATG5 dependent autophagy is induced by JQ1, utilizing the LKB1-AMPK-mTOR axis[157]. It was reported that inactivation of Akt (Ser473)-mTOR (Ser2448) contributed to cellular resistance to JQ1 in ovarian cancer cells and overexpression of AKT1 reversed the resistant phenotype[146]. To the contrary, Akt inhibitors are thought to overcome BET inhibitor resistance in primary prostate cancer cells harboring mutated Speckle Type POZ Protein[162].

Histone methylation

G9a (also known as EHMT2) is a histone methyltransferase (KMT) enzyme targeting the lysine. Specifically, this enzyme mediates the histone H3K9 mono-methylation and demethylation at histone 3 lysine 9 (H3K9me1 and H3K9me2). Functionally, this promotes the recruitment of additional epigenetic regulators and repressors of



transcription[163]. Gene silencing usually requires the methylation of H3K9. G9a silencing led to the formation of vacuole like structures in the pancreatic cancer cell line SU86.86. These findings indicate that G9a regulates the MAP1LC3B and WIP11 promoters, as well as, diabetes and obesity regulated (DOR) gene promoters. Starvation induced autophagy led to the reduction of H3K9me2 and an increased H3K9ac[164]. Treatment of MCF-7 breast cancer cells with the G9a inhibitor BIX0124 led to the recruitment of NF- κ B on the *BECN1* promoter and elevated the intracellular ROS. These events reduced the levels of H3K9me2, resulting in an open chromatin structure. This increased the upregulation of BECN1 and promoted autophagy. Breast tumor samples with high G9a and low BECN1 expression exhibited a poor prognosis[165]. It can be postulated that BECN1 is a tumor suppressor governed by G9a. Immunohistochemistry data of paired lung adenocarcinoma and lung squamous cell carcinoma samples revealed a significant higher expression of G9a correlating with metastasis and a poor prognosis of patients [166]. In comparison, low expressions of H3K9me2 and G9a could predict a better prognosis for patients with gastric cancer[167].

Autophagy is an essential pro-survival mechanism and provides adaptive responses. The inhibition of G9a elicits autophagy. mTOR is an integral part of nutrient and energy sensing. G9a inhibitor BIX01294 administration in HeLa, SHEP1 and U2OS cell lines induced LC3B. Interestingly, BIX01294 treatment decreased the phosphorylation of ribosome protein S6 kinase (S6K), an essential mTOR substrate [168]. RHEB overexpression studies in bladder transitional cancer cells attenuated autophagy and autophagic cell death capacity of BIX01294, indicating G9a inhibition is mTOR mediated[169]. Similarly, GA001, an G9 antagonist, induced autophagy in breast cancer cells via the AMPK-mTOR-ULK1 pathway [170]. Ding et al [168] suggests that G9a mediates H3K9 methylation, serving as a potential sensor between amino acid availability, cellular growth and proliferation functioning by the activation of transcription factor 4 (ATF4). ATF4 is part of the unfolded protein response triggered by metabolic stress[171]. Glioblastoma cell lines: A172 and U87MG, treated with BIX01294 and knockdown of *G9a*, revealed activation of LC3B dependent autophagy. Inhibition of G9a, activated Akt/HIF1a expression. Tumor cells treated with BIX01294 exhibited elevated LC3B and PKM2 protein levels resulting in activation of autophagy [172].

Hypoxic stress has shown to increase H3K9me2 and decrease in acetylated H3K9, in multiple cancer cell lines. Additionally, hypoxia mimetics similarly enhanced the global expression of H3K9me2, G9a expression and activity. Hypoxic stress decreased the mRNA levels of MIH1 (involved in mismatch repair) and DHFR (dihydrofolate reductase) genes and increased H3K9me2 levels in their promoter regions[173]. Hypoxia induced autophagy has been implicated in CSCs of different tumor types, including breast and glioma, and this correlated with poor clinical outcome [174,175]. Ablation of BECN1, ATG5 and ATG7 has been reported to enhance cell death in hypoxia condition[176]. Kaempferol (flavonoid, HDACi) was found to mediate autophagy in gastric cancer cells by increased protein expression of LC3B, BECN1 and ATG5 and reduced levels of SQSTM1[131]. Kaempferol induced autophagy by targeting G9a expression. G9a knockdown and Kaempferol co-treated experiments indicated a reduction in G9a binding to LC3B promoter. However, 3-MA rescued this effect by repressing LC3B and cell death[131]. It has been proposed that inhibition of HDAC-G9a pathway may potentiate anti-tumoral activity in cancer cells[177].

NCRNA REGULATING AUTOPHAGY

IncRNA

Transcriptome analysis detected upregulation of gallbladder cancer drug resistantassociated IncRNA1 (GBCDRInc1) in gallbladder cancer tissues, and this increase is implicated in chemoresistance of gallbladder cancer cells[178]. Phosphoglycerate kinase 1 (PGK1) was found to directly interact with GBCDRInc1 by preventing its ubiquitination and breakdown of PGK1, resulting to the formation of ATG5-ATG12 complexes. GBCRInc1 knockdown models treated with CQ reduced the autophagic activity and enhanced sensitivity to Doxorubicin in resistant gallbladder cancer cells in vitro and in vivo [178]. In colorectal cancer, the expression of LncRNA-H19^{High} is associated with poor recurrent free survival. H19 is associated to 5'Fluorouracil (5-FU) chemoresistance mediated by increased autophagy induction via SIRT1[179]. LncRNA MALAT-1 is upregulated in DLBCL compared to normal B lymphocytes. Silencing of MALAT-1 decreased lymphoma proliferation and invasion, enhanced cell cycle arrest and apoptosis. MALAT-1 knockdown promoted the generation of autophagosomes by



increasing the protein levels of LC3 I/II along with SQSTM1 expressions to induce autophagy. MALAT-1 silencing in xenograft model significantly reduced tumor volume and weight[180].

Short ncRNA and miRNA

Several studies have shown the controversial role of miRNA (miR) in the context of autophagy, tumorigenesis and chemoresistance of cancer cells. Indeed, miR-1251-5p levels were significantly elevated in advanced stages of primary ovarian tumors. MiR-1251-5p elicited oncogenic behavior through hyperproliferation, mediating cell cycle and initiating the LC3B dependent autophagy by targeting the tubulin binding cofactor CC (TBCC) in ovarian cancer[181]. Metastatic breast cancer invading lymphatic nodes, expressed increased miR-224-5p levels which correlated with low levels of LC3B protein and increased SQSTM1, suggesting the suppression of autophagy in a SMAD4 dependent manner [182]. SMAD4 protein is a crucial mediator of TGF- β [183]. Interactions between acute promyelocytic leukemia cells and bone marrow stromal cells activate NF-KB signaling, resulting in a negative regulation of miR-23a-5p. Consequently, increased levels of the autophagic proteins (for example BECN1, ATG5-ATG12 complex and LC3B), indicated the induction of cytoprotective autophagy. MiR-23a-5p overexpression led to Arsenic trioxide (APO) and Daunorubicin (DNR) sensitivity [184]. Autophagy inhibition with adjuvant ATO treatment reestablished chemotherapy sensitivity in leukemic cells[184]. Invasion and migration of glioma cells is dependent on P72 expression, the downregulation of BECN1 and autophagy, causing an increase in miR-34-5p and miR-5195-3P expression[185].

Similarly, glioma stem cells are reliant on *MIR93* (*miR-93*) for cell growth and sphere formation in vitro by repressing BECN1, ATG5, ATG4B and SQSTM1 proteins[186]. ATG7 gene overexpression facilitated in the degradation of the forkhead transcription factor FOXO4a mediated through autophagy. Subsequently, repressing miR-145 transcription and further reducing its binding to 3'UTR (3' untranslated region) of PD-L1, thus promoting PD-L1 expression. These events enhance the stem like property, tumorigenesis, and invasive features of bladder cancer cells[187]. Similarly, in cervical and lung cancer, MiR7-3HG targeted the 3'UTR of AMBRA1 mRNA promoting the downregulation of AMBRA1, acting as oncogenesis and MYC phosphorylation, leading to autophagy blockade[188].

Notably, certain tumor suppressor miRNAs elicit anti-tumoral activity through the regulation of autophagy. For instance, miR-1262 was detected in gastric cardia adenocarcinoma[189]. ULK1 gene expression was negatively regulated with the expression of miR-1262. Functional assays, such as, proliferation and cell cycle analysis, colony formation and wound healing elucidated the tumor suppressive function of *miR*-1262[189]. *MiR*-101 negatively regulates basal and Rapamycin-induced autophagy in breast cancer cells by targeting ATG4D, RAB5A and STMN1 genes[190]. Likewise, miR-137 overexpression inhibited ATG5 dependent autophagy in pancreatic cells by sensitizing the cells to the anti-tumoral activity of Doxorubicin in vitro and in vivo[191]. MiR-130a downregulated DICER1 and ATG2B mRNA expressions in chronic lymphocytic leukemia. This led to a reduction in the autophagosome generation due to autophagy inhibition and promoting apoptosis[192]. Consistent with the previous findings, autophagy inhibition is essential in treating AML by targeting HMGB1[193]. Increased MiR-32a levels accompanied by low HMGB1 expression, inhibited all-trans retinoic acid and induced autophagy in AML cells via stimulating LC3 Lipidation [193]. MiR-224-3p overexpression repressed glioblastoma cell proliferation and ablated hypoxia stimulated protective autophagy through targeting ATG5 and FIP200 genes 194].

CLINICAL IMPLICATIONS: TARGETING AUTOPHAGY THROUGH EPI-GENETIC MODULATIONS

Epigenetic therapeutics are promising targets to modify autophagy and to reactivate repressed tumor suppressor genes in different tumor types (Figure 3). Epigenetic abnormalities have been identified in several cancers modulating ATGs (Table 1). Inhibition of DNMTs and HDACs have been clinically developed to achieve the above objective.

It is reported that DAC treatment and additional administration of Panobinostat or valproic acid (HDAC inhibitors) downregulated oncogenic MYC expression and epigenetic modifiers, such as lysine demethylase KDM2B (demethylase for H3K36me2/ H3K4me3) and histone-lysine methyltransferase SUV39H1, leading to



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Epigenetic	Type of epigenetic modification	Cancer model	Genes	Autophagy modulation	Ref.
DNA methylation	Hypermethylation	Breast cancer	ATG2B, ATG4D, ATG9A, ATG9B, Beclin-1, ARHI	Repressed	Li et al <mark>[120]</mark> , Zhang et al[121] and Yu et al[203]
	Hypermethylation	Colorectal cancer	BTG1, PCDH17, BTG1, BTG3, MAP1LC3Av1	Repressed	Muhammad <i>et al</i> [124], Zhao <i>et al</i> [204], Hu <i>et al</i> [205] and Gou <i>et al</i> [206]
	Hypermethylation	Glioma and Glioblastoma	Ulk2, ANKDD1A	Repressed	Shukla <i>et al</i> [122] and Feng <i>et al</i> [207]
	Hypomethylation	Glioblastoma	ELFN2	Activated	Liu et al[115]
	Hypermethylation	Hepatocellular carcinoma	BCLB	Repressed	Liu et al[208]
	Hypermethylation	Liver cancer	PP2A	Activated	Shin et al[129]
	Hypermethylation	Lung cancer	TCF21, TUSC3	Repressed	Chen <i>et al</i> [123] and Peng <i>et al</i> [209]
	Hypomethylation	Lung cancer	LC3A	Activated	Nihira <i>et al</i> [116]
	Hypermethylation	Medulloblastoma	ATG16L1	Repressed	Cruzeiro et al[210]
	Hypermethylation	Melanoma	ATG5	Repressed	Liu <i>et al</i> [130]
	Hypermethylation	Ovarian cancer	ARHI	Repressed	Yu et al[203]
	Hypomethylation	Ovarian cancer	ATG4A	Activated	Liao et al[113]
Histone modification	Histone methylation or acetylation	Breast cancer	EHMT2, Beclin-1	Repressed	Park et al[165] and Sun et al[211]
	Histone methylation	Bladder cancer	SMYD3	Activated	Shen <i>et al</i> [212]
	Histone acetylation	Colorectal cancer	FOXO1	Activated	Zhao et al[213]
	Histone demethylation	Gastric cancer	KDM2B	Repressed	Zhao et al[214]
	Histone demethylation or deacetylation	Glioma	KDM4A, SIRT3	Repressed	Wang et al <mark>[215]</mark> and Qiao et al [<mark>216]</mark>
	Histone deacetylation	Hepatocellular carcinoma	HDAC6	Activated	Jung et al[141]
	Histone deacetylation	Neuroblastoma	HDAC10	Activated	Oehme et al[135]
	Histone methylation	Neuroblastoma	G9a	Repressed	Ke <i>et al</i> [217]
	Histone deacetylation	Prostate cancer	SIRT1	Activated	Powell <i>et al</i> [218]
	Histone deacetylation	Salivary mucoepidermoid carcinoma	HDAC7	Activated	Ahn and Yoon[139]

anti-leukemic activity in AML. Moreover, genes associated with metabolism were enriched under the combination therapy [195]. Monotherapy of DAC at low doses ablated clonogenicity of primary leukemic cells. Combined therapy of DAC and Azacitidine (DNMT inhibitor), decreased tumorigenicity in a xenograft model of breast cancer and in human primary breast cancer cells. Additionally, human breast CSCs displayed decreased self-renewal capacity in mammospheres[196]. In colorectal cancer, HDAC1 inhibitors, such as valproic acid and suberoylanilide hydroxamic acid, increased the expression of UVRAG (component of BECN1 complex). Increased UVRAG levels attenuated 5-FU mediated toxicity in colorectal cancer cells. HDAC1 inhibition potentiated cell death via DNA damage[197]. The novel HDAC8 inhibitor (HMC) elicited pro-apoptotic functions by activating ATG5 and LC3B autophagy proteins in MCF-7 breast cancer cells. Co-treatment of HMC with 3-MA or CQ autophagy inhibitors partially countered HMC-induced cell death, suggesting autophagy elicited a protective role[198].

Trichostatin A (HDAC inhibitor) and valproic acid promoted autophagy and apoptosis in pancreatic cancer cells[199]. CM-272 (G9a/DNMT dual methyltransferase inhibitor) elicited immunogenic cell death and apoptosis in human bladder cancer. Furthermore, CM-272 decreased proliferation, inhibited cell cycle progression and



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Figure 3 Epigenetic modulation of autophagy in resistance cancer cells and cancer stem cells. Cancer stem cells (CSCs) are a heterogenous collection of different cells that acquire genetic aberrations and epigenetic modifications during carcinogenesis. The protective role of autophagy in CSCs facilitates radio/chemotherapeutic resistance. Targeting specific epigenetic alterations could potentially repress autophagy and sensitize the CSCs population to cell death. CC: Cancer cell; TIL: Tumor-infiltrating lymphocytes.

induced autophagy; this correlated with a decrease in H3K9me2 and 5-methylcytosine. *In vivo* model demonstrated CM-272 enhanced the response to anti-PDL1 and attenuated tumorigenesis in *PIK3CA* mutated bladder cancer cells. DMNT1 inhibition enhanced MHC-I in breast cancer leading to the recruitment and activation of CD8⁺ T cells[200].

LncRNA-HOTAIR elicited anti-tumoral activity in chondrosarcoma by upregulating *miR-454-3p* leading to STAT3 activation and elevation of ATG12 protein[201]. Combination treatment of valproic acid and Temsirolimus (mTOR inhibitor/autophagy inducer) augmented cytotoxic effects by significantly inhibiting tumor cell proliferation and growth in murine xenograft model of Burkitt lymphoma[202].

CONCLUSION

Abnormal epigenetic alterations have been implicated in cancer initiation, development, and therapy resistance. Epigenetic mechanisms, such as DNA methylation, histone modification or ncRNAs, can regulate crucial cellular processes like autophagy. In aggressive tumors, epigenetic changes of autophagy can deliberately influence immunosurveillance, maintenance, therapy resistance and invasion. Therefore, understanding the underlying mechanisms involved in epigenetic regulation of autophagy can enhance cytotoxic effects, and thus eliminate tumor cell resistance and prevent disease reoccurrence. Moreover, the application of epigenetic modulators, such as demethylating agents or HDAC inhibitors not only aim to normalize atypical epigenetic patterns on DNA sequences or histones but provide a newer therapeutic opportunity to regulate autophagy in malignant cells. Preclinical and small cohort studies have provided evidence that this approach can be effective and improve cancer prognosis in patients. In hindsight, a challenge lies in using epigenetic modulators on a defined section of the genome. For instance, clinically approved DNA methylation inhibitors or HDACis act genome wide. Currently, patient-specific modification of target genes, using CRISPR/Cas9-based epigenome editors are being developed. It is therefore imperative to identify and validate novel therapeutic approaches to directly target epigenetic changes of autophagy-dependent genes or pathways in resistant cancer cells and CSCs, as this will potentially improve personalized cancer therapy and clinical outcome for cancer patients.

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