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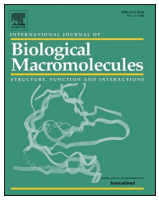

Review

Regulation of autophagy and cellular signaling through non-histone protein methylation

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ABSTRACT

Autophagy is a highly conserved catabolic pathway that is precisely regulated and plays a significant role in maintaining cellular metabolic balance and intracellular homeostasis. Abnormal autophagy is directly linked to the development of various diseases, particularly immune disorders, neurodegenerative conditions, and tumors. The precise regulation of proteins is crucial for proper cellular function, and post-translational modifications (PTMs) are key epigenetic mechanisms in the regulation of numerous biological processes. Multiple proteins undergo PTMs that influence autophagy regulation. Methylation modifications on non-histone lysine and arginine residues have been identified as common PTMs critical to various life processes. This paper focused on the regulatory effects of non-histone methylation modifications on autophagy, summarizing related research on signaling pathways involved in autophagy-related non-histone methylation, and discussing current challenges and clinical significance. Our review concludes that non-histone methylation plays a pivotal role in the regulation of autophagy and its associated signaling pathways. Targeting non-histone methylation offers a promising strategy for therapeutic interventions in diseases related to autophagy dysfunction, such as cancer and neurodegenerative disorders. These findings provide a theoretical basis for the development of non-histone-methylation-targeted drugs for clinical use.

1. Introduction

Autophagy is a process through which eukaryotic cells respond to environmental pressures, such as energy shortages, nutrient deprivation, or internal signals like metamorphosis and differentiation. During this process, autophagosomes from formed under the regulation of autophagy-related genes (ATGs), leading to the lysosome-dependent degradation and recycling of invasive pathogens, protein aggregates, and dysfunctional organelles in a lysosome-dependent manner [1,2]. Autophagy plays a crucial role in maintaining homeostasis, preventing metabolic stress, and promoting growth and metabolism [3,4]. However, understanding suggests that autophagy is a double-edged sword [5–7]. Research has increasingly revealed that dysregulated autophagy can contribute to diseases such as tumors, neurodegenerative disorders, and autoimmune deficiencies by either supporting cancer cell growth of harming normal cells [8,9]. Therefore, further elucidation of the regulatory mechanisms of autophagy is essential for advancing our understanding of this process and developing effective interventions.

Currently, autophagy is classified into three types based on the transported content and mode of action: macroautophagy (commonly referred to as autophagy), chaperone-mediated autophagy, and microautophagy [10,11]. This precisely regulated and highly conserved process that involves the rearrangement of the cell's inner membrane and comprises multiple stages: autophagy initiation of autophagy,

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autophagosome formation, fusion of autophagosomes with lysosomes, and the subsequent degradation and recycling of cellular components [12,13]. To date, more than 40 ATGs, conserved in both yeast and mammals, have been identified. Various proteins regulate autophagy by directly or indirectly interacting with ATGs [14]. For example, the kinases mammalian target of rapamycin (mTOR) and adenosine monophosphate-activated protein kinase (AMPK) sense nutritional and stress signals inside and outside cells, regulating autophagy by modulating the activity of the Unc-51-like autophagy-activated kinase 1 (ULK1) complex [15]. ULK1, the sole autophagy-associated protein with serine/threonine kinase activity, acts as both an effector and regulator of the upstream receptors such as mTOR and AMPK, driving the formation of downstream autophagosomes [16]. Typically, AMPK is inactive while mTOR is active when phosphorylated. Active mTOR inhibits autophagy by disrupting interaction between ULK1 and AMPK, phosphorylating of ULK1 (at Ser637 and Ser757) and ATG13 (at Ser258), and inhibiting the autophagy-promoting kinase activity of the ULK1 complex, thereby restraining autophagy [17–19]. In contrast, under conditions such as starvation or other stress conditions, AMPK becomes activated and inhibits mTOR phosphorylation, leading to mTOR inactivation and ULK1 dissociation. Activated AMPK mediates the phosphorylation of ULK1 at specific sites (Ser317, Ser467, Ser555, Ser574, Ser637, and Ser777), while ULK1 autophosphorylation at Thr180 enhances its activity. ULK1 phosphorylates various ATGs. The ULK1 complex is subsequently transferred to the endoplasmic reticulum, initiating autophagy [20,21].

The regulatory mechanisms of autophagy within signaling pathways are complex, and not fully understood. Studies suggest that epigenetic modification is indispensable for regulating autophagy [22,23]. Epigenetic modifications are changes to the genome that do not alter the DNA sequence but can affect gene expression, often through mechanisms like DNA methylation, histone modification, chromatin remodeling, microRNAs, and long non-coding RNAs, interact dynamically with environmental factors like nutrition, pathogens, and climate to regulate gene expression and the emergence of specific phenotypes [24,25]. These interactions underscore the complex and multilayered nature of gene regulation in eukaryotic systems, where gene expression is tissue-specific, developmentally regulated, and influenced by environmental cues [26]. Moreover, studies have demonstrated that genome and epigenome variations significantly impact health and productivity [27]. Epigenetic modifications play an intricate and critical role in regulating many biological processes, including genome transcription, stability and protein function [28–30]. Whole-genome DNA methylation profiling has been employed to distinguish rheumatoid arthritis cases from controls, illustrating the diagnostic potential of epigenetic studies [31]. Such findings provide a foundation for exploring non-histone protein methylation as a regulatory mechanism in autophagy.

Post-translational modifications (PTMs) are chemical changes that occur after protein synthesis, influencing their activity, stability, and interactions. Recent studies have provided important insights into the role of PTMs in various biological processes. For instance, Gao et al. [32] observed an increase in the expression of DOT1L and H3K79me2 during osteoclast differentiation. Inhibition of DOT1L was found to enhance autophagic activity, which is linked to osteoclast differentiation and bone resorption capacity. Similarly, Li et al. [33] demonstrated that EZH2 regulates the survival of vascular smooth muscle cells (VSMCs) by inhibiting apoptosis associated with aortic dissection. This is achieved through the catalysis of H3K27me2/3 and the subsequent suppression of the MEK-ERK1/2 signaling pathway. PTMs of histones is a significant epigenetic regulatory method, with various modifications occurring on the four histone proteins H2A, H2B, H3, and H4, which make up nucleosomes. These modifications include ubiquitination, methylation, acetylation, and phosphorylation [34–36]. Emerging evidence suggests that protein methylation often occurs in concert with other PTMs, such as acetylation and ubiquitination, forming a complex regulatory network. For example, the interplay between methylation and acetylation on transcription factors can dynamically influence autophagy-related gene expression, while ubiquitination can mediate the degradation of methylation-modified proteins, adding another layer of regulation [2]. Together, these modifications form the "histone code", a system regulating chromatin-related activities. Histone methylation modification is widely present in the PTMs of proteins [37,38]. This process involves the enzymatic transfer of methyl groups from the donor molecule S-adenosylmethionine to lysine or arginine residues on histone or non-histone proteins by methyltransferases, thereby modulating specific signaling pathways [39–42]. Lysine methylation can occur in mono-, di-, or trimethylated states, with each state affecting the expression of related genes (Fig. 1). Similarly, arginine can undergo mono- and demethylation resulting in either symmetric or asymmetric configurations depending on the methylation pattern (Fig. 2). Different modifications affect chromatin properties and can either activate or inhibit gene expression [43–45]. Recent advances in protein methylation research have unveiled its critical roles in diverse cellular functions and disease contexts, including cancer, neurodegeneration, and metabolic disorders. These findings underscore the importance of exploring methylation beyond histones, particularly its regulatory functions in pathways like autophagy [22,38].

In recent years, methylation modifications have been increasingly observed in non-histone proteins, indicating its role in regulating protein function as a common form of protein PTM [46,47]. Methylation of non-histone proteins has been shown to influence protein activity, protein-protein interactions, and other PTMs [47–49]. Many transcription factors can be methylated, suggesting that non-histone methylation modifications are extensively involved in epigenetic regulation [50–52]. Therefore, it is essential to review the research on non-histone methylation modifications and their relationship to autophagy, providing a theoretical basis and identifying new directions for the studying of PTMs [22,23,53]. This review aims to provide a comprehensive summary of the regulatory role of non-histone methylation in autophagy and clarified how ATGs induced changes in non-histone methylation modification-related signaling pathways across different biological processes [2,54]. Although non-histone methylation has been increasingly observed to regulate protein function, protein-protein interactions, and other PTMs, this review is one of the first to focus specifically on the interaction between non-histone methylation modifications and autophagy regulation. By providing an in-depth analysis of current findings, we aim to highlight the potential of targeting protein methylation as a therapeutic strategy for autophagy-related diseases.

2. Overview of autophagy

Autophagy is a conserved stress response that occurring widely in eukaryotes and is triggered by changes in both internal and external cellular environments [55–57]. It plays a crucial role in numerous physiological and pathological processes, including cell differentiation, development, immunity, metabolism, neurodegenerative diseases, and tumors, thereby helping to maintain cellular integrity and stability [58–60]. Based on the method of transporting intracellular substrates to lysosomes, autophagy is categorized into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy [8,61]. In macroautophagy, a separation membrane sequesters portions of the cytoplasm to form autophagosomes, which subsequently fuse with lysosomes to form autolysosomes that degrade their contents [62,63]. In microautophagy, the lysosome invaginates inward through its membrane to engulf small cytoplasmic components. In contrast, chaperone-mediated autophagy does not involve membrane reorganization [10]. Autophagy can also further classified into selective or non-selective autophagy based on cargo selectivity (Fig. 3). Non-selective autophagy involves the bulk transport of organelles and other cytoplasmic components to lysosomes, while selective autophagy specifically degrades certain substrates. The autophagy process [64] primarily includes four main stages: the initiation of autophagy, the formation of autophagosomes, the fusion of autophagosomes with lysosomes, and the

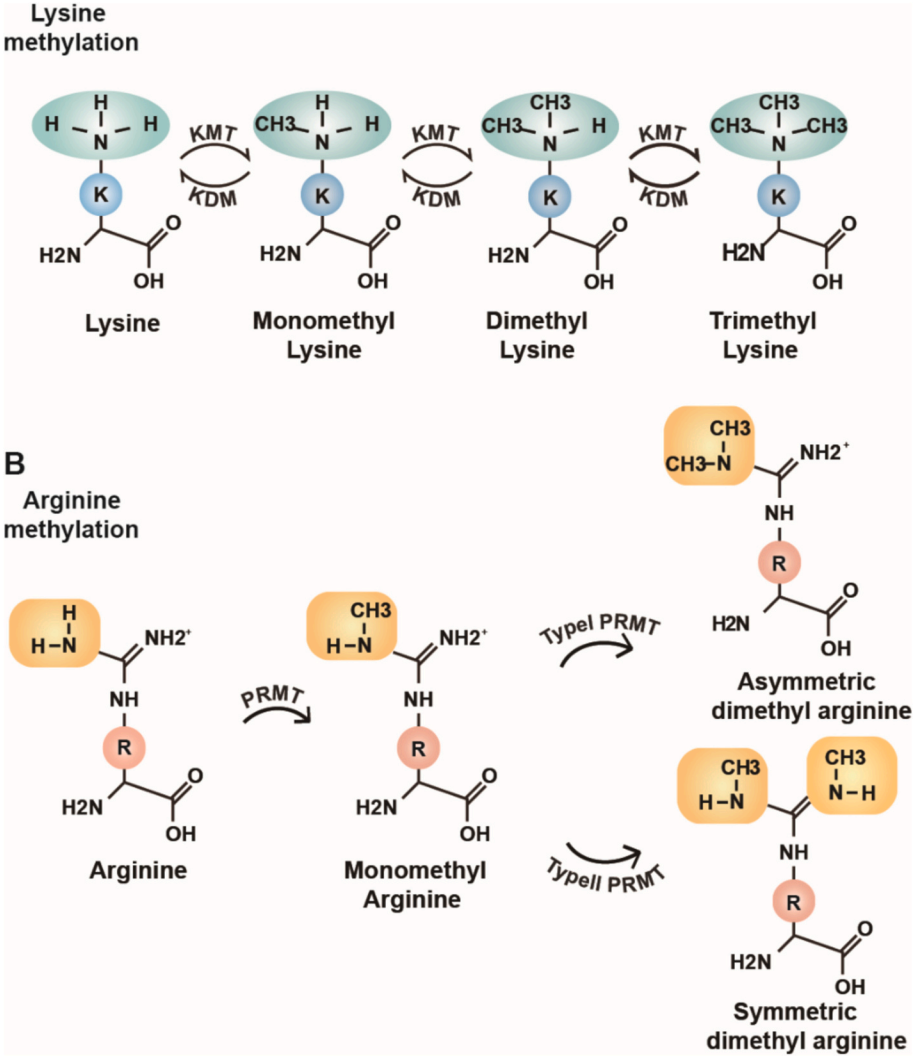


Fig. 1. Lysine and Arginine methylation. (A) Lysine and arginine methylation are a common type of post-translational modifications of proteins. Methyltransferase (KMT) catalyzes mono-, di- and trimethylation of lysine residues and can be reversibly regulated by lysine demethylase (KDM). (B) Arginine occurs under the action of arginine methyltransferase, and there are two types of dimethylation, namely asymmetric dimethyl arginine (ADMA) or symmetric dimethyl arginine (SDMA).

degradation of autophagosomes [11,55,65]. This process can be regulated by different ATGs. In yeast, the induction of autophagosome formation during macroautophagy is regulated by the ATG1-ATG13-ATG17-ATG31-ATG29 kinase complex, while in mammalian cells, it is regulated by the ULK1/2-ATG13-RB1CC1 complex [66,67]. Phagophore nucleation is mediated by the class III phosphatidylinositol 3-kinase (PtdIns3K) complex containing ATG14. The ATG9-ATG2-ATG18 complexes are involved in the expansion, elongation, and maturation of phagosomes, regulated by the ATG5-ATG12-ATG16 complex and microtubule-associated protein 1 light chain 3 (LC3). Finally, the autophagosomes fuses with the lysosomes, where lysosomal degrade the contents. The resulting nutrients are then released back into the cytoplasm for reuse by the cell [8,68].

The mTOR signaling pathway has been identified as a central regulatory mechanism for autophagy [69–71]. Xu et al. [72] revealed that the overexpression of silent information regulator 3 (SIRT3) inhibited the activation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway induced by interleukin-1 beta (IL-1β), thereby suppressing the autophagy process. Similarly, Cai et al. [73] demonstrated that miR-27a targets and silenced the PI3K gene by targeting its 3'-UTR. Compared to normal cells and tissues, PI3K mRNA levels were downregulated in osteoarthritis (OA) cartilage and IL-1β-treated articular chondrocytes were down-regulated, indicating that miR-27a promotes autophagy and apoptosis in IL-1β-treated chondrocytes by inhibiting the PI3K/Akt/mTOR signaling pathway. Wu et al. [74] used a passive rat model of Heymann nephritis and puromycin aminonucleotide *in vitro* to immortalize mouse podocytes and confirmed that mTOR disrupted podocyte homeostasis and induced podocyte damage through the mTOR-ULK1 pathway, leading to reduce autophagy. AMPK can modulate the autophagy process by sensing intracellular adenine nucleotides, It becomes activated when the intracellular AMP/ATP ratio increases [75–77]. Unlike the inhibitory phosphorylation of mTOR complex 1 (mTORC1), studies have shown that the ULK1 complex is activated by the direct phosphorylation of AMPK, which in turn activates the autophagy process [78]. Maria et al. [79] demonstrated that hepatocytes and mouse embryonic fibroblasts(MEFs) lacking AMPK or ULK1 have defects in mitophagy. Additionally, Lin et al. [80] showed that D-mannose may activate autophagy in IL-1β-treated rat chondrocytes by promoting the phosphorylation of AMPK, thereby mitigating OA degeneration.

3. Non-histone protein methylation of ATG proteins

ATG proteins are crucial for the formation of autophagosomes, where they form functional protein complexes that regulate various stages of autophagy. During this process, ULK1 complexes initiate

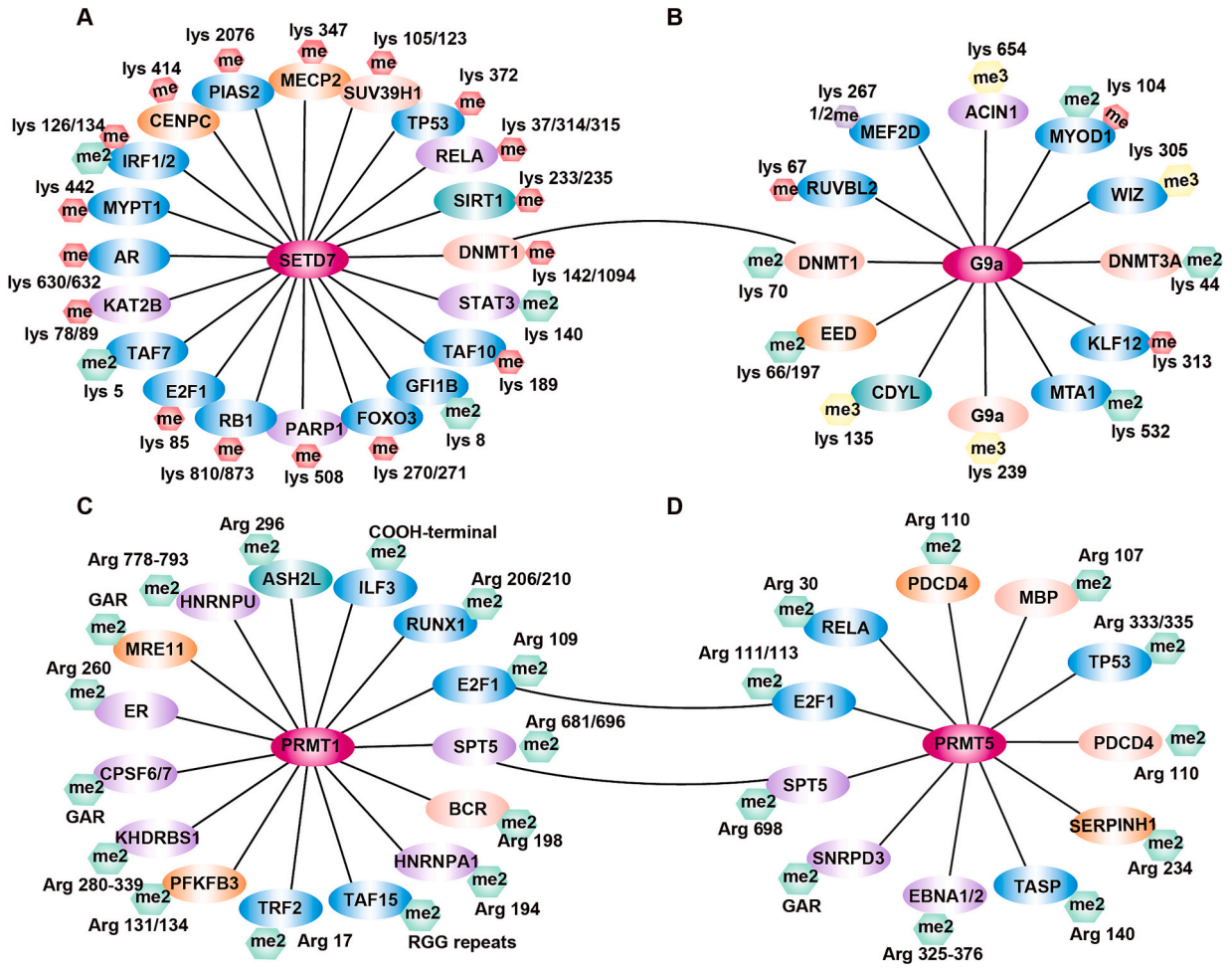


Fig. 2. Methyltransferase-non-histone methylation interaction networks. (A-B) An interaction network depicting the interaction between the lysine methyltransferases (SETD7, G9a) and non-histone lysine methylation is demonstrated based on published literature. For instance, DNMT1 has a complicated methylation interaction, which is dictated by the type of methyltransferases. (C-D). This interaction network illustrates how arginine methyltransferases (PRMTs), including PRMT1 and PRMT5, interact with non-histone arginine methylation. E2F1 and SPT5 exhibit intricate methylation that depends on the type of arginine methyltransferases.

autophagy, while Class III PI3K-Beclin-1 complexes control the nucleation of autophagosomes. These complexes are sequentially activated to regulate autophagy [81–83]. Song et al. [84] showed that the ATG5-ATG12-ATG16L1 ubiquitin-like conjugation system could be methylated by SET domain lysine methyltransferase 7 (SETD7) at lysine 151 (K151). This methylation disrupts the ability of ATG16L1 to bind to the ATG5-ATG12 conjugate, thereby inhibiting autophagy initiated by the gene. Furthermore, methylation at K151 also prevents casein kinase 2 (CSNK2) from phosphorylating ATG16L1 at serine 139, further inhibiting autophagy. However, ATG16L1 can be demethylated by lysine-specific demethylase 1 (LSD1), reactivating autophagy [22].

Additionally, the methylation of ATG16L1 by SETD7 can block its phosphorylation at serine 139 by tyrosine kinase 2, thus inhibiting the autophagy process. On the other hand, when ATG16L1 is phosphorylated, its interaction with SETD7 decrease, promoting autophagy [22,84]. Ultimately, the ATG12-ATG5-ATG16L1 complex recruits and activates the E2-like protein ATG3, facilitating the binding of microtubule-associated protein 1(LC3) to phosphatidylethanolamine (PE), converting LC3BI to LC3BII and promoting the elongation and closure of the autophagosome membrane. These findings suggest that the phosphorylation and methylation of ATG16L1 interact to regulate autophagy in a coordinated manner (Fig. 4).

ULK1 is a key regulator of autophagy initiation, and vacuolar protein sorting 34 (VPS34) is the only Class III PI3K in mammals [85–87]. Both of them are critical for the early stages of autophagy. Active ULK1 regulates the recruitment of ATG14L-containing VPS34 complexes, leading to the phosphorylation of Beclin-1, a binding partner of VPS34, and ultimately enhancing the activity of VPS34 complexes [88,89]. Two ubiquitin-binding systems then promote the lipidation of LC3 and allow autophagosomes to recognize and package cargo. Hypoxia-inducible factor 1-alpha (HIF-1α) can release Beclin-1 from Bcl-2, playing a crucial role in autophagy induction [20]. The symmetric dimethylation of ULK1 at arginine 170 (R170) is essential for autophagy induction. It is regulated by protein arginine methyltransferase 5 (PRMT5) and lysine-specific demethylase 5C (KDM5C), forming dynamic cycle that promotes autophagosome formation and mitochondrial clearance. Under hypoxic conditions, the activity of KDM5C, which requires oxygen as a cofactor, declines, leading to the accumulation of ULK1 symmetric dimethylation at R170, promoting the autophosphorylation of threonine 180 (T180) and activating ULK1. This activation triggers the phosphorylation of ATG13 and Beclin-1, inducing autophagy and reducing cellular oxygen consumption [20,90].

4. Non-histone protein methylation-induced signaling pathway activation and autophagy

The methylation of lysine and arginine residues on non-histone proteins is a critical regulatory mechanism for numerous signaling

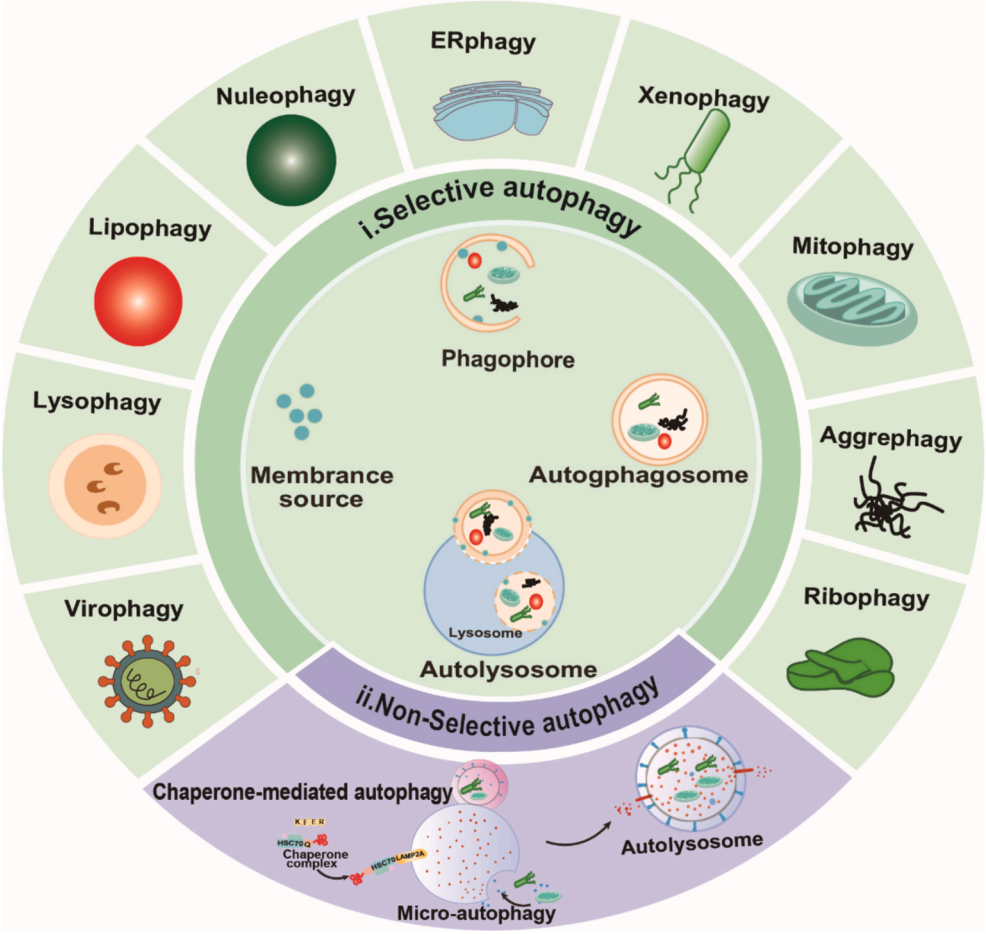


Fig. 3. Types of autophagy. Selective autophagy (i) such as mitophagy, ER-phagy, ribophagy and Lipophay *etc.* Non-selective autophagy (ii) During macroautophagy, abnormally aggregated proteins and microorganisms are recruited into the phagosome, which could then be extended and closed to form an autophagosome, subsequently fuses with lysosomes for degradation.

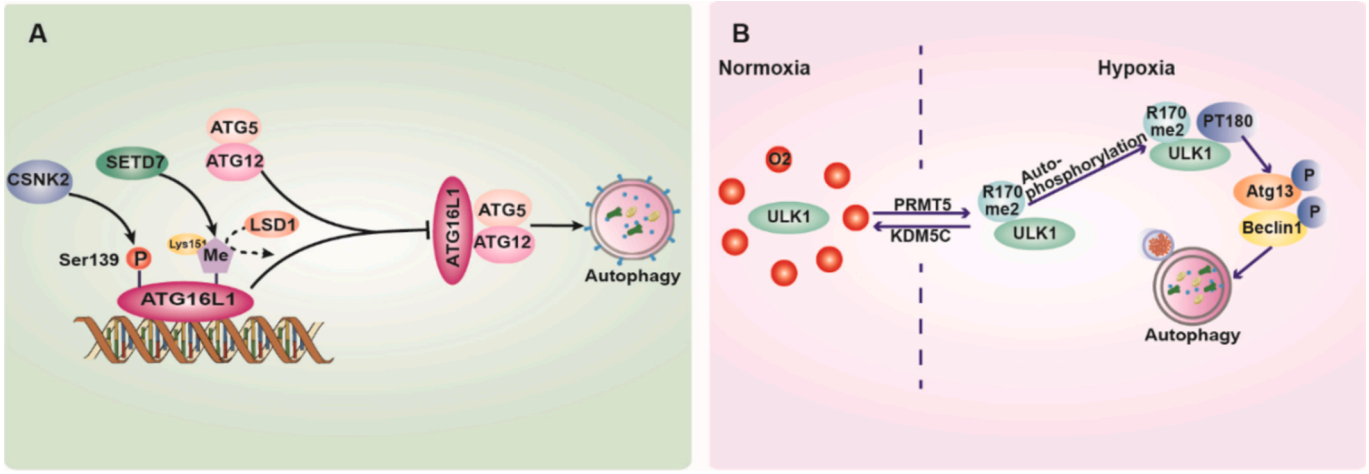


Fig. 4. Non-histone methylation regulates autophagy gene expression. (A) SETD7 methylates lysine 151 of ATG16L1 to inhibit the activation of autophagy genes, while LSD1 demethylates it to activate autophagy. (B) PRMT5 catalyzes the symmetric dimethylation of arginine 170 in ULK1, which promotes the phosphorylation of T180, and subsequent phosphorylation of Atg13 and Beclin 1 to form autophagosomes. KDM5C removes the modification at this site.

pathways. Increasing evidence suggests that non-histone protein methylation is connected to several key pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), signal transducer and activator of transcription 3 (STAT3), Akt, p53, Wnt/β-catenin, E2F transcription factor 1 (E2F1), HIF1, and the Hippo signaling pathway [91–94]. Autophagy is influenced by non-histone methylation through modulation of these different pathways (Table 1). This review summarized the changes in key signaling pathways affected by non-histone protein methylation and their relationship to autophagy (Figs. 5–7).

Table 1
List of protein methylation in autophagy.

Protein modification	Regulator	Target protein	Autophagy activation or inhibition	References
Non-histone methylation	FBXL11/ NSD1	p65(K218, K211)	Activation	[101]
	SMYD2	p65(K310)	Inhibition	[102]
	SETD9	p65(K314)	–	[103]
	SET7/9	p65(K37)	–	[104]
	PRMT1	p65(R30)	Inhibition	[105]
	JMJD1C	STAT3 (K140)	–	[115]
	NSD2	STAT3 (K163)	Activation	[117]
	E2H2	STAT3 (K180)	–	[118]
	TIFE1	STAT3 (R688)	–	[114]
	PRMT6	STAT3 (R729)	Inhibition	[92]
	LSD1	p53(K370)	Inhibition	[142]
	SMYD2/ SED7	p53(K30)	Inhibition	[140]
	KDM3A	p53(K372)	Activation	[143]
	G9a and GLP	p53(K373)	Activation	[144]
	SET8	p53(K382)	Inhibition	[139]
	AKT	E2H2(K49)	–	[160]
	LAST2	mTORC1	Inhibition	[169]
	SET1A	YAP(K342)	–	[174]
	STED6	E2F1 (K117)	Activation	[185]
	Set9	E2F1 (K185)	–	[188]
	Set7	HIF-1α (R32)	Inhibition	[198]
	PRMT3	HIF-1α (R282)	–	[197]

4.1. NF-κB pathway

NF-κB is a crucial transcription factor that regulates ATGs such as Beclin-1, LC3II, ATG7 and others, playing a significant role in diseases like colitis in mice, glioma, and liver fibrosis [95–97]. Peng et al. [98] found that autophagy, mediated by ATG5, sequestered p65 proteins in the cytoplasm, blocking NF-κB signaling and thereby inhibiting inflammatory responses in renal epithelium. Shen et al. [99] observed that chemokine receptor 5 (CXCR5) inhibited hippocampal autophagy during sepsis through NF-κB signaling, leading to cognitive dysfunction. However, the downregulation of CXCR5 restored autophagy and alleviated the pro-inflammatory environment in the hippocampus. In a mouse model of liver fibrosis induced by carbon tetrachloride (CCl4) injection, Fas/FasL facilitated NF-κB p65/p53 upregulated modulator of apoptosis (PUMA)-regulated hepatocyte apoptosis *via* autophagy, thereby exacerbating liver fibrosis [97]. Recent studies have shown that various methyltransferases can methylate different sites of NF-κB, influencing cellular autophagy [100]. For example, the overexpression of leucine-rich repeat protein 11 (FBXL11) inhibits NF-κB activity, and FBXL11/nuclear receptor binding SET domain protein 1 (NSD1) regulates the transcriptional activity of p65 through reversible lysine methylation at the lysine 218 (K218) and lysine 221 (K221) sites [101]. The SET and MYND structural domain-containing family protein 2 (SMYD2) methylates non-histone proteins such as p53, retinoblastoma protein (Rb), heat shock protein 90 (HSP90), and p65. SMYD2 can methylate p65 at lysine 310 (K310), promoting breast cancer cell growth [102]. Additionally, the methyltransferase SET domain containing 9 (SETD9) can methylate p65 at the lysine 314/lysine 315 (K314/K315) sites, leading to the degradation of promoter-associated p65 protein and inhibition of NF-κB activity [103]. Another study reported that SETD9 can also methylate p65 at lysine (K37), affecting its stability in response to TNF-α stimulation and regulating p65 binding to promoters [104]. Protein arginine methyltransferase 1(PRMT1) could methylates the arginine 30 (R30) site of p65, and asymmetric dimethylation at R30 inhibits p65 binding to DNA, thereby suppressing the response of NF-κB target genes to TNF-α [105]. Conversely, PRMT1-mediated methylation protects cellular FOS (c-Fos) from autophagic degradation and promotes gastric tumorigenesis [106].

4.2. STAT3 pathway

STAT3 is a transcription factor that regulates the expression of key genes involved in autophagy, cellular growth, and other biological processes, including ATGs, B-cell lymphoma 2 (BCL2), myeloid cell leukemia 1 (MCL1), and Bcl-2/adenovirus E1B 19-kDa-interacting protein 3 (BNIP3) upon cellular stimulation. It plays a crucial role in cellular growth, autophagy, and other biological processes [107–110]. In cases of sterile inflammatory osteolysis, the STAT3 signaling pathway is significantly activated in macrophages. Inhibiting STAT3 has been shown to activate the Phosphatase and tension homolog (PTEN)-induced kinase 1 (PINK1)-dependent mitochondrial autophagy pathway, mitigating the formation of osteoclasts induced by inflammatory macrophages [111]. Research by Liang et al. [112] demonstrated that amilorotinib induced apoptosis and autophagy in human lung cancer cells. In addition, blocking autophagy further enhanced the drug's cytotoxic effect and improved its anti-angiogenic properties through Janus kinase 2 (JAK2)/STAT3/vascular endothelial growth factor A (VEGFA) signaling. In a study using Trichostatin A in lipopolysaccharide-induced RAW264.7 cells, treatment reduced STAT3 phosphorylation in the nucleus, increased forkhead box O3a (FOXO3a) phosphorylation, and activated the STAT3/FOXO3a signaling pathway, which promoted macrophage autophagy and reduced inflammatory responses [113]. Therefore, the active state of STAT3 is crucial for the regulation of autophagy. Yang et al. [114] identified that tumor necrosis factor-alpha-induced protein 8-like 1 (TIPE1) inhibited the tumorigenesis and progression of osteosarcoma by modulating the PRMT1-mediated methylation of the arginine 688 (R688) site on STAT3. Yin et al. [115] demonstrated that histone demethylase jumonji domain-containing protein 1c (Jmjd1c) controlled plasma cell differentiation by demethylating lysine 140 (Lys140) on STAT3, thereby reducing antibody production, and alleviating rheumatoid arthritis. Additionally, PRMT5 enhanced STAT3 signaling by methylating arginine at position 57 of Smad7, promoting the proliferation, survival, and tumorigenicity of non-small cell lung cancer cells [116]. Based on mass spectrometry and fixed-point mutagenesis analyses, Song et al. [117] revealed that nuclear receptor-binding SET domain protein 2 (NSD2) methylated STAT3 at lysine 163 (K163), promoting the activation of the STAT3 pathway and enhancing tumor angiogenesis. Silencing NSD2 inhibited autophagy and alleviated pulmonary arterial hypertension in rat models. Luo et al. [118] reported that long non-coding RNA-p21 (lncRNA-p21) could enhance the methyltransferase activity of enhancer of zeste homolog 2 (EZH2), leading to increased lysine methylation of STAT3 and alterations in neuroendocrine differentiation in prostate cancer. PRMT6 dimethylated STAT3 at the arginine 729 (R729) site. Both *in vivo* and *in vitro* studies confirmed that PRMT6 overexpression was positively correlated with invasion-related gene expression in breast cancer cells, with the R729K mutant of STAT3 exhibiting the opposite effect, underscoring the significance of STAT3 methylation at R729 in PRMT6-mediated tumor metastasis [92].

4.3. Akt pathway

Akt, a serine/threonine kinase, is a key regulator of cellular autophagy [119]. And plays a crucial role in the development and progression of various inflammatory and tumor-related diseases, especially under conditions of starvation and cytokine influence [120,121]. For

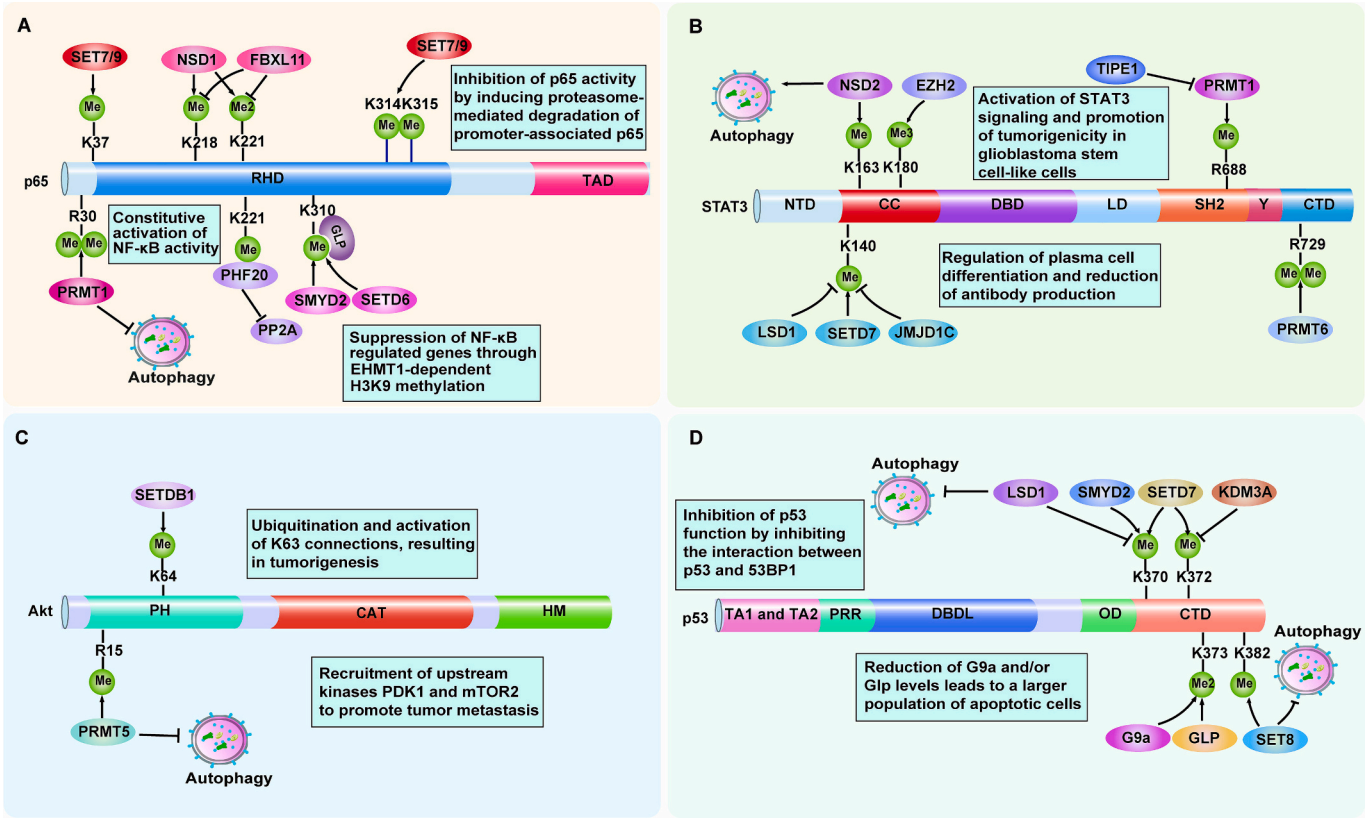


Fig. 5. Effects of methylation of non-histone lysine and arginine on transcription factors. (A) PRMT1 methylates the R30 site on p65 and protects c-Fos from autophagic degradation. Methylation of SET7/9 at the K37, K314, and K315 sites on p65 inhibits the stability of the DNA-p65 complex and promotes the degradation of p65 proteins, inhibiting NF-κB activity. FBXL11/NSD1 regulates p65 transcriptional activity by lysine methylation at the K218 and K221 sites to regulate the transcriptional activity of p65. SMYD2 methylates the K310 site on p65 to promote breast cancer cell proliferation. SETD6 monomethylates p65 at the K310 site to recruit GLP, leading to the repression of the p65 target genes. (B) SETD7 demethylates STAT3 at K140 to negatively regulate STAT3 target gene transcription. JMJD1C controls plasma cell differentiation and reduces antibody production by demethylating Lys140 of STAT3. NSD2 methylates STAT3 at K163 to promote STAT3 pathway activation and enhance tumor neogenesis. Knockdown of NSD2 inhibits autophagy. EZH2 trimethylates the K180 site of STAT3 and alters neuroendocrine differentiation in prostate cancer. TIPE1 inhibits osteosarcoma tumor progression by regulating PRMT1-mediated methylation at STAT3 arginine 688. PRMT6 is dimethylated at STAT3 arginine 729, thereby promoting tumor metastasis. (C) PRMT5 methylates Akt1 at R15 and recruits upstream-activated kinases PDK1 and mTOR2 to promote tumor metastasis. Additionally, it inhibits autophagy. (D) LSD1 demethylates p53 at K370, thereby inhibiting autophagy. SMYD2 and SETD7 monomethylate p53 at the K370 site, which inhibits its activity. SETD7 methylates p53 at K372, activating the transcriptional activity of p53. KDM3A demethylates p53 at K372 and inhibits its transcriptional activity, thereby inducing chemoresistance in breast cancer cells. G9a and GLP can demethylate p53 at K373 and inhibit its transcriptional activity. SET8 monomethylates p53 at K382, thereby inhibiting autophagy.

example, the antioxidant enzyme peroxiredoxin 1 (PRDX1) has been shown to enhance cellular autophagy by activating the PTEN-Akt signaling pathway, which in turn reduces reactive oxygen species (ROS) levels and apoptosis, thereby mitigating neuronal damage [122]. Additionally, mitochondrial ROS are involved in copper-induced autophagy through the Akt/AMPK/mTOR pathway. Silencing of ATG5, which inhibits autophagy, exacerbates $CuSO_4$-induced apoptosis [123]. He et al. [124] demonstrated that ginsenoside Rg2 could activate the Akt/mTOR pathway, suppress autophagy through inhibition of LC3II and upregulation of p62 expression, and ameliorate liver fibrosis induced by a high-fat diet and lipopolysaccharide-triggered activation of HSCT-6 cells. In a streptozotocin-induced diabetic mouse model, paeoniflorin bound to vascular endothelial growth factor receptor 2 (VEGFR2), promoted autophagy through the PI3K/AKT signaling pathway, and inhibited apoptosis, providing protective effects on diabetic nephropathic podocytes [125]. Non-histone lysine-specific methylation, is a prevalent PTM, plays a novel role in regulating protein function, mainly by affecting protein stability [126,127]. For instance, SET domain, bifurcated 1 (SETDB1)-mediated methylation of Akt at lysine 64 (K64) is involved plays a key role in tumorigenesis. SETDB1-mediated trimethylation of monocarboxylate transporter 1 (MCT1) at lysine 473 (K473) inhibits the interaction between MCT1 and Tollinteracting protein (Tollip), blocking Tollip-mediated autophagic degradation of MCT1 [128]. Zhang et al. [129] reported that arginine methyltransferase 1 (CARM1) methylated the arginine 23 (R23) site of protein phosphatase 1 catalytic subunit alpha (PPP1CA), leading to the dephosphorylation of Akt at threonine 450 (T450) and AMPK at threonine 172 (T172). Besides, this modification enhanced the activities of phosphofructokinase-1 and fructose-2,6-bisphosphate kinase 3, ultimately promoting glycolysis. Their study involving mouse embryonic fibroblasts (MEFs) under glucose starvation conditions revealed a significant upregulated level of CARM1, establishing a positive correlation between CARM1 and cellular autophagic activity [130]. Moreover, PRMT5 methylated Akt1 at arginine 15 (Arg15), facilitating the recruitment of upstream-activated kinases phosphoinositide-dependent kinase 1 (PDK1) and mTOR2, thereby promoting tumor metastasis [93].

4.4. p53 pathway

The p53 gene is a crucial tumor suppressor that plays a significant role in regulating apoptosis, senescence, and cellular autophagy through methylation of lysine residues and protein interactions [131,132]. Huang et al. [133] utilized CRISPR/Cas9 to knock down miR-34a and miR-34b in colorectal cancer cells, resulting in a significant decreased in

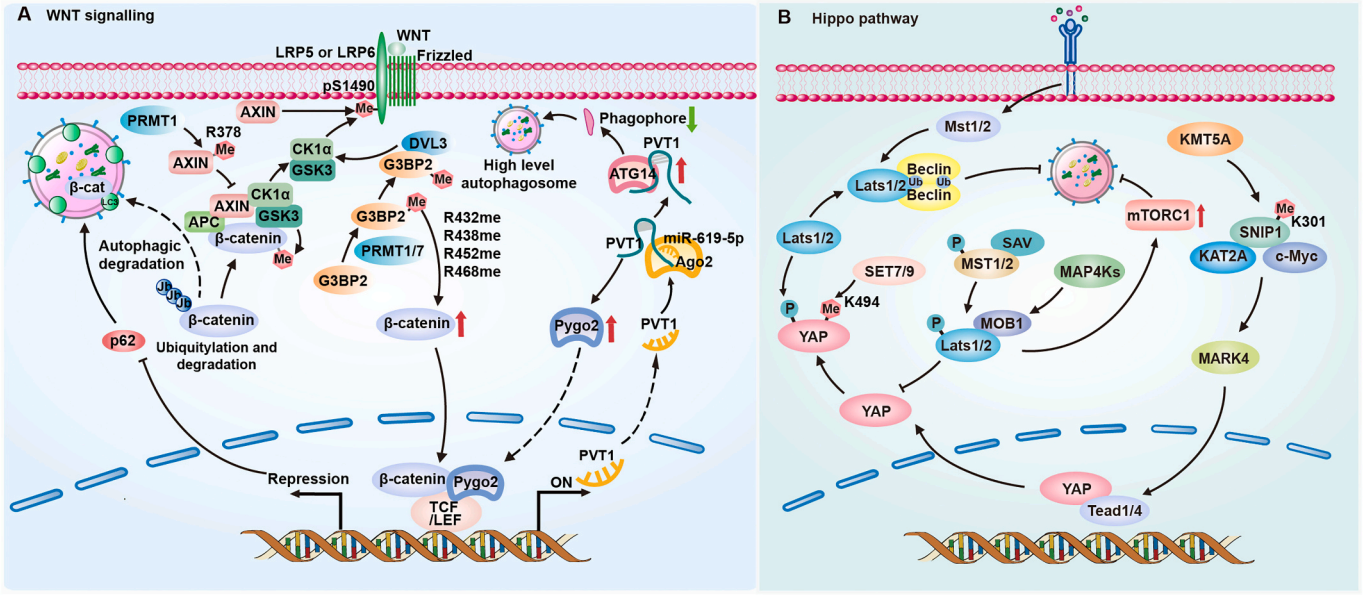


Fig. 6. Non-histone methylation regulates cell signaling pathways affecting autophagy. (A) PRMT1 can methylate Axin at the R378 site, increase Axin stability, and negatively regulate the Wnt signaling pathway mediating autophagy. PRMT7 can methylate multiple arginine sites of G3BP2, thereby up-regulating β-catenin expression and promoting autophagy. Plasmacytoma multiple ectopic gene 1 (PVT1) activates the Wnt/β-catenin and autophagy pathways by regulating Pygo2 and ATG14. (B) Under stress conditions, autophagy can enhance the autophagy protection mechanism by degrading LATS2, but continuous activation of LATS2 can lead to overactivation of mTORC1 and inhibition of autophagy. Set7 can monomethylate Yap at K494, which affects its autophagy transcriptional activity. KMT5A can mediate the methylation of SNIP1 at the K301 site and inhibit the Hippo kinase cascade, thus affecting the Hippo pathway regulation of autophagy.

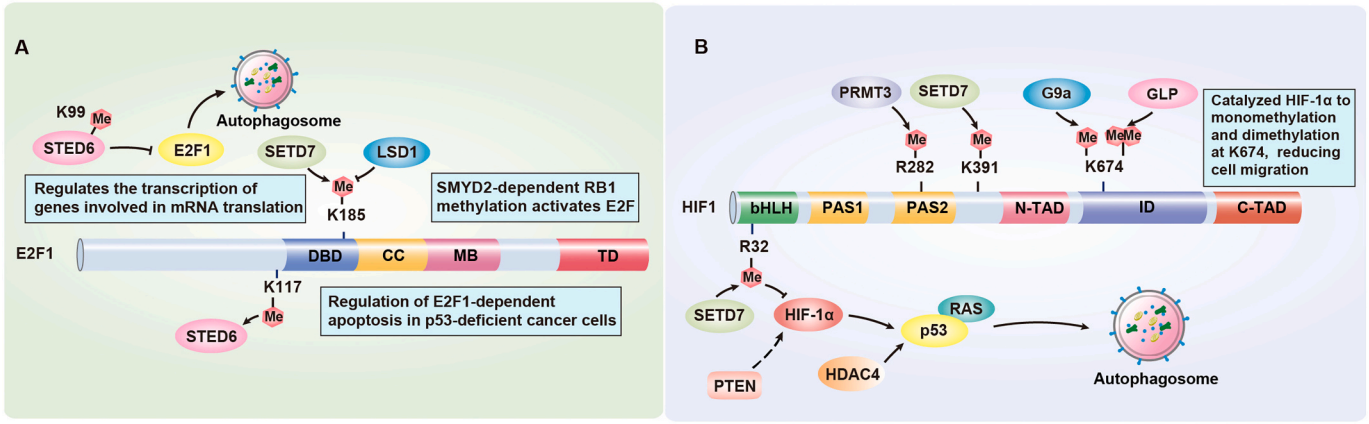


Fig. 7. Regulation of non-histone methylation in autophagy. (A) Methyl groups activated by E2F1 at K117 bind to the STED6 promoter and promote the transcription of STED6. SETD7 methylates E2F1 at K185, preventing the accumulation of E2F1 caused by DNA damage. (B)The lysine methyltransferase SETD7 methylates HIF-1α at the R32 site and inhibits HIF-1α expression, thereby suppressing its induction of p53-mediated autophagy. Arginine methyltransferase PRMT3 can influence the stability of HIF-1α by regulating the methylation of HIF-1α at R282. Lysine methyltransferase G9a and GLP are capable of catalyzing the monomethylation and dimethylation of HIF-1α at K674, significantly reducing cell migration.

tumor suppression following p53 activation, increased autophagic flux, and elevated expression of ATGs such as ATG9A. The mucolipo protein TRP cation channel 1 (MCOLN1)-induced autophagy inhibited mitochondrial damage and the subsequent massive release of ROS, which could activate p53 and suppress melanoma cell metastasis [134]. Additionally, SIRT4, a member of the Sirtuin (SIRT) family, regulated the expression of ATGs in pancreatic ductal adenocarcinoma cells. SIRT4 inhibited glutamine metabolism to activate AMPK, which promoted the phosphorylation of p53, and thereby inducing autophagy activation and inhibiting of pancreatic ductal adenocarcinoma development [135]. Another study demonstrated that bisphenol A (BPA)/bisphenol S (BPS) exposure enhanced ovarian cancer cell stemness by activating non-classical PINK1/p53-mediated mitochondrial autophagy, which in turn promoted ovarian cancer metastasis *in vivo* [136].

Moreover, methylation of p53 at different sites affects cellular autophagy in various ways [131,137,138]. Monomethylation of p53 by SMYD2 and SET8 at lysine 370 (K370) and lysine 382(K382), respectively, can inhibit its activity [139]. Additionally, SMYD2 also transcriptionally represses the expression of p53 target genes and inhibites autophagy-associated cell death induced by Bix01294 [140]. Huang et al. [141] found that histone LSD1 could demethylate p53 at K370, preventing its interaction with the coactivator p53-binding protein 1 (53BP1), thereby repressing p53 function. Knockdown of LSD1 activated cellular autophagy [142]. Lysine demethylase 3 A (KDM3A) demethylated non-histone p53 at K372, inhibiting its transcriptional activity, thereby inducing chemoresistance in breast cancer cells [143]. The homologous methylases G9a and GLP could methylate p53 at K373me2, and reducing the levels of both increased apoptosis and inhibited the

transcriptional activity of p53 [144]. Additionally, SETD7 was found to methylate p53 at K372, activating its transcriptional activity, while methylation at K370 inhibited its transcriptional activity [139].

4.5. Wnt /β-catenin pathway

The Wnt signaling pathway is a complex network of protein interactions primarily involved in embryonic development and cancer, influencing processes such as cell proliferation, autophagy, and apoptosis [145–147]. Regulatory feedback mechanisms between Wnt/β-catenin signaling and autophagy have been explored at various levels [148–150]. Zhou et al. [151] demonstrated that plasmacytoma diverse ectodomain 1 (PVT1) enhances drug resistance in pancreatic cancer by modulating Pygo2 and ATG14, thereby activating the Wnt/β-catenin and autophagy pathways. Fan et al. [152] found that autophagy promoted metastasis and glycolysis in hepatocellular carcinoma cells by upregulating monocarboxylate (MCT1) expression and activating the Wnt/β-catenin signaling pathway. Low-density lipoprotein receptor-related protein 6 regulated Rab7-mediated autophagy through the Wnt/β-catenin pathway, influencing trophoblast cell migration and invasion. Petherick et al. [153] revealed *in vivo* studies that the accumulation of β-catenin inhibited the p62/SQSTM1 promoter, thereby suppressing autophagy. Additionally, another study found that blocking Wnt signaling increased p62/SQSTM1 transcription in glioblastoma, leading to enhanced autophagy [154].

Recent studies have shown that Wnt/β-catenin can be by various methyltransferases, impacting cellular autophagy. Zhang et al. [155] observed that lysine-specific histone demethylase 1 A (KDM1A) demethylated H3K4me1/2 in the APC2 promoter and the non-histone substrate HIF-1α, downregulating Wnt pathway antagonists adenomatous polyposis Coli 2 (APC2) and dickkopf-related protein 1 (DKK1). This repression of APC2 transcription activated the HIF2α/microRNA-146a/DKK1 axis. PRMT1 enhanced β-catenin binding by methylating promoter R101, a member of the armadillo-repeat protein family (PKP2), thus promoting chemotherapy tolerance in lung cancer [156]. In contrast, reduced expression of PRMT7 inhibited β-catenin's symmetric dimethylation, contributing to cardiac hypertrophy and fibrosis in mice [157]. PRMT1 also directly methylated arginine 378 (R378) of the scaffolding protein Axin, enhancing Axin's stability and negatively regulating Wnt signaling [158]. In a rat model of Parkinson's disease, knockdown of Axin-2 modulated Wnt/β-catenin signaling, reducing cellular autophagy and the generation of ROS, while improving mitochondrial membrane potential and promoting dopaminergic neurogenesis [159]. Ghobashi et al. [160] demonstrated that AKT-mediated phosphorylation of EZH2 promoted the trimethylation of β-catenin at the K49 site, enhancing its binding to chromatin and influencing gene expression related to cell motility and metabolism.

4.6. Hippo pathway

The Hippo pathway is a conserved signaling mechanism that regulates various biological processes, including cell growth, death, and tissue regeneration [161–164]. Recent studies suggest Hippo pathway also plays a role in regulating autophagy, a crucial mechanism underlying lysosome-mediated cellular degradation that significantly impacts cell growth and death responses across different cell types [78,165,166]. Yuan et al. [167] observed that laminar flow inhibited the Hippo/YAP pathway by increasing the expression of autophagy proteins such as Beclin-1 and LC3II/LC3I, which ultimately reducing atherosclerotic plaque formation in mice. Another study found that Drosophila intestinal epithelial cells maintained intestinal homeostasis by eliminating p62 through autophagy, thereby suppressing the ROS-triggered Hippo pathway [168]. Under stress conditions, autophagy supported β-cell survival by degrading large tumor suppressor 2 (LATS2), which enhanced the protective autophagic mechanism through positive feedback. However, the prolonged LATS2 stimulation overactivated mTORC1 and inhibited autophagy, leading to the accumulation of LATS2 and the apoptosis of β-cell [169]. Tang et al. [170] demonstrated that LATS kinase in the Hippo pathway bound to and stabilized Beclin1, suppressing sorafenib-induced autophagy. In breast and ovarian cancer cells, Hippo-YAP signaling regulated drug resistance by enhancing autophagic flux through increased expression of proteins such as ATG3, ATG5, and LC3B [171,172].

Recent studies have also shown that the Hippo pathway is modified by various methyltransferases, significantly impacting biological processes including cellular autophagy. Oudhoff et al. [173] demonstrated that Yes-associated protein (YAP), a component of the Hippo pathway, interacted with the lysine methylase Set7 and was mono-methylated at the K494 locus. The mutant Yap (YapK494R) failed to remain in the cytoplasm. Methyltransferase SET1A also interacted with YAP, contributing to its lysine monomethylation at K342, It further YAP's nuclear retention and transcriptional activity [174]. Additionally, the lysine methyltransferase KMT5A methylated the K301 site of Smad nuclear-interacting protein 1 (SNIP1), inhibiting the Hippo kinase cascade and promoting metastasis in triple-negative breast cancer [175].

4.7. E2F1 pathway

E2F1 plays a critical role in cancer progression by driving cell cycle progression and regulating various biological processes related to proliferation and malignant transformation, including cell proliferation, autophagy, apoptosis, and metastasis [176–178]. In mice with silicosis, Beclin1 expression was reduced, while levels of kinase-related protein 2 (SKP2) and E2F1 were elevated [179,180]. MicroRNA-205-5p targeted E2F1, promoting autophagy by inhibiting SKP2-mediated ubiquitination of Beclin1. It consequently reduced pulmonary fibrosis in silicosis patients [179]. Metformin treatment prevented estrogen deficiency-induced upregulation of E2F1, and caused decreased levels of Beclin1 and BNIP3 proteins. This disruption interfered with BNIP3 binding to BCL2 while promoting Beclin1-BCL2 binding, triggering autophagy and reducing bone loss [181]. Additionally, E2F1 knockdown in mice enhanced white adipose tissue browning by suppressing ATGs, including LC3II and ATG5 [182].

In NB4 acute myeloid leukemia cells, LncSIK1 recruited E2F1 proteins to the promoters of LC3 and DRAM, leading to autophagy-dependent degradation of the oncoprotein PML-RARα and increased sensitivity to retinoic acid [183]. Moreover, resveratrol alleviated adriamycin-induced cardiotoxicity by disrupting E2F1-mediated autophagy inhibition of autophagy apoptosis [184]. Numerous studies have shown that lysine and arginine methylations at various sites on E2F1 affects cellular autophagy in multiple ways. Kublanovsky et al. [185] found that methylation of E2F1 at K117 influenced STED6 transcription, with methylated E2F1 binding to the STED6 promoter and stimulating its expression in a methylation-dependent manner. Similarly, methylation of STED6 at K99 regulated E2F1 expression, affecting the transcription of genes related to mRNA translation [186]. Inhibition of PRMT5 decreased E2F expression and symmetric dimethylation of E2F1, which reduced DNA damage repair and increased apoptosis [187]. Additionally, lysine methyltransferase Set9 methylated E2F1 at K185, blocking DNA damage-induced accumulation of E2F1 and activating the p73 gene [188].

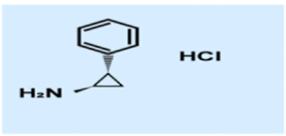
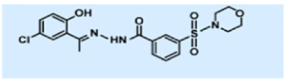
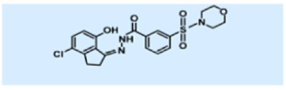
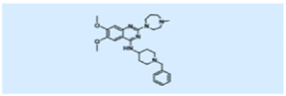
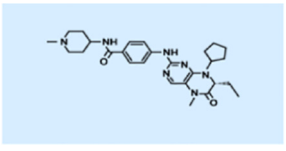
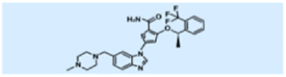
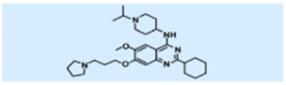
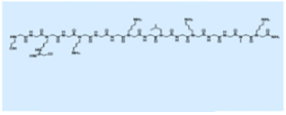
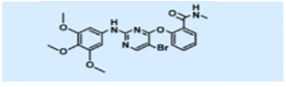
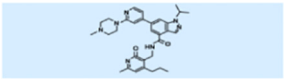
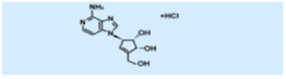
4.8. HIF1 pathway

HIF1 is a transcription factor with a helix-loop-helix structure that activates genes involved in the hypoxic response, which is essential for adapting to low oxygen levels. It also plays a significant role in cell proliferation, angiogenesis, and cellular autophagy [189,190]. The leucine-rich pentapeptide repeat (PPR) patterning protein (LRPPRC) acts as an autophagy suppressor, promoting metastasis and glycolysis by regulating autophagy and the ROS/HIF1α pathway in retinoblastoma

[189]. PTEN regulates HIF1α and mTOR *via* the PI3K/Akt pathway, reducing apoptosis and enhancing autophagy, which helps protect the kidney from acute injury [191]. HIF1α and histone deacetylase 4 (HDAC4) mediate interactions between p53 and RAS to inhibit ovarian cancer through both apoptosis and autophagy [192]. Li et al. [193] demonstrated that hypoxia reduced p62 and LC3II expression, triggering HIF/regulated in development and DNA damage responses 1 (REDD1)/mTORC1 signaling to control autophagy, which is crucial for erythroid differentiation. Research has shown that hypoxia damages mitochondria through HIF1α and regulates mitochondrial autophagy by controlling BNIP3 translocation to mitochondria [194].

Growing evidence suggests that PTMs of proteins can directly or indirectly regulate HIF-1α expression, influencing autophagosome formation and autophagy. Lysine methyltransferases G9a and GLP interact with HIF1α, catalyzing mono- and dimethylation at the lysine 674 (K647) site both *in vitro* and *in vivo*. Notably, methylation at K674 significantly reduced cell migration [195]. In multiple myeloma cells, G9a/GLP promotes autophagy-associated apoptosis by inactivating the

Table 2
Inhibitors of protein methylation and their effects in autophagy.

Methyltransferases	Non-histone protein targets	Inhibitors	Chemical structure	Impact to autophagy	Mechanisms of modulating autophagy	Cells	Clinical Trial Status	References
LSD1	p53 K370me1	2-PCPA		Activation	Accumulation of LC3II, formation of autophagosome and autolysosome, and SQSTM1/p62 degradation	U2OS cells	Early-phase clinical trials	[203,204,205]
		SP2509		Activation	Increased expression level of LC3-II protein	SH-SY5Y, SHEP Tet-21/N cells		
		ZY0511		Activation	Increaseed expression level of ATG9A gene	SU-DHL-4,SU-DHL-6 cells		
SMYD2	p53 K370me1	BIX-01294		Activation	Increased expression level of LC3B, ATG9A and ATG4A gene	HCT116 and U2OS cells	Preclinical studies in cancer and metabolic diseases	[140]
G9a	p53 K373me1	BI2536		Inhibition	Influences autophagy by regulating transcription factors involved in the autophagic pathway	HeLa α Kyoto cells	Early-phase clinical trials in solid tumors	[196,208,209]
		GSK461364		Inhibition	decreased expression level of LC3-I and LC3-II	MDA-MB-231 and T47D cells		
		UNC0638		Activation	Increased expression level of c-MYC gene	OPM2 cells		
PRMT1	c-Fos R287me1	P2		Activation	Modulates autophagy-related gene expression	MDA-MB-468 cells	Ongoing preclinical research for neurodegenerative diseases	[210]
PRMT5	ULK1 R170 me2	SBI-0206965		Inhibition	Reduction of autophagic vacuoles	A549 cells	Clinical trials in hematological cancers and solid tumors	[212]
EZH2	NF-κB	GSK343		Activation	Increased expression level of LC3B gene	HCT116 and DLD-1 cells	Ongoing clinical trials in cancer	[216,218]
		DZNep		Activation	Modulates autophagy-related gene expression	RKO and HCT116 cells		

mTOR/4E-binding protein 1 (4EBP1) pathway and decreasing c-MYC levels [196]. Arginine methyltransferase protein arginine methyltransferase 3 (PRMT3) facilitates colorectal tumorigenesis by modulating HIF-1α methylation at the arginine 282 (R282) site, locus and stabilizing its expression in colorectal cancer [197]. Additionally, lysine methyltransferase Set7 reduces HIF-1α expression by methylating it at the arginine 32 (R32) site [198].

5. Protein methylation as a therapeutic target and autophagy

Recent advancements in development of protein methyltransferase drugs have shown significant promise. These drugs selectively target specific methyltransferases, modulate autophagy, and have a crucial impact on inflammatory diseases, tumors, and cardiovascular and cerebrovascular conditions (Table 2). The intersection of autophagy and protein methyltransferase-targeted therapies is a key area of research, with significant potential for disease treatment [199,200]. Ongoing research aims to further our understanding of gene expression regulation mechanisms and provide novel strategies for disease management. Currently, Inhibitors are undergoing clinical trials for various cancers, with early-stage studies indicating potential efficacy in restoring autophagic flux in tumor cells [201]. The therapeutic potential of targeting protein methylation in autophagy-related diseases, such as cancer and neurodegeneration, is increasingly recognized. By modulating autophagic processes through the inhibition of methylation enzymes, these agents may offer novel strategies for restoring cellular homeostasis and improving disease outcomes.

LSD1, a histone demethylase, regulates autophagy through the demethylation of key autophagy-related proteins, such as ATG5, impacting the initiation of autophagy [202]. LSD1 demethylates the K151 site of ATG16L1, thereby activating autophagy [22]. It also demethylates p53 at K370 [141], and LSD1 knockdown increases ATG4B proteolytic activity, LC3II protein levels, and autophagy activation [142]. LSD1 inhibitors, such as 2-PCPA, GSK-LSD1, and SP2509, can promote LC3II accumulation, autophagosome and autolysosome formation, and activate autophagy [203,204]. Additionally, the LSD1 inhibitor ZY0511 promotes autophagy by upregulating ATG9A gene expression and inhibiting the proliferation of diffuse large B-cell lymphoma proliferation [205]. Lysine methyltransferase SMYD2 regulates tumor cell proliferation by monomethylating p53 at Lys370 (p53K370me1), thereby inhibiting its activity [206]. The small molecule BIX-01294 induces autophagy-related cell death, selectively activates p53 target genes, and inhibits SMYD2-mediated target gene activation. SMYD2 deficiency enhances p53 recruitment to p21 promoter, promoting autophagy-mediated cell death triggered by BIX-01294 [140]. The protein methyltransferase G9a can dimethylate p53 at Lys373, increasing the expression of polo-like kinase 1 (PLK1) expression and promoting colorectal cancer cell growth [207]. Inhibitors such as BI2536 and GSK461364 target PLK1, significantly reducing LC3II levels and inhibiting cellular autophagy [208,209]. G9a/GLP inhibitors, such as BIX01294 and UNC0638, can induce G1 phase arrest and apoptosis in multiple myeloma cells, reduce c-MYC expression, and enhance cellular autophagy [196].

PRMT1 methylates c-Fos at R287, protecting it from autophagic degradation. The autophagy inhibitor 3-MA enhances PRMT1-mediated c-Fos/AP-1 activity, resulting in increased c-Fos protein levels [106]. Brekker et al. [20] have constructed compound P2, which could selectively inhibited PRMT1 expression, induce LC3 expression in MDA468 cells, and promoted cellular autophagy [210]. PRMT5 catalyzes the symmetric dimethylation of the autophagy initiation protein ULK1 at arginine 170 (R170me2s), leading to the phosphorylation of ATG13 and Beclin 1, finally promoting autophagosome formation and autophagy. The ULK1 inhibitor SBI-0206965 mitigates its apoptosis [211]. Egan et al. [212] showed that SBI-0206965 could inhibit ULK 1-mediated phosphorylation events in cells, regulating autophagy and cell survival through the ULK1-Beclin1/VPS34 pathways.

EZH2, a methyltransferase, modulates autophagy *via* H3K27 methylation of transcription factors involved in autophagy regulation [213]. EZH2 is a key histone methyltransferase that promotes glioma stem cell-like self- renewal by methylating NF-κB [214]. Inhibitors targeting EZH2, such as GSK343, have shown promise in cancer treatment. GSK343 reduces glioblastoma cell viability and NF-κB protein expression, highlighting its potential as a therapeutic agent in glioblastoma [215]. Additionally, Hsieh et al. [216] showed that GSK343 could upregulate. The expression of the LC3B gene, thereby inducing autophagy and promoting cell death in colorectal cancer cells. In bone marrow-derived macrophages, the EZH2 inhibitor 3-Deazaneplanocin A (DZNep) promotes IKKα/β and IκB phosphorylation, leading to NF-κB nuclear translocation. This process enhances osteoclast formation in response to Receptor Activator of Nuclear Factor Kappa-β Ligand (RANKL) [217]. Furthermore, treatment of RKO and HCT116 cells with DZNep significantly increases LC3 II protein levels, inducing both autophagy and apoptosis [218].

6. The artificial intelligence in studying non-histone methylation and autophagy

Recent advancements in high-throughput technologies have significantly increased the amount of data generated in biology and biotechnology [219]. These data include complex datasets from DNA, RNA, proteins, and metabolites, requiring sophisticated analytical tools to uncover their roles in cellular processes [220]. Artificial intelligence (AI), particularly machine learning models like artificial neural networks, has emerged as a powerful tool to analyze omics data, including genomics and proteomics [221]. AI can handle large, noisy datasets and reveal complex patterns that traditional statistical methods might miss [222].

In the context of autophagy regulation, AI-driven approaches have been applied to predict protein interactions, model signaling pathways, and identify post-translational modifications (PTMs) with potential regulatory effects [223]. For example, AI methods have been used to prioritize potential non-histone protein methylation sites and predict their functional roles in autophagy-related signaling cascades [224]. Moreover, integrating AI with omics datasets could accelerate the discovery of novel targets for therapeutic intervention in diseases associated with autophagy dysregulation [225].

The integration of AI technologies into functional genomics and proteomics has enabled researchers to explore the dynamic roles of non-histone protein methylation in autophagy more comprehensively [226]. AI tools have been employed to predict interactions between methyltransferases and target proteins, evaluate the impact of these interactions on autophagy-related pathways, and identify novel regulatory mechanisms [227]. Such approaches not only enhance our understanding of PTMs but also pave the way for developing targeted therapies for autophagy-associated diseases.

7. Conclusion and future perspectives

So far, significant progress has been made in understanding how autophagy regulates cell growth, particularly in metabolism and tumor metastasis. The process of autophagy involves various types of protein PTMs of proteins, including initiation, autophagosome formation, substrate recognition, and degradation. Among them, lysine and arginine methylation modifications on non-histone proteins play specific roles at different stages of autophagy, affecting both non-histone and ATG proteins. These modifications influence the direct alteration of cytosolic proteins and the epigenetic regulation of target gene transcription. However, our current understanding has remained in its early stages, and several issues persist in the research on non-histone methylation and its role in regulating autophagy. For instance, the effects and mechanisms of non-histone methylation in autophagy are diverse and complex, often showing contradictory effects in promoting or inhibiting tumor

metastasis. Furthermore, the function of methylation modification has been varying with the specific site and the interacting enzyme. In addition, epigenetic changes in autophagy and cell signaling pathways are yet fully understood. Identifying new methylation sites is crucial for achieving a more comprehensive understanding of their functions.

Autophagy is a dynamic process, and targeting genes at different stages can lead to varying effects. It is important to explore how non-histone methylation affects autophagy different cells and diseases, as well as its role in tumor metastasis. Comprehensive and systematic research on non-histone methylation modifications could provide new insights into autophagy and uncover potential therapeutic targets for related diseases. Therefore, summarizing the current understanding of non-histone methylation in autophagy and identifying future research directions are essential.

Abbreviations

ATGs	Autophagy-related genes
AMPK	Adenosine monophosphate-activated protein kinase
BCL2	B-cell lymphoma 2
BNIP3	Bcl-2/adenovirus E1B 19-kDa-interacting protein 3
CARM1	Coactivator-associated arginine methyltransferase 1
E2F1	E2F transcription factor 1
HIF1α	Hypoxia-inducible factor 1-alpha
IL-1β	Interleukin-1 beta
KDM5C	Lysine-specific demethylase 5C
K370	Lysine 370
LATS2	Large tumor suppressor 2
LSD1	Lysine-specific demethylase 1
LC3	Microtubule-associated protein 1 light chain 3
mTOR	Mammalian target of rapamycin
MCT1	Monocarboxylate transporter 1
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B
R170	Arginine 170
PI3K	Phosphatidylinositol 3-kinase
PRMT5	Protein arginine methyltransferase 5
PRMT1	Protein arginine methyltransferase 1
PTEN	Phosphatase and tension homolog
PTMs	Post-translation modifications
ROS	Reactive oxygen species
STAT3	Signal transducer and activator of transcription 3
SETD7	SET domain lysine methyltransferase 7
ULK1	Unc-51 like kinase 1
VPS34	Vacuolar protein sorting 34
YAP	Yes-associated protein

CRediT authorship contribution statement

Yongfen Bao: Formal analysis. **Yaoyao Ma:** Writing – original draft. **Wentao Huang:** Writing – original draft. **Yujie Bai:** Investigation. **Siying Gao:** Software. **Luyao Xiu:** Investigation. **Yuyang Xie:** Writing – original draft. **Xinrong Wan:** Writing – original draft. **Shigang Shan:** Writing – review & editing. **Chao Chen:** Writing – review & editing. **Lihua Qu:** Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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Data availability

No data was used for the research described in the article.

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