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REVIEW ARTICLE

Epigenetic regulation of autophagy by histone-modifying enzymes under nutrient stress

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Autophagy is an evolutionarily conserved catabolic process that is induced in response to various stress factors in order to protect cells and maintain cellular homeostasis by degrading redundant components and dysfunctional organelles. Dysregulation of autophagy has been implicated in several conditions such as cancer, neurodegenerative diseases, and metabolic disorders. Although autophagy has been commonly considered as a cytoplasmic process, accumulating evidence has revealed that epigenetic regulation within the nucleus is also important for regulation of autophagy. In particular, when energy homeostasis is disrupted, for instance due to nutrient deprivation, cells increase autophagic activity at the transcriptional level, thereby also increasing the extent of overall autophagic flux. The transcription of genes associated with autophagy is strictly regulated by epigenetic factors through a network of histone-modifying enzymes along with histone modifications. A better understanding of the complex regulatory mechanisms of autophagy could reveal potential new therapeutic targets for autophagy-related diseases. In this review, we discuss the epigenetic regulation of autophagy in response to nutrient stress, focusing on histone-modifying enzymes and histone modifications.

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FACTS

- Transcriptional and epigenetic regulation of autophagy are essential for cellular homeostasis and survival during nutrient deprivation.
- Histone-modifying enzymes cooperatively regulate the transcription and histone modifications of autophagy genes.
- Understanding the complexity of the epigenetic regulation of autophagy provides important and useful clues for the treatment of numerous diseases.

OPEN QUESTIONS

- Are there differences in the regulatory mechanism of autophagy during nutrient deprivation?
- What is the role of non-histone substrates of histone-modifying enzymes in autophagy?
- How does the combination of histone modifications coordinately control autophagy?

INTRODUCTION

Macroautophagy (autophagy) is an essential self-digestion process in which cytoplasmic components are degraded by lysosomes [1, 2]. Autophagy is also constitutively active within cells, albeit at low levels, helping to maintain cellular homeostasis by eliminating unnecessary components and dysfunctional organelles. In addition, when cellular homeostasis is disturbed, for example due to lack of nutrients, cells can potently stimulate autophagic flux to obtain nutrients through the breakdown of non-essential components [3, 4]. On the other hand, excessive autophagy is associated with autophagic cell death [5, 6]. Therefore, autophagy must be tightly regulated; abnormal levels can disrupt normal cellular integrity and promote cell death. Dysregulated autophagy is closely associated with numerous diseases, including cancer, neurodegenerative diseases, and metabolic disorders [2, 7, 8].

The previous understanding of autophagy as a cytoplasmic event is supported by the observation that cells without a nucleus maintain the process of autophagy [9, 10]. However, emerging evidence suggests that nuclear components play a critical role in regulating autophagy, as recent studies have revealed a significant role of epigenetic and transcriptional factors in the regulation of autophagy [11, 12]. The continuous supply of proteins required for autophagy is carefully regulated through a combination of transcription factors and histone-modifying enzymes [13–15]. The interplay between these factors needs to be tightly controlled for precise regulation of autophagy, and understanding how these factors interact is crucial for gaining insight into the process of autophagy.

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In this review, we focused on histone-modifying enzymes and the corresponding histone modifications involved in the regulation of autophagy under nutrient deprivation.

SIGNALS ASSOCIATED WITH NUCLEAR REGULATION OF AUTOPHAGY

One of the most important questions in the field of autophagy is how cells sense stress and accordingly increase autophagic flux. Two nutrient-responsive kinases, mammalian target of rapamycin complex 1 (mTORC1) and AMP-activated protein kinase (AMPK), are responsible for sensing cellular energy and nutrient levels and regulating autophagy [16–18]. With sufficient nutrient availability, mTORC1 kinase integrates signals from nutrients and growth factors and acts as a junction for cellular signals to control growth and protein synthesis [19]. Nutrient deprivation leads to the inhibition of mTORC1, which subsequently leads to the induction of autophagy through altering the phosphorylation of autophagy-regulating proteins. In addition to cytoplasmic proteins, such as ATG13, ATG14, and ULK1, autophagy is also regulated by various mTORC1-associated nuclear proteins, such as transcription factors and histone-modifying enzymes.

AMPK is a conserved cellular energy sensor that monitoring the relative amounts of the AMP and ATP, as well as ADP and ATP levels [20, 21]. AMPK is activated when cellular AMP or ADP levels increase in response to energy stress, such as nutrient deprivation. AMPK positively regulates autophagy by suppressing mTORC1 activity and by regulating the activity autophagy associated proteins through its kinase activity. In addition, similarly to mTOR, AMPK is involved in the transcription of autophagy genes.

These two energy-sensing kinases affect various transcription factors and histone-modifying enzymes, leading to the transcriptional regulation of autophagy genes in the nucleus. The microphthalmia/transcription factor E (MiT/TFE) family of transcription factors, including transcription factor EB (TFEB), TFE3, and MITF, are considered the main regulators of autophagy and lysosomal genes. In nutrient-rich conditions, activated mTORC1 directly phosphorylates MiT/TFE family members, including TFEB, and the phosphorylated TFEB is retained in the cytosol by binding to the sequestering protein 14-3-3. However, during nutrient deprivation, inactivated mTORC1 does not phosphorylates the MiT/TFE family transcription factors, which subsequently translocate to the nucleus and induce autophagy [22, 23].

Forkhead box class O3 (FOXO3) is also regulated by nuclear/cytoplasmic shuttling. Under nutrient-rich conditions, FOXO3 is phosphorylated by AKT and sequestered in the cytoplasm. Similarly to MiT/TFE, during nutrient starvation, the dephosphorylated FOXO3 translocates to the nucleus and activates autophagy associated genes [24]. It has been reported that intracellular localization of other forkhead family transcription factors, including FOXK1 and FOXK2, is also regulated by mTORC1 [25]. The transcription factors FOXK1 and FOXK2 act as suppressors of autophagy genes and enter the nucleus when mTOR is activated.

In addition, various transcription factors can regulate the expression of autophagy-related genes. They bind to their specific responsive elements within the chromatin structure of autophagy genes and alter the level of transcription by changing the chromatin structure through various mechanisms, including histone modifications and chromatin remodeling.

AUTOPHAGY REGULATION BY HISTONE MODIFICATIONS AND HISTONE-MODIFYING ENZYMES

Histones are a family of basic proteins closely associated with chromatin architecture. Nucleosomes, the basic units of chromatin, are formed by the wrapping of DNA around histone octamers that are composed of two sets of histone proteins including H2A, H2B, H3, and H4 [26, 27].

Histone proteins undergo various post-translational modifications (PTM), such as phosphorylation, acetylation, methylation, ubiquitination, and SUMOylation, each of which is carried out by specific histone-modifying enzymes [28, 29]. Histone modifications are key epigenetic regulatory mechanisms that regulate gene transcription and chromatin structure. Certain modifications have been reported to alter chromatin accessibility by modulating the affinity between the histones and DNA. Depending on the accessibility of chromatin, proteins, such as transcription factors and transcriptional coregulators, can bind to DNA and consequently affect gene expression. Alternatively, proteins called epigenetic readers can directly recognize histone modifications, thereby modulating gene expression [30].

Compelling evidence has revealed that histone modifications and histone-modifying enzymes contribute to the regulation of autophagy. Through histone modifications and processes carried out by histone-modifying enzymes, the expression of genes associated with autophagic and lysosomal activity can be regulated to maintain a stable autophagic flux, and disruption of this process can lead to autophagy-related diseases. Therefore, understanding these autophagy programs in various diseases is crucial for developing effective therapeutic strategies for autophagy-related diseases.

Histone acetylation

Histone acetylation plays a central role in gene transcription by altering chromatin architecture. Generally, acetylation opens the closed chromatin structure by neutralizing the positive charge of the histones, thereby weakening the interactions between histone tails and DNA. Chromatin relaxation by histone acetylation allows transcription factors and cofactors to be more easily access the DNA, leading to the transcriptional activation of genes [31]. Histones acetylation is reversibly modulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), which add and remove acetyl groups from histones, respectively [32–34]. The epigenetic regulation of autophagy genes by histone acetylation and factors involved in this process are discussed in the following sections.

HDAC1/2-SIN3A-FOXK1/2. In nutrient-rich conditions, the Sin3A complex containing HDAC1/2 suppresses the expression of autophagy-associated genes by removing histone H4 acetylation [25]. The Sin3A-HDAC1/2 complex binds to chromatin through Forkhead box class K (FOXK) 1 and FOXK2, and acts as a transcriptional repressor of autophagy genes. Interestingly, FOXO3 and FOXK1/2, which are known as activators and repressors of autophagy, respectively, regulate gene expression by competing for the same shared response element. With sufficient nutrient availability, FOXK1/2 is phosphorylated by mTOR and then translocated to the nucleus, whereas phosphorylation of FOXO3 by AKT leads to cytoplasmic retention of FOXO3 [35]. Predominant FOXK1/2 recruits Sin3A-HDAC1/2 and deacetylates histone H4, thereby preventing the expression of autophagy-related genes (Fig. 1A). However, because nutrient starvation inhibits mTOR kinase activity, dephosphorylated FOXK1/2 is exported to the cytoplasm, followed by the removal of FOXK1/2-Sin3A-HDAC1/2 complexes from chromatin. In addition, AKT inhibition permits the nuclear localization of FOXO3, leading to the transcriptional activation of autophagy genes. Several cancer-derived FOXK mutations that are associated with impaired nuclear translocation have been reported to induce drug resistance by enhancing DNA damage-induced autophagy [36].

HDAC2-MYC. The HDAC2-MYC complex represses autophagy under nutrient-rich conditions. The CLEAR (coordinated lysosomal expression and regulation) motif is the most common motif in the

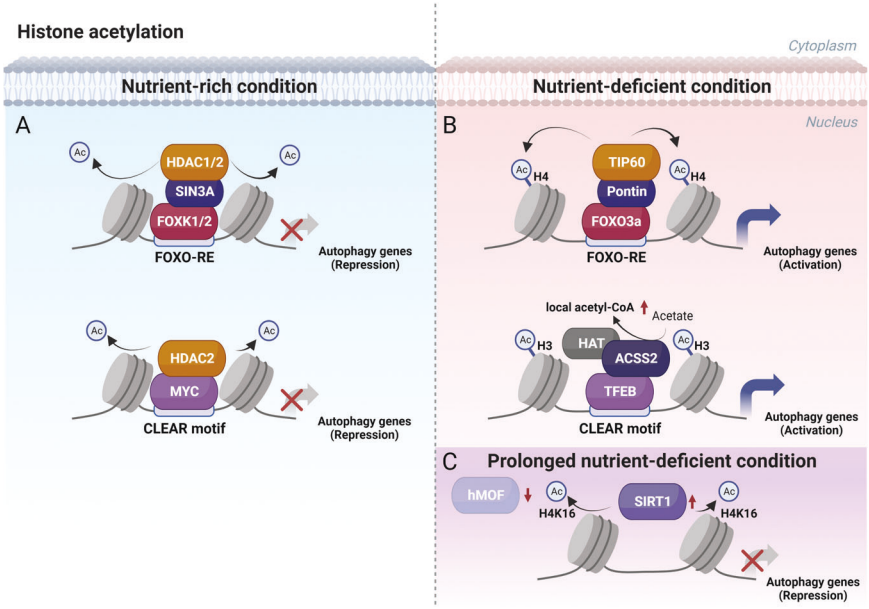

Fig. 1 Autophagy gene regulation via histone acetylation. A In nutrient-rich conditions, FOXK1/2 recruits Sin3A-HDAC1/2 complex to FOXO-response elements of autophagy genes for deacetylating histone H4. Additionally, MYC inhibits histone acetylation by recruiting HDAC2 to the CLEAR motif of autophagy genes. **B** In nutrient-deficient conditions, predominant FOXO3 repels FOXK1/2 and recruits Pontin-TIP60 complex to increase histone H4 acetylation. In a similar way, ACSS2 binds to CLEAR motif via TFEB and locally produces acetyl-CoA for promoting histone H3 acetylation. **C** During prolonged nutrient deprivation, degradation of hMOF and induction of SIRT1 act as a pair of molecular switches in the deacetylation of histone H4K16, thereby preventing excessive autophagy.

promoters of autophagy and lysosomal genes. The MiT/TFE family of transcription factors, which includes TFEB, TFE3, and MITF, directly bind to the CLEAR motif to promote gene transcription upon nutrient starvation [22, 37]. Recently, it was reported that c-MYC, the master regulator of cellular metabolism and proliferation, can recognize the same CLEAR motif bound by the MiT/TFE family [38]. HDAC2 is co-recruited to the CLEAR motif of autophagy genes by binding to c-MYC and inhibits gene transcription by reducing histone acetylation levels (Fig. 1A). In cancer, c-MYC and HDAC2 are found in the nucleus in certain groups of neoplastic adenocarcinoma cells, while TFE3 is typically seen in the cytoplasm in the same cells [38].

TIP60-Pontin/RUVBL1-FOXO3. Acetyl-coenzyme A (acetyl-CoA) is a crucial metabolite in cellular processes, and is the only donor of acetyl groups for histone acetylation. Nutrient deprivation that limits acetyl-CoA production, both from glucose and acetate intake, reduces global histone acetylation, and thus represses gene transcription. However, it has been reported that histone acetylation increases in certain genes important for survival, such as autophagy. Acetylation rearrangement is mediated by histone acetyltransferase TIP60 (also known as KAT5), which induces the expression of genes associated with autophagic and lysosomal activity by increasing histone H4 acetylation. During nutrient deprivation, Pontin (also known as RUVBL1), known as the binding component of TIP60, is methylated by arginine methyltransferase CARM1 (also known as PRMT4), which leads to the binding of TIP60 to the transcription factor FOXO3 [39]. Inhibition of TIP60 or Pontin methylation inhibits histone H4 acetylation near the FOXO3 binding regions, leading to the repression of autophagy and lysosome genes in response to nutrient starvation (Fig. 1B).

ACSS2. Histone acetylation can be altered by controlling the local concentration of acetyl-CoA. Acetyl-CoA synthetase 2 (ACSS2), a member of the acetyl-CoA synthetase family, catalyses the conversion of free acetate to acetyl-CoA. During glucose starvation, AMPK-mediated ACSS2 phosphorylation at S659 induces the nuclear translocation of ACSS2 by binding to importin α5 [40]. In the nucleus, ACSS2 binds to the promoter regions of autophagy-related and lysosomal genes via TFEB. Nuclear ACSS2 then locally produces acetyl-CoA using peripheral acetate, which elevates the level of histone H3 acetylation near the promoters of TFEB target genes, thereby activating their transcription (Fig. 1B). The regulation of genes associated with autophagy and lysosomal activity through ACSS2 is important for brain tumorigenesis and tumor survival [40], indicating that inhibition of the nuclear function of ACSS2 may be an efficient approach for the treatment of human cancers.

hMOF and SIRT1. H4K16 acetylation is a key determinant of survival versus cell death upon autophagy induction, which asserts its effects through regulating the transcription of autophagy genes. During long-term response to autophagy, degradation of human males absent on the first (hMOF) acetyltransferase (also known as KAT8) and activation of SIRT1 deacetylase act as a pair of molecular switches to turn off the acetylation of histone H4K16, thereby regulating autophagy at the transcriptional level (Fig. 1C). This regulation of histone H4K16 acetylation by hMOF and SIRT1 prevents autophagic cell death by inhibiting excessive autophagic flux [41]. Antagonizing H4K16 deacetylation upon autophagy induction using a SIRT1 specific inhibitor or hMOF overexpression has been reported to result in cell death.

Histone methylation

Histone methylation is a post-translational modification of histones, by which a variable number of methyl groups are transferred to the amino acids of histone proteins. Depending on which amino acids are methylated and the number of methyl groups attached, histone methylation is involved in positive and negative regulation of transcription [42, 43]. Methylation levels are reversibly modulated by the families of histone methyltransferases (HMTs) and histone demethylases (HDMs), which add and remove methyl groups, respectively. Histone methylation mainly occurs on arginine and lysine residues by HMTs that use S-adenosyl-l-methionine (SAM) as the methyl group donor. Arginine

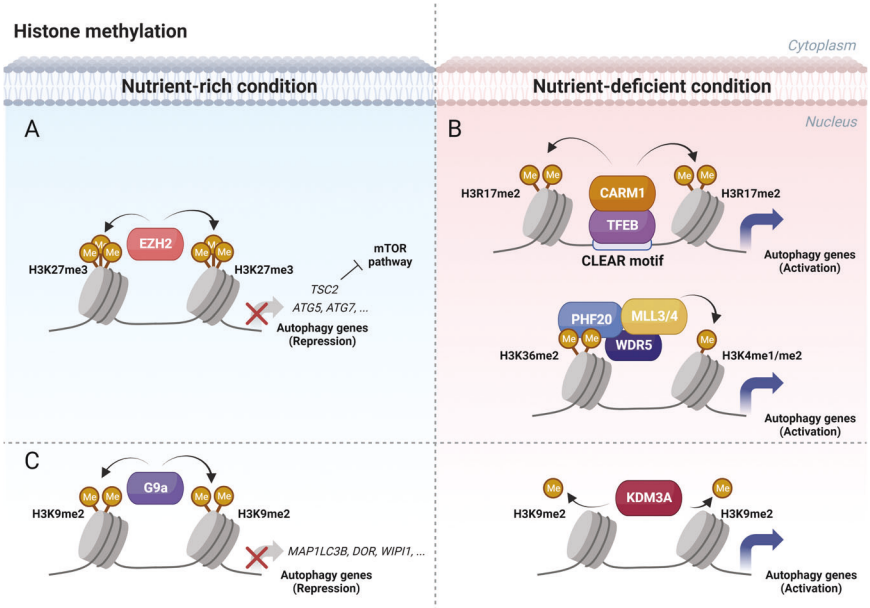

Fig. 2 Regulation of autophagy-associated genes via histone methylation. A In nutrient-rich conditions, EZH2 inhibits autophagy via histone H3K27me3 through two pathways: activation of mTOR signaling pathway through downregulation of TSC2, and inhibition of autophagosome formation genes such as ATG5 and ATG7. **B** In nutrient-deficient conditions, TFEB recruits CARM1 to the CLEAR motif on the promoter of autophagy genes, causing an increase in histone H3R17me2. Increased level of histone H3R17me2 is associated with upregulation of autophagy genes. Methyltransferase MLL3/4 is recruited to the histone H3K36me2 via PHF20, and increased levels of the histone H3K4me1/2 are important for enhancer activation. **C** In nutrient-rich conditions, G9a binds to the promoter of several autophagy genes and represses their transcription via histone H3K9me2. However, in nutrient-deficient condition, KDM3A activates transcription of autophagy genes by removing histone H3K9me2.

methylation results in the formation of three main types of methylarginine: mono-methylarginine (MMA), symmetric di-methylarginine (SDMA), and asymmetric di-methylarginine (ADMA), depending on the number and structure of the methyl groups [44]. Similarly, there are also three types of methylated lysines: mono-, di-, and tri-methyl lysine [45].

EZH2. Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of polycomb repressive complex 2 (PRC2) that catalyzes histone H3K27 tri-methylation and regulates transcriptional repression [46]. It has been reported that EZH2 regulates autophagy via the mTOR signaling pathway [47]. EZH2 is specifically recruited to the promoters of negative regulators of the mTOR pathway, such as tuberous sclerosis 2 (TSC2), via the metastasis-associated 1 family member 2 (MTA2), a component of nucleosome remodeling, and the histone deacetylase (NURD) complex (Fig. 2A). The downregulation of TSC2 by EZH2 leads to mTOR activation, which in turn inhibits autophagy. Additionally, EZH2 directly regulates autophagy by inhibiting autophagosome formation [48, 49], as EZH2 represses ATG5 and ATG7, which are essential for autophagosome formation (Fig. 2A).

CARM1-TFEB. CARM1, which induces histone H3R17 dimethylation, is crucial for the transcriptional activation of autophagy genes [50]. The CARM1 protein levels are strictly regulated by a ubiquitin-dependent degradation system. The level of nuclear CARM1 is maintained low by the S-phase kinase-associated protein 2 (SKP2)-containing E3 ubiquitin ligase in nutrient-rich conditions. Glucose deprivation leads to the accumulation of AMPKα2 in the nucleus and subsequently to the transcriptional repression of SKP2. Reduction in SKP2 levels has been reported to lead to stabilization of the CARM1 protein along with the induction of H3R17 di-methylation. Genome-wide analysis showed that CARM1 acts as a transcriptional co-activator of genes associated with autophagic and lysosomal activity via TFEB (Fig. 2B). Ellagic acid selectively inhibits histone H3R17 dimethylation and subsequently prevents autophagy induction during glucose deprivation. Inhibitors of H3R17 di-methylation, including ellagic acid, are potential therapeutic agents for autophagy-related diseases.

MLL3/4-PHF20. Histone methyltransferase mixed-lineage leukemia protein 3 (MLL3, also known as KMT2C) and MLL4 (also known as KMT2D) are histone-modifying enzymes that methylate histone H3K4 at enhancer regions [51, 52]. MLL3 and MLL4 activate the enhancer by inducing H3K4 monomethylation. Recently, that plant homeodomain (PHD) finger protein 20 (PHF20), a member of the PHF family containing two conserved tudor domains, was reported to be crucial for recruiting the MLL3/4 complex to autophagy genes for transcriptional activation [53]. Upon glucose starvation, PHF20 recognizes H3K36me2 via its tudor domain. The MLL3/4 complex is co-recruited to the H3K36me2 regions recognized by PHF20, resulting in increased histone H3K4 methylation and activation of autophagy genes (Fig. 2B).

G9a and KDM3A. Histone H3K9 methylation is a critical marker of transcriptional silencing and heterochromatin formation [54]. H3K9 di-methylation, mediated by the histone methyltransferase G9a (also known as EHMT2 and KMT1C) and the G9a-like protein (GLP, also known as EHMT1 and KMT1D), recruits transcriptional repressors and inhibits gene transcription. G9a binds to the promoters of several autophagy genes, including *MAP1LC3B, DOR*, and *WIPI1* in nutrient-rich conditions (Fig. 2C). However, during nutrient deprivation, G9a dissociates from the promoters of its target gene, resulting in subsequent demethylation of histone H3K9 [55]. In addition, demethylated histone H3K9 causes increased histone H3K9 acetylation, followed by RNA polymerase II binding, leading to increased transcription of autophagy-related genes.

In contrast, histone H3K9me2 demethylase KDM3A (also known as JHDM2A) is important in activating autophagy [56]. KDM3A expression increases in response to nutrient deprivation and it

helps the transcriptional activation of autophagy genes through histone H3K9 demethylation (Fig. 2C).

Other histone modifications

Ring Finger Protein 20 (RNF20), ubiquitin-specific protease 44 (USP44) and H2B mono-ubiquitination. H2B mono-ubiquitination functions as an important histone marker for autophagy regulation. In mammals, H2B mono-ubiquitination is mainly catalyzed by the ubiquitin-conjugating enzyme E2 A (UBE2A, also known as RAD6) and the RNF20 complex E3 ligase at lysine 120 of H2B, while the deubiquitinating enzyme USP44 cleaves ubiquitin from histones [57–59]. During nutrient deprivation, DNA methyltransferase (DNMT) 3A and DNMT3B are degraded via the ubiquitin-proteasome pathway, resulting in the activation of USP44 expression [60]. Induction of USP44 leads to the loss of histone H2B mono-ubiquitination at lysine 120, followed by transcriptional

Table 1. List of chromatin-modifying enzymes involved in autophagy regulation.

Histone modification	Chromatin-modifying enzyme	Histone residue	Transcription factor	Reference
Acetylation	TIP60	H4	FOXO3	Yu et al. [39]
	hMOF	H4K16		Füllgrabe et al. [41]
	SIRT1	H4K16		Füllgrabe et al. [41]
	HDAC1	H4	FOXK1/2	Bowman et al. [25]
	HDAC2	H3K14, H4	MYC, FOXK1/2	Annunziata et al. [38]; Bowman et al. [25]
	ACSS2	H3	TFEB	Li et al. [40]
Methylation	CARM1	H3R17	TFEB	Shin et al. [50]
	MLL3/4	H3K4		Park et al. [53]
	EZH2	H3K27		Wei et al. [47]; Hsieh et al. [49]
	G9a	H3K9		Narvajas et al. [55]
	KDM3A	H3K9		Kim et al. [56]
Ubiquitination	RNF20	H2BK120		Chen et al. [60]
	USP44	H2BK120		Chen et al. [60]; Zheng et al. [61]

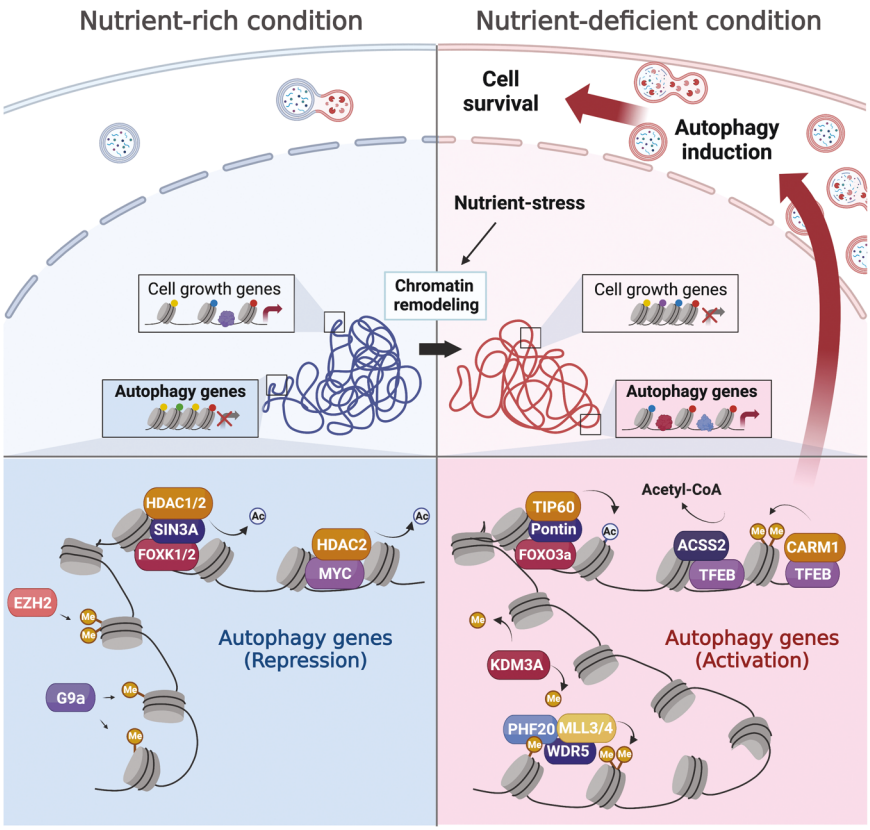

Fig. 3 Chromatin remodeling in nutrient-deficient condition promotes cell survival by inducing autophagy. During nutrient deprivation, histone-modifying enzymes and histone modifications alter the overall chromatin structure as well as the entire transcriptome to promote cell survival. For example, the expression of genes related to cell growth is suppressed, whereas the expression of genes required for survival, such as those associated with autophagy, is elevated. Changes in overall chromatin structure are precisely regulated by histone-modifying enzymes and histone modifications.

activation of autophagy genes [60]. It has been reported that radioresistance-associated long intergenic noncoding RNA 1 (linc-RA1) inhibits autophagy and promotes radioresistance by inhibiting the interaction between H2B and USP44 [61].

AMPK and H2B phosphorylation. AMPK is a sensor that helps to maintain energy homeostasis through phosphorylation of various substrates [20]. Histones can serve as direct substrates for AMPK under nutrient stress, and during glucose deprivation, increased AMPKα2 in the nucleus directly binds to histone H2B and phosphorylates histone H2B at serine 36 [62], which is essential for transcriptional activity and survival in low-glucose conditions.

CONCLUSION AND PROSPECTIVE

In this review, we summarized the role of each histone-modifying enzyme in autophagy regulation, along with the corresponding histone markers (Table 1). When the supply of nutrients is insufficient, chromatin remodeling enzymes suppress unnecessary gene transcription while activating the expression of genes necessary for survival, including those associated with autophagy (Fig. 3). Histone-modifying enzymes, along with the corresponding histone modifications, cooperatively regulate the transcription of autophagy-associated genes.

In addition to histone-modifying enzymes and histone modifications outlined in this review, various epigenetic regulations have been reported in response to nutrient deprivation. For instance, increases in histone modifications such as H3K4me3, H3K27Ac, and H3K56Ac have been reported in the promoters of autophagy genes during nutrient deprivation [63]. Further researches of which histone-modifying enzymes are involved in these histone modifications would helpful to understand the epigenetic regulation of autophagy.

Epigenetic regulation of autophagy has been implicated in various diseases. In cancer, autophagy is known to play a dual role, either inhibiting or promoting tumor growth. Specifically, in brain tumors, increased intranuclear ACSS2 expression promotes tumorigenesis, and inhibition of nuclear translocation of ACSS2 reduces autophagy and lysosomal biogenesis, thereby reducing tumor cell survival [40]. On the other hand, MYC-HDAC2 has been reported to help maintain the stemness of cancer cells and promote their growth. Moreover, in sialidosis, which is one of the lysosomal storage disorders (LSD) caused by a deficiency of an enzyme called neuraminidase 1 (NEU1), it has been reported that HDAC inhibition can restore the expression of NEU1 [38]. As autophagy is closely related to numerous pathologies, understanding the epigenetic regulation of autophagy will provide important and useful insight for developing effective strategies for the treatment of autophagy-related diseases.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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