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REVIEW

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Histone demethylases in autophagy and inflammation

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Abstract

Autophagy dysfunction is associated with changes in autophagy-related genes. Various factors are connected to autophagy, and the mechanism regulating autophagy is highly complicated. Epigenetic changes, such as aberrant expression of histone demethylase, are actively associated not only with oncogenesis but also with inflammatory responses. Among post-translational modifications, histone lysine methylation holds significant importance. There are over 30 members of histone lysine demethylases (KDMs), which act as epigenetic regulators in physiological processes and diseases. Importantly, KDMs are abnormally expressed in the regulation of cellular autophagy and inflammation, representing a crucial mechanism affecting inflammation-related diseases. This article reviewed the function of KDMs proteins in autophagy and inflammation. Specifically, It focused on the specific regulatory mechanisms underlying the activation or inhibition of autophagy, as well as their abnormal expression in inflammatory responses. By analyzing each KDM in epigenetic modification, this review provides a reliable theoretical basis for clinical decision marking regarding autophagy abnormalities and inflammatory diseases.

Keywords Histone demethylases, Autophagy, Inflammation

Introduction

Autophagy is a lysosomal degradation process in eukaryotic cells that plays a critical role in the renewal of cell components and the maintenance of cell homeostasis during states of nutrient or energy deficiency [1–3]. It can be adjusted by various autophagy-related genes and signaling pathways, involving the activation of innate and adaptive immunity, thereby promoting direct clearance of pathogens, and the processing and the presentation antigens [4–6]. Abnormal autophagy may lead to widespread inflammation and overactivation of immune responses [7–10]. There are several types of autophagy (Fig. 1), which can be divided into three classes based on their mechanisms: macroautophagy, microautophagy, and Chaperone-mediated autophagy (CMA) [11–13]. Among these, autophagy is the most widely studied process, involving de novo synthesis of a vesicle-like autophagosome using cellular membrane structure, followed by the translocation and fusion of the autophagosome with

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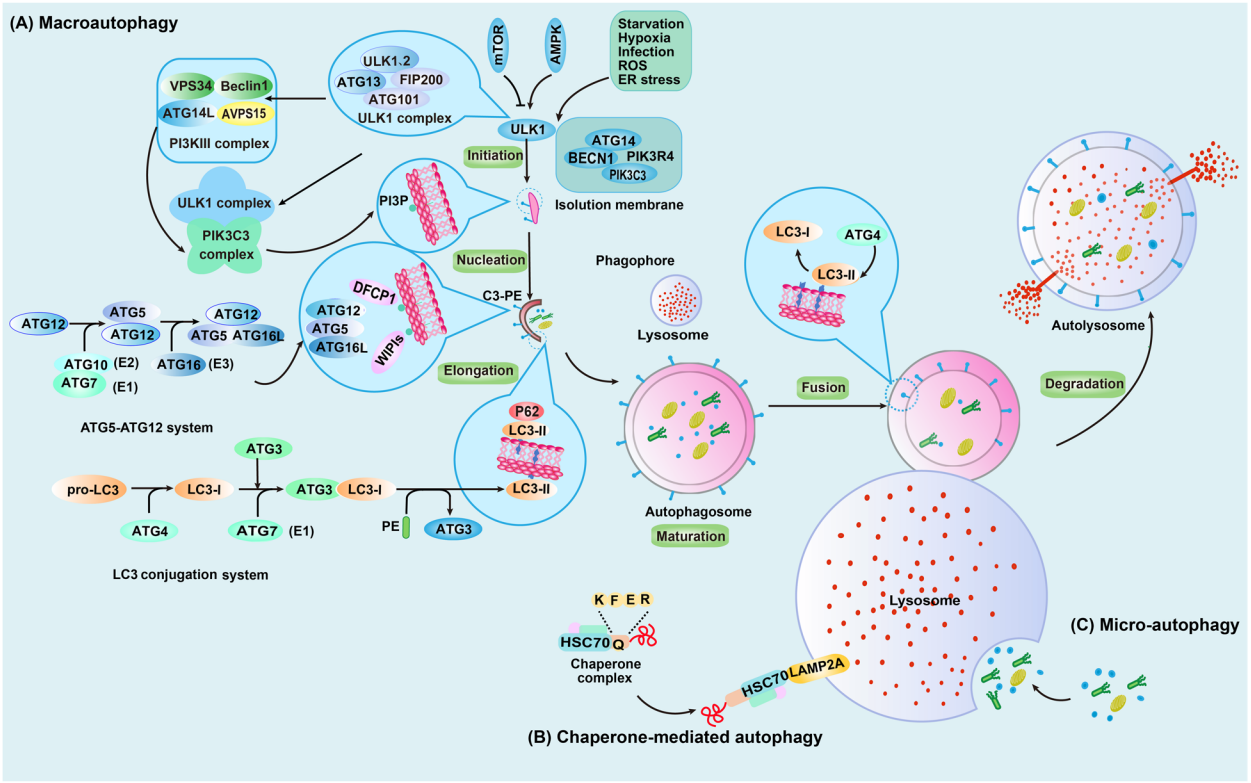

Fig. 1 Molecular mechanism of autophagy. **A** Macroautophagy: The process of autophagy includes the initiation of autophagy, nucleation of phagophore, membrane elongation, autophagosome maturation, autophagosome-lysosome fusion, and the final degradation and recycling of cellular content. **B** Chaperone-mediated autophagy (CMA): HSC70 specifically mediates protein transport into lysosomes through the LAMP2A receptor. **C** Microautophagy: It involves direct phagocytosis of aggregates by lysosomes

lysosomes to degrade the contents [14]. Autophagy is closely related to histone demethylase and inflammation [15–18].

The process of autophagy can be broken down into four main steps: initiation, extension and maturation of the phagophore, fusion of the autophagosome and lysosome, as well as degradation of the substrate [19–21]. Autophagy contains two types non-selective autophagy and selective autophagy each with different degradation substrates (Fig. 2). Selective autophagy includes processes such as mitophagy, pexophagy, endoplasmic reticulum-phagy, and ribophagy and so on [22–24]. Autophagy-related genes (ATGs) participate in the formation of autophagy and are regulated by multiple signaling pathways [25, 26]. The initiation of autophagy requires the interaction of Unc-51 like kinase 1 (ULK1), ATG13, ATG101, and FIP2000, forming the ULK1 complex that induces phagophore formation. This process is mainly regulated by cellular nutrition and energy status [27–29]. Amino acids and oxygen can activate mechanistic target of rapamycin complex 1 (mTORC1), leading to the phosphorylation of ATG13, thereby inhibiting the synthesis of the ULK1 complex and preventing the initiation of autophagy [11, 30]. Under conditions of low glucose ATP levels, the AMPK-PKA pathway can become activated, promoting autophagy through the phosphorylation of ULK1 [31]. Subsequently, the class III phosphatidylinositol 3-kinase complex is formed and catalyzes the production of phosphatidylinositol-3-phosphate on the membranes [32, 33]. Simultaneously, WD-repeat protein interacting with phosphoInositides (WIPI) and ATG2 facilitate in the recruitment of ATG9A vesicles, jointly regulating the extension of phagocytic membranes [34]. Additionally, two crucial ubiquitin-like conjugation systems, ATG12-ATG4-ATG16L and light chain 3 (LC3)-II, are involved in the extension and maturation of autophagosomes [35, 36]. Firstly, the E1-like protein ATG7 and the E2-like protein ATG10 co-catalyze the assembly of the ATG12-ATG4-ATG16L1 complex, which functions as an E3-like enzyme. Along with ATG7, ATG3, and the cysteine protease ATG4B, it catalyzes the aggregation of LC3 to phosphatidylethanolamine, forming LC3-II thereby promoting the closure and maturation of autophagosomes [37–40]. Subsequently, the autophagosomes are transported to the lysosomes, where they form autolysosomes and are degraded by

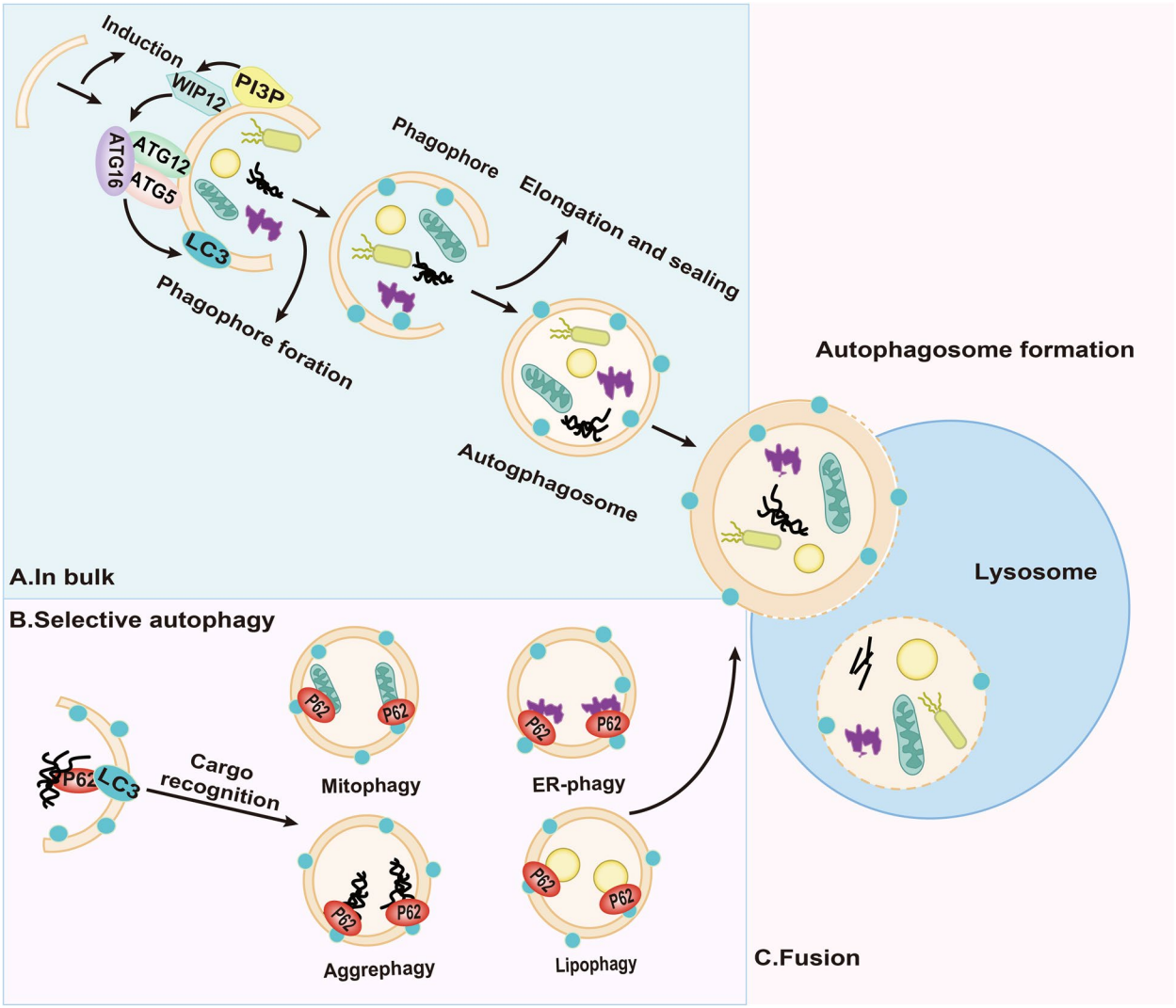

Fig. 2 Schematic of the autophagy pathway. **A** In Bulk: Cytoplasmic cargo is first trapped in double-membrane vesicles (autophagosomes), whose membranes are mediated by the autophagy-related protein LC3 with lipid phosphatidylethanolamine, along with other autophagy-related proteins (e.g., ATG5, ATG16, and ATG12). **B** Selective autophagy: Particular substrates, such as mitochondria, endoplasmic reticulum, aggregates, and lipid droplets, which are ubiquitinated, bind to the autophagy receptor, such as P62, which interact with LC3 on the phagosome membrane to transport the substrates into the vesicles. These specific substrates include mitochondria, endoplasmic reticulum, aggregates and lipid droplets. **C** Fusion of autophagosomes- lysosomes: autophagosomes fuse forms lysosomes, forming autolysosomes responsible for degrading the engulfed molecules

acidic hydrolases. The resulting materials are released into cytoplasm for reuse [41, 42]. This process is monitored by various proteins [43]. For example, microtubules are involved in the movement of autophagosomes, and inhibiting their polymerization or depolymerization will hinder autophagy [44–46]. Another example includes the soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) complex, which facilitates membrane fusion between autophagosomes and lysosomes [47]. Additionally, LC3-II can mediate the processes of selective autophagy [48–50]. For instance, during the maturation of red blood cells, BNIP3L on the mitochondrial outer membrane can interact with LC3-II to promote mitochondrial autophagy [51].

Chromatin is composed of DNA and surrounded by nucleosomes, forming a dynamic structure that continually changes depending on the external environment [52–54]. Each nucleosome consists of an octamer of four histones (H2A, H2B, H3, and H4) (Fig. 3), which affects chromatin compression and subsequently regulates transcription levels of different genes [55–58]. Histone modifications on specific residues include acetylation, methylation, phosphorylation, citrullination, ubiquitination, ADP-ribosylation, deamidation, formylation,

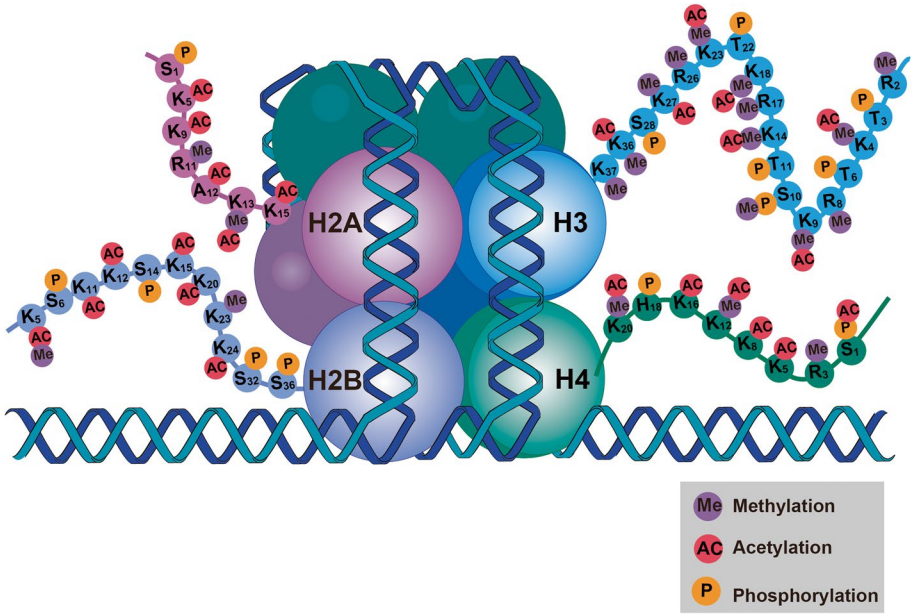

Fig. 3 Histone post-translational modifications (PTMs). Histones can undergo various PTMs at different amino acid residues. PTMs influences the interactions of histone with DNA and other proteins, thereby either promoting or repressing gene transcription. Common PTMs include methylation (purple), acetylation (red), phosphorylation (orange), etc

O-linked N-acetylglucosamine glycosylation (O-GlcNAC), propionylation, butylation, crotonylation, and proline isomerization. These epigenetic modifications play a critical role in regulating gene expression during disease development [59–63]. Methylation of lysine residues on histones is considered a significant class of post-translational modifications. The methylation of lysine is catalyed by histone lysine methyltransferases (KMTs) [64–66], resulting in monomethylation, dimethylation, or trimethylation (Kme1, Kme2, and Kme3). These enzymes recognize specific methylation marks on histones to mediate their effects. The removal of lysine methylation is carried out by lysine demethylases (KDMs) [67–69]. Based on sequence homology and structural similarity, KDMs can be further classified into eight subfamilies (KDM1-8). According to the catalytic mechanism, KDM1 is categorized as a flavin adenine dinucleotide (FAD)-dependent amine oxidase (LSD family), whereas KDM2-8 (Fig. 4) are demethylases containing the JumonjiC (JmjC) domain (JMJD family) [68, 70, 71].

Both types of KDMs catalyze N-methyl-lysine demethylation through oxidation mechanisms but in different ways [72, 73]. LSDs use FADs and electron transfer. Since the electron pairs required for demethylation are only present on monomethylated and dimethylated histones, LSDs cannot remove trimethylation from lysine residues [74, 75]. In contrast, the JmjC domain of the Jumonji C domain-containing (JMJD) family proteins contains 170 amino acids. The 2-oxoglutarate and O_2 are used as the co-substrate, and $Fe^{(II)}$ is used as a cofactor to promote the enzyme's oxygenase reaction and exert its activity [76, 77]. This means that JmjC demethylase can remove monomethyl, dimethyl, and trimethyl labels on histone lysine residues [78]. JMJD family members can be further categorized based on the molecular weight (> 100 kDa or < 100 kDa), lysine demethylation specificity, or the presence of functional domains [79]. In recent years, an increasing number of studies have shown that autophagy plays an essential role in inflammation by affecting the differentiation and maturation of inflammatory cells. Autophagy also participates in modulating gene transcription and the secretion of cytokines [80]. Autophagy and cytokines mutually regulate each other to maintain cellular homeostasis [81]. This review focused on the specific mechanisms by which histone demethylation could activated or inhibited autophagy regulation, providing a reliable theoretical basis for the clinical search for identifying efficient therapeutic targets for inflammatory diseases.

KDMs in autophagy

Increasing evidence has demonstrated that, in addition to traditional metabolic-related signals, epigenetic modifications are also key mechanisms in autophagy regulation, in which histone demethylases play an important role [82]. The KDM protein family consists of KDM1-KDM8 subfamilies. These subfamilies act on different histone

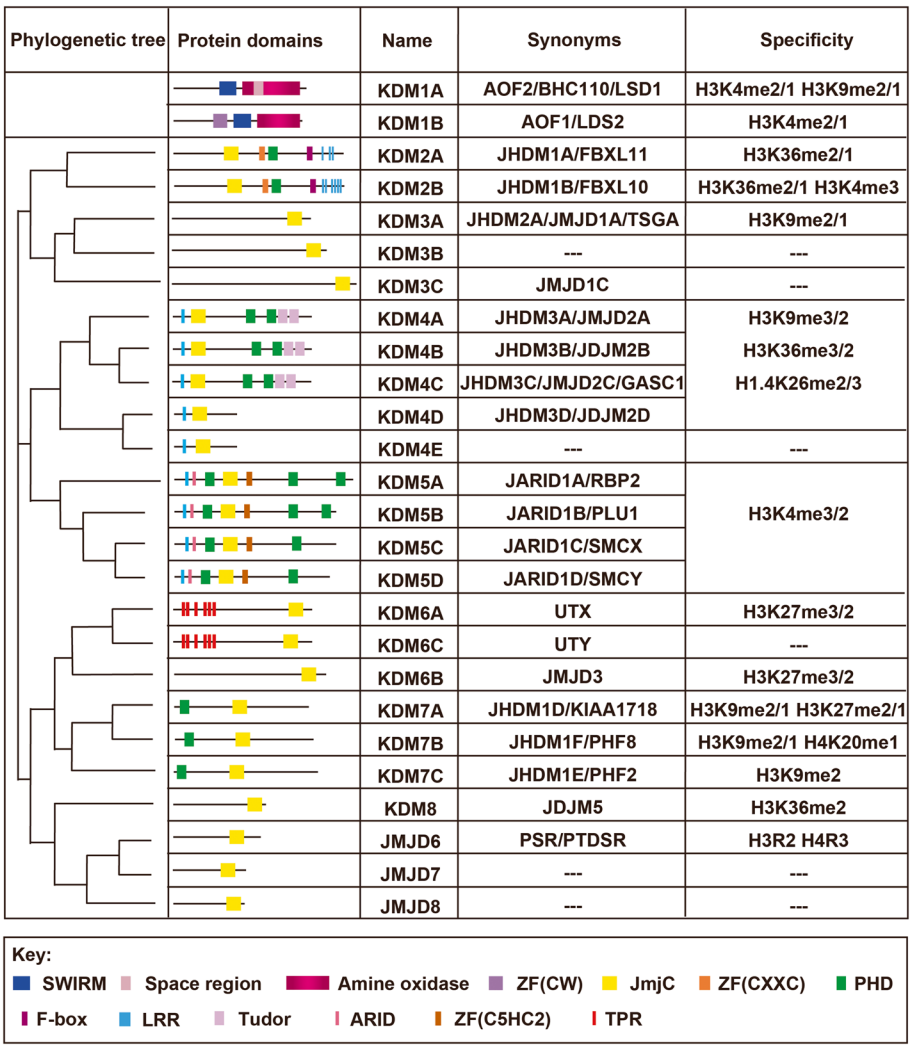

Fig. 4 Phylogenetic tree of the KDMs family. KDMs are classified into two major families based on substrates and reaction mechanisms: lysine-specific histone demethylases (LSD) and JmjC demethylases. Notably, LSD1 was the first demethylase to be identified. Additionally, KDM2-8 are JmjC domain-containing demethylase

methylation sites and exert different regulatory effects on gene expression and autophagy (Fig. 5).

KDM1

Current studies have identified KDM1A as one of the proteins potentially closely associated with the regulation of autophagy. KDM1A, also known as LSD1, belongs to the KDM1 subfamily Unlike the rest of the KDM2-KDM8 subfamily, KDM1A does not contain the JmjC domain, but has FAD-dependent amine oxidase activity [83]. KDM1A can form a co-suppressor complex with corepressor of repressor element-1 silencing transcription factor (CoREST) to remove histone modification of histone H3 lysine 4 dimethylation/trimethylation (H3K4me2/3), thereby inhibiting target gene transcription [84, 85]. Furthermore, in specific instances, KDM1A can act upon histone h3 lysine 9 monomethylation/dimethylation (H3K9me1/2) to activate target gene expression [86]. Predominantly, KDM1A exerts inhibitory effects on autophagy, and the modulation of the mTORC1 pathway is one of its pivotal mechanisms. Feng et al. [87]reported that KDM1A regulated the initiation of autophagy through regulating the protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway. Treatment with the KDM1A inhibitor S2101 reduced the levels of phosphorylated (p)-AKT, p-mTOR, and p-70S6K in ovarian cancer cells, thereby enhancing autophagy and inhibiting ovarian cancer cells proliferation. Subsequently, Ambrosio et al. [88] elucidated that the regulation of mTORC1 activity by KDM1A relied

on the expression of Sestrin2 (SESN2). SESN2, an intracellular leucine receptor, interacted with GATOR2 to inhibit the activity of mTORC1. By suppressing of SESN2 expression, KDM1A increased mTORC1 activity, thereby inhibiting autophagy. Importantly, KDM1A bound to the transcriptional starting site of SESN2. Upon KDM1A inhibition or knockdown, the level of H3K4me2 significantly increased in this area, accompanied by enhanced histone H3 acetylation, reduced H3K27me3, and no obvious change in H3K9me2 levels. These findings suggest that KDM1A-mediated epigenetic changes play a key role in regulating mTOR. The KDM1A/SESN2/mTORC1 pathway contributes to modulating autophagy in various tumors and inflammatory diseases. A novel LSD1 inhibitor, ZY0511, was found to augment autophagy and apoptosis in diffuse large B-cell lymphoma cells by inhibiting mTORC1 activity, leading to suppressed tumor proliferation in mouse models [89]. Knockdown of KDM1A promoted autophagy in macrophages through the KDM1A/SESN2/mTORC1 pathway and inhibited oxidized low-density lipoprotein (ox-LDL)-induced NLRP3 inflammasome activation and the release of inflammatory cytokines [90]. In rats with kidney failure, the histone deacetylase histone deacetylase 1 (HDAC1) was shown to negatively regulated KDM1A transcription. Consequently, inhibition of KDM1A led to heightened activation of the SESN2 promoter and enhanced autophagy, and exacerbated vascular calcification [91]. In addition, Shi et al. [92] demonstrated that knocking down KDM1A could hinder phosphatase and tensin homolog (PTEN) ubiquitination, thereby promoting its stability. Given that PTEN is also an inhibitor of the AKT/mTORC1 pathway, the KDM1A/PTEN/mTORC1 axis represents another mechanism for regulating autophagy.

In addition to the mTORC1 pathway, KDM1A regulates autophagy through other targets. P62 is an important carrier that mediates the binding of autophagy substrates to autophagosomes. In various tumor cells, KDM1A binds to the p62 protein and reduced its stability by regulating ubiquitination, thereby inhibiting autophagy and promoting the occurrence of gynecological tumors. The regulatory impact of KDM1A on p62 depends on its catalytic activity [93]. Furthermore, KDM1A suppresses the transcription of p62 by eliminating H3K4me2, which contributes to the regulation of programmed oocyte death [94]. Byun et al. [95] observed an increase in hepatic fibroblast growth factor after food consumption. In this context, KDM1A was recruited by small heterodimer partner (SHP) to the cAMP response element binding protein (CREB) target gene locus, where it removed H3K4me2/3 and H3K9/14 acetylation modifications, while enhancing H3K9me2. It further resulted in the suppression of autophagy-related genes such as TFEB, ATG3, and ATG10, leading to a reduction in lipid autophagy within hepatocyte phagocytic vesicles. Moreover, KDM1A inhibits autophagy in diseases, such as acute myeloid leukemia, prostate cancer, hypopharyngeal cancer, and other diseases. Knockdown or inhibition of KDM1A often hinder the occurrence and progression of these tumors. However, the specific mechanism and clinical implications of KDM1A in these contexts need to be further clarified [96–98].

KDM1A can also promote autophagy through other mechanisms. For instance, in studies on Alzheimer's disease (AD), KDM1A was found to interact with proteins associated with mRNA methylation, enhancing the autophagic degradation of p-Tau by increasing the activity of the transcription factor EB (TFEB). This process helped impede the progression of AD [99]. Additionally, KDM1A targeted the promoter of methyltransferase-like 3 (METTL3), resulting in a decrease in the levels of H3K9me3 [99]. METTL3 subsequently activated the ubiquitin ligase STUB1 through m6A methylation modification, which facilitated the degradation of

(See figure on next page.)

Fig. 5 KDMs in autophagy regulation. **A** KDM1A inhibits autophagy by depleting histone H3K4me2, thus suppressing SESN2 and p62 transcription. It is recruited by SHP to CREB target genes, removing H3K4me3 and repressing the expression of autophagy-related genes such as TFEB, ATG3, and ATG10. Additionally, KDM1A directly mediates the demethylation of K151me1 of ATG16L1, enhancing the phosphorylation of ATG16L1 and its binding to ATG12-ATG5, consequently promoting the extension and maturation of autophagosomes. In addition, knockdown of KDM1A can block PTEN ubiquitination and enhance its stability, thereby regulating mTOR activity and inhibiting autophagy. **B** NUPR1 binds to KDM3A, reducing H3K9me2 at the TFEB promoter and promoting TFEB-mediated autophagy; **C** KDM3B activates autophagy by inducing GABARAPL1 transcription. **D** Nutlin treatment promotes KDM4B expression, which activates ULK1 and ATG16L1 transcription by decreasing H3K9/K36me3, thereby promoting autophagy and inhibiting apoptosis. On the contrary, Nutlin treatment reduces KDM4B expression in MHM and SJSA1 cells by activating p53, thereby inhibiting autophagy and promoting apoptosis. KDM3B mediated H3K9me3 demethylation also inhibits the expression of LC3B and promotes autophagy. **E** KDM6A may interact with MLL3 to regulate the increase of H3K4me3 and promote the expression of autophagy genes. **F** KDM6B enhances autophagy by inhibiting H3K27me3 at the TFEB promoter. In addition, ecdysone recruits dUTX to regulate autophagy-related genes by managing H3K27me3 at the promoter. FGF21 activates KDM6B phosphorylation and promotes the expression of TFEB, ATG7, ULK1, and other genes by regulating H3K27me3, thereby enhancing autophagy. **G** KDM5C interacts with ULK1 to mediate the demethylation of R170me2. Hypoxia weakens the catalytic activity of KDM5C, activating ULK1 by enhancing R170me2 and promoting the initiation of autophagy. **H** KDM7B activates ATG17/FIP200 transcription by binding to its promoter region, thereby activating autophagy

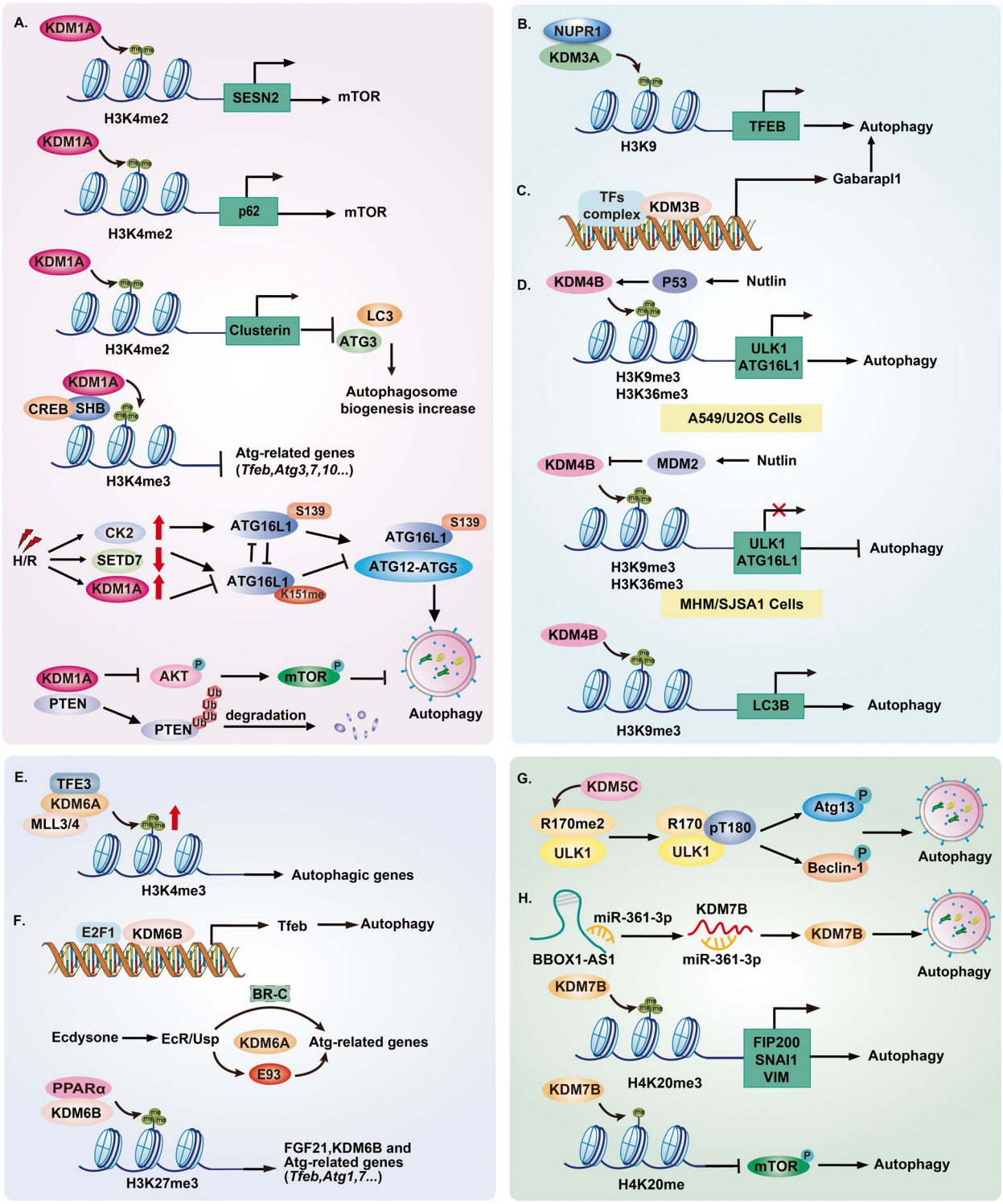

Fig. 5 (See legend on previous page.)

inactivated p-TFEB while increasing activated TFEB levels. This, in turn, promoted the expression of autophagy-related genes [100]. Furthermore, KDM1A functions as non-histone demethylase by directly mediating the demethylation of ATG16L1 at the K151me1 site. This enhanced the phosphorylation of ATG16L1, thereby

strengthening its binding to ATG12-ATG5 complex, ultimately promoting the extension and maturation of autophagosomes [101]. In hypoxia/reoxygenation-stressed cardiomyocytes, the expression of the demethylase KDM1A was up-regulated, while the methylase SET domain containing 7 (SETD7) was down-regulated. KDM1A and SETD7 antagonized each other, collectively regulating the methylation of ATG15L1 at the K151 site. This interaction promoted autophagy and protected the survival of cardiomyocytes under stress conditions [101].

JmjC proteins and autophagy

KDM2

The KDM2-KDM8 proteins are members of the JmjC family, whose catalytic activity depends on JmjC activity and requires the participation of cofactors such as α-ketoglutaric acid (α-KG) and Fe^{2+} [102]. Among them, KDM2A/KDM2B mainly target the methylation of H3K36 to activate the expression of target genes [103, 104]. In ovarian cancer, the high expression of KDM2A have been implicated in the ubiquitination-mediated degradation of Beclin-1. Knockdown of KDM2A enhances the stability of Beclin-1 and promotes the activation of autophagy [105]. Similarly, the high expression of KDM2B can be observed in gastric cancer or lung squamous cell carcinoma tissues. However, knocking down KDM2B leads to the reduced p-Akt/mTOR activity, increased the ratio of LC3-II/LC3-I, and decreased p62 protein levels, indicating enhanced autophagy and inhibited of tumor cell growth [106, 107]

KDM3

The KDM3 family mainly includes KDM3A and KDM3B. It acts on H3K9me1/2 to activate the transcription of target genes [108]. KDM3 proteins primarily promotes autophagy by activating autophagy-related genes. Nutrient deprivation, such as glycogen or amino acid starvation, is a common trigger for inducing autophagy. Kim et al. [109] found that starvation-induced autophagy depended on the up-regulation of KDM3A, which could bind to the promoters of autophagy-related genes such as Map1lc3b and Atp6v1c1 to reduce H3K9me2 levels, thereby promoting autophagy in mice liver. In glioma cells, hypoxia enhanced the expression of the promoting gene Nupr1, which bound to KDM3A to reduce H3K9me2 levels at the promoter of TFEB, promoting TFEB mediated autophagy and inducing tumor resistance to temozolomide [82]. Similarly, in colon cancer cells, starvation culture upregulated KDM3B protein, which promoted autophagy by regulating H3K9me2 at the promoters of ATG5 and ATG7 [110]. Furthermore, Song et al. [111] discovered that in acute myeloid leukemia (AML) cells, KDM3B can activated the transcription of GABA(A) receptor-associated protein like 1 (GABARAPL1). GABARAPL1, belonging to the ATG8 protein family along with LC3, plays a key role in autophagosome elongation. Thus, KDM3B-mediated transcriptional activation facilitates autophagy in AML cells. Overall, KDM3 proteins are activated by nutrient deficiency and play a pivotal role in promoting autophagy.

KDM4

The KDM4 family, consisting of KDM4A-KDM4D, targets inhibitory sites marked by H3K9me2/3 or H3K36me3 [112, 113]. Recent studies have established their close association with autophagy. KDM4A was highly expressed in glioma cells, and silencing KDM4A (siKDM4A) promoted autophagy, leading to decreased cell viability and increased apoptosis [114]. Duan et al. [115] revealed that Nutlin treatment stimulated the expression of KDM4B, activating the transcription of ULK1 and ATG16L1 by demethylating H3K9/K36me3 in A549 cells, thereby promoting autophagy and inhibiting apoptosis. Similarly, Tan et al. [116] demonstrated that in colon cancer cells, glycogen deprivation increased KDM4B expression and suppressed LC3B expression through demethylating H3K9me3 at its the promoter, thereby improving the level of autophagy and favoring cell survival. In castration-resistant prostate cancer, KDM4B promoted autophagy by activating the activity of the Wnt/β-catenin signaling pathway [117]. Additionally, KDM4C has been implicated in stress-induced autophagy. In a mouse model of kidney injury, knockdown of KDM4C inhibited autophagy, suggesting that KDM4C may positively regulate autophagy under stress conditions [118]. Moreover, KDM4D is involved in selective autophagy during autoimmune encephalomyelitis. Optineurin (OPTN) mediated the interaction of ubiquitinated-KDM4D interacting with LC3 in autophagosomes. TRIM14 inhibited the autophagic degradation of KDM4D by recruiting deubiquitination enzymes, resulting in increasing KDM4D protein levels, and enhanced expression of pro-inflammatory factors through H3K9me3 [119]. Overall, the KDM4 family proteins can either promote or inhibit autophagy in different contexts. Further studies are needed to confirm these mechanisms.

KDM5

KDM5 primarily functions as an H3K4 demethylase, with its members including KDM5A-C [120, 121]. Wang et al. [122] observed an increase in the promoter H3K4me3 level at the PIK3C3 gene promoter upon KDM5B knockdown in esophageal squamous cell cancer cells, consequently activating autophagy and apoptosis while enhancing the sensitivity of mouse models to

radiotherapy. Li et al. [123] identified a distinctive demethylase activity of KDM5C, which targeted arginine residues within the autophagy protein ULK1, thereby inhibiting hypoxia-induced autophagy. In hypoxia-cultured tumor cells, the ULK1 protein was found to be symmetrically dimethylated at the arginine 170 site (R170me2s). Mutations at the R170 site inhibited hypoxia-induced autophagy. The demethylase KDM5C could interact with ULK1 to mediate the methylation of R170me2 through the catalytic activity of the JmjC domain. Under hypoxic conditions, the catalytic activity of KDM5C was diminished, leading to increased R170me2s of ULK1. This modification activated ULK1 by promoting its phosphorylation at T180, subsequently inducing the phosphorylation of ATG13 and Beclin-1, and activating downstream autophagy pathways. Furthermore, in LN229 glioma cells, hypoxia-induced autophagy promoted mitochondrial clearance and reduced oxygen consumption by inducing autophagy, ultimately favoring cell survival [123].

KDM6

The KDM6 family, including KDM6A (UTX), KDM6B (JMJD3), and KDM6C (UTY), demethylates H3K27me2/3 to activated the expression of related genes, thereby promoting autophagy [124–126]. Similarly, in Drosophila, demethylase UTX (dUTX), a homolog of KDM6A, is recruited by the steroid hormone ecdysone to regulate autophagy and apoptosis-related genes, including ATG 1, ATG 2, ATG 7, ATG 9 and ATG 18, by regulating H3K27me3 at the promoters. Therefore, dUTX is an important regulator of ecdysone-mediated programmed death in Drosophila salivary glands [127]. Yin et al. [128] observed a significant upregulation of KDM6B expression in dental pulp stimulated by tumor necrosis factor-alpha (TNF-α), thereby promoting autophagy. However, silencing KDM6B inhibited the expression of autophagy-related genes such as ATG5, LC3B, FIP200, and ATG12, by regulating H3K27me3 levels at their promoters. Wang et al. [129] further demonstrated that KDM6B enhanced autophagy in thyroid cancer cells by decreasing H3K27me3 levels at the TFEB promoter. KDM6B promoted TFEB transcription, thereby upregulating lysosomal-related gene expression and promoting autophagy. Additionally, KDM6B participated in lipid autophagy in the liver. The starvation-sensing hormone Fibroblast growth factor 21 (FGF21) mediated the activation of KDM6B via PKA-mediated phosphorylation, elevating the expression of TFEB, ATG7, and ULK1 by reducing H3K27me3. This enhanced liver autophagy, promoting the decomposition of triglycerides and β-oxidation of fatty acids [17]. Furthermore, KDM6A may regulate autophagy via another mechanism. During starvation, transcription factor E3 (TFE3) translocated to nucleus and recruited KDM6A to target gene promoters such as MAP1LC3B and WIPI2. This recruitment increased H3K4me3 levels, ultimately promoting autophagy and cell proliferation in renal cancer cells. Interestingly, mutant variants of KDM6A lacking catalytic activity still promoted autophagy, indicating its regulatory role on target genes is partially independent of its enzyme activity [130]. Knockout of KDM6A also reduced the recruitment of methyltransferase mixed-lineage leukemia 3 (MLL3) to the target gene promoters, suggesting a potential interaction between KDM6A and MLL3 in the regulation of autophagy [130].

KDM7

The KDM7 family members, including KDM7A, KDM7B, and KDM7C, target H3K9/K27 as their substrates [131]. They are also the only KDM proteins capable of demethylating histone H4. Particularly, KDM7B (PHF8) can positively regulate autophagy. In hepatocellular cancer (HCC) cells, KDM7B promotes autophagy by binding to the transcriptional initiation domain of ATG17/FIP200, thereby enhancing its transcription. This process leads to the degradation of E-cadherin, which in turn increases the invasion and migration of HCC cells. Moreover, KDM7B-mediated autophagy is implicated in Sorafenib resistance of HCC mice, further promoting tumor progression [132, 133]. However, Witucki et al.'s study on AD revealed that KDM7B inhibited autophagy by enhancing the H4K20me1 modification at the mTOR promoter, leading to increased activation of the mTOR pathway and inhibiting autophagy. Therefore, it contributes to increased Aβ protein aggregation in AD models [134].

KDMs in autophagy and inflammation

Histone modifications contribute to significant changes in genome structure and function. The KDMs family is involved in signaling pathways that regulate autophagy and inflammation (Fig. 6). Substantial evidence underscores that dysregulated expression of KDMs is closely associated with multiple inflammatory responses.

KDM1

KDM1 primarily removes monomethylated and dimethylated modifications on histones, participating in the regulation of autophagy and inflammation through epigenetic modifications [135]. Zhou et al. [90] found that downregulation of KDM1A/LSD1 promoted autophagy by inhibiting SESN2-mediated activation of the mTOR pathway in atherosclerotic disease, which in turn reduced ox-LDL-stimulated activation of the NLRP3 inflammasome and cytokine production. However, Xie et al. [136]

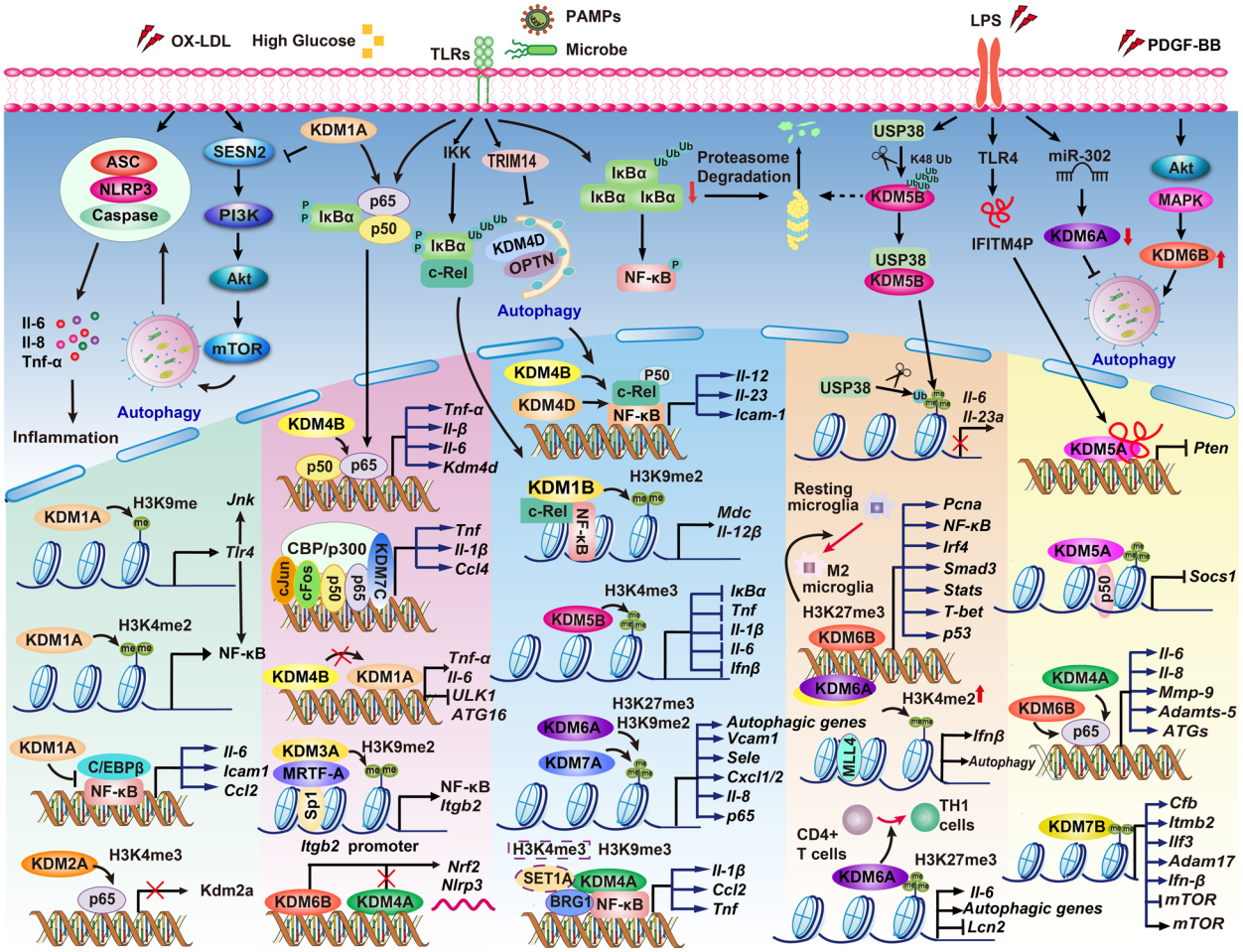

Fig. 6 Mechanisms of KDMs in regulation of inflammatory factors. KDMs regulate the expression of inflammatory factors in response to LPS, PAMPs, and various other stimuli. 1) KDM1A is stimulated by ox-LDL, which suppresses the PI3K/mTOR inhibitor SESN2 and inhibits autophagy of NLRP3 inflammasome, resulting in elevated inflammatory cytokines. Additionally, KDM1A and KDM1B interact with the NF-κB pathway and modulate the expression of IL-6, CCL2, and IL-12β through histone demethylation. 2) KDM2A is driven by NF-κB and negatively regulates inflammation by demethylation and consequently inhibiting p65. 3) KDM3A interacts with MRTF-A, promoting inflammation by removing H3K9me2 of ITGB 2. 4) KDM4A is recruited to NF-κB binding sites and promotes the production of IL-1β, CCL2, and TNF by altering histone methylation. Additionally, KDM4B and KDM4D control the activation of NF-κB and the expression of cytokines such as IL-12β and IL-23. 5) KDM5A is recruited by p50 and suppresses the expression of Socs1 to activate NK cells. Upon LPS stimulation, KDM5A is enriched at the PTEN promoter and inhibits its expression. KDM5B can be recruited to the promoter of IL-6, IL-23a, and Th1 cytokines, including TNF, IL-1β, and IFN-β, inhibiting their production by H3K4me3 demethylation. 6) KDM6A removes the H3K27me3 of Lcn2 and IL-6. Additionally, KDM6A interacts with MLL4 to induce the expression of IFN-β by promoting H3K4me2. KDM6B regulates macrophage polarization by removing H3K27me3 of M2 transcriptional factors, such as STAT6, IRF4, and T-bet. KDM6A and KDM7A mediate the transcription of VCAM1, Cxcl1/2, IL-8, and p65 via H3K27me3 and H3K9me2, respectively.7) KDM4A/6B and KDM7B participate in the regulation of IL-6, IL-8, IFN-β, and others through histone methylation. KDM7C can interact with the CBP/p300 coactivator to promote TNF, CCL4, and IL-1β expression by H4K20 demethylation

discovered in homocysteine upregulated the expression of SNF5 through KDM1A in a mouse model of atherosclerosis, regulated the monomethylated modification of histone H3K4 in macrophages, and then led to an increase in the interleukin (IL)−1β level, aggravating the inflammation of macrophages and ultimately promoting the formation of atherosclerosis. KDM1A inhibitors significantly reduced the protein expression level of aortic inflammatory factors [137]. In Addition, KDM1A has been found to positively regulate the expression of toll-like receptor 4 (TLR4) by catalyzing H3K9me2 in the promoter region of HBV-associated glomerulonephritis. Knockdown of KDM1A inhibited the TLR4-nuclear factor-kappaB (NF-κB)/ Jun N-terminal kinase (JNK) signaling axis in HBV-induced HK-2 cells, reducing the production of pro-inflammatory mediators [135]. Wang

et al. [138] observed that inhibition of KDM1A activity by GSK-LSD1 led to elevated H3K4me2 and H3K9me2 modifications, which further inhibited the activation of NF-κB signaling, subsequently inhibiting the production of cytokines (TNF-α, IL-6, and IL-1β), thereby alleviating the inflammatory response of mastitis. In rheumatoid arthritis (RA), KDM1A has promoted the proliferation of $CD4^{+}$T cells and the production of inflammatory cytokines IL-17 and immune interferon (IFN)-γ [139]. In lipopolysaccharide (LPS)-induced sepsis, phosphorylation of KDM1A has promoted the demethylation of p65 K314/315 to activate NF-κB targeted genes and recruited KDM1A and p65 to the NF-κB promoter, thus activating PKCα-KDM1A-NF-κB signaling to promote the inflammatory response in sepsis [140]. In the adipose tissue of obesity, knockout of KDM1A has promoted the binding of CCAAT/enhancer binding protein beta (C/EBPβ) and NF-κB at the IL-6 promoter, subsequently increasing the transcription of inflammatory genes including carbon tetrachloride (CCL)2, CCL20, IL-6, IL-15, and C/EBPβ [141]. KDM1B also regulates inflammation by interacting with the NF-κB protein through the connection between AO-N and AO-C subdomains. Disrupting the interaction prevents KDM1B recruitment to CCL22 and IL-12b, mitigating inflammatory responses [142].

JmjC protein autophagy and inflammation

KDM2

KDM2A can either positively or negatively regulate inflammatory cytokines and inflammatory signaling pathways in different situations, while KDM2B positively regulates the expression of inflammatory cytokines [143]. High expression of KDM2A in ovarian carcinoma participates in the ubiquitination degradation of Beclin-1. Knockdown of KDM2A enhances the stability of Beclin-1 and promotes the activation of autophagy [105].KDM2A could demethylate the lysine K218 or K221 residues of p65 inhibit its expression. This process was antagonized by nuclear receptor binding SET domain protein 1 (NSD1), which serves as a methyltransferase to K218 or K221 residue of p65 to promote the transcriptional activity of NF-κB [144]. In psoriasis-like dermatitis, KDM2A reduced the inflammatory response of epidermal keratinocytes by suppressing the activity of NF-κB, while KDM2A inhibitors enhanced the expression of cytokines such as IL-8 and CCL20 induced by poly (I:C) [145]. In high-fat diet -treated mice, deletion of KDM2A significantly reduced the expression of inflammatory factors IL-6, IL-1β, and CCL2, thereby suppressing chronic inflammation in adipose tissue. Deletion of KDM2A has increased the H3K36me2 level at the peroxisome proliferator-activated receptor gamma (PPARγ) site, promoting the binding of STAT6 and mediating the polarization of M2 macrophages [146]. In osteoarthritis (OA) mice, the levels of KDM2A, IL-1β, IL-6, and TNF-α were significantly reduced, and overexpression of miR-31 has downregulated the expression of KDM2A and activated the E2F1/PTTG1 axis, thereby reducing the expression levels of IL-1β and TNF-α in OA [147]. Hypoxia increased the expression of KDM2A in stem cells of apical papilla, and KDM2A has inhibited the transcription of secreted Frizzle-related protein 2 by reducing the methylation of histone H3K4 and H3K36 in its promoter, inhibiting the canonical Wnt/β-catenin pathway, and then inhibiting the NF-κB signaling pathway [148]. Zhou et al. found that KDM2B bound to the SWI/SNF complex containing Brg1 in macrophages and dendritic cells (DCs) to catalyze chromatin remodeling of the IL-6 promoter. In addition, KDM2B has directly engages RNA polymerase II to further initiate IL-6 transcription, thereby promoting IL-6 production in the inflammatory response [149].

KDM3

KDM3 regulates the inflammatory response by controlling proinflammatory factors and NF-κB pathways. In high glucose and hypoxia-treated human umbilical vein endothelial cells(ECs), KDM3A has increased inflammatory damage by up-regulating the expression of IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1), and promoted oxidative stress progression by enhancing the levels of reactive oxygen species(ROS) and malondialdehyde (MDA) while reducing the activity of superoxide dismutase(SOD) [150]. Inhibition of KDM3A significantly reduced insulin-induced cytokines such as IL-6 and MCP-1 and suppressed the activation of phosphorylated mitogen-activated protein Kinases (p-MAPKs) and NF-κB/p65 pathways in vascular smooth muscle cells [151]. In glioma cells, hypoxia enhanced the expression of the promoting gene Nupr1, which bound to KDM3A to reduce H3K9me2 of TFEB promoter, promoting TFEB mediated autophagy and thus inducing tumor resistance to temozolomide [82]. Zhang et al. [152] have demonstrated that KDM3A enhanced the transcription of NF-κB/p65 to drive the continuous inflammatory response in diabetic myocardial injury. Liang et al. [153]found that leukocidin enhanced the transcriptional activity of transforming growth factor β inducible factor 1 by promoting the ubiquitination and degradation of KDM3A, which inhibited the activation of the TGF-β1/Smad2/3 signaling pathway and suppressed the inflammatory response in diabetic nephropathy. The interaction between KDM3A and myoglobin-associated transcription factor A (MRTF-A) might contribute to integrin beta 2(ITGB2) transcription, leading to macrophage adhesion to ECs, and cardiac inflammation was suppressed in macrophage MRTF-A conditional knockout mice [154].

In ECs, the collaborative action of KDM3A alongside Brg1 serves to initiate the transcription of colony-stimulating factor 1(CSF1), thereby facilitating the recruitment of macrophages, consequently perpetuating vascular inflammation [155]. In colon cancer cells, the KDM3A peptide was recruited to the 15-LOX-1 promoter, subsequently demethylating H3K9me2 and ameliorating carcinogenesis [156]. In KDM3C knockdown THP-1 cells, LPS induced the phosphorylation of NF-κB p65 and its nuclear translocation, and stimulated the expression of TNF-α, IL-1β, and IL-6. In contrast, overexpression of KDM3C inhibited NF-κB signaling and osteoclast generation, thereby enhancing the anti-inflammatory function of macrophages against oral bacterial infection [157].

KDM4

The KDM4 family predominantly assumes a proinflammatory role in regulating inflammatory responses. Various studies have highlighted the critical role of KDM4A in the inflammation cardiovascular system. In a study involving mice with kidney injury, it was found that knockdown of KDM4C inhibited autophagy under stress conditions, promoted the secretion of inflammatory cytokines [118]. The TRIM14-USP14-BRCC3 complex inhibits OPTN-mediated autophagic degradation of KDM4D by reducing K63 ubiquitination on KDM4D, thereby removing the H3K9me3 modification from the promoters of IL-12 and IL-23, promoting the expression of the pro-inflammatory cytokines IL-12 and IL-23, and enhancing the inflammatory response [158].Upon exposure to ox-LDL, KDM4A is upregulated in macrophages, provoking pro-inflammatory M1 polarization. Knockout of KDM4A significantly reduces the expression of M1 inflammatory factors such as TNF-α, IL-1β, and MCP-1, independent of NF-κB or HIF pathways activation, suggesting that KDM4A may exert its proinflammatory role through alternative pathways such as epigenetic modification [159]. In the LPS-induced inflammatory response of vascular ECs, KDM4A was recruited to the NF-κB target gene promoter, removing H3K9me3. Subsequently, methyltransferase SET1A was recruited, leading to an increase in H3K4me3, thereby activating the expression of IL-1β, CCL2, and TNF [160]. Compound Danshen dripping pills inhibited the activity of KDM4A and block the transcription of p65 in a mouse model of heart failure induced by a high-fat diet, consequently reducing the inflammatory response [161]. Moreover, KDM4A/4B is involved in nervous system inflammation. In a rat cerebral ischemia model, knockdown of KDM4A inhibited NF-κB signaling in microglia, reducing the neuroinflammatory response and promoting the recovery of stroke [162]. LPS-induced inflammation in nerve cells, and knockdown of KDM4B inhibited the expression of inflammatory factors upon KDM4B knockdown by recruiting inhibitory H3K9me3 to Notch1, IL-1β, and IL-2 promoters [163]. Choi et al. [164] found that KDM4B could bind to intercellular adhesion molecule 1 (ICAM1) promoter to reduce H3K9me2, mediating the expression of ICAM1 and inhibiting inflammatory-induced leukocyte extravasation, consequently suppressing nervous system inflammation. Furthermore, KDM4D is also involved in inflammatory responses. Jin et al. [165] showed that upon LPS stimulation activated TLR receptors in DCs and increased the stability of KDM4D protein through inducing the expression of deubiquitinase Trabid. KDM4D promotes the expression of IL-12a, IL-12b, and IL-23a by regulating their H3K9 methylation, inducing the differentiation of Th cells into T-helper 17 (Th17) subtypes and fostering autoimmune inflammation in mice. TRIM14 interacts with USP14 and BRCC3 to inhibit OPTN mediates the interaction of ubiquitinated KDM4D with LC3 in autophagosomes in experimental allergic encephalomyelitis (EAE) mice. TRIM14 inhibits KDM4D autophagic degradation by recruiting deubiquitinating enzymes, resulting in increased KDM4D protein and the expression of inflammatory cytokines such as IL-12 and IL-23 through the removal of H3K9me3, which leads to inflammation-related T cell differentiation [119]. TNF-α upregulates KDM4D expression in dextran sulfate sodium (DSS)-induced UC mice. KDM4D inhibits epithelial cell apoptosis and promotes colitis recovery by activating the Hedgehog signaling pathway [166].

KDM5

KDM5A/5C/5D positively regulates the inflammatory response. Zhao et al. [167] revealed that p50 recruited KDM5A and inhibited its transcription by removing H3K4me3 binding on the Socs1 promoter, which in turn stimulated NK cells to release a substantial quantity of IFN-γ through the JAK2-STAT4 signaling pathway. In contrast, the activation of NK cells in mice with KDM5A knockout was inhibited [167]. Liu. et al. [168] found that dexamethasone (DEX) could inhibit KDM5A activity, leading to increased H3K4me3 modification of inflammation-related genes such as TNF-α, nitric oxide synthase 2 (NOS2), and CCL2. Inhibiting KDM5A could weaken the inflammatory response in mice with renal injury. Qi et al. [169] demonstrated higher expression of KDM5C/6A in aged female microglia compared to males. They highlighted that KDM5C inhibited the expression of the IRF4 gene through H3K4 demethylation. The IRF4 signal mainly directed the production of anti-inflammatory cytokines. Consequently, knockout of KDM5C significantly reduced the expression of anti-inflammatory factors such as IL-4 and CD206/Arg1, and other anti-inflammatory factors, indicating that the poor

prognosis of cerebral ischemia in elderly females may be related to the inflammatory regulation of KDM5C. In addition, LOXL1 antisense RNA 1 (LOXL1-AS1) was up-regulated in OA and enhances KDM5C expression via miR-423-5p, thereby intensifying the inflammatory response and apoptosis, ultimately promoting OA development [170]. Ebadi et al. [171] found that KDM5D was the most significantly up-regulated gene in patients with myocardial infarction and coronary artery disease (CAD) through bioinformatics analysis. Moreover, the expression of inflammatory genes such as CCL20, IL-1β, and IL-17 was also significantly enhanced.

Specifically, Wang et al. [122] observed an increase in the promoter H3K4me3 level of the PIK3C3 gene upon KDM5B knockdown in esophageal squamous cell cancer cells, consequently activating autophagy and apoptosis while enhancing the sensitivity of mouse models to radiotherapy. KDM5B may exert multiple effects on the regulation of the inflammatory response. In LPS-induced bone marrow-derived DCs (BMDMs), LPS induced KDM5B to bind to IL-6 and IL-23a promoters. KDM5B can inhibited NF-κB binding to them by reducing H3K4 trimethylation, thereby contributing to inflammation dissipation [172]. Moreover, KDM5B was closely associated with inflammatory damage caused by respiratory syncytial virus (RSV) infection. RSV infection upregulated the expression of KDM5B and inhibits the generation of Th1 antiviral cytokines, such as IFN-β, IL-6, and TNF-α by regulating H3K4me3 modification, consequently promoting the differentiation of $CD4^+$ T cells to the Th2 type. However, in RSV-infected KDM5B knockout mice, the levels of Th2 inflammatory factors IL-4, IL-5, and IL-13 were reduced, and the secretion of mucus was less, alleviating lung injury [173]. In addition to histone demethylation, KDM5B also promotes protein translation by maintaining the length of the 3 'UTR and increasing mRNA stability. Vascone et al. [174] discovered that soluble epoxide hydrolase (SEH) plays a crucial role in Angiotensin (Ang) II-mediated vascular endothelial inflammation, and KDM5B can increase the stability of SEH mRNA through this mechanism. Conversely, knockdown or inhibition of KDM5B can reduce endothelial inflammatory damage.

KDM6

KDM6A/6B is widely implicated in the regulation of inflammatory genes and primarily plays a pro-inflammatory role [175]. Previous studies have indicated that TLR4 is activated in LPS-stimulated macrophages and induces the up-regulation of KDM6B in a manner dependent on the NF-κB. However, KDM6B does not affect the overall level of H3K27me3 but forms complexes with Wdr5, RbBP5, and Ash2L, as well as Polycomb group proteins, which selectively regulates H3K27me3 demethylation of target genes such as Bmp-2 to enhance their transcriptional activity [176].Approximately 70% of the genes activated by LPS were targeted by KDM6B, including CCL5, IL-12b, CXCL11, and CCL9 [177]. Knockdown of KDM6B affected the expression of various key genes in NF-κB, chemokine, and CD40 signaling in THP-1 cells. Wang et al. [129] demonstrated that KDM6B enhanced autophagy in thyroid cancer cells by inhibiting TFEB promoter H3K27me3. KDM6B promoted TFEB transcription, thus amplifying lysosomal-related gene expression and promoting autophagy. In fact, knockout of KDM6B can inhibit the expression of NF-κB-mediated inflammatory genes by recruiting the H3K27me3 to their promoters to inhibit the inflammatory response [178]. Li et al. [179] found that KDM6A demethylated the promoter through H3K27me3 to enhance the expression of IL-6 in macrophages, while KDM6A indirectly promoted the expression of IFN-β through the transcription of specific enhancer S-IRE1. Kruidenier et al. [180] developed a small molecule inhibitor GSK-J4 targeting the H3K27 demethylation activity of KDM6A/6B, enabling a more intuitive study of the effects of KDM6A/6B-mediated histone demethylation on inflammatory gene expression. Surprisingly, knockout of KDM6B alone did not result in a significant enhancement of H3K27me3 at the target gene. However, treatment with GSK-J4 or inhibition of both KDM6A and KDM6B by RNA interference suppressed TNF-α transcription and upregulated H3K27me3 at the transcription start region [177, 180]. Inhibition of KDM6B and KDM6A by GSK-J4 also antagonized the production and release of IL-1β in macrophages induced by zoledronic acid, consequently ameliorating the inflammatory response in mice [181]. Moreover, GSK-J4 treatment in NK cells reduced the secretion of IFN-γ, TNF-α, granulocyte–macrophage colony stimulating factor (GM-CSF), and IL-10 by up-regulating H3K27me3, although it did not affect the cytotoxic activity of NK cells against cancer cells [182]. This suggests that KDM6A and KDM6B may play similar proinflammatory functions in inflammation, and subsequent studies have revealed their involvement in various inflammatory diseases. Wang et al. [183] observed an upregulation of KDM6B expression in LPS-induced mastitis, whereas GSK-J1 alleviated mammary inflammation. It was further demonstrated that knockout of KDM6B reduced the expression of TLR4 by regulating H3K27me3, thereby inhibiting the downstream NF-κB proinflammatory signal transduction and inhibiting the production of TNF-α, IL-1β, and IL-6 in breast tissues. Additionally, Johnstone et al. [184] demonstrated the up-regulation of KDM6B in the prefrontal cortex and nucleus accumbens of alcohol-dependent mice, where it regulated H3K27me3 demethylation of

multiple genes in the IL-6 pathway. Knockout of KDM6B significantly reduced IL-6 expression in macrophages, suggesting a close relationship between alcohol dependence and KDM6B-mediated inflammatory response.

KDM6 plays a crucial role in the regulation of macrophage polarization, in which KDM6B mainly promotes anti-inflammatory M2-type polarization, while KDM6A favors pro-inflammatory M1-type polarization. Ishii et al. [185] discovered that IL-4-stimulated macrophages induced KDM6B expression through the activation of the STAT6, which then targeted H3K27me2/3 at the promoter of M2 marker genes such as Chitinase-like 3 (Chi3l3), Resistin-like alpha (Retnla), and Arginase 1 (Arg1) and activated their expression, thus mediating IL-4-induced M2 polarization. Similarly, Satoh et al. [186] demonstrated that KDM6B was essential for M2 polarization. In chitin-stimulated or helminth-infected mouse peritoneal macrophages, KDM6B inhibited H3K27me3 at the IRF4 promoter. Conversely, knockdown of KDM6B enhanced H3K27me3 and suppressed IRF4 expression, consequently impeding the generation of M2 macrophages. Moreover, Salmonella Typhimurium infection led to increased host KDM6B expression and reduced the H3K27me3 mark. KDM6B was recruited to the promoter of WNT pathway genes, including PPARδ, and activated its transcription, thereby promoting M2 polarization of macrophages, leading to the prolonged survival of S. typhi in the intestinal tract and the formation of chronic infection [187].Additionally, KDM6B also participated in the polarization of microglial cells. In Parkinson's disease, IL-4 induced the production of KDM6B and was associated with the microglia phenotype. KDM6B enhanced the expression of Arg 1 by modifying histone H3K27me3. It further promoted the anti-inflammatory M2-type polarization of microglia and antagonized the pro-inflammatory M1-type response, ultimately alleviating the death of dopaminergic neurons [188]. Alexaki et al. [189] observed that during the process of dehydroepiandrosterone (DHEA) inhibiting nervous system inflammation, DHEA bound to the receptor of tropomyosin receptor kinase A (TrkA) and activated Akt1/Akt2 and cAMP, inducing the expression of KDM6B, thereby regulating the polarization of microglia and suppressing the expression of M1 pro-inflammatory genes.

In contrast, KDM6A promotes M1 polarization and inhibits M2 polarization. Chen et al. [190] discovered that LPS or IL-4 stimulation did not change the expression level of KDM6A in BMDM cells. However, knocking out KDM6A significantly impeded the M1 polarization induced by LPS while facilitating the M2 polarization induced by IL-4. KDM6A was found to promote the expression of M1 markers including Nos2 and IL-6 while inhibiting the expression of M2 markers such as Arg1 and Retnla [190]. Similarly, knocking out KDM6A can enhance the expression of miR-467b-3p in ECs, which subsequently induce M2-type polarization of macrophages after spinal cord injury (SCI) through the PI3K/AKT/mTOR pathway [191].

Moreover, in a mouse model of bladder cancer, the knockout of KDM6A enhanced the secretion of pro-inflammatory factors IL-6 and CCL-2, inducing the polarization of M2 macrophages, thereby promoting bladder cancer cell proliferation by activating inflammatory pathways such as STAT3 [192]. In the periodontitis model, the expression of KDM6A protein increased in macrophages infiltrating periodontal tissue, and the disruption of circadian rhythm further upregulated KDM6A. Knockdown of KDM6A in macrophages reduced the expression of M1 cytokines including IL-6, IL-1β, and TNF-α, but did not affect the expression of M2 cytokines, indicating that KDM6A may aggravate periodontitis by inducing pro-inflammatory M1 polarization [193]. Additionally, in diabetic retinal microglia and macrophages, KDM6A promoted Lipocalin-2 (Lcn2) expression by removing H3K27me3, thereby regulating metabolic status and inhibiting the inflammatory response. However, the knockout of KDM6A reduced retinal inflammatory factors, such as TNF-α, NOS2, and inhibited M1 polarization [194]. Furthermore, Qi et al. [169] observed that the expression of KDM5C/6A in microglia in aged females was higher compare to that in males and was associated with a poor prognosis of cerebral ischemia. KDM6A promoted the expression of the IRF5 gene through H3K27 demethylation, and IRF5 signaling further induced the transcription of pro-inflammatory cytokines. Knockout of KDM6A significantly reduced the expression of inflammatory factors such as TNFα and NOS2.

KDM6A/6B can also regulate T helper cell function and contribute to the pathogenesis of autoimmune diseases. Doña et al. [195] demonstrated that inhibiting KDM6B with GSK-J4 induced immune tolerance in DC cells. The expression of co-stimulatory molecules and secretion of pro-inflammatory cytokines (IL-6, IFN-γ, and TNF-α) were reduced in GSK-J4-treated DC cells, while the secretion of anti-inflammatory mediators such as TGF-β1 was enhanced, leading to an increase in regulatory T cell (Treg) generation. Transfer of GSK-J4-treated DCs into EAE mice significantly suppressed the degree of inflammatory $CD4^+$ T cell infiltration in the central nervous system. Similarly, knockout of KDM6A in $CD4^+$ T cells induced Th2 differentiation and substantially reduced the neuroinflammatory response in mice by inhibiting CD44 expression through H3K27me3 demethylation. In the $CD4^+$ T cells of EAE mice, KDM6A downregulated the expressions of IL-2, IFN-γ, and IL-17A,

but upregulated the expression of IL-5, indicating that KDM6A can participate in Th2 differentiation during autoimmune inflammation [196]. Cribbs et al. [197] found that GSK-J4-induced inhibition of KDM6A and KDM6B reduced differentiation and proliferation of Th17 and decreased the release of Th17-type proinflammatory cytokines including IL-17 and IFN-γ. GSK-J4 treatment increased the repressive H3K27me3 modification, leading to the reduced expression of vital Th17-type TFs such as MYC, PPARγ, and peroxisome proliferator-activated receptor gamma coactivator 1-related protein 1 (PPRC1), which ultimately diminished the inflammatory response in ankylotic arthritis. Additionally, KDM6 is associated with autoimmune diseases such as colitis, RA, and OA. Doñas et al. [198] showed that GSK-J4 could reduce the secretion of IL-6 and IL-17, weaken the response of Th17, thereby alleviating inflammatory colitis. Inhibition of KDM6B by GSK-J4 enhanced H3K27 methylation at the Nrf2 gene promoter and downregulated Nrf2 expression in macrophages, which is essential for NLRP3 inflammasome activation. Consequently, GSK-J4 reduced NLRP3-mediated inflammatory response and mitigated intestinal injury in mice with colitis [199]. The expression of KDM6B was upregulated in RA patients. In mice with collagen-induced arthritis(CIA), GSK-J4 could reduce the levels of pro-inflammatory factors and like IL-1β inflammatory cell infiltration by inhibiting KDM6B, thereby reducing the severity of arthritis in CIA mice [200]. In OA, KDM6B is overexpressed. GSK-J4 inhibited the NF-κB signaling pathway activated by IL-1β, reducing the production of pro-inflammatory factors such as IL-6 and IL-8, and consequently decreasing cartilage damage [201].

KDM7

The KDM7 family might also contribute to promoting inflammation, although current research in this area is limited. KDM7A was rapidly recruited to the NF-κB binding site in TNF-α-stimulated human ECs and can promote the expression of downstream inflammatory factors such as vascular cell adhesion molecule 1 (VCAM1) and selectin E (SELE) by regulating H3K9me2 [202]. In human brain microvascular ECs, KDM7A increased the stability of ICAM1 protein by regulating TFEB-mediated lysosomal activity and upregulated the expression of ICAM1, which was closely related to leukocyte migration and adsorption, thus promoting brain inflammation [203]. In hepatocellular cancer cells, KDM7B triggers ATG17/FIP200 transcription by binding with the startup domain, thereby activating autophagy. In LPS-stimulated macrophages, KDM7B may facilitate the activation of NF-κB by mediating H3K9me2 demethylation of NF-κB, promoting the expression of inflammatory factors and enhancing the activation and proliferation of T cells [204]. Furthermore, KDM7C is involved in TLR4-stimulated inflammatory responses. TLR4 signaling and the downstream NF-κB pathway can lead to the activation of KDM7C, which in turn triggers the expression of inflammatory factors such as TNF and CXCL10 in macrophages by removing the inhibitory histone H4 lysine 20 trimethylation (H4K20me3) [205].

KDMs as therapeutic targets

Autophagy is closely related with inflammatory diseases [8, 18]. On one hand, it constitutes an important component of the immune response. Through xenophagy, pathogens such as bacteria entering cells are recognized by selective autophagy receptors and transported to lysosomes for degradation, thereby playing an anti-infective role and restraining excessive inflammatory responses. On the other hand, autophagy often functions as an anti-inflammatory mechanism. Mitophagy can degrade the aged or damaged mitochondria and inhibits the activation of the NLRP3 inflammasome, thus playing an anti-inflammatory role in diseases such as chronic obstructive pulmonary disease, and inflammatory bowel diseases, and other conditions [206]. Autophagy also interrupts inflammatory pathways activated by viral DNA or RNA and negatively regulates type I interferon (IFN-I) production. Moreover, it exerts anti-apoptotic effects, inhibits pyroptosis, and promotes the clearance of necrotic cells, thereby preventing the overactivation of the inflammatory response [207]. However, effective strategies to regulate autophagy are still lacking, and the potential regulation of autophagy through epigenetic modifications is holds promise for drug development.

Evidence shown that inhibitors of KDMs, particularly KDM1A/LSD1 inhibitors, can regulate the autophagy process. Tranylcypromine (TCP, 2-PCPA) is a monoamine oxidase inhibitor and the first identified KDM1A inhibitor. It antagonizes the demethylase activity of KDM1A [75].Subsequently, selective inhibitors of KDM1A, such as SP2509 [208], GSK-lysine-specific demethylase 1 (GSK-LSD 1) [209], and S2101 [210], have been developed, with many novel inhibitors continually discovered. TCP activates the SESN2 promoter by regulating modifications such as H3K4me2, leading to the inactivation of mTOR pathway and promoting autophagy, thereby impeding the growth of cells such as neuroblastoma and ovarian cancer [211, 212]. Treatment with SP2509 promotes p62 transcription and enhances p62 protein stability, thereby activating cellular autophagy, inducing apoptosis of uterine serous cell carcinoma ARK 2 cells, and inhibiting tumor growth in mice [94, 213]. Addition of S2101 to ovarian cancer serous cystadenocarcinoma ovarian cell line 3 (SKOV3) cells inhibits the

p-AKT-mTOR pathway, promoting cellular autophagy, subsequently inducing apoptosis and hindering SKOV3 cell growth [87]. In addition, novel inhibitors, such as NCL1, JL1037, and ZY0511, were all capable of inhibiting tumor growth in mouse models by promoting autophagy and apoptosis [89, 97, 214].

Within the JmjC family proteins, JIB04 is a widely used JmjC inhibitor [215]. JIB04 inhibited KDM4C, aggravates apoptosis of HEK29 cells after oxidative stress, and aggravated kidney injury caused by ischemia–reperfusion in mice [118]. Additionally, 5-Carboxy-8-Hydroxyquinoline (IOX-1) acts as a small-molecule 2-oxoglutarate (2-OG) dependent oxygenase inhibitor antagonizing the catalytic activity of JmjC proteins [216]. Using IOX-1 or si-KDM4B, inhibiting the expression of ULK1 and ATG16L1 by increasing H3K9/H3K36 levels and then inhibiting autophagy could induce apoptosis of glioma A549 cells and exert a unique anti-tumor effect [115]. However, GSK-J1/4 showed selective inhibition of KDM6 family proteins. In TNF-α-stimulated dental pulp cells, GSK-J4 inhibited the expression of autophagy genes such as LC3B, ATG5, and ATG12 and cellular autophagy in pulpitis [128].

Inhibitors of KDMs play pivotal regulatory roles in multiple inflammatory diseases. In hepatitis B (HBV)-induced glomerulonephritis, KDM1A regulated H3K9me1/2 and promoted TLR4 transcription. However, the KDM1A inhibitor TCP alleviated inflammation by downregulating TNF-α, IL-1β, and IL-6 expression in the kidney cortex by inhibiting TLR4/NF-κB signaling in the HBV mouse model [135]. For instance, the KDM6 protein inhibitor GSK-J1/4 could downregulate the inflammatory response in conditions such as inflammatory bowel disease, RA, multiple sclerosis, and mastitis [182, 183, 195, 198, 217]. KDM6B-mediated H3K27me3 modification is critical for Th17/Treg cell differentiation in ulcerative colitis mice. However, Treg cells were increased and Th17 was decreased in colon tissues following GSK-J1 treatment, leading to reduced secretion of inflammatory factors [218]. In the context of inflammatory diseases, inhibitors of KDMs have the potential to modulate inflammatory responses by regulating autophagy. SESN2 activation in si-LSD1 treated macrophages promotes autophagy and inhibits the activation of ox-LDL-induced NLRP3 inflammasome and the release of proinflammatory factors such as IL-1β, IL-6, and TNF-α [90].Furthermore, KDM4D can be regulated by OPTN-mediated selective autophagy in macrophages in experimental allergic encephalomyelitis (EAE) mice, while IOX-1 mitigates inflammatory symptoms in KMD4D by increasing H3K9me3 modification in IL-12b, IL-12a, and IL-23a promoters, thereby inhibiting EAE in mice [119].

Therefore, the potential clinical applications of KDMs inhibitors in regulating autophagy and inflammation are evident. Nevertheless, several issues remain to be addressed. Firstly, our understanding of the roles and mechanisms of autophagy in inflammation is not yet complete. Secondly, existing evidence indicates that the regulatory effects of KDMs on autophagy and inflammation vary across different disease states, tissues, and organs. Further trials are necessary to explore the specific conditions under which KDMs inhibitors are most suitable for use. In addition, some KDM1A inhibitors have been used in clinical studies of tumors and hematological diseases [219, 220]. However, additional clinical trials are need to validate the effectiveness and safety of other KDM inhibitors.

Conclusion and future perspectives

Under different external conditions, the KDMs family affects multiple signaling pathways through the demethylation modification on histones, thereby regulating autophagy and the secretion of inflammatory factors. Accumulating studies have shown that KDMs play a significant role in the development of various diseases, thus small molecule inhibitors related to KDMs, aimed at delaying disease progression and treating diseases, have gained increasing recognition. Substantial evidence has elucidated the mechanisms by which KDMs regulate autophagy in different diseases. In addition, KDMs can also regulate inflammation-related genes to influence the of inflammatory progression. Current studies have provided a solid theoretical basis for the treatment of KDMs protein inhibitors in inflammatory diseases. However, there are some obstacles that need to be overcome before their extensive application in clinical practice. Firstly, the altered expression of KDMs in cells, whether increased or decreased, can serve as a marker for the activation of autophagy or inflammation activation. For example, KDM1A can inhibit autophagy and promote gynecological tumors. However, it can also enhance the autophagic degradation of p-Tau, therefore slowing down the progression of AD. However, KDM6A can both positively and negatively regulate the inflammatory response. The behavior of KDMs varies across different cells. Therefore, understanding the unique efficiency of each KDM protein in autophagy and inflammation under different conditions is crucial for the targeted therapy of inflammatory diseases. Secondly, although the various active domains of the KDMs family have been elucidated, there are still obstacles to the successful construction of effective JMJD inhibitors due to the high polarity of the 2-OG binding pocket of the JMJD family. The efficacy of some developed JMJD inhibitors that have been developed so far is not very high. Furthermore, with the continuous

Table 1 Application of epigenetic drugs in autophagy

KDMs	Inhibitors	Functions	Mechanisms of modulating autophagy by KDM inhibitors	References
KDM1A	TCP, SP2509	promoting autophagy	activating SESN2 promoter by inhibiting KDM1A, leading to suppressed mTORC1	[210]
	TCP, GSK-LSD1	promoting autophagy	enhancing the expression of autophagy-related genes	[95, 211]
	SP2509, GSK-LSD1, GSK2879552	promoting autophagy	stablizing PTEN by inhibiting KDM1A-dependent ubiquitination, suppressing mTORC1	[91]
	GSK-LSD1, SP2509	promoting autophagy	promoting p62 transcription or reducing p62 degradation by suppressing KDM1A	[93, 212]
	S2101	promoting autophagy	inactivating AKT-mTOR pathway	[86]
	NCL1	promoting autophagy	-	[96]
	JL1037	promoting autophagy	-	[213]
	ZY0511	promoting autophagy	inactivating AKT-mTOR pathway	[88]
	si-LSD1	promoting autophagy	activating SESN2 promoter by inhibiting KDM1A, leading to suppressed mTORC1	[89]
KDM4C	JIB04	suppressing autophagy	-	[117]
KDM4B	IOX-1	suppressing autophagy	inhibiting H3K9 demethylation of ATGs by KDM4B	[114]
KDM5C	IOX-1	promoting autophagy	activating ULK1 by enhancing KDM5C-dependent R170me2s and phosphorylation, inducing autophagy initiation	[122]
KDM6B	GSKJ-4	suppressing autophagy	inhibiting the expression of autophagy-related genes	[127]
KDM6B	si-KDM6B	suppressing autophagy	inhibiting H3K27 demethylation of TFEB by KDM6B	[128]

development of research on KDMs inhibitors, there have been no inhibitors that can be universally applied for autophagy regulation in diverse cells or for various inflammatory diseases currently (Table 1). The impact of interactions between various KDMs proteins on disease makes the development of effective targeted drugs more challenging. For example, JMJD2 inhibitors have been used in cancer treatments, but only one drug is currently undergoing clinical evaluation. To screen for the interference of non-selective target interference and improve the precision of targeted therapy with KDMs inhibitors, further investigation into the structural and functional information of KDMs proteins and protein interactions is needed.

Abbreviations

KDMs	Histone lysine demethylases
ATG	Autophagy-related genes
ULK1	Unc-51 like kinase 1
LSDs	Flavin adenine dinucleotide-dependent amine oxidase
JmjC	JumonjiC
JMJD	JumonjiC domain
SESN2	Sestrin2
ox-LDL	Oxidized low-density lipoprotein
PTEN	Phosphatase and tensin homolog
CREB	CAMP response element binding protein
TFEB	Transcription factor EB
METTL3	Methyltransferase-like 3
GABARAPL1	GABA(A) receptor-associated protein like 1
OPEN	Optineurin
PIK3C3	Class III phosphatidylinositol 3-kinase complex
R170me2s	Arginine 170 site
MLL3	Mixed-lineage leukemia 3
DCs	Dendritic cells
MRTF-A	Myoglobin associated transcription factor A
MCP-1	Monocyte chemoattractant protein-1
ICAM1	Intercellular adhesion molecule 1
RSV	Respiratory syncytial virus
SHE	Soluble epoxide hydrolase
DHEA	Dehydroepiandrosterone
TCP	Tranylcypromine
EAE	Encephalomyelitis
PTMs	Post-translation modifications

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Authors' contributions
LHQ designed and supervised the manuscript. YG, WTL, TY and YYM were writing the manuscript and depicting the figures and tables. YJB, ZQL, CC, WJY, JYF, WBQ, RLT, YTS and SGS reviewed the manuscript and revised the references. LHQ, HFD and YFB revised and edited the manuscript. YG, WTL, TY and YYM contributed equally to this manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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