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Review

Lysine demethylase 6 (KDM6): A promising therapeutic target in autoimmune disorders and cancer

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ABSTRACT

Epigenetic dynamics, which influence gene expressions independent of DNA sequence alterations, play a pivotal role in regulating chromatin structure and transcription. Among these modifications, the dynamic methylation and demethylation of histone 3 lysine 27 (H3K27me2/3) by the Lysine Demethylase 6 (KDM6) subfamily are pivotal regulators of both physiological and pathological processes. In immune cells, KDM6A and KDM6B fine-tune the transcription of pro- and anti-inflammatory genes, influencing differentiation, polarization, and activation states in monocytes, macrophages, dendritic cells, T helper cells, and other key immune subsets. Dysregulated KDM6 activity underlies aberrant cytokine production, Th17 cell expansion, and imbalances in tissue repair responses, thus contributing to autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. Concurrently, KDM6A and KDM6B can act as either tumor suppressors or oncogenes in a context-dependent manner, mediating cellular proliferation, DNA damage repair pathways, and immune evasion in cancers ranging from hematologic malignancies to solid tumors of the bladder, breast, and brain. Recent efforts to exploit this duality include developing small-molecule inhibitors, notably GSK-J4, which block KDM6 demethylase activity and show promising therapeutic effects in models of chronic inflammation and cancer. Nonetheless, challenges such as incomplete target specificity, the interplay with other epigenetic mechanisms, and variations in tumor microenvironment emphasize the complexity of translating these findings into clinical practice. This review highlights the structural features, regulatory mechanisms, and disease associations of KDM6 demethylases, positioning them as compelling biomarkers and therapeutic targets at the intersection of autoimmunity and cancer.

1. Introduction

Epigenetics is classically described as heritable and inducible changes in gene expression that occur without altering the underlying DNA sequences. These changes determine genome structure and accessibility, controlling gene activation. They enable cellular specialization despite identical genetic content [1–3]. Dysregulation of epigenetic mechanisms can contribute to the onset of various pathologies, including autoimmune disorders and cancers. Epigenetic mechanisms include, but are not limited to DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation, which together shape the chromatin landscape [3]. Chromatin exists in a dynamic range from compact heterochromatin to accessible euchromatin, and epigenetic changes can shift this balance to control gene activity [3,4]. In immune or cancer cells, condensing chromatin into heterochromatin can silence tumor suppressor or pro-inflammatory genes, whereas loosening chromatin into euchromatin can increase accessibility for transcription factors that drive proliferation or inflammation [5,6]. To date, over 20 histone modifications have been identified, among which lysine methylation plays a key role in regulating chromatin state and gene expression [1,7,8]. These marks are dynamically modified by lysine methyltransferases (KMTs) and lysine demethylases (KDMs), also known as epigenetic writers and erasers, which add or remove methyl groups from histone tails [1,7].

Histone methylation involves the transfer of methyl groups from methionine to specific amino acids, such as lysine (K) or arginine (R) on histone proteins. The exact position of the amino acid that is modified plays a crucial role in determining the outcome of this modification. Depending on where the methylation occurs on the histone, it can lead to different effects on gene expression [9]. Mono-methylation (me1) of

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histone 3 lysine 4 (H3K4me1) is generally linked to enhancer regions and serves as a marker of poised or active enhancers. On the other hand, H3K4me2 and H3K4me3 are closely associated with active gene promoters. H3K4me3, in particular, marks the promoters of genes that are actively being transcribed and plays a key role in recruiting transcription factors that enhance gene activation [8,10]. Di-methylation (me2) or tri-methylation (me3) of histone 3 lysine 27 (H3K27me2/3), particularly at gene promoter regions, are known to be associated with a compact chromatin conformation and the suppression of gene expression [11,12]. The H3K27me3 epigenetic mark is self-maintained during DNA replication, which leads to sustained gene silencing [13,14]. These heritable epigenetic marks can be retained through cell division, reinforcing specific transcriptional states across multiple cell generations [6, 15]. Methylation on H3K27 is reversible. Removing this methyl group is essential for reactivating genes that need to be expressed in response to certain signals. These repressive epigenetic marks are added by the Enhancer of Zeste Homolog 2 (EZH2) methyltransferase and removed by the demethylating activity of two members of the KDM6 family: KDM6A and KDM6B [9]. The capacity of KDM6A and KDM6B to reprogram chromatin accessibility makes them vital for developmental processes, immune cell differentiation, and the modulation of inflammatory responses [1,2]. Furthermore, H3K27 demethylation by KDM6A and KDM6B is associated with excessive inflammatory and autoimmune responses by regulating the inflammatory gene expression and functions of both innate and adaptive immune cells [13]. Notably, when KDM6 enzymes are dysregulated, the resulting chronic activation of proinflammatory genes can shift immune homeostasis toward autoimmune pathology [16,17]. This review highlights the critical role of KDM6 histone demethylases in promoting both autoimmune responses and cancer (Fig. 1). We begin by examining KDM6 structure, expression, and function, including their known protein and non-histone substrates across diverse immune pathways. We then focus on how dysregulation of KDM6A/B drives pathological inflammation and tumorigenesis and conclude with emerging therapeutic strategies that leverage these enzymes as potential treatment targets.

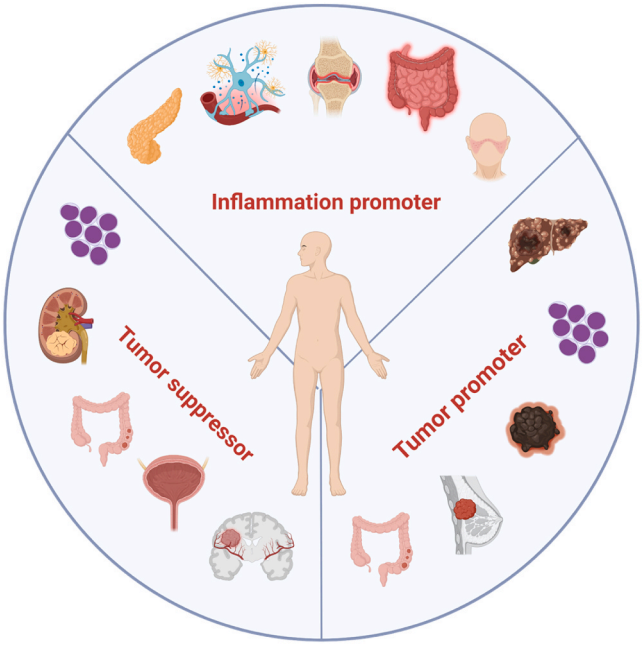

Fig. 1. The inhibiting and promoting effects of the KDM6 demethylase family in different types of cancers and autoimmune diseases. The roles of KDM6 are highlighted in three primary sections: 1) promoter of inflammation in autoimmune disorders, including type 1 diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus; 2) tumor promoter in liver cancer, hematologic malignancies; melanoma, breast cancer, pancreatic, and colorectal cancers and 3) tumor suppressor in glioblastoma, bladder, colorectal, kidney, and various hematologic cancers (Created with BioRender.com).

2. Structural insights into KDM6 demethylases

Understanding the KDM6 structure helps clarify their unique functions and regulatory mechanisms. The KDM6 demethylases were identified in 2007 [13,14,18,19]. Since then, numerous studies have revealed that the KDM6 family plays essential roles in maintaining homeostasis [18,20], regulating cell metabolism [21], influencing cell development [18,22,23], differentiation [24], proliferation, and the immune response [20] as well as modulating a wide range of physiological and pathological contexts, either by activating or repressing gene transcription through the regulation of related signaling pathways [11, 25]. Early breakthroughs in understanding KDM6 function came from studies linking KDM6B to macrophage activation and inflammatory responses, highlighting its significance in immune regulation [26].

The KDM6 family belongs to the Jumonji C (JmjC) domain-containing histone demethylases and consists of three proteins: KDM6A (also known as UTX), KDM6B (also known as JMJD3), and KDM6C (also known as UTY) [22]. The KDM6 family structure shares a high degree of homology within their JmjC domain but differs in other distinct regions: tetratricopeptide repeat motifs (TPR), a helical domain, a linker region, and a GATA-like zinc finger domain (Fig. 2) [9,13,22,26, 27].

All KDM6 enzymes remove methyl groups from histone H3 lysine 27 (H3K27me2/3) via their highly conserved JmjC catalytic domain. Notably, KDM6C exhibits minimal demethylase activity (inactive protein) due to a mutation in its JmjC catalytic domain [27–29]. KDM6C remains less studied because its role in chromatin regulation appears to be primarily scaffolding rather than enzymatic. Additionally, KDM6C shares functional redundancy with KDM6A, and its mutations are rare which results in limited disease associations and lower research interest compared to its paralogs [27,29].

KDM6A and KDM6C possess an additional TPR motif near their N-terminus which distinguishes them from KDM6B. These motifs consist of a series of 34 amino acid repeats that form helical structures, specifically, two α-helices that align in tandem to form a superhelical structure and contribute to their unique functional activities. KDM6A, due to its TPR motifs, can bind with MLL/COMPASS ((Mixed-Lineage Leukemia/Complex of Proteins Associated with Set1) complexes (MLL3 and MLL4), which regulate gene activation by modifying histone H3K4 [30,31]. This TPR motif enables KDM6A and KDM6C to serve as scaffolds for protein-protein interactions, particularly those involved in chromatin remodeling and transcription factors. In contrast, KDM6B lacks this TPR motif, limiting its ability to participate in the same range of protein interactions and potentially influencing specific or distinct regulatory functions (Fig. 2) [26,32]. All KDM6s share a similar C-terminal zinc finger domain that aids in their interaction with various transcriptional co-regulators in chromatin remodeling [13]. The zinc finger domain within the KDM6 family demonstrates DNA binding capability, which is crucial for gene regulatory regions. However, the nature of these interactions can be context-dependent, potentially varying based on the cellular environment and biological function. The helical domain of the KDM6 family is speculated to mediate specific protein-protein interactions in chromatin-protein and other protein-complex assemblies [26]. However, the exact role of the helical domain in the KDM6 family remains unclear, as the amine oxidase-like domain serves as the active site for substrate and cofactor binding [28].

The demethylation process carried out by KDM6 enzymes involves several key steps. First, the enzyme binds to the methylated lysine residue on histone H3. The JmjC domain is responsible for demethylase activity and relies on ferrous iron (Fe (II)), α-ketoglutarate (α-KG), and oxygen as co-factors to carry out the demethylation reaction, resulting in the sensitivity of KDM6 activity to metabolic modifications within cells

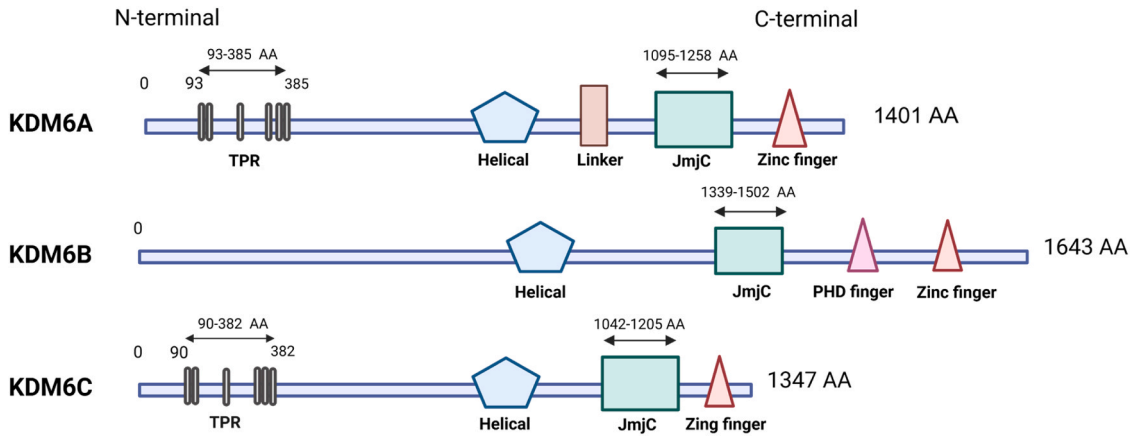

Fig. 2. Structural domains of KDM6 family proteins. This figure explains the structure of three KDM6 family proteins, KDM6A, KDM6B, and KDM6C. Each protein is represented with its unique combination of functional domains, including TPR tetratricopeptide repeats, helical domain, JmjC domains, linker region, and zinc finger domain (Created with BioRender.com).

[33,34]. The JmjC domain catalyzes the demethylation of H3K27me3 to H3K27me0 by hydroxylating the methyl group, leading to its removal. The hydroxylated methyl group then spontaneously decomposes to produce formaldehyde, leaving behind a demethylated lysine residue [22,26]. The JmjC domain is highly conserved and is essential for the oxidative demethylation catalytic mechanism. The JmjC domain forms a double-stranded β-helix (DSBH) fold, creating a pocket that assists the H3K27me3 substrate, Fe (II), and α-KG. This structural arrangement is crucial for the hydroxylation of the methyl group, leading to demethylation [28,33].

While the KDM6B gene is located on chromosome 17p13.1 [19], KDM6A (UTX) and KDM6C (UTY) are respectively located on the X and Y chromosomes [27]. The structural features of KDM6A, particularly its TPR motif and its ability to form complexes with the MLL3 and MLL4 chromatin modifiers, allow it to play a role in this sex-specific regulatory process [31]. KDM6C is the Y-linked homolog of UTX and shares structural similarities with KDM6A but exhibits minimal demethylase activity on H3K27 [13,27]. The increased expression of KDM6 family demethylases generally results in gene activation by demethylating H3K27me3/2 at target promoters and leading to the remodeling of transcriptionally accessible states [12,35]. For instance, in activated T cells, KDM6A and KDM6B can remove repressive H3K27me3 marks on from specific gene promoters such as *Tbx21* (encoding T-bet) and *Prdm1* (encoding Blimp-1), promoting their rapid transcription and shaping immune responses [36–38]. Studies have primarily focused on the impact of KDM6 demethylation on H3K27, but little is known about its interaction with other histone modifications such as acetylation and phosphorylation. Whether KDM6 influences the crosstalk of multiple post translational modifications, such as H3K27 acetylation or phosphorylation, remains to be elucidated.

KDM6B has also been implicated in the regulation of non-histone substrates, such as p53 [39,40], NF-κB (p65 subunit) [41,42], STAT3 [43], and RUNX1 [44], influencing transcriptional control, cell cycle progression, immune regulation, and metabolic adaptation. These findings suggest that KDM6B function extends beyond H3K27 demethylation, integrating broader epigenetic and transcriptional networks that govern immune responses, differentiation, and tumorigenesis [6]. Hence, KDM6 plays a critical role in the dynamic regulation of chromatin states, balancing gene repression and activation. Emerging evidence indicates that the abnormal expression of the KDM6 family is associated with autoimmune diseases and the progression of certain types of cancer which may contribute to the uncontrolled activation of oncogenic pathways [5,11]. This makes KDM6 enzymes compelling therapeutic targets for conditions where pathological immune activation and tumor progression share an epigenetic basis. Understanding the structural and functional aspects of the KDM6 demethylases is thus crucial for clarifying their roles in healthy physiological processes and their potential as therapeutic targets in diseases such as cancer and autoimmunity.

3. Biological functions of KDM6 demethylases

Current studies have shown that KDM6A and KDM6B modulate the epigenetic landscape of both innate and adaptive immune cells. Through their demethylase activity on histone H3 lysine 27 (H3K27me2/3), KDM6 enzymes influence the transcriptional programs and functions of various immune cells to maintain homeostasis. Understanding the specific mechanisms by which KDM6s regulate immune cells is critical for deciphering their roles in health and disease. This section covers KDM6 regulation in key immune subsets, including monocytes/macrophages, dendritic cells, NK cells, and T cells.

3.1. *Regulation of immune cell development by KDM6 demethylases*

The onset of various diseases is often linked to an imbalance in the number or functionality of immune cells, a process significantly influenced by epigenetic regulation. Histone demethylation, in particular, affects cellular differentiation by modulating the activity of gene enhancers specific to certain cell types including T cells, monocytes, macrophages, and dendritic cells. Recent evidence has shown that KDM6A and KDM6B regulate several innate immune genes by transcriptional activation through the removal of repressive epigenetic markers. [45]. KDM6B ensures a rapid and appropriate innate immune response to various stimuli through the removal of H3K27me3 from pro-inflammatory cytokine and chemokine promoters, enabling the swift induction of IL-1β, IL-6, TNF-α, IFN-α/β, and other inflammatory mediators [46–48]. This regulation helps in controlling the magnitude and duration of inflammation, preventing excessive tissue damage during the resolution of inflammation.

3.1.1. *KDM6 demethylases in hematopoietic stem cell differentiation*

Hematopoietic stem cells (HSCs) are multipotent stem cells responsible for the constant production of all immune cell lineages. The differentiation of HSCs into various immune cells is a tightly regulated process involving a complex interplay of transcription factors, signaling pathways, and epigenetic modifications [45,49]. KDM6A-mediated demethylation is necessary for the activation of genes required for erythropoiesis and myelopoiesis, therefore HSC differentiation into erythroid/myeloid lineages. Demethylation of repressive H3K27me3 allows for the appropriate expression of lineage-specific transcription

factors, such as GATA1 (GATA Binding Protein 1), RUNX1 (RUNX Family Transcription Factor 1), and PU.1 (Spi-1 Proto-Oncogene) to ensure the development of HSCs into distinct cell lineages [44,50]. Whereas KDM6B overexpression has been associated with compromised HSC differentiation, the exact molecular interplay remains to be fully characterized. KDM6B is involved in the regulation of the NOTCH signaling pathway, which is known to play a critical role in HSC self-renewal [18]. KDM6B regulates the AP-1 transcription factor complex (Fos and Jun) and immediate early response genes (*Egr1*, *Csrnp1,* and *Dusp1*) leading to a pro-differentiation poised state during HSC inflammatory and proliferative stress response [51]. It has been reported that KDM6B is overexpressed by hematopoietic stem and progenitor cells (HSPCs) found in the bone marrow of patients with myelodysplastic syndromes (MDS) [45,52]. Furthermore, overexpression of KDM6B results in overexpression of S100a9 in BM HSPCs and can mediate the activation of innate immune signaling in HSPCs [45,52].

3.1.2. KDM6A/B in B cell development and plasma cell differentiation

KDM6 demethylases are essential epigenetic regulators influencing B cell development from early activation to germinal center (GC) formation and ending in plasma cell (PC) generation. KDM6A supports the GC phenotype partly by activating the transcription of BCL6 (B-cell lymphoma 6) [53,54]. Upon IL-4 stimulation, STAT6 recruits KDM6A to the *BCL6* enhancer, where KDM6A demethylates H3K27me3 to maintain the GC reaction. Mice lacking KDM6A in B cells exhibit enlarged yet functionally impaired GCs, frequently displaying heightened plasma cell numbers but impaired class-switch recombination [55]. Recent studies show that KDM6A plays a dominant role in restraining PC formation. Its deletion, but not KDM6B's, enhances PC generation in response to T cell-independent antigens, increases B cell proliferation, and alters metabolism toward oxidative phosphorylation. KDM6A loss also elevates H3K27me3 at pro-apoptotic loci, reducing PC apoptosis and prolonging survival. Despite some compensation by KDM6B, KDM6A deletion alone is sufficient to drive excessive plasmablast formation and disrupt class-switch recombination. These findings highlight KDM6A as a key epigenetic regulator of B cell fate, ensuring balanced differentiation and antibody production [56].

3.1.3. KDM6B in myeloid cell phenotype and differentiation

In monocytes/macrophages, KDM6B serves as an epigenetic switch for polarization and differentiation [14,16,46,57,58]. KDM6B exhibits a context-dependent role in immune regulation, acting as either a proinflammatory (classically activated) or pro-reparative (alternatively activated) factor depending on the surrounding signals. Whether this switch is fixed or reversible may depend on ongoing stimuli, such as cytokines IL-4 or IFN-γ, emphasizing the dynamic nature of macrophage epigenetics [57,59]. KDM6B amplifies inflammatory responses in macrophages by erasing the H3K27me3 repressive mark at promoters of NF-κB–driven cytokines, thus making these gene regions more accessible to transcription factors like NF-κB. This change leads to elevated production of proinflammatory mediators, including IL-1β, TNF-α, and IL-12, which in turn accelerate aortic aneurysm development. Additionally, KDM6B expression is enhanced by the type I interferon IFN-β via the JAK/STAT1 pathway, further reinforcing the proinflammatory phenotype of macrophages [48]. Increased KDM6B in diabetic wound macrophages directs early macrophage-mediated inflammation via JAK1,3/STAT3 signaling and increased IL-6 levels. In healthy wounds, early IFN-β signaling transiently induces KDM6B; however, in diabetic wounds, lack of an IFN-β spike and excess IL-6 lead to sustained, pathological KDM6B expression. During healing, prolonged KDM6B activity demethylates H3K27me3 at the *STING1* (signaling effector stimulator of interferon genes) locus, further amplifying inflammation in addition to NF-κB-mediated inflammatory gene transcription [47].

LPS stimulation increases KDM6A protein levels and decreases repressive H3K27me3 marks at the promoter of the *Il6* gene and *IFNB1*-specific enhancer r-derived RNA (eRNA) *S-IRE1*, leading to the promotion of IL-6 and IFN-β transcription in macrophages [16]. It has been shown that LPS stimulation upregulates KDM6B and decreases H3K27me3 levels on the *NRF2* (Nuclear factor erythroid 2-related factor 2) promoter. This epigenetic modification enhances the activation of the NLRP3 inflammasome bone marrow-derived macrophages [60]. In serum amyloid A-stimulated macrophages, KDM6B is highly inducible and decreases H3K27me3. Silencing of KDM6B significantly reduces the expression of proinflammatory cytokines, such as IL-23p19, G-CSF, and TREM-1, by increasing H3K27me3 at their promoters in stimulated macrophages [58].

KDM6B is critical for the epigenetic regulation of genes required for the differentiation of alternatively activated macrophages, which are pivotal in promoting anti-inflammatory responses and tissue repair [61,62]. IL-4 treatment leads to increased KDM6B expression and decreased H3K27me2/3 at the promoter of alternatively activated macrophage genes such as *Chi3l1* (non-enzymatic chitinase-3 like-protein-1 known as *Ym1*) and *Arg1* (Arginase 1). After IL-4 stimulation, activated STAT6 increases, binds to consensus sites at the KDM6B promoter, and activates these specific anti-inflammatory genes in alternatively activated macrophages [61]. Furthermore, the production of α-KG induced by GM-CSF leads to the polarization of macrophages into the alternatively activated phenotype through the KDM6B/IRF4 (Interferon Regulatory Factor 4) axis. In contrast, IFN-β reverses this process, shifting macrophages back to the classically activated phenotype [59]. Targeting KDM6B pharmacologically could bias macrophage populations away from a pathologically proinflammatory state in chronic inflammatory conditions. However, KDM6 enzymes are integral to monocyte-macrophage differentiation and inflammation, yet their impact on trained immunity and immune memory remains poorly understood.

KDM6 enzymes modulate the maturation and function of dendritic cells (DCs) by regulating the expression of genes involved in antigen processing and presentation. A study by Malinczak et al. demonstrated that respiratory syncytial virus (RSV) infection induces the upregulation of KDM6A and KDM6B in both bone marrow-derived dendritic cells (BMDCs) and pulmonary DCs. This upregulation of KDM6 enzymes enhanced the production of pro-inflammatory cytokines and chemokines including IL-6, CCL2, CCL3, and CCL5. Additionally, it increased the expression of antigen-presenting cell (APC) maturation markers such as CD80/CD86 and MHC II [63].

3.1.4. KDM6B regulation in natural killer (NK) cells

Furthermore, it has been shown that KDM6B is a key regulator of cytokine production in human NK cell subsets. KDM6B inhibition increases the repressive H3K27me3 mark on effector cytokine genes' transcription start sites, reducing levels of IFN-γ, TNF-α, GM-CSF, and IL-10 in cytokine-stimulated NK cells while sparing their cytotoxic killing activity against cancer cells [64]. This suggests the potential to modulate inflammatory cytokine release without compromising NK-mediated tumor or viral clearance.

3.1.5. KDM6 demethylases in T cell differentiation and function

In the context of the adaptive inflammatory response, KDM6A and KDM6B are required for the differentiation and function of T cells [36,37]. During thymocyte development, KDM6A-mediated demethylation of H3K27me3 at key regulatory genes facilitates the expression of T cell receptor (TCR) components and related signaling molecules. Manna et al. discovered that KDM6A and KDM6B were essential players in T cell maturation and differentiation by demethylating H3K27me3 at the promoters of target genes, including *S1pr1* (Sphingosine-1-Phosphate Receptor) and the transcription factor *Klf2* (KLF Transcription Factor 2), which are critical proteins for T cell maturation [36,65].

T cell activation induces KDM6B expression. Upon TCR stimulation, KDM6B expression is rapidly induced, preceding the first cell division, and facilitates the removal of repressive histone marks at locations encoding critical transcription factors, including *Tcf7*, *Eomes*, *Id3*, and *Myc*. This chromatin remodeling enables robust expression of genes

involved in T cell expansion (*Il2* and *Myc*), cytokine production (TNF-α and IFN-γ), and long-term survival (*BCL-2* and *BCL-6*) [66]. Qingtian et al. clarified that KDM6B can mediate Th1 differentiation by promoting Th1-related genes such as the transcription factor *Tbx21* (T-Box Transcription Factor 21) and *Smad3* (SMAD Family Member 3). They showed that T cell-specific KDM6B-deficient mice promote Th2 and Th17 differentiation and inhibit Th1 and Treg cell differentiation [37, 67]. A large body of evidence revealed that KDM6B is a positive regulator of pro-inflammatory Th17 cells and a negative regulator of anti-inflammatory Tregs. This function is particularly relevant in autoimmune diseases, as dysregulated Th17 responses are central to the pathogenesis of conditions such as multiple sclerosis (MS) and rheumatoid arthritis (RA) [68–71]. KDM6B crucially regulates the differentiation of naïve T cells into T helper 17 (Th17) cells *in vitro* and *in vivo*. Liu et al. demonstrated a positive regulation of KDM6B in the differentiation of Th17 cells by binding and removing the methyl group from genomic loci of key Th17-related genes such as *Il17A, Il17F, and Il22*, and the key transcription factor *Rorc* (encoding RORγt, RAR-related orphan receptor γt) [38]. Using a combined chemical-genetic approach, Cribbs et al. identified KDM6A and B as central regulators of human Th subsets. KDM6 inhibition led to the suppression of RORγt during Th17 differentiation and profound metabolic reprogramming with reduced mitochondrial biogenesis resembling a resting state [68]. Finally, KDM6B inhibits TGFβ-induced FOXP3 expression, thereby hindering the development of Tregs. Instead, KDM6B promotes the differentiation of T cells into proinflammatory phenotypes, such as Th17 or Th1 cells, which exacerbate inflammatory responses [42,72]. This emphasizes the therapeutic potential of KDM6B inhibition to rebalance T cell subsets in autoimmune settings. The interplay between KDM6A and KDM6B in controlling the balance between different T cell subsets is an area of ongoing research, with implications for understanding how dysregulation of these enzymes may contribute to autoimmune diseases and cancer. It remains unclear why KDM6A and KDM6B can have overlapping vs. unique functions in immune regulation; future studies should examine their individual contributions.

3.2. Regulation of activated signaling pathways by KDM6 demethylases

By regulating histone methylation, KDM6 enzymes can activate or repress multiple signaling pathways that control cellular processes such as proliferation, differentiation, and immune responses (Fig. 3). The KDM6A and KDM6B demethylases can be directly influenced by cellular metabolites, such as Fe (II) or TCA (Tricarboxylic Acid) cycle intermediates like succinate, acetyl coenzyme A (CoA), fumarate, and α-KG [34,73,74]. The availability of α-KG is a key determinant of KDM6 enzyme activity, as it serves as a cofactor essential for their function. A sufficient supply of α-KG ensures the proper functioning of KDM6 demethylases, which efficiently maintain the epigenetic landscape and regulate gene expression. The production of α-KG occurs by the oxidative decarboxylation of isocitrate by IDH1 and IDH2 (Isocitrate Dehydrogenase 1 and 2) or by the deamination of glutamine. Glucose and glutamine are transported into cells and converted to pyruvate and then to acetyl-CoA and glutamate [21,34,74,75]. Notably, mutations in *IDH1* or *IDH2* can result in the generation of the oncometabolite 2-HG (2-Hydroxyglutarate), which competes with α-KG and inhibits α-KG-dependent dioxygenases, including KDM6A and KDM6B enzymes [75]. Metabolic alterations, such as IDH mutations producing 2-HG, directly inhibit KDM6 function by competing with α-KG, leading to epigenetic dysregulation and a block in cell differentiation [21,75].

The hypoxic tumor microenvironment leads to decreased α-KG concentration and increased 2-HG levels, contributing to the inhibition of α-KG-dependent KDM6A activity [21]. KDM6A has been identified as a potential oxygen sensor, where its activity drops under hypoxic conditions, leading to increased H3K27 hypermethylation and suppression of transcriptional reprogramming. Under hypoxia, HIF-1α (hypoxia-inducible factor 1) is stabilized and interacts with ARNT (Aryl Hydrocarbon Nuclear Translocator) to drive hypoxia-induced gene programs, further linking oxygen availability, metabolic states, and KDM6A function [21,76].

KDM6B's role in cell proliferation and differentiation is regulated by growth factors, cytokines, and ligands through distinct signaling

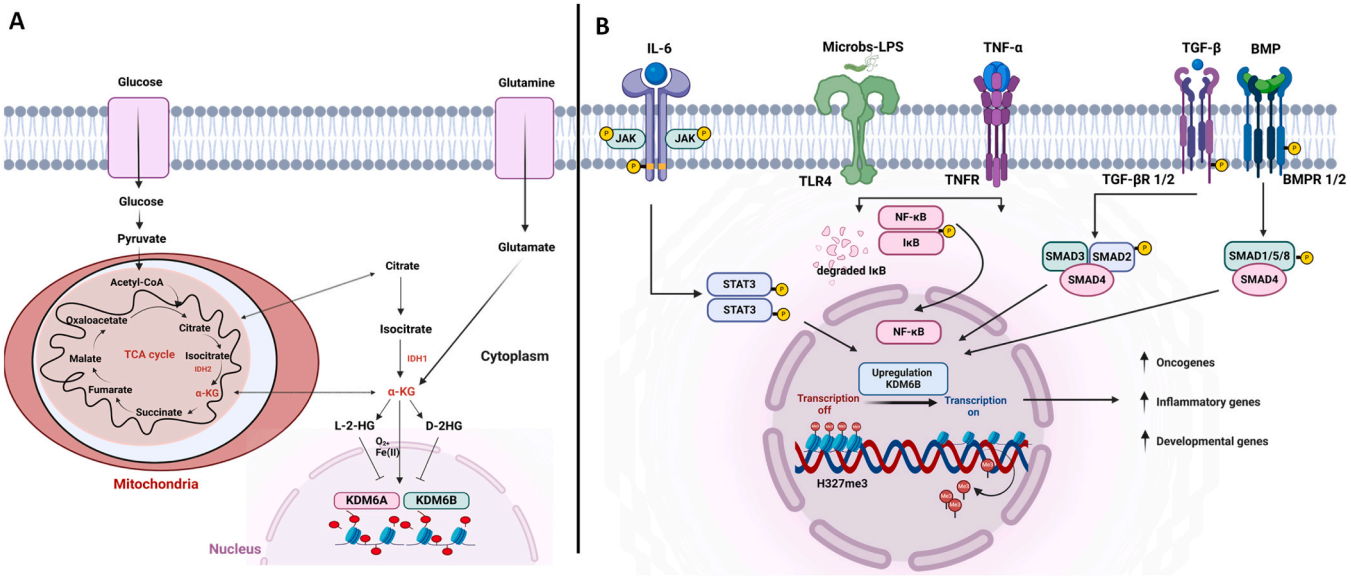

Fig. 3. The regulation of KDM6A and KDM6B. a) the metabolic and epigenetic interplay control by α-kg production, and the subsequent impact on nuclear KDM6A and KDM6B demethylase activity. KDM6A and KDM6B are recruited to the chromatin and respond to the transcription by metabolic and hypoxic stress through modulating gene expression associated with cell proliferation, differentiation, and function of immune cells. D-2HG D-2-hydroxyglutarate, L-2HG L-2- hydroxyglutarate, IDH1/2 isocitrate dehydrogenases 1 or 2, α-KG α-ketoglutarate. b) KDM6B is upregulated by several stimuli, cytokines, and cellular stresses by the JAK2/STAT3, TLR4/NF-κB, and TGF-β/SMAD signaling pathways. KDM6B is recruited to the chromatin and modulates oncogenic, inflammatory, and developmental genes through the demethylation of histone H3 at lysine 27 (H3K27me3). BMP bone morphogenetic protein, BMPR1 bone morphogenetic protein receptor 1, BMPR2 bone morphogenetic protein receptor 2, IκB inhibitor of nuclear factor-κB, JAK Janus kinase, LPS lipopolysaccharide, NF-κB nuclear factor-κB, STAT3 signal transducer and activator of transcription 3, TGF-β transforming growth factor-b, TLR4 toll-like receptor 4, TNF-α tumor necrosis factor-α, TNFR tumor necrosis factor receptor (Created with BioRender.com).

pathways in inflammation and cellular senescence [7,9,18,77]. Under steady-state conditions, KDM6B expression remains low but increases significantly in response to inflammatory stresses or stimuli such as LPS, serum amyloid A, IFNs and LL37/self-DNA complexes [42,46,58]. KDM6B exerts its regulatory function through interactions with key transcription factors, including NF-κB, STAT3, AP-1, IRF4, and TGF-β/Smad3 [14,46,47,59]. Beyond histone demethylation, KDM6B can influence non-histone proteins, broadening its impact on gene expression independent of H3K27me3 levels, as seen in the TGF-β/Smad3 pathway [35]. Future studies should clarify whether these non-histone targets undergo direct demethylation by KDM6B or if the enzyme also has a scaffolding role in these interactions.

KDM6B enhances both pro-inflammatory and anti-inflammatory responses by targeting distinct transcription factors in a context-dependent manner at gene promoters. KDM6B regulates TGF-β signaling by demethylating H3K27me3 at TGF-β/Smad3-binding sites on target promoters such as *Ccn2* (Cellular Communication Network Factor 2), *Snai1* (Snail Family Transcriptional Repressor 1), and *Snai2*. This activity mediates cellular responses to TGF-β signaling via activation of Smad3 and influences fibrosis, immune regulation, tolerance, and tumor progression [78]. KDM6B interacts with distinct transcription factors and is upregulated via different signaling pathways, such as NF-κB signaling [14,46,79,80] and STAT3 signaling [43]. KDM6B, often induced by inflammatory signals such as IL-1β, TNF-α, IL-6, and IFNs, is recruited by NF-κB and STAT3 transcription factors to pro-inflammatory genes [47]. KDM6B participates in feed-forward loops that amplify immune responses, whereby NF-κB and STAT3 signaling induce KDM6B, which, in turn, reinforces NF-κB and MAPK pathways, leading to sustained pro-inflammatory gene expression even after the initial stimuli has been removed. Such feed-forward loops, if left unchecked, can perpetuate chronic inflammation and tissue damage. KDM6B deletion affects several inflammatory and immune responses, including chemokines (CCL3, CCL4, CCL5, CCL9, and CXCL11) and cytokines (IL-12B and IL-6) [14,46]. In human monocytic cells, KDM6B deletion leads to the accumulation of repressive H3K27me3 at NF-κB target promoters, suppressing the expression of MCP-1 (Monocyte Chemoattractant Protein-1) and IL-1β [79,81].

KDM6B expression is partially determined by the STAT3, which binds to and inhibits the promoter region of KDM6B. STAT3 inhibition results in histone H3K27 demethylation of neural differentiation genes, such as *Myt1* (Myelin Transcription Factor 1), *Fgf21* (Fibroblast Growth Factor 21), and *Gdf15* (Growth Differentiation Factor 15) in tumor stem cells from glioblastoma [43]. However, KDM6B's role in STAT3 signaling varies by cell type: while it inhibits differentiation in glioblastoma stem cells, it promotes pro-inflammatory gene expression in immune cells. It has been shown that KDM6B regulates NF-κB and MAPK (Mitogen-Activated Protein Kinase) signaling pathways. Induction of KDM6B by TNF-α or bone marrow stromal cell culture supernatants is prevented by the IKKβ (Inhibitory kappa B kinase beta) inhibitor, indicating regulation through NF-κB signaling. KDM6B is recruited to loci of genes in the MAPK signaling pathway and upregulates their expression independently of H3K27 methylation levels [80]. Cell type-specific transcription factor repertoires likely determine whether KDM6B acts as a pro- or anti-differentiation factor, underscoring the need to interpret its function within each unique signaling context. This context-dependent function of KDM6B underscores its dual role in different cell types, promoting inflammation in immune cells while limiting differentiation in tumor stem cells. KDM6B's role in NF-κB and STAT3 signaling is particularly critical in macrophages and monocytes, where it fine-tunes a feed-forward loop in inflammation to amplify immune responses. Understanding these context-specific roles of KDM6B will be essential for designing therapeutic strategies that either block its pro-inflammatory function in autoimmune diseases or enhance its activity in anti-tumor immune responses.

4. KDM6-mediated regulation of inflammatory diseases and cancers

Growing evidence shows that the aberrant activity of KDM6A and KDM6B is associated with autoinflammatory diseases and certain cancers [17,67,82]. While the role of KDM6A and KDM6B in cancer progression and immune regulation is established, the precise mechanisms through which they interact with specific signaling pathways remain unclear. Future studies should focus on defining the molecular networks that these enzymes regulate in different disease contexts. Inhibitors targeting KDM6A and KDM6B often aim at the active site of the JmjC domain, binding competitively with α-KG and chelating Fe (II). The most well-studied selective inhibitor of KDM6B, GSK-J4, has shown potential as a therapeutic approach in cancer and autoimmune diseases [26,83]. In models of T-cell acute lymphoblastic leukemia and rheumatoid arthritis, GSK-J4 demonstrated significant anti-inflammatory and anti-tumor effects, respectively. GSK-J4 shows a higher selectivity and stronger binding affinity for KDM6B than KDM6A. The half-maximal inhibitory concentration (IC50) of GSK-J4 for KDM6B is approximately 60–90 nM, whereas the IC50 of GSK-J4 for KDM6A is reported to be around 100–150 nM. Chemically, GSK-J4 is a cell-permeable derivative of the 2, 4-pyridine dicarboxylic acid scaffold. The structure contains a key ethyl ester modification, which allows it to penetrate cells and then convert to the active acid form, GSK-J1. The conversion to GSK-J1 is crucial as it is the form that interacts directly with the KDM6 enzymes [26,84]. However, there is limited knowledge of the potential off-target effects of KDM6 inhibitors. More research is required to evaluate their selectivity and long-term epigenetic consequences.

4.1. KDM6 regulation in autoimmune diseases

KDM6A and KDM6B have been shown to contribute to pro-inflammatory responses by activating different transcription factors that bind cytokine promoters via numerous signaling pathways. Many studies have shown that the dysregulation of KDM6B is largely related to the occurrence and development of immune-mediated diseases (Table 1), including rheumatoid arthritis [64,85–87], systemic lupus erythematosus diseases [82], and multiple sclerosis [67].

4.1.1. Rheumatoid arthritis (RA)

RA is a chronic, systemic autoimmune disease characterized by persistent inflammation of synovial joints, leading to progressive joint damage, pain, and disability [71]. KDM6B is upregulated in the peripheral blood and tissues of RA patients in comparison to healthy controls. Most findings center on KDM6B, with KDM6A less studied in RA. In RA, KDM6B promotes arthritis development by inducing the transcription of PCNA (proliferating cell nuclear antigen), which promotes the migration and proliferation of fibroblast-like synoviocytes (FLS) [85]. Likewise, Zhang et al. found that KDM6B promoted the release of various pro-inflammatory cytokines and aggravated RA by activating the STAT3 signaling pathway in FLS [87]. Wu et al. investigated the interplay between cystathionine-γ-lyase (CSE) and KDM6B in regulating inflammation in RA. They found both enzymes upregulated in synovial fibroblasts from RA patients and arthritic mice. CSE negatively regulates KDM6B by modulating *Sp1*, which affects H3K27me3 demethylation at the inflammatory gene promoter of *Il1b* [88]. Furthermore, KDM6B inhibition suppressed the expression of RANKL and reduced the cytokine-stimulated production of IFN-γ, TNF-α, GM-CSF, and IL-10, thus suppressing the inflammatory response in NK cells [64]. H3K27me3 plays a crucial role in macrophage polarization and the pathogenesis of RA. Loss of H3K27me2/3 increases IL-6, TNF-α, and IFN-β production in macrophages. In the collagen-induced arthritis (CIA) mouse model of RA, the KDM6B inhibitor GSK-J4 alleviated RA symptoms and prevented IL-6 transcription in M-CSF-derived macrophages [86]. These findings remain preclinical; clinical trials evaluating KDM6 inhibitors in RA have yet to be initiated.

Table 1
Effects and mechanisms of KDM6B in different autoimmune and inflammatory diseases.

Inflammation type	Mechanism of Action	Study Model	Reference
SLE	Inhibition of demethylases leads to decreased interferon-stimulated gene (ISG) expression in patient monocytes	SLE Patients	[82]
SLE	Inhibition of B cell differentiation by lowering the expression of *BLIMP1*, *BCL6*, and other transcription factors essential for B cell lineage commitment	$CD19^+$ B cells from Healthy donors	[54]
Hashimotos thyroiditis (HT)	Suppression of TNFα-induced chemokines (CXCL10, CCL2) and inhibition of thyrocyte apoptosis	HT Patients	[92]
Rheumatoid Arthritis	Downregulation of *PDGF* induced *PCNA* expression, decreased PDGF mediated synoviocyte proliferation, and migration	CIA (Collagen-Induced Arthritis) mouse model	[85]
Rheumatoid Arthritis	Amelioration of collagen-induced arthritis in vivo, increased H3K27me3 levels and reduced proinflammatory cytokine expression	CIA mouse model	[86]
Rheumatoid Arthritis	Reduction of inflammatory response in IL−1β-treated synovial fibroblasts	CIA mouse model	[88]
Encephalomyelitis (EAE)	Attenuation of EAE development and progression by inducing a tolerogenic phenotype in DCs, GSKJ4 treated DCs promote generation, stability, and suppressive function of induced Tregs	EAE (MS) mouse model	[17]
Colitis	Inhibition of NLRP3 inflammasome activation and decreased IL−1β secretion	DSS (dextran sulfate sodium) induced colitis model	[60,91]
Hepatic fibrosis	Enhancement of cell growth and morphological transformation of quiescent hepatic stellate cells into myofibroblasts and upregulating fibrotic markers	CCl_4 (carbon tetrachloride) induced toxic injury, bile duct ligation	[93]
Psoriasis	Reversal of the trained immune response in LL−37/self-DNA-trained monocytes and psoriatic monocytes	*In vitro* two hit model	[42]
Mastitis	Increase in the deposition of H3K27me3 marks on the promoter regions of proinflammatory cytokines such as *Il1b, TNF*, and *IL6*	LPS induced mastitis model	[94]

4.1.2. Systemic lupus erythematosus (SLE)

SLE is a complex chronic autoimmune disease characterized by the production of autoantibodies and a breakdown in immune tolerance, leading to the activation of autoreactive B and T cells [89]. The expression of KDM6B increases at the *Itgal* (Integrin Subunit Alpha L) promoter in SLE $CD4^+$ T cells compared to healthy controls, and its H3K27me3 demethylation activity enhances the expression of *Itgal*, thus promoting T cell autoreactivity and production of autoantibodies [90]. Moreover, Montano et al. showed that SLE monocytes exhibit heightened glycolysis and oxidative phosphorylation compared to healthy controls, accompanied by increased levels of α-KG. Inhibiting KDM6B, to a lesser extent KDM6A, with GSK-J4 decreased ISG expression in SLE monocytes and mitigated autoantibody production and kidney pathology in mouse models of IFN-driven SLE [82]. These findings position KDM6B as a promising target in SLE, though the safety and specificity of such epigenetic therapy remain to be addressed. Thus, in lupus, KDM6B contributes to T-cell autoreactivity, and B-cell help (via *Itgal* upregulation) and sustains inflammatory gene expression in monocytes (via high α-KG-fueled demethylation), both of which are central to SLE pathology.

4.1.3. Multiple sclerosis (MS)

MS is a chronic demyelinating disease of the central nervous system, characterized by the immune system's aberrant attack on myelin, the protective sheath around nerve fibers. In MS, autoreactive T cells, particularly $CD4^+$ T cells, cross the blood-brain barrier, recognize myelin antigens, and release pro-inflammatory cytokines which recruit and activate macrophages and microglia [70]. KDM6A was identified as a key sex-linked factor in MS. Female T cells express more KDM6A, which limits Th1/Th17 responses in humans and the experimental autoimmune encephalomyelitis (EAE) mouse model. Sex hormones and X-chromosome inactivation patterns may influence KDM6A expression, adding another layer to MS pathophysiology. KDM6A was identified as the top sexually dimorphic gene in $CD4^+$ T cells, with higher expression in females across humans and mice. KDM6A downregulated Th1 and Th2 activation pathways in $CD4^+$ T cells, as well as their polarization into T cells producing IL-17. Importantly, deleting KDM6A in $CD4^+$ T cells alleviated disease symptoms and reduced neuropathology in the EAE model [67]. Using GSK-J4, Doñas et al. reported that the dual inhibition of KDM6A/B demethylase reduced the severity of inflammation in both EAE and colitis murine models [91]. Furthermore, the inhibition of H3K27 demethylase activity with GSK-J4 significantly suppressed Th17 cell differentiation in EAE. KDM6B directly reduced H3K27 trimethylation at the genomic sites of *Rorc* (encodes the Th17 master transcription factor RORγT) and Th17 cytokine genes [38]. GSK-J4 can act on dendritic cells and T cells in vivo and induce the tolerogenic profile of DCs, which promotes the polarization of $CD4^+$ T cells and the differentiation of anti-inflammatory Treg cells as well as the secretion of IL-10 [17,91]. These findings suggest that GSK-J4 could potentially translate into a new MS therapy, pending further translational and clinical evaluations.

4.1.4. Other autoimmune and inflammatory diseases

GSK-J4 showed a broad anti-inflammatory effect in most *in vivo* models of autoinflammatory diseases and efficiently reduced the production of pro-inflammatory cytokines like IFN-α, TNF-α, IL-1, and IL-6. Targeting H3K27me3 may offer an effective approach to treating autoimmune inflammatory disorders. Beyond RA, SLE, and MS, KDM6B is implicated in other inflammatory conditions. In psoriasis, KDM6B inhibition reversed trained immunity in monocytes, reducing the hyperactive inflammatory response characteristic of psoriasis including increased glycolysis, oxidative phosphorylation, and elevated IL-6, IL-8, and TNF-α production [42]. In inflammatory colitis, it restricted NLRP3 inflammasome activation and prevented excessive intestinal inflammation [60,91]. KDM6B expression is significantly elevated in the thyroid tissues of Hashimoto's thyroiditis (HT) patients, accompanied by an upregulation of pro-inflammatory chemokines CXCL10 and CCL2. Using

thyroid epithelial cell line models, it was shown that TNF-α stimulation induces KDM6B expression and promotes chemokine production, which can be effectively suppressed by GSK-J4 treatment. Additionally, GSK-J4 inhibits TNF-α-induced thyrocyte apoptosis, suggesting a protective role in HT pathogenesis [92]. These examples underline KDM6B's broad involvement in inflammatory pathologies, demonstrating its role in immune cell reprogramming across multiple autoinflammatory diseases.

4.2. KDM6 regulation in cancers

KDM6A and KDM6B play crucial roles in tumor initiation, progression, and metastasis. By modulating the levels of H3K27 methylation, KDM6A and KDM6B influence the transcriptional landscape of cancer cells, enabling them to switch between different phenotypic states. The aberrant functions of KDM6 appear to act as either tumor suppressors or oncoproteins depending on the specific cancer cell type and tumor milieu [95,96]. This dual nature is influenced by cell type, signaling environment, and the presence of cofactors. Co-occurring genetic alterations with tumor suppressor genes, such as IDHs (Isocitrate Dehydrogenases) [21], TP53 [39,40,97], or Kirsten rat sarcoma viral oncogene homolog (KRAS) [98,99] mutations, can further shape whether KDM6 exerts tumor-suppressive or oncogenic activities.

4.2.1. KDM6A as a tumor suppressor in hematologic malignancies

Current studies suggest that KDM6A may contribute to tumor suppression and tumor maintenance or progression **(**Table 2**)** in different types of cancers [100,101]. In hematologic malignancies, such as leukemia and lymphoma, KDM6A mutations are frequently observed, consistent with a tumor suppressor role.

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive hematologic malignancy characterized by the aberrant proliferation of immature T cells. The loss of KDM6A function resulted in increased levels of H3K27me3 at the promoters of tumor suppressor genes, such as *Cdkn2a* (Cyclin Dependent Kinase Inhibitor 2A, p16) and *Cdkn2b* (p15), which are critical for cell cycle regulation and apoptosis [102,103].

Acute myeloid leukemia (AML) is a heterogeneous hematological malignancy characterized by the rapid proliferation of abnormal myeloid progenitor cells in the bone marrow and blood. KDM6A and KDM6B are critical in regulating *DDR* (DNA damage repair) gene expression in AML. Genotoxic stress influences KDM6 expression, and loss of KDM6A or KDM6B impairs DDR activation, increasing genomic instability and chemoresistance. Interestingly, combining KDM6A restoration or inhibition of EZH2 with standard chemotherapy could enhance tumor clearance in AML, suggesting a potential combination therapy. *KDM6A loss-of-function mutations are linked to chemoresistance, yet paradoxically, some relapsed AML cases exhibit increased KDM6A expression, suggesting dynamic regulation in different disease stages* [104]. Notably, EZH2 inhibitors can counteract the effects of KDM6A loss by reducing H3K27me3 levels and restoring the expression of silenced tumor suppressor genes. Thus, in AML and T-ALL, KDM6A functions as a bona fide tumor suppressor, and its loss contributes to malignancy. Therapeutically, EZH2 inhibition may mitigate the effects of KDM6A loss [96].

Multiple myeloma (MM) is a malignancy of plasma cells, characterized by the clonal proliferation of abnormal plasma cells in the bone marrow. Loss of KDM6A expression is common in MM, promoting the proliferation, clonogenicity, adhesion, and tumorigenicity of MM cells. MM patients with low KDM6A expression exhibited reduced *NLRC5* and *CIITA* levels, leading to decreased MHC expression and impaired T-cell infiltration [105]. Ezponda et al. have shown that KDM6A mutant cells display increased sensitivity to EZH2 inhibition both *in vitro* and *in vivo*, which is associated with decreased levels of *IRF4* and activation of IRF4 repressors such as *BCL6* and *IRF1*. Therefore, they suggested that rebalancing H3K27me3 levels at specific genes by targeting EZH2 may offer a better therapeutic strategy for MM cases harboring KDM6A mutations [101].

Table 2
Diverse oncogenic and tumor suppressor functions of KDM6A in different cancer types.

Activity	Cancer Type	Target Genes	Study Model	Reference
Oncogene	Hepatocellular Carcinoma (HCC)	FGFR4 and PI3K-AKT-mTOR	The xenograft tumor model	[112]
Oncogene	Glioblastoma	Periostin	Human glioblastoma stem cells (LN229 and U251 MG) from patients	[113]
Suppressor	Pancreatic Ductal Adenocarcinoma (PDAC)	GATA6	Human pancreatic tissue and PDAC cell line (HPNE)	[114]
Suppressor	Pancreatic Cancer	HDAC/BET pathways	Human PDAC cell lines (BxPC3, PANC1, KLM1 and MIA PaCa2)	[30,115]
Suppressor	Bladder Cancer	EZH2 and FOXA1	Human urothelial bladder carcinoma cell lines (RT4, SW780, and SCaBER) and bladder cancer patients	[116]
Suppressor	Breast Cancer	E-cadherin and Dicer	Human mammary epithelial cells (HMLE)	[117]
Suppressor	Multiple Myeloma	EZH2, MHC-I and II, NLRC5, and CIITA	Human multiple myeloma cell lines (ARD and ARP−1) and myeloma tumor cells	[101, 105]
Suppressor	T-ALL	NOTCH1, CDKN2A and CDKN2B	Bone marrow samples from T-ALL patients, Human T-ALL cell lines (PEER, TALL−1, and PF−382)	[102, 103]
Suppressor	AML	ETS、GATA、ENT1	Samples from AML patients, patient-derived xenografts (PDX), and leukemia cell lines	[104, 118–120]
Suppressor	Colorectal Cancer	HIF−1α, p15INK4B	Human colorectal cancer cell lines (HCT116, RKO, HCT8, HT29) and normal epithelia cell line (NCM460)	[121, 122]
Suppressor	Lung Cancer	KRAS and E-cadherin	Human lung cancer cell lines (A549 and LC−2/ad)	[99]

4.2.2. Context-dependent roles of KDM6A in solid tumors

In solid tumors, KDM6A exhibit heterogeneous roles, acting as either oncogenes or tumor suppressors depending on the type of cancer. KDM6A has also been identified as a tumor suppressor in bladder carcinoma (BCa) [106]. Mutations in the KDM6A gene are commonly found in urothelial carcinomas, where the loss of function leads to increased H3K27me3 levels at the promoters of genes that regulate cell cycle arrest and differentiation. Dee Ler et al. indicated that approximately 70 % of

KDM6A mutations resulted in the loss of KDM6A expression and demethylase function in bladder cancer. The loss of KDM6A expression leads to the activation of EZH2-regulated signaling, and bladder carcinoma can develop through H3K27me3 dysregulation, which leads to the accumulation of EZH2-mediated transcriptionally repressive regions [107]. This positions KDM6A as a crucial tumor suppressor in BCa and suggests EZH2 inhibitors or restoring KDM6A function as potential therapeutic strategies. Kaneko et al. showed that KDM6A knockout in mice reduces the expression of *Cdkn1a* and *Perp* (P53 Apoptosis Effector Related to PMP22), genes targeted by the tumor suppressor p53, increasing BCa risk in female mice. In humans, mutations or reduced expression of KDM6A are associated with a poor prognosis in female BCa patients. The study suggests that the X chromosome protects against BCa in females through a KDM6A-dependent epigenetic mechanism, highlighting KDM6A as a key sex-biased tumor suppressor with both demethylase-dependent and independent functions [106]. These insights could pave the way for sex-specific treatment strategies or biomarker profiling in bladder cancer.

In breast cancer cells, the KDM6A and H3K4 methyltransferase MLL4 (KMT2D) co-regulate gene expression programs that promote cell proliferation and invasion. KDM6A interacts with the C-terminal region of MLL4, and together they control a set of genes, including oncogenes and pro-metastatic genes. KDM6A and MLL4 work interdependently, with KDM6A demethylating H3K27me3 and MLL4 mediating H3K4 trimethylation at co-target genes. Clinically, high levels of KDM6A or MLL4 correlate with poor prognosis in breast cancer patients [31,108]. KDM6A is physically associated with the ER (Estrogen Receptor) and creates a permissive chromatin state on ER targets. Genome-wide chromatin immunoprecipitation-seq analysis identified KDM6A targets, including genes like *CXCR4*, which are crucial for breast cancer tumorigenesis and metastasis. KDM6A expression increases during ER^+ breast cancer progression, correlating positively with CXCR4 expression, and negatively with overall survival in ER^+ breast cancer patients [109].

KDM6A expression is lost in about 30 % of liver cancer patients. Deletion of KDM6A accelerates tumor development in mouse models of liver and pancreatic cancer, resulting in hyperactivation of the mTORC1 (mTOR complex 1) signaling pathway. KDM6A directly binds to and activates transcription of mTORC1 negative regulators like *DEPTOR* (DEP domain-containing mTOR interacting protein). In human tumors, KDM6A expression is inversely correlated with mTORC1 activity, and KDM6A-deficient tumors are more sensitive to mTORC1 inhibition. This suggests that targeting mTORC1 could be an effective treatment for cancers with low KDM6A expression, although clinical data are still pending [110]. Conversely, recent findings suggest that KDM6A overexpression in hepatocellular carcinoma can drive tumor progression and influence treatment response. KDM6A enhances *FGFR4* expression, leading to activation of the PI3K–AKT–mTOR pathway, which promotes tumor growth and metabolic reprogramming. Inhibiting KDM6A-FGFR4 signaling may enhance lenvatinib efficacy, positioning KDM6A as both a prognostic biomarker and a potential therapeutic target in liver cancer. These findings highlight the context-dependent roles of KDM6A, with its loss driving mTORC1 activation and sensitivity to mTOR inhibitors, while its overexpression confers resistance to lenvatinib via FGFR4 signaling [111].

The dual role of KDM6A as both a tumor suppressor and oncogene has been demonstrated, but the factors determining this switch remain unidentified. Further research could explore the interplay between KDM6A, p53, and MLL4 to determine how context dictates pro- or anti-tumor outcomes.

4.2.3. Context-dependent roles of KDM6B in hematological malignancies

Unlike KDM6A, which predominantly acts as a tumor suppressor, KDM6B is known to play a controversial dual role in human cancers in diverse types of cancer (Table 3) depending on the cellular context and type of cancer [123]. Its role can pivot based on tumor microenvironment cues, immune cell infiltration, and metabolic adaptations, illustrating the complexity of targeting KDM6B. While KDM6B is crucial for disease initiation and maintenance by controlling oncogenic gene targets through H3K27 methylation modulation in T-ALL, KDM6A plays an opposing role as a tumor suppressor, frequently inactivated in T-ALL. Importantly, the small molecule inhibitor GSK-J4, which targets KDM6B activity (to a lesser extent KDM6A), has been shown to impede T-ALL growth. This highlights an intriguing contrast where proteins

Table 3
Diverse oncogenic and tumor suppressor functions of KDM6B in different cancer types.

Activity	Cancer Type	Target Genes	Study Model	Reference
Oncogene	Clear Cell Renal Carcinoma (ccRCC)	SLUG	Human ccRCC cell lines (Caki−2 and ACHN)	[131]
Oncogene	Diffuse Large B-cell Lymphoma (DLBCL)	IRF4	DLBCL cells and tumor tissues from the mouse model, NOD/SCID mice, human DLBCL cell lines (Karpas422, OCI-Ly1, and OCI-Ly8)	[53,127]
Oncogene	Cervical Squamous Cell Carcinoma	PFKFB2	Human cervical squamous cell carcinoma (THP−1, SiHa and C33A)	[132]
Oncogene	Multiple Myeloma (MM)	ELK1 and FOS	Human MM lines (MM.1S, RPMI 8226, KMM−1, NCI-H929, KMS−11 and KMS−27)	[80]
Oncogene	Acute Myeloid Leukemia (AML)	HOX and AP1	C57Bl/6 Kdm6bfl/fl and Utx1fl/fl mice, primary cells from AML patients and human AML cell lines (Kasumi−1, THP−1, KG−1, and KG−1a)	[51,119]
Oncogene	Melanoma	STC1 and CCL2	Human melanoma cell lines (A375-LM3 and MeWo-LM2), BALB/c nude and NOD/SCID mice	[41]
Oncogene	Ovarian Cancer	Erbeta, TGF-b1, and HER2	Human ovarian cancer cell lines (SKOV3 and A2780cis) and human tissue samples of ovarian cancer	[133, 134]
Suppressor	Non-Small Cell Lung Cancer (NSCLC)	FOXO1 and E-cadherin	Human NSCLC cell lines (A549, SK-MES−1, H1650, H292, and H358), tumors and paracancerous tissues from NSCLC patients	[135, 136]
Suppressor	Colon Cancer	p15INK4B	Human cancer cell lines (colo201, DLD1, HCT116, LOVO, and SW620)	[122]
Suppressor	Pancreatic Cancer	C/EBPa	Human pancreas tissue and pancreatic cancer cell lines (BxPC3, PANC1, SU.86.86, and MiaPaCa2)	[98]
Suppressor	Prostate Cancer	EZH2, cyclin D1, and p53	Human tissue samples of patients and human prostate cancer cell lines (DU 145, LNCaP, PC−3, and C42B)	[137, 138]

with similar enzymatic functions exhibit opposing effects in the same disease [102].

KDM6B is located adjacent to the p53 tumor suppressor and directly interacts with it, decreasing H3K27me3 occupancy at the TP53 gene promoter [39,40]. Its tumor-suppressive role is evident in AML, particularly in M2 and M3 subtypes, where KDM6B is expressed at low levels while activating a transcriptional myeloid differentiation program centered on *C/EBPβ* (CCAAT/enhancer-binding protein beta) and *HOXA* gene clusters (*HOXA5*, *HOXA7*, *HOXA9*, and *HOXA11*) [119,124,125]. Neomorphic H3K27M/I mutations in AML are associated with RUNX1 mutations, significantly altering the leukemia epigenetic landscape. The presence of H3K27M/I mutations resulted in global reductions of H3K27me2/3 levels. Mouse models further demonstrate that these mutations act as disease accelerators, particularly in AML cases with RUNX1-RUNX1T1 translocations [44]. Research indicates that KDM6B is highly expressed in several AML cell lines as well as in primary bone marrow-derived mononuclear cells from AML patients. Interestingly, the accumulation of H3K27me3 facilitates the proliferation and colony formation of both primary AML cells and AML cell lines, suggesting that KDM6B may exert opposing roles depending on the AML subtype [96, 124,125]. Notably, KDM6B can function as an oncogenic protein through various mechanisms, promoting proliferation, inflammation, and migration, thus enabling cells to evade differentiation and apoptosis [126].

KDM6B plays a role in the antigen-driven differentiation of germinal center B-cells. In the context of DLBCL (diffuse large B-cell lymphoma), particularly the activated B-cell-like (ABC) subtype, KDM6B is frequently overexpressed and contributes to oncogenic pathway activation. KDM6B enhances the phosphorylation of proteins involved in the B-cell receptor (BCR) signaling pathway. Moreover, KDM6B was found to have an anti-apoptotic effect by promoting the expression of *IRF4* through mediation of the NF-κB signaling pathway and BCL-2 [127]. Similarly, in Hodgkin lymphoma (HL), KDM6B often acts as an oncogene. KDM6B activation influences the downstream BCL6 protein, which plays a crucial role in maintaining normal B cell survival and the development of B cell non-Hodgkin lymphoma (NHL) [75].

4.2.4. Context-dependent roles of KDM6B in solid tumors

KDM6B function in solid tumors also varies widely based on tissue type and signaling context. Patients with glioblastoma often experience a decrease in H3K27me3 marks and high levels of KDM6B expression. It was found that STAT3 inhibition suppresses KDM6B in glioblastoma stem cells (GSCs). KDM6B expression is significantly upregulated in glioblastoma tissues compared to healthy brain tissues, and the pharmacological inhibition of KDM6B with GSK-J4 reduces tumor cell proliferation, migration, and enhances apoptosis [43]. However, some studies suggest a tumor-suppressor role for KDM6B in glioma. KDM6B modulates the expression of key transcription factors, including p53, and may directly regulate p53 activity independently of chromatin modification, contributing to glioblastoma stem-cell differentiation. This dual function suggests that KDM6B may either promote tumor growth or drive differentiation depending on the glioblastoma subtype [39]. Tumor heterogeneity within glioblastoma likely underlies these apparently conflicting roles, underscoring the necessity for subtype-specific research. Furthermore, the STAT3-mediated regulation of KDM6B maintains the repression of differentiation-specific genes such as *Myt1* (Myelin Transcription Factor 1), *FGF21* (Fibroblast Growth Factor 21), and *GDF15* (Growth Differentiation Factor 15), thereby promoting the self-renewal capacity of both normal neural stem cells and GSCs [43].

KDM6B expression is critical for melanoma growth and metastasis [128]. Overexpression of KDM6B promotes a tumor-supportive microenvironment by stimulating angiogenesis and macrophage recruitment. It also activates pro-tumorigenic PI3K signaling through interactions with stromal components. Additionally, KDM6B overexpression in melanoma cells promotes tumor expansion by activating NF-κB and BMP (Bone Morphogentic Protein) signaling pathways, which regulate STC1 (stanniocalcin 1) and CCL2, essential for self-renewal and macrophage recruitment [41]. Further research could clarify if KDM6B also modulates immune checkpoint molecules, such as PD-L1, to enhance immune evasion in melanoma. These findings highlight the crucial role of KDM6B dysregulation in melanoma tumor progression. Baksh et al. underscore how metabolism-driven changes in α-KG modulates KDM6B and H3K27me3 dynamics, thereby influencing epidermal stem cell differentiation and the initiation of malignant squamous cell carcinomas. Persistent H3K27 trimethylation, due to a lack of KDM6B activity, can sustain a stem-like program with hyperproliferative and tumorigenic potential in the epidermis [129].

4.2.5. KDM6B in the tumor microenvironment

Beyond intrinsic cancer cell roles, KDM6B regulates tumor-associated myeloid cells of the tumor microenvironment (TME). In glioblastoma, the KDM6B is highly expressed by myeloid cells including monocytes, macrophages, and dendritic cells, and drives an immune-suppressive phenotype within the tumor microenvironment. $KDM6B^{high}$ myeloid cells co-express markers such as KLF2, IL-10, CXCL8, and MAFB, and are spatially distinct from CD8 + T cell-rich regions, suggesting their role in forming an immunosuppressive niche. Mechanistically, KDM6B knockout myeloid cells exhibit enhanced antigen presentation, a stronger interferon response (upregulation of *ISG15*, *IRF7*, *CXCL9*, and *CXCL10*), and increased phagocytic capacity (via *FCGR1* and *FCGR4*). Loss of KDM6B prevents the usual demethylation of *MAF*, *SOCS3*, and *SIRPA*, which typically restrain pro-inflammatory pathways by curbing cytokine production and phagocytosis [130]. Though direct studies on KDM6B in tumor-infiltrating Tregs are limited, evidence indicates that KDM6B has been implicated in the stabilization and suppressive function of Tregs, with potential consequences for tumor immune evasion. Browning et al. demonstrated that BMPR1a (bone morphogenic protein receptor 1a) signaling maintains FOXP3 expression in peripheral Tregs by preventing the upregulation of KDM6B, which otherwise destabilizes the Treg program and promotes Th1/Th17-like effector differentiation. Inhibition of KDM6B with GSK-J4 restored FOXP3 expression and suppressed pro-inflammatory gene programs, underscoring the key role of the BMP–KDM6B axis in regulating Treg stability and immune homeostasis [72].

The findings underline the dual role of KDM6B in acting as an oncogene in certain contexts by promoting cell survival and proliferation as well as serving as a tumor suppressor by modulating epigenetic marks that control gene expression and cellular growth. Beyond intrinsic tumor cell effects, KDM6 enzymes also shape the tumor immune microenvironment (e.g., influencing myeloid cell behavior in gliomas). This crosstalk could be crucial for cancer immunology and therapy. Combining KDM6-targeted strategies with checkpoint inhibitors might help overcome the immunosuppressive niche formed by tumor-associated macrophages. This functional dichotomy suggests that KDM6B is a potential therapeutic target in cancer, but its inhibition or activation must be precisely tailored to the cancer type and microenvironment.

5. Discussion and future perspectives

This review highlights the critical role of KDM6 family members, KDM6A and KDM6B, in the pathogenesis of autoimmune diseases and cancer. In autoimmune disorders, genetic predisposition, environmental triggers, and hormonal factors collectively activate autoreactive T cells, particularly $CD4^+$ T helper cells. Once activated, these cells initiate an immune cascade that involves the recruitment of various immune cells, including monocytes, macrophages, and neutrophils. These immune cells secrete pro-inflammatory cytokines such as IFN-α, TNF-α, IL-1, and IL-6, which further drive inflammation and tissue damage. KDM6 demethylases play a pivotal role in shaping immune responses, and their inhibition has shown promising potential in modulating inflammation.

KDM6 inhibition could be studied in combination with established biologics, such as TNF-α blockers in RA or B-cell–depleting agents in SLE, to enhance therapeutic efficacy.

KDM6B inhibition has been shown to suppress Th17-driven inflammation, as demonstrated by its ability to downregulate RORγT, a key transcription factor for Th17 differentiation. Given that Th17 cells are central to autoimmune pathology, targeting KDM6B could serve as an effective strategy for reducing chronic inflammation. Small-molecule inhibitors such as GSK-J4 have gained traction for their ability to suppress pro-inflammatory immune cell differentiation (e.g., Th17 cells and classically activated macrophages), restoring the balance between pro- and anti-inflammatory signals. By preventing excessive immune activation, KDM6B inhibition may mitigate long-term tissue damage in autoimmune conditions. However, because KDM6 demethylases regulate numerous genes involved in both innate and adaptive immunity, their inhibition may also impair host defense mechanisms. Thus, future studies must carefully weigh the benefits of immune modulation against the potential for immune suppression, particularly in patients with latent infections or compromised immunity.

While GSK-J4 has demonstrated broad anti-inflammatory effects, several challenges must be addressed before translating these strategies into clinical practice. One of the major difficulties is the incomplete understanding of KDM6B's function across different diseases. KDM6B regulates numerous genes via both histone demethylase-dependent and independent mechanisms, and its effects are highly context-dependent. Multi-omics approaches, integrating transcriptomics, proteomics, and metabolomics, could solve the complex networks regulated by KDM6B in diverse cell types. For example, while KDM6B inhibition in monocytes and macrophages may limit inflammation in autoimmune diseases, enhancing KDM6A activity in Tregs might improve immune tolerance. This distinction underscores a broader challenge in precision therapy: how to select the appropriate KDM6-targeting strategy (inhibition or activation), and which paralog to target, depending on disease context, patient gender (given KDM6A's X-linkage), tissue-specific roles, and microenvironmental cues. These variables must be carefully considered in future preclinical and clinical studies to avoid unintended consequences.

Moreover, KDM6C (also known as UTY), the Y chromosome paralog of KDM6A, adds further complexity to the functional landscape of the KDM6 family. Although enzymatically inactive or only weakly active, KDM6C may act as a chromatin scaffold and contribute to transcriptional regulation. Evidence from knockout models suggests that KDM6C can partially compensate for KDM6A loss, particularly in developmental and hematopoietic contexts. This compensatory role is especially relevant in sex-biased diseases such as MS, where X chromosome dosage and escape from X-inactivation influence immune function.

This functional divergence within the KDM6 family underscores a broader challenge for precision therapy: determining when to inhibit or activate specific KDM6 paralogs depending on disease type, tissue context, patient gender (given the X-linked nature of KDM6A), and microenvironmental cues. These variables must be carefully considered in future preclinical and clinical studies to optimize therapeutic outcomes while minimizing unintended effects.

These enzymes play dual roles in cancer, acting as both tumor suppressors and oncogenes depending on the tumor microenvironment, disease stage, and cellular context. By targeting H3K27me2/3, KDM6A and KDM6B are activated by inflammatory and stress-induced transcription factors, driving key pathways involved in immune regulation, tumor progression, and therapy resistance. While their role in host defense mechanisms involves promoting pro-inflammatory cytokine expression and cell cycle arrest, their overactivation can result in widespread transcriptional dysregulation, genomic instability, and loss of nuclear homeostasis. Therapeutically, combining KDM6 inhibitors with EZH2 inhibitors may help restore normal H3K27 methylation patterns and resensitize tumors to conventional therapies. In addition to their interplay with EZH2, KDM6A/B also functionally intersect with histone deacetylases (HDACs), particularly HDAC1–3, adding a second regulatory layer to chromatin remodeling. While KDM6B activates transcription by removing H3K27me3, HDACs repress it by deacetylating H3K27ac. This antagonism was demonstrated in pancreatic ductal adenocarcinoma, where KDM6A loss impaired p300 recruitment, reduced H3K27ac at tumor suppressor promoters (e.g., CDKN1A), and enhanced tumor aggressiveness. Notably, KDM6A-deficient cells showed heightened sensitivity to HDAC inhibitors like vorinostat, which restored gene expression and suppressed tumor growth [115]. These findings support co-targeting H3K27 methylation and acetylation, such as dual inhibitors like JMJD3/HDAC-IN-1 [139], as a promising precision epigenetic strategy.

The potential of KDM6 enzymes as prognostic biomarkers for cancer is significant. Their expression and mutational status provide insights into tumor aggressiveness, therapy resistance, and treatment response. For example, loss of KDM6A expression is associated with an aggressive phenotype and poor prognosis, particularly due to EZH2 activation, which represses tumor suppressor genes. This suggests that in KDM6A-deficient cancers, such as bladder cancer, therapies targeting EZH2 could selectively eliminate tumor cells, positioning KDM6A as a predictive biomarker for selecting patients who might benefit from EZH2 inhibitors.

Monitoring the activity of KDM6 enzymes could also inform treatment strategies, particularly for adjusting targeted therapies. Given KDM6B's role in immune regulation and inflammation, its expression could help predict a patient's response to immunotherapies, such as immune checkpoint inhibitors. KDM6 enzymes not only drive tumor initiation but also influence tumor progression and therapeutic resistance. As tumors evolve, changes in KDM6A and KDM6B expression could signal which cancers are more likely to respond to epigenetic therapies, making these enzymes dynamic markers of therapeutic susceptibility. Integrating KDM6 profiling into precision oncology could streamline personalized therapeutic decisions, optimizing patient outcomes. Alterations in KDM6A and KDM6B occur across multiple cancer types, such as bladder, breast, and hematological cancers, making them less specific for diagnostic purposes. However, their ability to influence the tumor microenvironment, by modulating immune cell infiltration and inflammatory signaling pathways, positions them as more effective predictors of treatment response rather than general diagnostic markers. For instance, KDM6B's ability to shape the immune response may help forecast tumor responses to immune checkpoint blockade, reinforcing its value in immunotherapy prediction.

KDM6A and KDM6B are central to chromatin remodeling, immune regulation, and tumor progression, making them particularly useful as predictive biomarkers for informing treatment decisions and anticipating therapeutic outcomes. However, their widespread occurrence across different types of cancer and their dynamic roles in therapy resistance and tumor evolution limit their application for early cancer diagnosis [40,118]. Therefore, incorporating KDM6 expressions or mutation data into multi-parameter precision therapy frameworks may enhance its clinical efficiency, especially when combined with genomic and immunological markers.

Despite promising preclinical evidence, no clinical trials have evaluated KDM6 inhibitors like GSK-J4 in humans, posing a major translational gap. GSK-J4, while potent, is a broad-spectrum inhibitor of JmjC domain-containing demethylases, raising concerns about potential off-target effects. Studies have demonstrated that at high concentrations, GSK-J4 also inhibits KDM5 family, particularly KDM5B and KDM5C, suggesting potential off-target effects. This lack of selectivity raises concerns that some of GSK-J4's observed biological activities may result from unintended KDM5 inhibition, which is undesirable in a therapeutic setting. For instance, KDM5C acts as a tumor suppressor in ovarian and renal cancers through regulation of chromatin structure and immune signaling [21]. Its off-target inhibition by GSK-J4 could compromise genome integrity or disrupt antitumor immunity, raising safety concerns in clinical contexts. Such limitations in selectivity are common among

first-generation epigenetic probes and significantly hinder their clinical translatability. Furthermore, KDM6B overexpression has been implicated in chemotherapy resistance, particularly under hypoxic conditions [21]. In these settings, elevated KDM6B can promote survival pathways and stem-like phenotypes, contributing to drug tolerance. These resistance mechanisms underscore the need to stratify patients based on KDM6B expression when considering KDM6-targeted therapies. Another critical challenge is the complex interplay between histone modifications. Histone demethylation does not act in isolation but intersects with other epigenetic mechanisms, such as DNA methylation and histone acetylation, to regulate gene expression. Altering H3K27me3 levels without accounting for compensatory epigenetic changes may lead to unpredictable biological consequences. Therefore, a systems-level understanding of epigenetic crosstalk is necessary to predict and mitigate unintended outcomes of KDM6 inhibition. To address these issues, next-generation compounds such as KDM6B-selective PROTACs have been developed. These proteolysis-targeting chimeras enable precise degradation of KDM6B while sparing related demethylases, thereby reducing off-target toxicity and improving specificity. Such strategies represent a promising direction for overcoming the limitations of GSK-J4 and advancing KDM6-targeted therapy toward clinical application. Future efforts should focus on refining small-molecule inhibitors that selectively target KDM6B while preserving essential chromatin functions regulated by other demethylases.

The roles of KDM6A and KDM6B in both autoimmune diseases and cancer are highly context-dependent and complex. Rather than blanket inhibition, future therapies must be tailored to specific diseases, patient profiles, and stages of progression. Genome-wide analyses and comprehensive integration of epigenetic data will be crucial in identifying precise therapeutic windows for KDM6-targeted interventions. This will help identify the exact roles these enzymes play in gene regulation across different diseases, enabling more precise targeting. Additionally, future studies should explore how KDM6 inhibition might be combined with other therapeutic interventions, whether through direct targeting of other epigenetic mechanisms or by modulating immune and inflammatory pathways in tandem.

Although preliminary studies with KDM6B inhibitors like GSK-J4 have demonstrated promising anti-inflammatory effects, further preclinical and clinical validation is essential before these compounds can advance to human trials.

In its current form, GSK-J4 faces several substantial limitations that hinder its translational potential. Particularly concerning are its poor target selectivity and the high doses required for efficacy. In some preclinical models, achieving meaningful in vivo effects requires relatively high doses, typically in the range of 50–100 mg/kg per day in mice [140–142]. Such dosing poses practical challenges for human translation, as it increases the risk of off-target interactions and toxicity. Additionally, its low aqueous solubility and poor compatibility with oral delivery further complicates its formulation and therapeutic use. These issues are compounded by its chemical structure: GSK-J4 is an ethyl ester prodrug of the active compound GSK-J1, a design that contributes to its overall suboptimal pharmacokinetic profile. Together, these limitations emphasize why, despite encouraging biological data, GSK-J4 remains a useful tool compound rather than a viable drug candidate for clinical development.

Research should not only confirm the therapeutic potential of KDM6 inhibition but also elucidate its broader epigenetic consequences. A finer understanding of KDM6 regulation across immune cell subsets and cancer lineages will help refine therapeutic strategies. Ultimately, the clinical application of KDM6-targeted therapies will depend on the ability to fine-tune these treatments to the specific disease context. Given the heterogeneity of both cancer and autoimmune diseases, personalized approaches that integrate genetic, epigenetic, and environmental factors are likely to yield the most effective therapeutic outcomes. With continued research and innovation, targeting KDM6A and KDM6B could become a key component of future treatment strategies, offering new hope for patients suffering from complex immune and oncologic disorders.

CRediT authorship contribution statement

Mahsa Nastaranpour: Writing - original draft. **Aman Damara:** Writing - original draft. **Stephan Grabbe:** Writing - review & editing. **Fatemeh Shahneh:** Writing - original draft, Writing - review & editing, Supervision, Funding acquisition, Conceptualization.

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Declaration of Competing Interest

I hereby declare that I have no conflicts of interest to disclose in relation to the manuscript entitled " **Lysine Demethylase 6: A Promising Therapeutic Target in Autoimmunity and Cancer**".

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Data availability

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

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