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KDM 6B (JMJD3) in Cancer: Unlocking Epigenetic Targets for Effective Therapeutic Strategies

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ABSTRACT
An aberration of the epigenetic landscape represents a commonality of cancers. Histone-modifying enzymes mediate the epigenetic landscape and serve to initiate solid tumors, support tumor progression, and facilitate immune escape. Among these enzymes, KDM6B (also known as JMJD3) a histone demethylase with a Jumonji-C domain, has a central role in regulating gene expression by facilitating the removal of repressive histone marks, specifically the demethylation of H3K27me3.The focus of this review is to summarize the biological functions of KDM6B, highlight its dual oncogenic and tumor-suppressive roles, and explore the therapeutic potential of KDM6B in various cancers while also considering the limitations of available inhibitors and future directions for clinical application. We drew upon evidence derived from molecular oncology, epigenetics, and pharmacological studies to characterize the role of KDM6B across tumor types. We particularly focused on inhibitor development (e.g., GSK-J4, QC6352), combination strategies, and biomarker-driven precision oncology. KDM6B functions in a context-dependent manner: it can suppress certain hematological cancers and promote solid tumors, including gliomas, breast cancer, and prostate cancer. Molecular pharmacological inhibition has demonstrated preclinical efficacy particularly in combination with standard-of-care chemotherapy or immune checkpoint inhibitors; however, specificity and drug resistance is a dilemma, as is personal safety. KDM6B represents an exciting and complex epigenetic target for cancer therapy. The structural advances in drug discovery will impact the potential for successful clinical outcomes.

1. INTRODUCTION:

Cancer remains one of the leading causes of global death. It is an important indication of the complex and multiple origins of this disease. There are many factors involved in cancer development, mostly including genetic mutations and epigenetic modifications that can subtly impact epigenetic or cellular behaviors. of these important factors, epigenetic dysregulation changes in gene expression that can be inherited but do not alter the DNA sequence are one of the major influences on tumorigenesis, tumor growth, metastasis, and the rising clinical issue of treatment resistance, which complicates efficacy[1].

Fundamental epigenetic mechanisms, such as DNA methylation, histone modifications, and the activities of various non-coding RNAs, are critical in remodeling chromatin and altering gene availability, and they actuate many biological functions that are essential for normal cell function and proliferation[2]. These processes are similar to coordinating an orchestra; each must work in a concerted manner for

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correct gene regulation. A histone modification that has an important association with cancer is trimethylation of lysine 27 on histone H3 (H3K27me3). This specific modification is also often associated with the silencing of tumor suppressor genes, which ultimately allows tumor cells to overcome growth control[3]. The consequence of incorrect regulation will be the unregulated proliferation of cells, which is a defining characteristic of cancer.

Within this vast area of cancer epigenetics, histone demethylases, especially those of the Jumonji C (JmjC) domain-containing family, stand out as important player(s) with potentially serious implications for tumorigenesis. Histone demethylases are not merely spectator enzymes; rather, they reverse histone methylation marks, meaning they directly impact the expression of genes needed for cells to function properly. A particularly noteworthy example is KDM6B (JMJD3), which has an incredible ability to demethylate H3K27me3 to H3K27me1/0 and is involved in processes relevant to cell cycle, immune response, cellular aging, and differentiation[4,5]. KDM6B exemplifies a regulatory player on the cancer biology stage because it can activate gene expression for a broad spectrum of functions.Moreover, KDM6B is tightly regulated by both internal cellular signals, such as cytokines, oxidative stressors, and other developmental indicators, as well as external environmental elements.It acts downstream of significant transcription factors like NF-kB,STAT, and IRFs, thus orchestrating vast transnational responses that are closely intertwined with processes of inflammation, differentiation, and tissue regeneration[6,7]. By serving as a central nexus through which many cellular signals converge, KDM6B wields influence not only in maintaining normal physiological conditions but also in the pathologies encountered in cancer.

The role of KDM6B is highly context-dependent in the field of oncology, embodying a certain duality that may represent both difficulty and opportunity in the development of future therapies. such duct rause features like cell cycle arrest and senescence and it presumably eliminates the unlimited proliferation of cancerous cells. In contrast, firm tumors along the lines of breast cancer, prostate cancer, and glioblastoma often reach KDM6B when considered within the oncogenic connotative framework, enacting similar features like inflammation, epithelial-mesenchymal transition, and eventually metastasis[8,9].As the Epigenetic therapy space develops with increasing interest, KDM6B has emerged as a new and exciting target for possible therapeutic agents. There are currently clinical approaches with DNA methyltransferase (DNMTs) and histone deacetylase (HDACs) inhibitors, but KDM6B is still mainly in pre-clinical development[10]. Nevertheless, there are promising developments on the horizon, including GSK-J4, a cell-permeable prodrug of the selective KDM6 inhibitor GSK-J1.Since the community is working hard to develop next-generation small molecules, PROTACs (proteolysis-targeting chimaeras), and agents that act via dual epigenetic mechanisms, this novel agent showed strong anti-cancer effects in a number of in vitro and in vivo experimental models [11,12].

2. Biological Role Of Kdm6b In Normal Physiology:

KDM6B is critical for the precise modulation of gene expression through diverse epigenetic changes to chromatin structure. In particular, KDM6B catalyzes the removal of the H3K27me repressive histone mark, which represents a succinct model of the transcriptional activation of genes requiring regulation for vital biological processes, including inflammation, differentiation, immunity, senescence, and development[13,14].

2.1 Inflammation and Immune Response:

KDM6B plays a central role in coordinating pro-inflammatory responses in both the innate and adaptive arms of immunity, an activity that is emerging as complex and critical for understanding inflammatory disorders.KDM6B is directly transcriptionally activated by the NF-kB signaling pathway after stimulation by several TLR (Toll-like receptor) ligands and pro-inflammatory cytokines, such as TNF-a and IL-1v. This activation underlines its important role in stimulating inflammatory responses, indicating that KDM6B is an important regulator in the early stages of the immune response, thereby ensuring that the cell is sufficiently trained to provide a potent defense against pathogen invasion or tissue injury [15,16].Thus, KDM6B is actively involved in transcriptional activation of the inflammatory cytokines IL-6, IL-12, TNF-a and interferons (IFNs) by demethylating H3K27me3 at their respective gene promoters. Demethylation is a critical process, not only for the potential cytokine expression but also for the general inflammatory environment, which affects both the intensity and duration of the immune response triggered in response to pathogens or cellular stress [17].This modulation not only impacts immediate immune responses but also participates in the long-term functionality of adaptive immunity by influencing the differentiation and performance of different types of immune cells [18,19].

2.2 Cell Differentiation and Development

In many tissues, KDM6B plays a crucial role in controlling lineage definition and differentiation, which is crucial for the growth and upkeep of tissues.Appropriately, KDM6B is an important mediator of the transition from a pluripotent state to a

Journal of Molecular Science
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specific cell fate in ESCs. This is important for ensuring that lineage-specific genes are activated correctly, and ultimately, stem cells can complete their fate decisions, culminating in specialized cells that are components of various tissues and organs in the body[20]. KDM6B contributes to neurogenesis, a complex developmental process, by disrupting Polycomb-mediated silencing to enhance the expression of critical neurogenic factors (such as NeuroD1 and Mash1), which promote neuronal differentiation and maturation.The correct development and operation of the nervous system depend on both KDM6B's promotion of neuronal differentiation from progenitor cells and its involvement in the temporal and spatial regulation of neuronal maturation[21,22].

2.3 Senescence and Cell Cycle Regulation:

KDM6B occupies an important role in the promotion of oncogene-induced senescence (OIS), an essential tumor-suppressive mechanism that mitigates unrestricted cell proliferation: In response to oncogenic RAS activation or significant DNA damage, KDM6B demethylates H3K27me3 at the crucial p16^INK4a^/ARF locus, promoting cell cycle arrest and starting the senescence program to reduce the proliferation of damaged cells and ultimately reduce tumorigenesis while maintaining tissue integrity during oncogene-induced stress[23].By cooperating with the p53 and RB tumour suppressor pathways to increase cellular responses to stress and play a significant role in tumour suppression, KDM6B further strengthens the senescence program[24].

KDM6B is necessary for the development of immune lineages, largely influencing the building of a responsive and functional immune system. KDM6B meets this functional role when mature blood cells are formed from hematopoietic stem cells (HSCs), because it regulates both the unexpected differentiation of HSCs toward myeloid and lymphoid lineages, which is an important facet of hematopoiesis, and the dynamic transcriptional networks coordinating these differentiation pathways, which allow for the proper generation of various blood cell types essential for sustaining

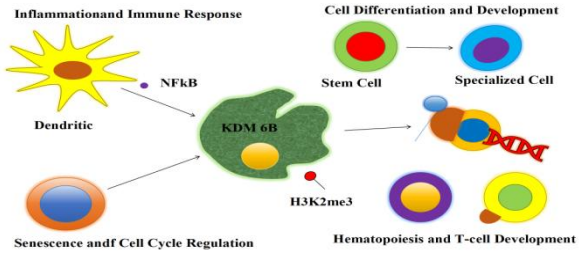

Figure 1. Biological Role of KDM6B in Normal Physiology.

effective immune responses and overallfunction.KDM6B also promotes the differentiation of Th1 (type 1 T-helper) and Th17 cells, which are T-helper subsets responsible for special immune responses related to the activation of transcription factors including T-bet and RORγt amplifying their cytokine profile. This detailed precision is important in building a T-cell cytokine profile that allows the immune system to orchestrate specific responses to various pathogens, demonstrating their role in immune defense mechanisms[25,26].

2.4 Hematopoiesis and T-cell Development

Table 1. Major Physiological Functions of KDM6B

Sl.no	Biological Process	KDM6B Role	Key Target Genes	References
1	Inflammation	Enhances cytokine expression via NF-κB/STAT1	IL-6, TNF-α, IL-12	27
2	Neuronal differentiation	Activates neurogenic transcription factors	Mash1, NeuroD1	28
3	Osteogenesis	Promotes bone differentiation via RUNX2	ALP, OCN	29
4	Senescence	Induces cell cycle arrest via p16/ARF	p16^INK4a^, ARF	30
5	T-cell differentiation	Regulates Th1/Th17 pathways	T-bet, RORγt	31

3. KDM6B In Cancer: A Dual-Edged Sword:

KDM6B, sometimes referred to as JMJD3, plays a crucial part in the biology of cancer and is highly paradoxical because it may function as either an oncogene or a tumour suppressor.This complex double-edged sword is deeply affected by multiple variables, such as the cancer type itself, the epigenetic environment around it, and the cellular context in which KDM6B functions. This amazing complexity highlights the possibility of one gene having drastically different effects in different cell types or under different biological conditions[32]. KDM6B's unique capacity to demethylate H3K27me3, a sign of transcriptional repression, and release the expression of both tumor-suppressive and pro-oncogenic genes is one of the intricate mechanisms behind this duality.This multifunctional activity makes KDM6B a central player in the complex web of cellular mechanisms that determine tumor behavior and progression. [33,34].

3.1 Tumor Suppressor Role of KDM6B

In cases of Hematologic Malignancies-Acute Myeloid Leukemia (AML): Multiple independent studies have described a significant loss of KDM6B expression or actual inactivation in many different AML subtypes. Such decreases are of great concern as they are strongly associated with worse patient

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outcomes, hence highlighting the critical role of KDM6B as a tumor suppressor in this setting[35].The protective mechanism of KDM6B is multifactorial; one of the most important KDM6B functions is the activation of the INK4A-ARF locus (mainly p16INK4a and p14ARF). This senescence is critical in oncogene-induced senescence and acts as a key roadblock against leukemogenesis, effectively suppressing cancer progression [36].Recently, studies in mouse models of AML deficient in KDM6B have revealed worrying dynamics: these models have significantly improved self-renewal potential and defective myeloid differentiation. These changes are strongly associated with leukemia progression and indicate that KDM6B deletion may promote the development of a more aggressive cancer phenotype and outcome[37].

Lymphoma: KDM6B is a critical negative regulator of NOTCH1 signaling in T-cell acute lymphoblastic leukemia (T-ALL). The authors demonstrate how inhibiting this crucial route enabled KDM6B to significantly lower oncogenic transcriptional activity while simultaneously boosting apoptotic processes, hence providing a protective impact that may be utilised in the development of novel therapeutic strategies[38].Furthermore, the demethylase activity of KDM6B has important implications for tumor suppression in that it mediates the restoration of expression of several tumor suppressor genes, including the well-characterized p21. Thus, this restoration reflects the protective function of KDM6B in lymphoid malignancies, which points to its possibility of being explored as a target to improve the success of current therapeutic interventions[39].

3.2 Oncogenic Role of KDM6B

Breast Cancer: In contrast to its tumor-suppressive functions in hematopoietic malignancies, KDM6B is over expressed in many types of solid tumors, particularly in estrogen receptor-positive (ER+) and triple-negative breast cancers (TNBC), both of which have aggressive phenotypes and few therapeutic options[40,41].Furthermore, pharmacological inhibition of KDM6B using compounds such as GSK-J4 has shown encouraging results in preclinical models of TNBC. These studies show not only a slowing of tumor growth but also an increase in the sensitivity of these tumors to chemotherapeutic agents, suggesting that targeted inhibition of KDM6B may be a novel and effective therapeutic strategy for treating difficult types of breast cancer [42].

Prostate Cancer: It is a similar situation in prostate cancer, where overexpression of KDM6B significantly enhances androgen receptor (AR) signaling pathways which are a key driver of prostate cancer cell proliferation and survival. This amplification facilitates cell cycle progression and thus highlights KDM6B's oncogenic potential in this malignancy[43,44].

Glioblastoma: In the difficult setting of glioblastoma multiforme (GBM), a fatal tumor with a very poor prognosis, KDM6B seems to have a key auxiliary function for the self-renewal of glioma stem-like cells. This involvement is mediated via its regulatory role on neurodevelopmental genes, which in turn maintain the CSC phenotype that is characteristic of GBM tumor heterogeneity and resistance [45].

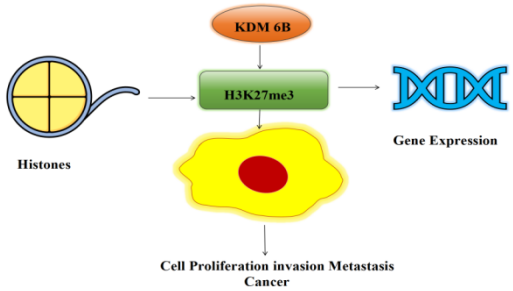

Figure 2. KDM 6B role in cancer

Table 2. Context-Specific Role of KDM6B in Cancer

Sl.no	Cancer Type	KDM6B Role	Key Targets / Pathways	Outcome	Reference
1	Acute Myeloid Leukemia	Tumor suppressor	p16^INK4a^, ARF, p53	Inhibits transformation	46
2	T-cell Leukemia	Tumor suppressor	NOTCH1 downstream genes	Promotes apoptosis	47
3	Breast Cancer (TNBC)	Oncogene	SNAIL, IL-6, ZEB1	Promotes EMT, proliferation	48
4	Prostate Cancer	Oncogene	AR signaling, Cyclin D1	Enhances tumor growth	49
5	Glioblastoma	Oncogene	Neural stem cell genes	Maintains stemness	50

4. THERAPEUTIC TARGETING OF KDM6B:

The identification of KDM6B (JMJD3), a dominant member of the Jumonji domain- containing family of histone demethylases, as an important regulatory component of multiple important biological activities, including the growth of tumors, inflammatory responses, and immune evasion, has garnered a significant amount of attention in both research and clinical fields. A large part of this interest is attributed to its integral role in the complex processes of epigenetic regulation, where the expression of genes can be altered without changing the sequence of DNA. As a result, KDM6B has been considered a high-potential pharmacologic target in oncology, a setting where signaling aberrations often lead to accelerated proliferation of cells or increased tumor growth. While several epigenetic medications, especially DNA methyltransferase (DNMT) inhibitors

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Journal of Molecular Science
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and histone deacetylase (HDAC) inhibitors, have advanced in the clinic, treatments targeting KDM6B are usually restricted to preliminary studies or early-stage clinical trials[51].

4.1 Small Molecule Inhibitors:

GSK-J1 acts as a cell-impermeable alpha-ketoglutarate analog and enables specific binding to the Fe(II)-binding active site of KDM6B to inhibit its demethylase activity. This is relevant here because, by inhibiting the activity of KDM6B, GSK-J1 inhibits the demethylation of the lysine on histones leading to changes in gene expression and significant tumorigenesis.Acute lymphoblastic leukaemia (ALL) is one of the several cancers for which GSK-J4, a prodrug intended for cell permeability, has shown notable anti-tumor activity. GSK-J4 has proven to be quite effective against this aggressive leukaemia disease [52].Triple-negative breast cancer (TNBC), where the absence of therapeutically targeted pathways presents challenges in treating malignant tumors, shows that GSK-J4 demonstrates the ability to inhibit tumor growth. Pediatric gliomas, where the need for quality therapeutics for pediatric patients is often neglected in the normal treatment regimen, are of universal concern[53].

4.2 Emerging Therapeutic Strategie- PROTACs (Proteolysis Targeting Chimeras)

The advent of PROTAC technology represents a new and innovative therapeutic approach that uses the recruitment of E3 ligases to target the degradation of KDM6B, and instead of simply inhibiting it, now has an advanced mechanism of action that allows for a much greater dismantling of pathological proteins, which could be the change needed to enable prolonged and efficacious therapeutic responses. Early research on KDM6B-PROTACs provides preliminary, promising results that suggest these compounds might allow for irreversible degradation of JMJD3, which may represent a significant advancement in the development of targeted treatments, with the first studies showing increased efficacy and specificity in initial studies[54].

4.3 Natural Compounds

Multiple natural compounds that include polyphenols such as curcumin and flavonoids, indirectly regulate KDM6B by modifying the upstream signaling pathways or the modulation of key co-factors. This parsing out of nuanced modification shows how complicated the biological interactions are that regulate cancer progression and cellular outcomes. While these natural agents may show non-specific actions, they are excellent scaffolds to launch semi-synthetic drugs from and chemically create molecules that show increased selectivity and potency against KDM6B, thus enhancing therapeutic responses[55].

Table 3. Selected KDM6B Inhibitor and Their Characteristics

Sl.no	Inhibitor	Type	IC_{50} (KDM6B)	Selectivity	Model Tested	Stage	References
1	GSK-J1	Cell-impermeable inhibitor	~60 nM	KDM6A/KDM6B	In vitro only	Preclinical	56
2	GSK-J4	Cell-permeable prodrug	~50–70 nM	KDM6A/B > others	ALL, glioma, TNBC	Preclinical	57
3	QC6352	Selective small molecule	~15–30 nM	High KDM6B selectivity	Neuroblastoma	Preclinical	58
4	KDOBA67	Improved analog of GSK-J4	~40 nM	Improved selectivity	Colorectal, prostate cancer	Preclinical	59

5. FUTURE PERSPECTIVES:

The epigenetic regulator KDM6B (JMJD3) is quickly becoming recognized as a key target in developing new cancer therapies. Ongoing studies are revealing the many different roles epigenetic factors play in cancer development, and KDM6B is emerging as a focus of increasing interest for both robotic improvements and medical practice. Below are some key areas that offer exciting opportunities for further research to help realize KDM6B's potential as a therapeutic target.

CONCLUSION:

KDM6B (JMJD3) is a fundamental player in the complex realms of cancer epigenetics, immune regulation, and cell fate determination. It is both a tumor suppressor in hematological malignancies and an oncogenic driver in multiple solid tumors, which reveals the complication of epigenetic regulation that varies by context.

The initial inhibitors, like GSK-J4, have demonstrated (and validated) their therapeutic potential; however, the development of next-generation inhibitors is critically needed to address issues of selectivity, resistance, and systemic toxicity. We need to provide a meaningful foundation for the potential therapeutic opportunities for KDM6B by continuing to study the biological functions, structural features, and interaction networks for KDM6B; we will also employ innovative approaches under the rubric of precision medicine.

In conclusion, KDM6B represents an important yet complex target in the dynamic, ever-changing world of cancer therapy. Success in the clinical uptake pathway will depend on novel developments in innovative chemistry, an exhaustive understanding of

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Volume 35 Issue 4, Year of Publication 2025, Page 1661-1667
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complex biological processes, and the employment of personalized epigenomic profiling for each patient.

CONFLICT OF INTEREST:

The author declares no conflict of interest, financial or otherwise.

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