Targeting menin in lysine methyltransferase 2A/nucleophosmin-mutated leukemia: A novel strategy from epigenetic dysregulation to clinical therapy (Review)

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Abstract. Menin protein is encoded by the multiple endocrine neoplasia type 1 gene, which typically serves an oncogenic role in endocrine organs. However, in mice, menin protein is a key mediator of leukemic transformation, particularly in acute myeloid leukemia (AML), and is involved in the disease process through epigenetic regulatory mechanisms. This functional paradox may be due to the unique gene expression regulatory properties of menin, which can both activate and inhibit the expression of target genes. At the molecular level, menin protein regulates the gene transcription process by interacting with multiple protein complexes and forms a complex network with multiple signaling pathways. As the core hub of transcriptional regulation, menin protein is essential for the maintenance of cellular homeostasis and its aberrant function can lead to gene expression disorders, which contributes to the development of AML. Despite the druggability challenges of several transcriptionally regulated proteins, inhibitors of menin protein have made breakthroughs in clinical development. Particularly in AML subtypes [for example, lysine methyltransferase 2A (KMT2A) rearrangement or nucleophosmin (NPM1) mutation], menin protein inhibitors have demonstrated favorable efficacy. The present study systematically reviewed biological functions of the menin protein and its application in targeted therapy for specific AML subtypes. Notably, menin inhibitors have demonstrated potential in KMT2A/NPM1-mutant leukemia, however, the off-target effects, resistance mechanisms and a lack of biomarkers due to the extensive nature of their binding interface remains to be elucidated.

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Contents

1. Introduction

Acute myeloid leukemia (AML) is a hematological malignancy characterized by the aberrant proliferation of hematopoietic stem cells and is the most prevalent form of acute leukemia in adults, accounting for ~80% of cases in this group (1,2). Despite the continuous development of medical technology, the 5-year survival rate of patients with AML is 32% (with the rate as high as 50% in younger patients and lower than 10% in those over 60 years old) and the prognosis remains poor (3-5). Although traditional cytotoxic chemotherapy has been the foundation of AML treatment for the past 50 years, researchers are investigating therapeutic approaches aimed at enhancing patient survival (6,7).

Transcription is a complex biological event involving the interaction of transcription factors, RNA polymerase II and transcriptional cofactors with DNA regulatory elements. This process is key for maintaining essential cell functions such as cell proliferation, differentiation, and metabolic homeostasis (8). It converts DNA sequences into translatable mRNA, which regulates protein synthesis. Organisms achieve precise gene expression through a sophisticated transcriptional regulatory network that ensures internal environmental stability and

regulates normal cell development (9-11). When transcriptional dysregulation occurs, it can lead to abnormal cell proliferation and differentiation, which ultimately results in tumors (12). Consequently, small-molecule targeted therapies aimed at key proteins in transcriptional regulation have become a focal point of current research (13). Menin protein inhibitors have emerged, with several preclinical studies confirming their notable potential as chromatin regulators (14-16).

The menin protein, encoded by the multiple endocrine neoplasia type 1 gene, functions primarily as a scaffolding protein that modulates gene transcription via interactions with various gene regulators, such as histone methyltransferases and transcription factors including JunD and SMAD (15,17,18). In AML, menin serves a key role in epigenetic regulation by interacting with genes such as lysine methyltransferase 2A (KMT2A) and mutant nucleophosmin 1 (NPM1), thereby facilitating the progression of AML (19,20). Inhibitors of the menin protein may reverse aberrant transcription associated with tumors and restore normal gene expression and cellular function by targeting this essential epigenetic regulator (21). The present review aimed to provide a comprehensive evaluation of the role of menin protein, assess the data supporting its mechanisms in KMT2A/NPM1 mutations and discuss the pharmacological characteristics and clinical challenges associated with current inhibitors, such as functional disparities of menin in various cellular contexts and optimization pathways for combinatorial therapeutic strategies.

2. Direct epigenetic regulation network of the menin protein

Menin protein modulates the mixed lineage leukemia (MLL) complex. AML is categorized into subtypes based on genetic and transcriptomic characteristics, one of which is defined by the homeobox (HOX) gene upregulation and primarily includes NPM1-mutant (NPM1-mut) and MLL-rearranged leukemia (22). MLL proteins (MLL1 and MLL2) belong to the histone H3 position 4 lysine (H3K4) methyltransferase family, which is essential for the maintenance of high HOX gene expression, and activate myeloid ecotropic viral integration site 1 (MEIS1) through direct epigenetic regulation (16). Notably, MLL fusion proteins contain specific Su(var)3-9, Enhancer-of-zeste, Trithorax) structural domains, whereas the crystal structure of menin proteins exhibits a rectangular conformation, which allows for the formation of deep binding pockets that bind specifically to the N-terminal fragment of MLL fusion proteins (23,24). This interaction designates menin protein as an oncogenic cofactor that facilitates histone H3 lysine trimethylation at position 4 (H3K4me3) via its engagement with MLL, subsequently enhancing HOX/MEIS1 gene expression and precipitating leukemia (25). Utilizing a structure-based drug design approach targeting the menin-MLL interaction interface, Krivtsov *et al* (15) developed a highly selective small molecule inhibitor, VTP50469, which displaces menin from the fusion protein and prevents the recruitment of MLL to target genes. Both cell and animal studies (immunodeficient NSG mice xenotransplanted with human KMT2A-r leukemia cells) have demonstrated notable anti-leukemic efficacy (15,26). While preclinical data indicate that the small molecule inhibitors exhibit potential anti-leukemic efficacy, the extensive menin-MLL binding interface reveals that the crystal structure of VTP50469 occupies a subregion of the menin-MLL interface (15,27). This indicates the necessity for potentially higher inhibitor concentrations to achieve complete menin-MLL disruption, consistent with the typical dose-response association of partial protein-protein interaction inhibitors (28,29). This technical barrier may represent a notable impediment in the translation of menin-MLL-targeted therapies from laboratory research to clinical application.

Menin protein modulates the sirtuin (SIRT) family. The sirtuin family comprises seven highly conserved members (SIRT1-SIRT7) that share evolutionary conservation, all of which possess highly conserved catalytic structural domains, differing markedly only at their N- and C-terminus (30,31). This structure enables each member to exhibit NAD^+-dependent deacetylase and ADP-ribosyltransferase activity (31). As components of histone deacetylases, SIRTs serve a key role in cell proliferation, survival, maintenance of genomic stability and metabolic regulation by modulating gene expression and chromatin dynamics. A direct interaction between the menin protein and SIRT1 has been identified (30). Menin binds directly to the deacetylase structural domain of SIRT1 through its C-terminal domain, which forms a functional complex that regulates epigenetic processes. In mouse hepatocytes, SIRT1 modulates CD36 gene expression and intracellular triglyceride accumulation via histone deacetylation, a process that is contingent upon the involvement of the menin protein (32). Furthermore, in hepatocellular carcinoma cells, menin enhances NF-κB (p65) deacetylation by recruiting SIRT1, which underscores its key role in the SIRT regulatory network (33). Numerous studies have demonstrated that SIRT1 impacts apoptosis and inflammatory activation by modulating the NF-κB pathway (34-36). For example, in murine models, upregulation of SIRT1 promotes B lymphocyte proliferation, inhibits apoptosis and advances inflammatory responses by suppressing the NF-κB pathway (37,38). Therefore, it is hypothesized that in acute leukemia, the menin-SIRT interaction may also influence apoptosis and inflammatory activation via the NF-κB pathway, potentially inhibiting or promoting acute leukemia (39).

Menin protein regulates the protein arginine methyltransferases (PRMT) family. The human genome encodes a total of 11 PRMTs, which regulate cell signaling networks by modifying arginine residues in both histone and non-histone proteins (40). As important epigenetic regulators in eukaryotes, all members of the PRMT family contain highly conserved S-adenosylmethionine (SAM)-dependent methyltransferase structural domains that facilitate the transfer of methyl groups from SAM to the nitrogen atom of substrate arginine residues (41,42). Menin protein can recruit PRMT5 to the growth arrest-specific protein 1 (GAS1) gene locus, inhibiting GAS1 gene expression by promoting the symmetric dimethylation of histone H4 at position 3 (H4R3me2) (43). However, in MLL, the interaction between menin protein and PRMT5 leads to decreased levels of H4R3me2 and

Table I. Menin-mediated direct epigenetic regulatory networks.

Interacting protein	Epigenetic modification	Leukemogenic effect	Limitations	(Refs.)
MLL complex	H3K4me3	HOX gene upregulation	Small-molecule inhibitors fail to fully disrupt protein-protein interactions	(15,23,25)
SIRT family	HDACs	NF-κB suppression via p65 deacetylation	Precise mechanistic insights remain elusive	(32,33)
PRMT5	H4R3me2	Dysregulation of GAS1	Reduced H4R3me2/GAS1 inhibition in AML; H4R3me2 promoted to inhibit GAS1 in MEN1 tumors	(43,44)
SUV39H1	H3K9me3	Aberrant IL-6 activation	Limited therapeutic targeting of IL-6 signaling	(47)

MLL, mixed lineage leukemia; H3K4me3, histone H3 lysine trimethylation at position 4; H4R3me2, symmetric dimethylation of histone H4 at position 3; PRMT5, protein arginine methyltransferase 5; SIRT, silent information regulator; HDAC, histone deacetylase; GAS1, growth arrest-specific protein 1; SUV39H1, heterochromatin protein 3-9 homolog 1; AML, acute myeloid leukemia.

fails to effectively inhibit GAS1 expression (44,45). This suggests that the regulation of PRMT by menin protein may be context-dependent (43). In MEN1 tumor syndrome and mixed-lineage leukemia (MLL), the regulation of GAS1 by the menin-PRMT5 complex exhibits opposite outcomes, suggesting an oncogenic isoform of the menin-PRMT5 complex that reverses epigenetic manifestations by altering the conformation of the complex (43,44).

Menin protein regulates heterochromatin protein 3-9 homolog 1 (SUV39H1). SUV39H1 is a histone H3 lysine 9 methyltransferase (H3K9). Menin protein enhances trimethylation of H3K9 in the promoter regions of target genes by interacting with SUV39H1, thereby silencing transcription of associated genes (24,46). In a previous study on IL-6 gene regulation, Song *et al* (47) detected the enrichment of menin protein and SUV39H1 around the IL-6 gene using chromatin immunoprecipitation (ChIP). The aforementioned study reported that menin protein and SUV39H1 are specifically recruited to the auxiliary region of the IL-6 promoter and the recruitment of SUV39H1 decreases with the depletion of menin protein, which suggests menin protein may serve a key role in the regulation of SUV39H1. Further analysis indicated that menin protein and SUV39H1 may regulate IL-6 gene expression at the protein level through H3K9 methylation (47). Numerous preclinical and clinical studies have confirmed that IL-6 serves a notable role in the development of acute leukemia (48-50). Anti-IL-6 antibodies, such as cetuximab, have potential therapeutic value in the treatment of various malignancies, including acute leukemia, either alone or in combination with chemotherapy regimens (51). However, the pathogenesis of leukemia involves a complex regulatory network of multiple signaling pathways - such as JAK/STAT, NF-κB and Wnt/β-catenin - which limits the therapeutic efficacy of targeting IL-6 alone (52-54). Following blocking IL-6 signaling, leukemia cells sustain their survival and proliferative capacity by activating alternative pathways (for example, Janus kinase/STAT), which markedly reduces the clinical benefit of single-agent therapy. These direct epigenetic regulatory interactions mediated by menin are summarized in Table I.

3. Menin protein indirect signaling pathway regulatory network

JunD proto-oncogene transcription factors. Agarwal*et al* (18) demonstrated, via a yeast two-hybrid assay using a galactose-responsive transcription factor 4 (Gal4) DNA-binding domain fusion of full-length menin protein, that JunD, a member of the activator protein 1 family, interacts with menin protein. This interaction is contingent upon the structural domains located at the N-terminal end of menin protein. The aforementioned study identified the N-terminal region of JunD binding to menin protein as the menin binding sequence (JunDMBL). Notably, although the binding modes of JunDMBL and the MLL binding sequence exhibit similarities, they exert opposite effects on transcriptional regulation (55). Menin-JunD complexes may interfere with JNK-mediated phosphorylation of JunD and c-Jun, thereby inhibiting the Ras signaling pathway (56,57). However, the specific target genes regulated by the menin-JunD complex remain unclear and further research is warranted to explore its potential application in leukemia treatment (55).

SMAD signaling protein. SMAD proteins are key downstream effector molecules in the TGF-β signaling pathway and serve a direct role in TGF-β signaling and gene transcriptional regulation (58). As transcriptional regulators, menin protein binds SMAD proteins, thereby indirectly influencing the activity of the TGF-β signaling pathway and regulating the transcription of target genes. In pituitary secretory tumor cell lines, menin protein markedly enhances the binding specificity of SMAD3 to DNA sequences via interaction with SMAD3 (59,60). More importantly, during osteoblast differentiation and maturation, menin protein forms complexes with SMAD1, SMAD5 and the key regulator of osteogenesis Runt-related transcription factor 2 to promote the differentiation of mesenchymal stem

cells into osteoblasts (59,61). While the interaction of menin protein with SMAD1, SMAD3 and SMAD5 has been demonstrated (59), the specific molecular mechanisms underlying their synergistic activation of transcription warrant further investigation.

Myc proto-oncogene. As a key proto-oncogene, the dysregulated expression of Myc is closely associated with >50% of malignant tumorigenesis (62). Myc serves primarily as a transcription factor through the classical enhancer-box (E-box) region (63). Wu *et al* (64) demonstrated that Myc forms a regulatory complex with positive transcription elongation factor b (P-TEEb) within the E-box region to activate transcription, with the menin protein being a key factor in this process. Menin regulates Myc-mediated transcriptional activity by influencing the transcriptional elongation regulator P-TEEb. In the KMT2A rearrangement (KMT2A-r) AML model, the expression of Myc and its characteristic genes is markedly suppressed in leukemia cells following treatment with a menin inhibitor (65). Zhou *et al* (65) found a notable positive correlation between menin protein levels and Myc expression, which suggests Myc may serve as a common target of menin protein. Based on these findings, co-targeting menin protein and Myc may represent a novel therapeutic strategy for leukemia treatment in future.

Forkhead box (FOX) transcription factor family. The FOX family is an evolutionarily conserved group of transcription factors, all of which possess the distinctive forkhead DNA-binding structural domain and are key for cell proliferation and differentiation (66). Previous studies have indicated that menin protein engages with several members of the FOX family, such as FOXG1, FOXA1 and FOXO1 (67-69). In FOXG1-associated encephalopathy, menin protein influences α-thalassemia X-linked mental retardation protein-mediated FOXG1 transcription via modulation of the FOXG1 transcripts (67). Bonnavion *et al* (70) established that menin protein interacts with FOXA2, which influences its trans-auto reactivation ability and serves a role in the control of FOXA2 expression in adult pancreatic α-cells.

β-catenin signaling pathway. The inaugural member of the Wnt family was identified in 1982 and research has consistently validated the essential function of the Wnt/β-catenin signaling pathway in embryonic development and tissue regeneration (71-73), Dysregulation of this system results in numerous illnesses, such as colorectal and gastric cancer (74-77). Menin protein serves as a reciprocal partner of β-catenin proteins, the principal effector molecules of this signaling pathway, and can facilitate their nuclear translocation. ChIP and chromosome conformation capture (3C) studies demonstrated that the menin protein augments the association of β-catenin proteins with the Myc promoter (78-80). The mechanism of action of menin protein inhibitors in the treatment of AML may partially arise from their suppression of the Wnt/β-catenin protein signaling pathway (81-83).

Nuclear receptor classification. Nuclear receptors are a class of receptor proteins located in the nucleus, which include the androgen receptor (AR), estrogen, thyroid hormone, glucocorticoid, retinoid X, peroxisome proliferator-activated, liver X and retinoic acid receptors (84). These receptors not only serve as biosensors to regulate key cellular activities such as proliferation, differentiation, and apoptosis but also directly bind to DNA to exert transcriptional regulation (85,86). The interactions between nuclear receptors and tumor growth have attracted notable research regarding their role in tumor progression (87-89). Luo *et al* (90) identified that the menin protein exhibits distinct pro-oncogenic actions in androgen receptor-dependent prostate cancer cells by modulating AR transcription and its target genes. Based on the presence of nuclear receptor interaction sites in the amino acid sequence of the menin protein, menin serves as an important coactivator of nuclear receptor-mediated transcription (68,90).

NF-κB transcription factors. The NF-κB family comprises five members: Rel or c-Rel, RelA or p65, RelB, NF-κB1 or p50 and NF-κB2 or p52. Each member exists in dimeric form and possesses a Rel homology domain (91). The pro-carcinogenic role of NF-κB is prevalent in hepatocellular carcinoma (92). Previous studies have demonstrated that menin protein engages with NF-κB and suppresses p65-mediated transcriptional activation via the recruitment of SIRT1 (33,93). Another previous study revealed that the degree of menin-NF-κB interaction changes the production of cell cycle protein D1, a downstream signaling molecule of NF-κB that governs the G1/S phase transition and affects cell proliferation (55). Irregularities in this mechanism may result in tumorigenesis.

4. Clinical translation of epigenetic regulation: Key function of the menin-MLL-HOX/MEIS1 axis in KMT2A-r/NPM1-mut leukemia

The menin-MLL complex activates the expression of the HOX/MEIS1 gene cluster by mediating aberrant H3K4me3, a well-established axis of epigenetic regulation implicated in KMT2A-r and NPM1-mut leukemia (Fig. 1 (17,94). This mechanism was first elucidated by Yokoyama *et al* (94), who demonstrated that blocking the interaction between menin and the methyltransferase KMT2A markedly decreases leukemia incidence in mice (95). Further research has confirmed the key role of menin protein in NPM1-mut leukemia (96). Specifically, menin protein contributes to KMT2A-r leukemia by binding to fusion proteins and to NPM1-mut leukemias via aberrant nucleoplasmic transport pathways (97). The role of the menin protein in KMT2A-rearranged leukemia and NPM1-mutant leukemia cause the dysregulated expression of the HOX and MEIS1 genes (98,99). Menin inhibitors effectively suppress the abnormal proliferation and differentiation of leukemia cells by specifically disrupting the interaction between menin and KMT2A or NPM1, while simultaneously downregulating the expression of HOX and MEIS1, thereby demonstrating notable therapeutic potential (21).

Role of menin protein in KMT2A-r leukemia. Patients with acute leukemia characterized by KMT2A-r, previously referred to as MLL, exhibit a long-term survival rate <60% and poor prognosis across all age demographics (100,101). This leukemia variant exhibits a high prevalence among infants and children, accounting for >70% of new acute

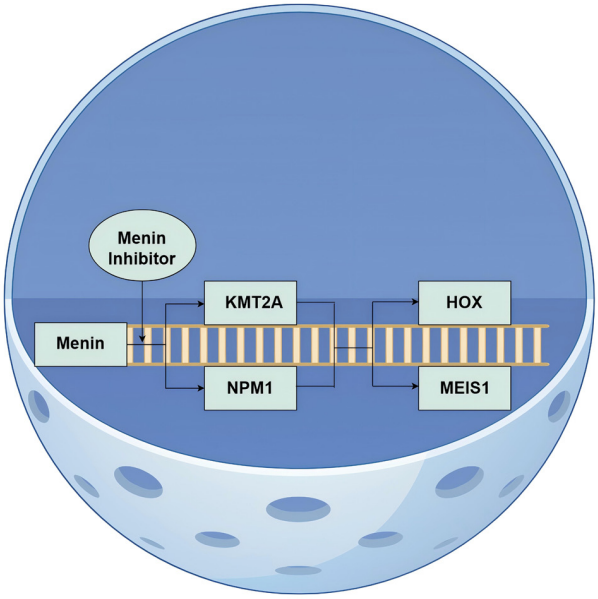

Figure 1. Mechanism of menin inhibitors KMT2A, Lysine Methyltransferase 2A; NPM1, Nucleophosmin 1; HOX, Homeobox; MEIS1, myeloid ecotropic viral integration site 1.

lymphoblastic leukemia (ALL) diagnoses in infants, is marked by notable aggressiveness, frequent relapse, substantial medication resistance and presents considerable challenges for therapeutic management as a high-risk genetic subtype (101).

KMT2A-r may lead to aberrant expression of the HOX gene and its DNA-binding cofactor MEIS1, which may inhibit hematological development and precipitate leukemia (21,102). Although no specific medications have been approved for KMT2A-r leukemia, preclinical studies have identified the chromatin regulatory protein menin as a promising therapeutic target (14,103,104). In KMT2A-driven leukemia, all KMT2A fusion proteins contain menin-binding sequences, with menin protein serving as a key cofactor that facilitates the interaction between the KMT2A protein complex and the HOX gene promoter. In a study using the KMT2A-mut leukemia model (105), it was demonstrated that the inhibition of menin protein markedly reduces the transcript levels of HOX and MEIS1, thereby reversing the leukemogenesis process.

Function of menin protein in NPM1-mut leukemia. Through the examination of gene expression in pediatric and adult patients with primary AML, researchers discovered that NPM1-mut leukemia exhibits notable similarities to the KMT2A-r subtype and NPM1 is associated with the HOX/MEIS1 gene cluster (106). NPM1-mut is among the most prevalent genetic alterations in AML, affecting ~30% of the total patient population (107). These mutations, primarily located in the terminal exons of the NPM1 gene, enhance nuclear export signaling activity and impair nucleolus localization signaling, which results in the dysregulated expression of the HOXA/B and MEIS1 genes (108). NPM1 may serve as a transcriptional amplifier of gene expression, potentially constituting a notable factor in the development of AML (109). Dillon *et al* (110) identified microscopic residual lesions in patients with AML through pre-transplantation DNA sequencing of hematopoietic stem cells, which revealed that patients with NPM1-mut AML experience a significantly higher recurrence rate and shorter survival compared with those without NPM1-mut.

The persistence of NPM1-mut AML in an undifferentiated state is attributed to the HOX-associated pathway, which underscores the therapeutic potential of targeting this pathway. Menin protein serves as a cofactor to promote H3K4me3 through interactions with MLL, thereby modulating the expression of HOX and MEIS1 genes. This mechanism highlights the feasibility of targeting menin protein for therapeutic interventions (96). *In vivo* experiments have demonstrated that inhibitors of menin protein exhibit notable anti-leukemic activity in NPM1-mut leukemia (20,21,111). Previous studies conducted in NPM1-mutant leukemia models have indicated that treatment with the menin inhibitor VTP50469, a precursor drug to revumenib, leads to downregulation of oncogenic cofactors such as MEIS1 and a marked reduction in the self-renewal capacity of leukemic stem cells (15,104).

5. Advancements in the development of menin protein inhibitors

Understanding of the menin formation mechanism in leukemia, alongside advancements in high-throughput screening techniques and structural biology, facilitate creation of highly selective small chemical inhibitors (112). Based on the efficacy of menin inhibitors in KMT2A-r and NPM1-mut leukemia, a growing array of menin inhibitors (such as revumenib and ziftomenib) exhibiting enhanced pharmacological efficacy against these AML subtypes has recently been introduced into clinical practice (21,113,114).

A total of seven menin inhibitors are undergoing different phases of clinical development for acute myeloid leukemia, with numerous candidates in development (Table II). The leading candidate is revumenib, which demonstrated a promising safety and effectiveness profile in a phase I open-label, dose-escalation and extension study (AUGMENT-101) assessing the menin inhibitor revumenib for KMT2A-r leukemia treatment (21,113). The occurrence of grade ≤3 treatment-related side events was minimal in treated patients, with asymptomatic QT interval prolongation being the sole dose-limiting effect. Revumenib achieved an overall remission rate of ≤53% and a complete remission rate of ≤30% with partial hematological recovery (98,113). In the subsequent phase II trial (AUGMENT-101), a total of 94 patients with KMT2A-r acute leukemia (comprising 78 patients with AML, 14 with ALL and two with an indeterminate subtype) received menin inhibitors, which achieved an overall remission rate of 63.2% (of which, 68.2% exhibited no measurable residual disease; unpublished data). In 57 patients with assessable efficacy, the combined complete response and complete response with incomplete hematological recovery rate reached 22.8% (113). Grade ≥3 adverse events included neutropenia (37.2%), differentiation syndrome (16%) and QT interval prolongation (13.8%). Most of these events were controllable and transitory and menin inhibitors had a predictable safety profile.

The combination therapy of menin inhibitors with other targeted leukemia medications has potential due

Table II. Summary of menin inhibitors.

Drug	Molecular formula	Targeted disease	Development status	Trial no.	Patient recruitment status
Revumenib	$C_{32}H_{47}FN_6O_4S$	KMT2A-r AML and NPM1-mut AML	Approved (FDA; 2023)	NCT04065399	Recruiting
Ziftomenib	$C_{33}H_{42}F_3N_9O_2S_2$	NPM1-mut AML and mixed phenotype acute leukemia	Phase III	NCT07007312	Not yet recruiting
JNJ-75276617	$C_{32}H_{50}FN_7O_3$	Acute leukemia	Phase III	NCT06852222	Recruiting
DS-1594	$C_{27}H_{29}F_3N_6O_3S$	NPM1-mut AML and Philadelphia chromosome-positive chronic myelogenous leukemia	Phase I/II	NCT04752163	Terminated
DSP-5336	$C_{33}H_{43}FN_6O_3$	Acute lymphoblastic leukemia and refractory AML	Phase I/II	NCT04988555	Recruiting
BN-104	$C_{31}H_{35}FN_8O_2$	Refractory AML	Phase I/II	NCT06746519	Recruiting
BMF-219	$C_{31}H_{34}N_8O_3$	Refractory or relapsed acute leukemia and patients with previously treated subjects with active CLL	Phase I	NCT05153330	Terminated
Balamenib	$C_{33}H_{34}F_3N_7O_2$	NPM1-mut AML	Phase I	NCT06780124	Recruiting

KMT2A, lysine methyltransferase 2A; NPM1, nucleophosmin; mut, mutant; AML, acute myeloid leukemia; FDA, Food and Drug Administration.

to the promising efficacy and safety profile of menin inhibitor monotherapy in the treatment of acute leukemia. Miao *et al* (115) administered a menin inhibitor and kinase inhibitor to NUP98-r leukemia samples, which demonstrated that the combination therapy outperformed monotherapy, with a combination index between 0.12 and 0.65, as determined by the Chou-Talalay method, which indicated notable synergistic effects. The combinatorial therapy induced a more pronounced decrease in both the quantity and size of leukemic blasts in NUP98-r leukemia specimens and was more effective in promoting cell proliferation arrest and differentiation. Furthermore, the combination of Brahma-related gene 1/Brahma inhibitors with menin inhibitors for acute leukemia treatment has demonstrated notable preclinical efficacy, resulting in a more substantial reduction in leukemia burden and extended survival duration in mice compared with monotherapy (116). A clinical trial is currently examining menin inhibitors in conjunction with azacitidine/vincristine for the treatment of acute leukemia, specifically evaluating JNJ-75276617 with AML-targeted treatments (trial no. NCT05453903) (117). The combined regimen inhibits the immune evasion of acute leukemia cells following monotherapy and diminishes relapse in treatment-resistant leukemia (117).

Common adverse effects of menin inhibitors include gastrointestinal reactions, QT interval prolongation, cytopenia and differentiation syndromes, however, these adverse effects are within manageable limits and menin inhibitors are generally safe (113,118). Furthermore, menin inhibitors are not associated with notable off-target toxicity, which has enabled the clinical scale-up of menin inhibitors and their emergence as a potential option for long-term therapy (112). However, recent data have also demonstrated that certain patients have menin mutations that prevent binding of the inhibitor and thus mediate clinical resistance, which leads to clinical relapse; therefore, resistance to menin inhibitors remains a challenge (21,119).

6. Conclusion

Although menin inhibitors have demonstrated significant efficacy in KMT2A-r and NPM1-mut leukemia, their clinical application faces key challenges such as drug resistance and optimization of combination strategies (21,98). Future research should focus on overcoming resistance mediated by menin protein mutations, including the development of allosteric inhibitors and combination with epigenetic regulatory drugs to block compensatory pathways. In terms of combination therapy, it is necessary to optimize combination regimens with other drugs based on synergy indices (such as the Chou-Talalay model) and explore the potential advantages of sequential therapy. Furthermore, the indication scope of menin inhibitors should be expanded to include other subtypes dependent on the HOX/MEIS1 pathway, such as NUP98-r leukemia and predictive biomarkers based on HOX gene expression profiles or menin-MLL complex activity should be developed to screen beneficiary populations. From a technical perspective, structural biology and artificial intelligence-assisted design should be leveraged to develop high-affinity inhibitors and targeted delivery systems should be developed to enhance

efficacy and safety. In-depth studies of the menin protein regulatory network may reveal its functional heterogeneity in different cell environments and provide a theoretical basis for dual-targeting strategies (such as menin-Myc co-inhibition). With the advancement of multidisciplinary collaboration, menin inhibitors may become a key therapy for specific leukemia subtypes and provide novel directions for epigenetically targeted therapy.

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Authors' contributions

HZ conceived, designed and supervised the study and edited the manuscript. JB wrote the manuscript. Data authentication is not applicable. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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