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Review

NUP98 Rearrangements in AML: Molecular Mechanisms and Clinical Implications

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Simple Summary: *NUP98* rearrangements are frequent events in myeloid malignancies, especially in acute myeloid leukemia (AML). AML patients carrying *NUP98* fusions show poor response to standard treatments and adverse outcomes. This review focuses on recent progress in understanding the underlying mechanisms of NUP98 fusion driven leukemias and the development of therapeutics against them.

Abstract: *NUP98* fusions constitute a small subgroup of AML patients and remain a high-risk AML subtype. There are approximately 30 types of *NUP98* fusions identified in AML patients. These patients show resistance to currently available therapies and poor clinical outcomes. NUP98 fusions with different fusion partners have oncogenic transformation potential. This review describes how the *NUP98* gene acquires oncogenic properties after rearrangement with multiple partners. In the mechanistic part, the formation of nuclear bodies and dysregulation of the HoxA/Meis1 pathway are highlighted. This review also discusses mutational signatures among *NUP98* fusions and their significance in leukemogenesis. It also discusses the clinical implications of *NUP98* fusions and their associated mutations in AML patients. Furthermore, it highlights therapeutic vulnerabilities in these leukemias that can be exploited as therapeutic strategies. Lastly, this review discusses the gaps in our knowledge regarding NUP98 fusions in AML, as well as future research opportunities.

Keywords: leukemia; AML; translocations; fusion genes; *NUP98* fusions; *NUP98::NSD1*; *NUP98::KDM5A*; FLT3-ITD

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1. Introduction

Acute myeloid leukemia (AML) is a myeloid malignancy characterized by genomic abnormalities and a high number of blast cells in the bone marrow [1]. Like other cancers, fusion genes are also reported in AML. Fusion genes are formed by chromosome aberrations such as translocations, inversions, deletions, and insertions [2]. Fusion genes can lead to oncogenic transformation by activating oncogenes or inactivating tumor suppressors [3]. Whenever a 3′ oncogene is linked to a strong promoter of a 5′ gene, it becomes overexpressed. In *TMPRSS2::ETS* fusions in prostate cancer, expression of ETS family transcription factor is driven by *TMPRSS2* gene promoter [4]. An oncogene can lose its 3′ UTR microRNA binding site through fusion and lead to higher expression of the oncogene. For example, *MYB::NFIB* fusion in adenoid cystic carcinomas (ACC) activates critical MYB targets through the loss of the 3′ UTR-regulating microRNA binding site [5]. Similarly, a gene can inactivate its tumor suppressor function in a fusion.

As a result of recent advances in high-throughput sequencing technologies, it has been possible to detect cryptic fusion genes that are usually skipped by conventional karyotyping [6]. For example, one-third of *KMT2A* fusions in AML are missed by karyotyping and require additional tests like FISH or RT-PCR. These methods fail to identify rare fusion genes [7]. However, next-generation sequencing (NGS) successfully identifies rare fusions in patient samples [8,9]. The discovery of these fusion genes has improved the diagnosis, prognosis, and treatment of cancer patients.

In addition, a malignancy caused by a fusion gene opens the door to targeted therapies. Since fusion genes are exclusive to neoplastic cells and not expressed in healthy cells, they are excellent drug targets for treatment. For instance, imatinib was discovered against the *BCR::ABL* fusion gene that is expressed in 95 percent of chronic myeloid leukemia (CML) patients [10]. Discovery of fusion genes in AML helps with risk stratification and treatment of AML patients. Approximately 30–40 percent of AML patients carry at least one fusion gene, and *NUP98* fusions frequently occur in AML [11,12].

2. NUP98: A Commonly Translocated Gene in AML

Nucleoporin 98 (*NUP98*) is a gene located on chromosome 11p15 and encodes a precursor protein that results in NUP98 and NUP96 nucleoporins, which are structural components of the nuclear pore complex (NPC) [13,14]. The NPC facilitates the nucleo-cytoplasmic transport of ions, mRNAs, and proteins. Large molecules are transported via nuclear transport receptors that recognize nuclear export signals (NES) or nuclear localization signals (NLS), while smaller molecules can pass easily through them [15,16].

NUP98 is located on both sides of the nuclear pore complex and migrates on and off the NPC [17]. One-third of nucleoporins have phenylalanine–glycine [FG] repeats, but NUP98 has a unique FG repeat signature of Gly-Leu-Phe-Gly (GLFG) repeats [18,19]. In addition to the GLFG repeats, the N terminal part of the NUP98 protein contains a GLE2-binding sequence (GLEBS) motif, and the C terminal part contains an RNA-binding motif. The GLFG repeats interact with Exportin 1 (XPO1) and mediate nuclear protein export (Figure 1) [20]. The GLFG repeats also interact with importin-β family proteins for nuclear import [19]. RNA export factor RAE1 (Gle2) binds to the GLEBS motif to mediate the nuclear export of mRNAs [21,22]. Additionally, NUP98 is involved in the regulation of transcription. NUP98 is a mobile component of NPC and forms nuclear bodies, known as GLFG bodies [23]. The GLFG repeats interact with histone deacetylases (HDACs) and transcriptional co-activators CBP/p300, suggesting involvement of NUP98 in transcriptional regulation [24]. Furthermore, Kalverda showed that altered expression of nucleoplasmic NUP98 affects its target gene expression, supporting its involvement in gene regulation [25].

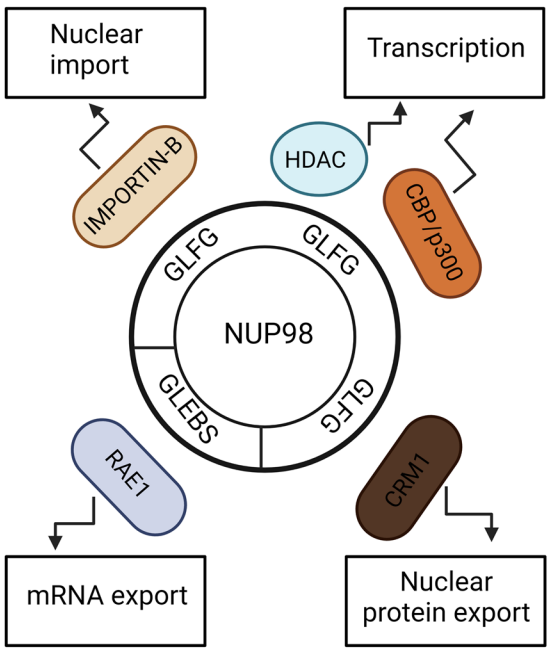

Figure 1. Schematic representation of general functions of important NUP98 protein motifs. GLEBS motif of NUP98 aids nuclear export of mRNAs. GLFG repeats of NUP98 protein are required for multiple functions. It binds to IMPORTIN-B family members for nuclear import, and it binds to CRM1/XPO1 for nuclear export of proteins. By interacting with HDAC and CBP/p300, it drives gene expression. The figure was created with BioRender.com.

NUP98 gene alterations have been implicated in several hematological malignancies including AML, chronic myeloid leukemia (CML), juvenile myelomonocytic leukemia (JMML), T-cell acute lymphoblastic leukemia (T-ALL), and myelodysplastic syndrome (MDS) [26]. Notably, *NUP98* fusions are majorly reported in myeloid and T-cell malignancies and rarely observed in B-cell malignancies. Around 5% of pediatric AML patients exhibit *NUP98* rearrangements [27–30].

3. Fusion Partners of NUP98 in NUP98-Rearranged AML

The *NUP98* gene is rearranged with approximately 30 partners in AML (Table 1). *NUP98::NSD1* and *NUP98::KDM5A* are frequently occurring *NUP98* fusions in AML [30]. The NUP98 fusion proteins retain the N-terminal of NUP98, which contains GLFG repeats and GLEBS motif. NUP98 fusion proteins lack the C-terminus portion of NUP98 containing the RNA binding motif. The C-terminus of the fusion protein is contributed by the partner gene [31].

Overall, *NUP98* fusions can be divided into three broad parts (Figure 2). The first category includes *NUP98* fusions with transcription factors as partners, which can change the expression of target genes through DNA binding domains. The second category is *NUP98* fusions with epigenetic modifiers that modify chromatin to change target gene expression. The third category of *NUP98* fusions has neither the DNA binding nor chromatin remodeling domain. Transcription factor partners of *NUP98* mostly include homeobox genes, including "class I" *HOX* genes (*HOXA9*, *HOXA11*, *HOXA13*, *HOXC11*, *HOXC13*, *HOXD11*, and *HOXD13*) and "class II" *HOX* genes (*PMX1*, *PMX2*, *HHEX1*, and *POU1F1*) and non-homeobox genes (*RARA* and *RARG*) [26]. RARA and RARG are the nuclear receptor (NR) superfamily members [32,33]. The *LEDGF* (lens epithelium-derived growth factor) gene encodes p75 and p52, which act as transcriptional coactivators [34].

Table 1. Different fusion partners of NUP98 in AML, its functional category, and the associated FAB subtypes.

Fusion Partner	Functional Category	AML Subtype	Chromosome Rearrangement	Refs.
HOXA9	Transcription factor	M2, M4	t(7;11)(p15;p15)	[35,36]
HOXA11	Transcription factor	M2	t(7;11)(p15;p15)	[37]
HOXA13	Transcription factor	M2	t(7;11)(p15;p15)	[38]
HOXC11	Transcription factor	M1, M2, M5	t(11;12)(p15;q13)	[39,40]
HOXC13	Transcription factor	M2, M4	t(11;12)(p15;q13)	[41,42]
HOXD11	Transcription factor	M4	t(2;11)(q31;p15)	[43]
HOXD13	Transcription factor	t-AML, M4	t(2;11)(q31;p15)	[44,45]
PMX1	Transcription factor	M2	t(1;11)(q23;p15)	[46]
PMX2	Transcription factor	t-AML	t(9;11)(q34;p15)	[[47]
HHEX	Transcription factor	M1, M2	t(10;11)(q23;p15)	[48,49]
RARA	Transcription factor	M3 or APL	t(11;17)	[32]
RARG	Transcription factor	M3 or APL	t(11;12)(p15;q13)	[33,50]
POU1F1	Transcription factor	t-AML	t(3;11)(p11;p15)	[51]
LEDGF/PSIP1	Transcription coactivator	M1, M2	t(9;11)(p22;p15)	[34,52,53]
PHF23	Epigenetic modifier	M0, M1, M4, M5	t(11;17)(p15;p13)	[54,55]
JADE2/PHF15	Epigenetic modifier	M3 or APL	t(5;11)(q31;p15)	[56]
JARID1A/KDM5A	Epigenetic modifier	M0-M7	t(11;15)(p15;q35)	[57,58]
NSD1	Epigenetic modifier	M1, M2, M4, M5, M6	t(5;11)(q35;p15.5)	[27,59–61]

Table 1. *Cont.*

Fusion Partner	Functional Category	AML Subtype	Chromosome Rearrangement	Refs.
NSD3	Epigenetic modifier	M1	t(8;11)(p11.2;p15)	[62]
MLL/KMT2A	Epigenetic modifier	M1, M2	inv(11)(p15q23)	[63]
C6orf80/CCDC28A	Unknown	M7	t(6;11)(q24.1;p15.5)	[64]
HMGB3	High-mobility group (HMG) protein	t-AML	t(X;11)(q28;p15)	[65]
IQCG	Calcium signaling	AML (Unknown)	t(3;11)(q29q13;p15)	[66]
RAP1GDS1	GTPase activity	AML (Unknown)	unknown	[67]
ADD3	Cytoskeletal protein	AML (Unknown)	t(10;11)	[68]
DDX10	RNA helicase	M6	inv(11)(p15q22)	[69,70]
TOP1	DNA Topoisomerase	M4, M5	t(11;20)(p15;q11)	[27,71]
TOP2B	DNA Topoisomerase	M5	t(3;11)(p24;p15)	[72]
ANKRD28	Signaling protein	AML (Unknown)	t(3;5;11)(p25;q35;p15)	[73]
LOC348801	Unknown	M2	t(3;11)(q12;p15)	[74]

Undifferentiated acute myeloblastic leukemia (M0), acute myeloblastic leukemia with minimal maturation (M1), acute myeloblastic leukemia with maturation (M2), acute promyelocytic leukemia (APL) (M3), acute myelomonocytic leukemia (M4), acute monocytic leukemia (M5), acute erythroid leukemia (AEL) (M6), acute megakaryoblastic leukemia (M7), therapy-related acute myeloid leukemia (t-AML).

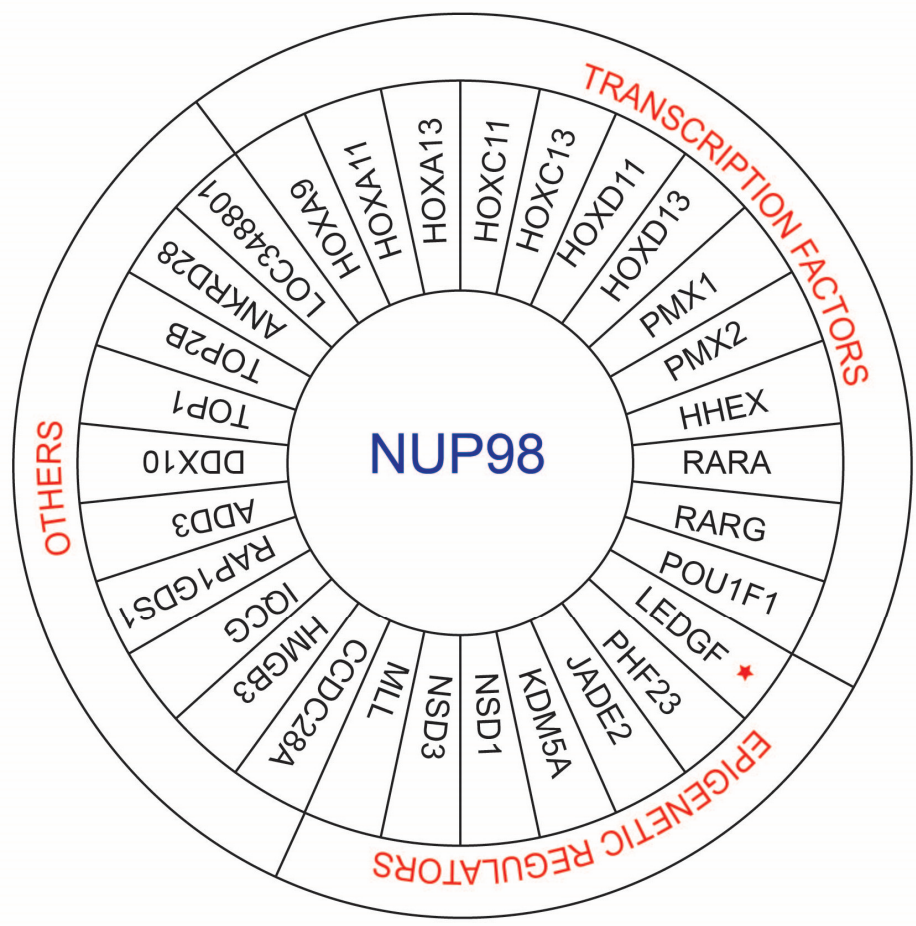

Figure 2. Fusion partners of *NUP98* in AML. NUP98 fusion partners can be divided into three groups. In the first group, NUP98 has a transcription factor as a fusion partner. In the second group, NUP98 has an epigenetic regulator as a fusion partner. In the second group, the star marked LEDGF is a transcriptional coactivator. The last group includes fusion partners of NUP98 that have neither transcription factor nor epigenetic regulation properties.

NUP98 fusions with epigenetic modifiers typically have plant homeodomain (PHD) domains (PHF23, JADE2, KDM5A, MLL, NSD1, and NSD3) and SET domains (MLL, NSD1, and NSD3) [26,31]. Among the third group, there are a number of partners that have topoisomerase and RNA helicase activities or are involved in signaling activities (Table 1).

AML patients with *NUP98* fusions display different French-American-British (FAB) subtypes. *PML::RARA* fusion is usually a characteristic of acute promyelocytic leukemia (APL) or the M3 subtype of AML [75]. However, certain AML types with NUP98 translocations like *NUP98::JADE2*, *NUP98::RARA*, and *NUP98::RARG* resemble the APL phenotype [32,33,56]. The PML::RARA fusion inhibits RARA target genes that block differentiation at the promyelocyte stage, which leads to APL [76]. This may indicate that the NUP98 rearrangements associated with the APL phenotype prevent the expression of RARA target genes. However, the mechanism of APL transformation and the response to ATRA therapy by these NUP98 fusions is not clearly understood yet. Compared to other *NUP98* fusions, the *NUP98::KDM5A* fusion is enriched in the M6/M7 subtype of AML. *NUP98::KDM5A* fusion occurs in about 20 percent of acute erythroid leukemia (AEL) cases. *NUP98-KDM5A* fusion also occurs in approximately 10 percent of pediatric acute megakaryoblastic leukemia (AMKL) cases [57,77]. Although *NUP98::NSD1* fusion appears in different AML subtypes, it is more frequent in M4/M5 subtypes [70]. *NUP98::HOX* fusions mostly occur in undifferentiated or minimally differentiated AML subtypes (Table 1).

4. NUP98 Fusions Represent a Poor Prognostic and Chemoresistant AML Subgroup

NUP98 fusions are associated with adverse clinical outcomes in AML. Patients with *NUP98* rearrangements, predominantly *NUP98::NSD1* fusion, showed poor overall survival [OS] and disease-free survival (DFS) in a pediatric AML cohort [78]. Additionally, more than 70% of *NUP98* fusion positive patients were refractory after the induction therapy [27]. In this line, other studies reported induction failure and chemotherapy resistance in pediatric AML patients carrying *NUP98::NSD1* fusion [79,80]. Shiba et al. demonstrated that *NUP98::NSD1*-like patients, with the similar gene expression signature as *NUP98::NSD1*, confer poor overall survival like *NUP98::NSD1* patients. *NUP98::HOXA13*, *DEK::NUP214*, *MLL::MLLT4* were observed in the *NUP98::NSD1*-like subgroup [81]. Furthermore, a study by the Children's Oncology Group (COG) and the European AML study groups demonstrated poor survival and higher relapse risk in *NUP98::KDMA+* pediatric AML patients [58]. In a study including acute erythroid leukemia (AEL) patients, *NUP98* fusions showed adverse clinical outcomes with estimated OS less than 10 percent [60]. Similarly, *NUP98::KDM5A* fusion showed unfavorable outcomes in pediatric AMKL patients [77]. A report from the AIEOP AML group, which includes multiple *NUP98* fusions, observed worse event-free survival (EFS) and nearly double the relapse rate in *NUP98* fusion positive AML patients compared to AML patients without known mutations [28]. Another study conducted by the French ELAM02 study group grouped *NUP98* fusions in an adverse subtype together with mutations in *WT1*, *PHF6*, and *RUNX1*. In this study, *KMT2A* rearrangements were classified as intermediate subtypes, whereas *CBF* rearrangements, *NPM1* mutations, and double *CEBPA* mutations were classified as favorable subtypes [78]. Similarly, *NUP98* fusions confer poor prognosis in the adult AML cohort [70,82]. *NUP98* fusions often co-occur with *WT1* and *FLT3-ITD* mutations. Therefore, it is always a question as to how these cooperating mutations affect survival and the response to chemotherapy. Niktoreh et al. found that co-occurrence of *NUP98* fusion, *WT1*, and *FLT3-ITD* mutations, or any of these two abnormalities, shows significantly low 3-year OS compared to patients with none of these mutations or patients with either one of these mutations [83]. Ostronoff et al. reported that the addition of *FLT3* mutations decreases the survival chances of patients with *NUP98::NSD1* AML [84]. An interesting study showed that no *NUP98::NSD1* relapsed AML patients exhibit *FLT3* mutations after chemotherapy, but four out of six exhibit WT1 mutations [79].

5. Mechanism of NUP98 Fusion Mediated AML

The NUP98 fusions mostly retain the N terminus of NUP98 and C terminus of the partner protein [85]. From the N terminus of NUP98, the GLFG repeats play a crucial role in leukemogenesis through recruiting the transcriptional coactivator complex CBP/p300, refs. [24,86] but the GLEBS domain is dispensable for leukemogenesis [87]. A mechanistic question is whether NUP98 or its partner gene plays a key role in leukemogenesis. Various studies have shown that NUP98 fusions lose their transformation properties when either partner is deleted. For example, deletion of NUP98 or the SET domain of NSD1 in NUP98-NSD1 fusion prevents myeloid progenitor immortalization [86]. Further overexpression of neither NUP98 nor its partner protein is sufficient for oncogenic transformation [88,89]. These studies indicate that the fusion protein has unique oncogenic properties in comparison to its associated components.

NUP98 fusions can form distinct nuclear dots, suggesting their involvement in gene regulation [48,90,91]. These GLFG nuclear bodies are distinct from Cajal bodies, PML bodies [in APL], and splicing-factor speckles [23]. NUP98 fusion proteins can bind CRM1 in a distinct manner from wild-type NUP98, thus preventing transcription factors, such as NFAT and NFKB, from being exported from the nucleus. The NUP98::IQCG, NUP98::HOXA9, and NUP98::DDX10 fusion proteins cause nuclear accumulation of P65, which has the potential to activate the NFKB pathway, which may contribute to the development of leukemia mediated by NUP98 fusion proteins [91,92]. Recent studies observe that membraneless organelles are formed within the nucleus through liquid–liquid phase separation (LLPS) that facilitates active transcription [93]. NUP98 fusion oncoproteins have intrinsically disordered FG motifs that create nuclear puncta and promote leukemogenesis through formation of these transcription centers [94–96].

Different NUP98 fusion proteins regulate *HOX* genes expression to drive leukemogenesis. NUP98 fusions bind near the *HOX* genes loci and activate their expression through chromatin remodeling. Results from different studies confirm that the HoxA/Meis1 pathway is the major mechanism through which NUP98 oncoproteins drive leukemogenesis. The expression of distal *HoxA* cluster genes (*Hoxa7*, *Hoxa9*, and *Hoxa10*) and *Meis1* are downregulated as hematopoietic stem and progenitor cells differentiate and overexpression of these promote self-renewal [86,97,98]. EZH2, which is part of the polycomb repressive complex 2 (PRC2), silences *HOXA* genes during differentiation [86]. Cooperation of *Hoxa9* with *Meis1* causes rapid leukemia induction in mice, indicating a crucial pathway through which leukemogenesis happens [99]. NUP98 fusions activate silenced *HoxA* cluster genes. While histone acetylation, H3K4, and H3K36 methylation around the HoxA locus confirm active chromatin, H3K27 marks by polycomb repressor complex silence HoxA genes [86,100]. NUP98 fusions prevent the H3K27me3 repressive mark and add few activation marks to induce expression of *HoxA* genes and *Meis1* (Figure 3) [86]. NUP98 fusions acetylate histones through the recruitment of enhancer factors, CREB-binding protein (CBP) and p300, by NUP98 [24,86,101]. NUP98 fusions with a chromatin-modifier partner change the chromatin near the *HoxA* cluster and *Meis1* locus. Histone H3 Lys 36 (H3K36) methylation on the *HoxA* locus by the SET domain of NUP98::NSD1 activates distal *HoxA* gene expression and causes bone marrow (BM) immortalization [86]. NSD2 is translocated in multiple myeloma patients and shows its oncogenic activity dependent on dimethylation of histone H3 at lysine 36 (H3K36me2) [102]. Other epigenetic-modifying partners of NUP98, such as PHF23 or KDM5A, dysregulate *Hox* genes expression through recognition of H3K4me3/2 marks by the plant homeodomain (PHD) finger domain. NSD1 also contains PHD fingers, but it lacks residues that interact with H3K4me3 [101]. Small molecules that inhibit the binding of the PHD domain to H3K4me3 can inhibit leukemogenesis [103,104]. *NUP98* fusions with a homeobox partner gene like *NUP98::HOXA9*, *NUP98::HOXA10*, and *NUP98::HOXD13* cooperate with *Meis1* and cause lethal AML [105–107]. However, the overexpression of Meis1 does not affect the survival of mice with leukemia induced by NUP98::TOP1 [88]. It indicates that NUP98 fusions might have distinct oncogenic potential. However, it is unclear how NUP98::HOX oncogenes collaborate with MEIS1 as compared to

NUP98::HOXA9, as only HOXA9 has a MEIS1 binding site. Additionally, the lack of *Hoxa9* does not affect the immortalization properties of an *NUP98::HOXA9* fusion oncogene [108]. Based on these findings, there may be redundant functions of *Hoxa9* in *NUP98* fusion mediated leukemogenesis. Other *Hox* genes can also drive leukemogenesis, which could be clarified in future studies. NUP98 fusion carrying patients show upregulation of both *HOXA* and *HOXB* cluster genes [57,70], but the significance of the upregulation of *HOXB* cluster genes in NUP98-fusion oncoprotein-driven AML remains unknown.

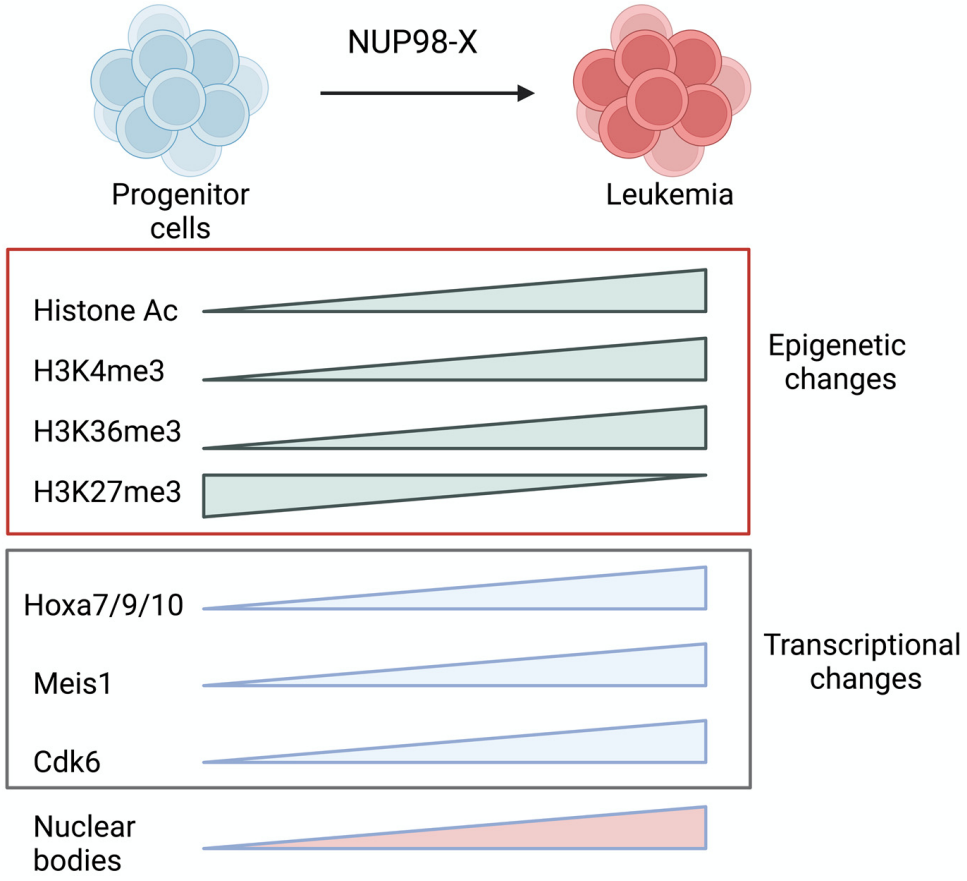

Figure 3. Mechanism of leukemic transformation by NUP98 fusions. Epigenetic and transcriptional changes that occur when hematopoietic stem and progenitor cells (HSPCs) are transformed using an *NUP98* fusion oncogene. The figure was created with BioRender.com.

In addition to transcriptional regulation, NUP98 fusions also facilitate aneuploidy [109]. The anaphase promoting complex/cyclosome (APC/C) plays a key role in the transition from metaphase to anaphase during the cell cycle, and misregulation of this complex can make the cell susceptible to malignant transformation [110]. APC/C^{Cdc20} ubiquitinates securin, leading to its degradation, and activates separase to allow chromosome segregation. Furthermore, the spindle checkpoint protects from improper chromosome segregation by inhibiting APC [111]. NUP98 fusion proteins interact with APC/C^{Cdc20} and mediates aneuploidy through obstructing the interaction of the mitotic checkpoint complex to the APC/C^{Cdc20} and premature securin degradation [109,112].

6. Cooperating Abnormalities in NUP98 Rearranged AML

NUP98 rearranged AML patients show frequent mutations in signal transduction genes (*FLT3*, *NRAS*, *KRAS*, and *KIT*) and *WT1* [113]. Different *NUP98* fusions show different co-occurring mutational signatures. For example, *NUP98::KDM5A* positive AEL cases are often associated with *RB1* deletions [60]. A recent report indicated that del(13q) is a frequent event in *NUP98::KDM5A* AML patients, indicating co-occurrence of *NUP98-KDMA* fusion

with *RB1* deletion [30]. *FLT3-ITD* mutation is a recurring event in *NUP98::NSD1* positive AML patients [70,84,114]. *FLT3-ITD* mutation is also observed in some *NUP98::HOXA9* AML patients [114,115]. *WT1*, *NRAS*, and *KRAS* mutations frequently co-occur with *NUP98::NSD1* and *NUP98::HOXA9* [78,116,117]. Patients with *NUP98* rearranged AML also have mutations in other genes, such as *ASXL1* and *MYC* [117,118].

Multiple subtypes of AML (myeloid, erythroid, and megakaryoblastic) exhibit *NUP98::KDM5A* fusion. *NUP98::KDMA* positive acute megakaryoblastic leukemia (AMKL) cases usually do not show any additional mutations [57]. It is not yet clear whether different types of AML can be attributed to different origins of cells or the presence or absence of specific additional genetic changes. Mice transplanted with hematopoietic stem and progenitor cells (HSPCs) expressing NUP98::KDM5A fusion oncoprotein develop a myeloid leukemia phenotype [60]. This suggests that additional alterations, such as *RB1* deletion, are required for the development of erythroid leukemia, thus explaining why *RB1* deletion occurs concurrently with *NUP98::KDM5A* positive AEL. There is, however, a need for more studies to clarify how the same fusion can lead to different types of AML.

One genetic alteration alone does not cause AML; at least two types of genetic alterations must be present for the disease to manifest. While Class-I mutations provide proliferative advantage to cells, Class-II mutations impair differentiation [119]. Class-I mutations include mutations in proliferative genes like *FLT3*, *RAS*, or *KIT*, but Class-II mutations include different translocations like *MLL* rearrangements, *RUNX1::ETO*, and *PML::RARα* fusion [119,120]. Several studies have demonstrated that *BCR::ABL* positive CML progresses to AML (CML blast crisis) through the acquisition of the *NUP98::HOXA9* fusion gene (Figure 4) [121,122]. Interestingly, another study observed cooperation of *NUP98::HOXA9* with *BCR::ABL* for causing AML with features of a CML blast crisis in a murine model [123]. Additionally, *NUP98::HOXA13* and *NUP98::HOXA11* were also reported in a CML blast crisis [37,124]. Another intriguing study observed the appearance of *NUP98::DDX10* fusion as a resistance mechanism to imatinib in CML and caused a blast crisis [125]. Fusions involving *NUP98* induce *HOX* genes expression and stem cell renewal, which are considered Class-II mutations. *NUP98* fusions often show mutations in signaling genes like *FLT3*, *NRAS*, and *KIT*, indicating the requirement of Class-I mutations for *NUP98* fusion mediated AML development [113,116]. Different murine model studies have also shown that *NUP98* fusions alone induce long-latency myeloid disease, but when they collaborate with different proliferative events like *FLT3* or *NRAS* mutations, they induce a lethal short-latency AML phenotype [126–130]. Retroviral insertional mutagenesis is an excellent tool to identify cooperative events for carcinogenesis [131]. A retroviral insertional mutagenesis study using *NUP98::HOXD13* fusion showed insertional events near *Meis1*, several signal transduction genes, and cell-cycle genes [132]. Similarly, another study observed spontaneous mutations in *Nras* and *Kras* in NUP98::HOXD13 mice with the AML phenotype, but these mutations were absent in NUP98::HOXD13 mice with the MDS phenotype [133]. Our study demonstrated that the addition of the NRAS p.G12D mutation further elevates the expression of distal *Hoxa* genes in NUP98::NSD1 immortalized cells [128]. Overall, the above studies support why signaling mutations are more frequent with *NUP98* rearrangements in AML (Figure 4). However, additional future studies are required to understand and clarify the clonal evolution pattern of NUP98 fusion mediated AML. Furthermore, the future studies can explain the mechanistic significance of the co-occurrence of *NUP98::NSD1* fusion with *WT1* mutation and *NUP98::KDM5A* fusion with deletion of *RB1*.

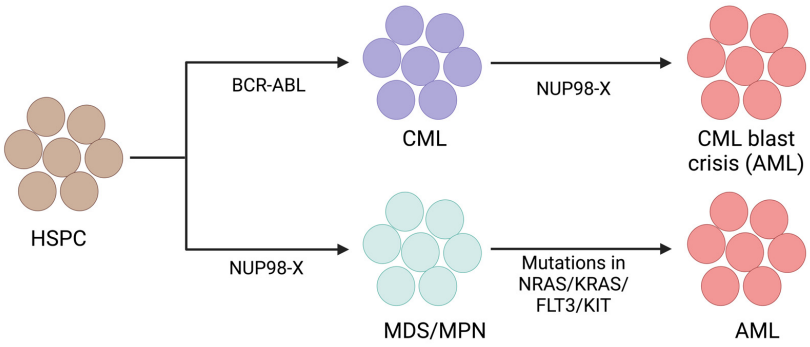

Figure 4. Generalized model of AML development by NUP98 fusions in cooperation with other oncogenic abnormalities. The BCR::ABL oncogene causes a CML-like phenotype and undergoes a CML blast crisis (AML phenotype) when it acquires a NUP98 fusion oncogene. The NUP98 fusion oncogene shows the MDS or MPN phenotype and transforms into AML when it acquires mutations in signaling genes. The figure was created with BioRender.com.

7. Therapeutic Strategies to Treat NUP98 Fusion Positive AML Patients

As discussed above, AML patients carrying a NUP98 fusion show low response to conventional therapies. Therefore, we should explore more targeted therapies for this subset of AML patients. Acute promyelocytic leukemia (APL), a subtype of AML that express *PML::RARα* fusion, is now the most curable AML through targetable degradation of fusion protein using all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) [134]. Therefore, eliminating the NUP98 chimeric protein or its potential downstream target can be developed as a curative treatment option for AML patients carrying NUP98 fusions. There are different ways to target chimeric oncoproteins. In order to eliminate AML, the oncoprotein itself can be targeted directly, or downstream targets of this fusion oncogene or its interactors can be targeted [135]. Several approaches have been proposed for treating *NUP98* rearranged AML (Figure 5).

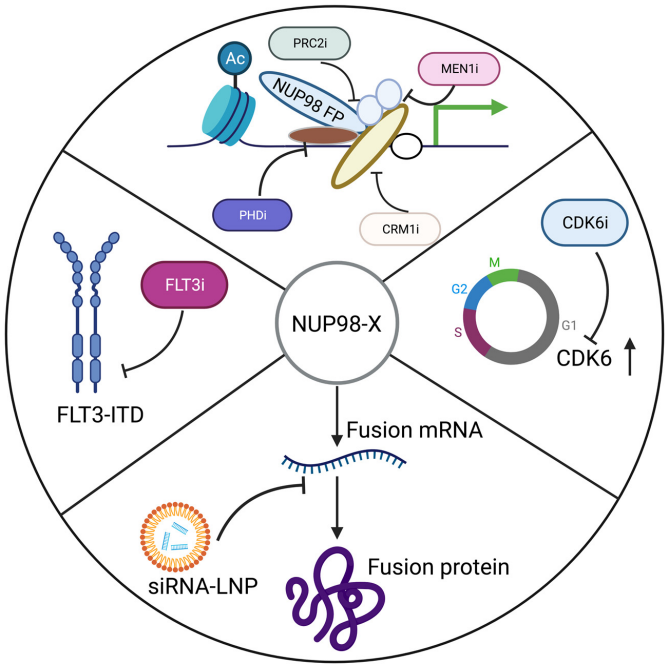

Figure 5. Potential therapeutic options for leukemia with *NUP98* rearrangements. NUP98 fusions can be directly targeted using siRNA-LNP formulations. The downstream targets of NUP98 fusion like CDK6 can be inhibited by a small molecule inhibitor. Further CRM1/XPO1, MEN1, or PRC2 inhibitors can be used to eradicate NUP98 fusion driven leukemia. A small-molecule inhibitor can be used to inhibit the FLT3-ITD mutation that is commonly associated with *NUP98* rearrangements. The figure was created with BioRender.com.

Because these fusion genes are expressed only in leukemia cells and not in healthy cells, siRNAs targeting fusion junctions can be designed specifically to target these leukemia cells. Using the patient-derived xenograft (PDX) model, we showed that siRNA lipid nanoparticle formulations can be used as a therapeutic strategy against *NUP98::NSD1* leukemia [128]. This approach is validated against *BCR::ABL*, *TCF3::PBX1*, and *RUNX1::ETO* fusion oncogenes [136–138]. However, a same fusion protein with a different breakpoint can appear as a resistance mechanism to this kind of therapy.

CDK6, which is required for G1- to S-phase transition, is upregulated by different NUP98 fusion oncoproteins. NUP98 fusion positive human and mouse samples treated with palbociclib, a CDK4/CDK6 inhibitor, show a reduction in leukemia growth [67,139]. Different FDA-approved CDK 4/6 inhibitors, which are palbociclib, ribociclib, and abemaciclib, are used for the treatment of metastatic breast-cancer patients [140].

Previously, it was demonstrated that the menin (MEN1)-MLL interaction is critical for MLL-rearranged and NPMc-mutant leukemias, and small molecules disrupting this interaction are effective against these leukemias [141,142]. Disruption of this interaction downregulates leukemic gene expression. Different menin inhibitors (SDNX-5613, JNJ-75276617, BMF-219, DSP 5336, and KO-539) are currently in early phase clinical trials [143]. A recent study shows that menin–MLL interaction is critical in *NUP98*-rearranged AML. VTP50469, an inhibitor of menin–MLL interaction, abrogates leukemogenesis and upregulates differentiation in leukemic cells carrying the *NUP98* fusion. Inhibition of menin–MLL interaction downregulates the expression of *Meis1* [144]. Overall, leukemias with *KMT2A* rearrangements, *NUP98* rearrangements, or *NPM1* mutations depend upon the HOXA/MEIS1 pathway and are susceptible to menin inhibition [145]. These genotypes account for the majority of patients with AML, indicating that menin inhibitors may have a beneficial effect on a large proportion of AML patients [145]. A recent clinical trial report for revumenib (SNDX-5613), a potent oral menin inhibitor, showed that it was effective in treating relapsed or refractory AML with *KMT2A* rearrangements or *NPM1* mutations [146]. Even though the report indicates promising clinical efficacy, minimal toxicity, and good tolerance for revumenib, clinical resistance could result from mutations in menin that prevent the drug from binding to the target [147].

The NUP98 fusions interact with XPO1; therefore, XPO1 inhibitors may be effective against NUP98 leukemia [26]. Oka et al. found that Crm1 recruits Nup98-Hoxa9 to *Hox* cluster genes to drive its expression [148]. Selinexor, an XPO1 inhibitor, has been approved for the treatment of multiple myeloma [26].

Ren et al. showed that the PRC2-KDM5B axis is crucial for NUP98::NSD1 AML. An inhibitor of polycomb repressive complex 2 (PRC2), UNC1999, reduced the leukemic burden in NUP98::NSD1-bearing mice and improved their survival [149]. PRC2 forms silenced chromatin through H3K27me3. The enhancer of zest homolog 2 (EZH2) is a catalytic subunit of PRC2, so EZH2 inhibitors can also be tested against NUP98 fusion AML [150]. Tazemetostat, an FDA-approved EZH2 inhibitor, is currently used for the treatment of epithelioid sarcoma and follicular lymphoma patients [151]. Another study shows that NUP98::PHF23 and NUP98::JARID1A leukemias are sensitive to disulfiram or a small molecule that inhibits binding of the PHF23 plant homeodomain (PHD) motif to H3K4me3, which is essential for *HOXA* and *MEIS1* aberrant expression [103,104].

Since NUP98 fusions are frequently associated with other kinase mutations, primarily *FLT3* mutations, kinase inhibitors present an interesting aspect if they are capable of effectively eradicating these leukemic cells. Leukemic cells that express NUP98::NSD1 and FLT3-ITD are effectively inhibited by a potent FLT3 inhibitor [129]. However, it has been demonstrated that leukemic clones with kinase mutations disappear after chemotherapy [79]. Therefore, kinase inhibitors might alone be insufficient to eliminate major leukemic clones, but they should be used in combination with other inhibitors targeting NUP98 fusions. The BCL2 inhibitor navitoclax and SRC/ABL inhibitor dasatinib show synergistic effects against AML cells co-expressing NUP98::NSD1 and FLT3-ITD [152].

In these AML patients, allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is an effective treatment method to prevent relapse. In different studies, relapse was observed despite allo-HSCT [58,116]. According to a study, allo-HSCT in the first complete remission (CR1) is more effective than HSCT in the second complete remission (CR2) for AML patients with *NUP98::HOXA9* fusion [153]. These studies indicate that allo-HSCT is partially effective for *NUP98* rearranged AML patients.

Future research may lead to the development of other treatment options for *NUP98* rearranged AML. Since fusion oncoproteins are exclusively expressed on cancer cells, novel ways to target fusion oncoprotein can be explored. The proteolysis-targeting chimeras (PROTACs) technology can be used to target and degrade the fusion oncoprotein and can be developed as a potential treatment approach for *NUP98* fusion positive AML patients [154]. As an ideal source of neoantigens, fusion genes can be exploited for the development of immunotherapy, such as the development of adoptive cell therapy, vaccines, and checkpoint blockade therapy [155,156]. The benefit of checkpoint blockade therapy for patients with an *NUP98* rearrangement remains undetermined. The identification of unique cell-surface proteins in the *NUP98* fusion subtype AML, which are not expressed in healthy counterparts, may be used for developing chimeric antigen receptor (CAR) T-cell therapy. A recent study demonstrated that CD123 is highly expressed in *NUP98::NSD1* positive AML patients and can be exploited as an therapeutic target [157].

8. Concluding Remarks

In recent years, new fusion partners of *NUP98* have been discovered in patients with AML.. Although many mechanisms are proposed to explain the leukemogenic activity of NUP98 fusion proteins, HOXA/MES1 appears to be the major player. There is remarkable progress in developing disease models to understand the oncogenic function of NUP98 fusion proteins. These models have been instrumental in validating therapeutic targets and assessing drug responses. Furthermore, the development of patient-derived xenograft (PDX) models of NUP98 fusions recapitulates the disease well and is an effective method to track patient cells' response to different drugs. We currently have PDX models for only a few *NUP98* rearrangements, but we will need to establish PDX models for all common *NUP98* rearrangements in the near future [26,158,159]. In different NUP98 fusion mouse models, the siRNA-LNP formulations, CDK6 inhibitor, and menin inhibitor show promising antileukemic activity.

Future studies may focus on discovering the new therapeutic vulnerabilities of NUP98 fusions and developing immunotherapies for these patients. Further research into the shared and unique mechanisms of leukemogenic transformation among NUP98 fusion oncoproteins is necessary to clarify whether a single agent can be used for the treatment of all AML patients with different *NUP98* rearrangements.

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