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EDITORIAL

Paraspeckle component 1 in acute myeloid leukemia: prospects for therapeutic targeting

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PLAIN LANGUAGE SUMMARY

Acute myeloid leukemia (AML) is a blood cancer that is hard to treat. AML contains special cancer cells called leukemia stem cells. These cells survive treatment and cause the cancer to return. Doctors need new ways to target these cells. Scientists found a protein called PSPC1 that becomes elevated in AML. When PSPC1 levels are high in AML patients, it blocks cancer cells from maturing into normal blood cells and helps them survive. This keeps the cancer cells in an immature state where they keep growing and resist treatment. The good news is that normal blood cells do not need PSPC1 to function properly. This means blocking PSPC1 mainly affects cancer cells while leaving healthy blood cell production alone. This makes it an excellent target for new treatments. PSPC1 works in an unusual way. Most similar proteins must attach to RNA to function. But PSPC1 does not need RNA. Instead, it connects with other proteins like PU.1. Together, they control which genes turn on or off in cancer cells. This finding is important because it means doctors can design drugs that break these protein connections. Breaking RNA connections with drugs is much harder. Researchers are testing several ways to stop PSPC1. Some drugs can destroy PSPC1. Others can block it from connecting with partner proteins. Some treatments use genetic tools to reduce PSPC1 levels. Early lab tests show these approaches work well. Targeting PSPC1 may help doctors remove leukemia stem cells better. This could lead to better outcomes and longer remissions for AML patients. This research is an important step toward more effective treatments for this disease.

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1. Introduction

Cancer stem cells (CSCs) [1] are a small but essential subpopulation within both solid and hematologic tumors that drive resistance to therapy, relapse, and metastatic spread. CSCs are characterized by key features, including persistent self-renewal, blocked differentiation, stress resistance, and cellular plasticity, and they represent a common vulnerability across malignancies such as breast, liver, lung, pancreatic, gastric, and hematologic cancers, including acute myeloid leukemia (AML).

In particular, AML stands out as a disease heavily influenced by CSCs, often called leukemia stem cells (LSCs) in this context. These LSCs drive the initiation, progression, and relapse of AML because of their unique abilities for self-renewal and resistance to standard therapies [2]. Despite advances in supportive care and some targeted treatments, AML still has poor long-term survival rates in most patients, mainly due to recurrence caused by residual LSCs. This underscores an urgent need to identify molecular regulators essential for LSC maintenance and AML progression as new therapeutic targets.

Recent studies have linked RNA-binding proteins, including Paraspeckle Component 1 (PSPC1), to promoting cancer stemness in various tumors, such as hepatocellular carcinoma, lung, breast, and nasopharyngeal cancers, where it reprograms gene expression, epithelial-to-mesenchymal transition (EMT) signaling, and pro-stemness transcriptional pathways (see review [3]). In the following sections, we describe PSPC1's roles in regulating leukemic transcriptional programs and stemness, highlighting new vulnerabilities in AML.

1.1. PSPC1 as a leukemia-selective oncogenic co-regulator

PSPC1 was first identified among 14 other genes within the minimal overlapping copy number alteration (CNA) locus after aligning a recurrent CNA region at chromosome 13q12.11 in different cancer cells, including AML [4]. Our recent research showed that PSPC1 is abnormally elevated in AML patient samples. Genetic inactivation of PSPC1 significantly hampers AML cell growth and colony formation, promotes terminal myeloid differentiation, and prevents leukemic engraftment *in vivo*, all while largely sparing normal hematopoietic stem and progenitor cell functions [5]. These findings indicate that AML cells and LSCs uniquely depend on PSPC1, setting it apart from other DBHS (*D*rosophila *b*ehavior, *h*uman *s*plicing) family members and offering a promising therapeutic target.

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In addition to AML, PSPC1 has gained attention as a mediator of cell plasticity and adaptation in various tumor contexts; for example, its involvement in TGF-β-driven EMT and metastasis in carcinomas is well documented [4]. In pancreatic adenocarcinoma, PSPC1 is stabilized by SKP2-mediated suppression of TRIM21-mediated ubiquitination, which promotes tumor progression [6]. These previous studies and our findings establish PSPC1 as a context-specific oncogenic co-regulator, likely guiding different transcriptional programs to influence tumor plasticity in solid cancers or maintain leukemic identity in AML. However, these features make PSPC1 a promising candidate for developing leukemia-specific therapeutic strategies.

1.2. Mechanistic insights: PSPC1 at the intersection of transcription, chromatin, and stemness

Mechanistically, PSPC1 physically interacts with PU.1, a key regulator of myeloid differentiation, forming a transcriptional complex that directly activates pro-leukemic genes, including NDC1, and suppresses differentiation signals. Importantly, we showed that the RNA-binding domain of PSPC1 is not necessary for its oncogenic activity in AML; its pro-leukemic role functions independently of traditional RNA binding or paraspeckle formation, emphasizing the modular and context-dependent nature of DBHS protein activity. Loss of PSPC1 leads to a significant reorganization of the AML transcriptome, marked by decreased expression of stemness-promoting genes and increased expression of differentiation genes.

Recent studies on pluripotent [7–9] and cancer stem cells from solid tumors [4] further reveal that PSPC1 also participates in higher-order chromatin organization and interacts with the long noncoding RNA *NEAT1*, a structural component of paraspeckles, as well as with related chromatin modifiers such as TET1 and PRC2, and with transcription factors Smad2/3. It remains to be tested whether this broader influence on genome architecture also contributes to PSPC1-mediated gene expression and cell fate determination in AML. Since the RNA-binding domain of PSPC1 is not essential for its pro-leukemic roles in AML cells, our latest data emphasize its context-dependent recruitment to AML-specific chromatin loci and the dependence of leukemic hematopoietic cells on this recruitment.

Although PSPC1 has not been directly examined in AML within the context of Wnt or TGF-β signaling, its interactions with these pathways in solid tumors may provide mechanistic insights. Given that these pathways are frequently deregulated in leukemia, they may intersect with PSPC1-driven regulatory networks. Together, PSPC1 may serve as a master regulator of LSC identity at multiple regulatory layers.

1.3. Therapeutic targeting of PSPC1 in AML

The unique PSPC1 dependency observed in AML opens the door to several therapeutic strategies. Targeting PSPC1 via RNA interference (RNAi), antisense oligonucleotides (ASOs), or small-molecule inhibitors disrupts leukemic growth and induces differentiation in preclinical models. PROTACs (proteolysis-targeting chimeras) and molecular glue degraders offer powerful strategies to eliminate 'undruggable' nuclear proteins by recruiting them to the ubiquitin-proteasome machinery [10].

Although PSPC1 is part of the DBHS protein family associated with nuclear paraspeckles that also include SFPQ and NONO [11], its pro-leukemic roles in AML, such as promoting hyperproliferation and inhibiting myeloid differentiation [5] occur independently of paraspeckle formation or NONO activity. This functional independence implies that PSPC1 could be targeted selectively without broadly disrupting paraspeckle biology or other DBHS family functions.

Emerging studies also highlight the potential for targeting protein interfaces. In hepatocellular carcinoma, the PSPC1 C-terminal fragment CT131 acts as a dual PSPC1/PTK6 inhibitor, disrupting PSPC1-driven oncogenic signaling [12]. Additionally, small molecules covalently bound to a reactive cysteine on NONO induce sequestration in nuclear condensates and interfere with transcriptional programs in prostate cancer [13]. As high-resolution structural biology and proteome editing techniques advance, opportunities for rational drug design targeting specific DBHS family members in AML will grow. These findings collectively demonstrate that DBHS proteins are druggable targets, raising the exciting possibility that PSPC1 could be targeted to treat AML.

2. Expert opinion

PSPC1 is quickly emerging as a critical vulnerability in AML. The evidence so far indicates that targeting PSPC1, which is key for LSC maintenance, could selectively eliminate leukemia-initiating cells while sparing normal blood cell production (Figure 1A), offering a promising therapeutic window. However, several challenges and questions still need to be addressed. Important research goals include thoroughly mapping PSPC1's interactome and genomic targets in primary patient samples (Figure 1B), differentiating its context-specific functions from those that are broadly conserved across cell types, and exploring potential resistance mechanisms that could develop during prolonged inhibition. Additionally, understanding how PSPC1 dependency in AML differs from other myeloid diseases and lymphoid cancers is essential for ensuring clinical safety and expanding its potential applications.

The next few years will likely see renewed efforts to develop PSPC1 inhibitors using advanced methods, including molecule-glue degraders, PROTACs, ASOs, and small molecules targeting protein-protein interfaces, along with leveraging combination therapies (Figure 1C). The potential of nucleic acid therapeutics has been recognized for transforming myeloid leukemia treatment [14]. Clearly, ASOs and siRNA platforms [15] could silence PSPC1 expression *in vivo*, especially in hematologic cancers where nanoparticle delivery to the bone marrow is becoming more practical. Additionally, PSPC1's relatively long half-life, nuclear presence, and scaffold-like properties make it an ideal target for degradation using small molecules or PROTACs. These strategies could be used alone or together to block or disrupt PSPC1 functions for therapeutic benefit.

Therapeutically, targeting RBPs like PSPC1 is difficult because they lack enzymatic domains. However, as our study

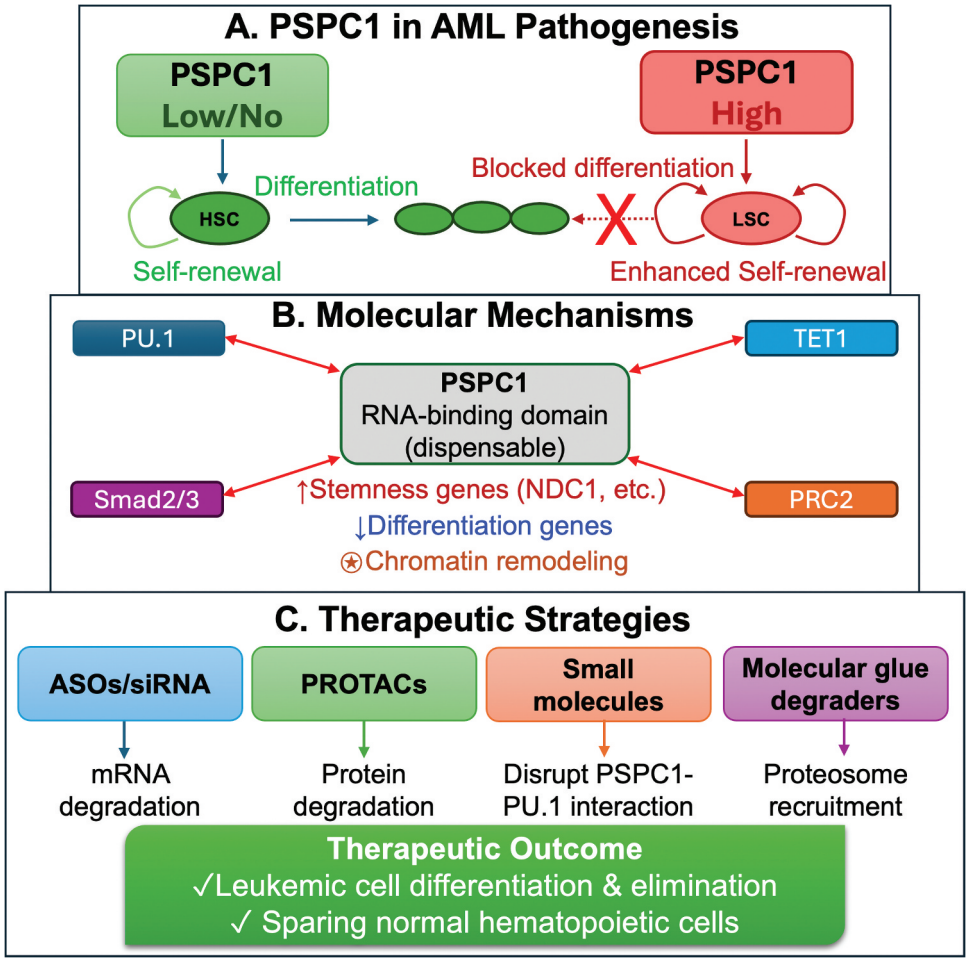

Figure 1. PSPC1 as a therapeutic target in acute myeloid leukemia. (A): PSPC1's Role in AML Pathogenesis. Normal hematopoiesis (left) depends on low or no PSPC1 expression with balanced self-renewal and differentiation. In AML (right), elevated PSPC1 drives enhanced self-renewal and blocked differentiation of leukemia stem cells (LSCs). (B): Molecular Mechanisms. PSPC1 could potentially interact with PU.1, TET1, PRC2, and Smad2/3 to regulate leukemic transcriptional programs. The RNA-binding domain is dispensable for PSPC1's oncogenic function. These interactions upregulate (↑) stemness genes, downregulate (↓) differentiation genes, and remodel (⊛) chromatin. (C): Therapeutic Strategies. Multiple approaches target PSPC1: ASOs/siRNAs (mRNA degradation), PROTACs (protein degradation), small molecules (disrupting PSPC1-PU.1 interaction), and molecular glue degraders (proteasome recruitment). These strategies eliminate leukemic cells while sparing normal hematopoiesis.

Abbreviations: AML, acute myeloid leukemia; ASO, antisense oligonucleotide; LSC, leukemia stem cell; PRC2, Polycomb repressive complex 2; PROTAC, proteolysis targeting chimera; siRNA, small interfering RNA.

shows, the oncogenic and transcriptional coactivator roles of PSPC1 in AML do not depend on its RNA-binding ability, suggesting that treatments could target its protein-protein interactions instead of its RNA-binding interface. Advances in cryo-EM and AlphaFold have begun to determine RBP structures at atomic resolution, allowing for the rational design of drugs.

The field now faces several key challenges and opportunities. First, developing selective ligands that distinguish PSPC1 from NONO and SFPQ will require high-resolution structures and structure-activity relationship (SAR) frameworks. Second, although *in vivo* delivery of ASOs or PROTACs to hematopoietic tissues is technically feasible, it remains a significant obstacle for effective AML treatment. Third, understanding the functional effects of PSPC1 inhibition on the chromatin landscape will be essential for predicting therapeutic responses. Ultimately, the goal is not only to target PSPC1 but also to reprogram the transcriptional and epigenetic circuits it influences in cancers.

Compared to targeted therapies such as the recently approved FLT3 inhibitors and IDH1/2 inhibitors, as well as the Menin inhibitors under clinical evaluation for specific AML subentities (reviewed in [16]), PSPC1 inhibition represents a potential universal therapeutic strategy across various AML subentities. We envision a future where a strategic combination of PSPC1 inhibition with epigenetic modulators or immunotherapies could selectively deplete the CSC population, including LSCs. From a translational perspective, PSPC1 represents an ideal candidate for integration into a broad oncology approach for AML, with the ultimate goal of durable remissions and cure. A comprehensive table summarizing the therapeutic targeting potential of PSPC1 is provided in Table 1. With the right tools, PSPC1 may be transformed from a 'villain' of malignancy into a 'hero' and cornerstone of cancer cure strategies.

Table 1. Therapeutic targeting strategies for PSPC1 in acute myeloid leukemia.

Therapeutic modality	Mechanism of action	Advantages	Challenges	Development status	Key considerations for AML
Antisense Oligonucleotides (ASOs)	• Target PSPC1 mRNA • Induce RNase H-mediated degradation • Reduce protein expression	• High specificity • Proven delivery to bone marrow/ hematopoietic tissues • Clinical precedent in hematologic malignancies • Reversible effects	• Off-target effects • Delivery optimization needed • Potential immunogenicity • Manufacturing complexity	Preclinical	• Leverage existing nanoparticle delivery platforms • Monitor normal hematopoiesis • Combination with chemotherapy
Small interfering RNA (siRNA)	• Target PSPC1 mRNA • RISC-mediated cleavage • Potent knockdown	• High potency (low doses) • Transient silencing • Rapid development timeline • Tunable duration	• Delivery vehicles required • Stability in circulation • Potential for off-target effects • Immune activation	Preclinical	• Lipid nanoparticle formulations • Bone marrow tropism • Dose optimization for LSC targeting
PROteolysis TArgeting Chimeras (PROTACs)	• Bifunctional molecules • Recruit E3 ubiquitin ligase to PSPC1 • Induce proteasomal degradation	• Catalytic mechanism (substoichiometric dosing) • Complete target removal • Can target 'undruggable' proteins • Potentially overcome resistance	• Large molecular size (bioavailability) • Complex synthesis • E3 ligase expression dependence • Potential for degradation resistance	Preclinical (proof-of-concept)	• Nuclear localization required • Screen multiple E3 ligases (CRBN, VHL, etc.) • Selective vs. NONO/SFPQ • Test in patient-derived xenografts
Molecular Glue Degraders	• Small molecules inducing neo-protein interactions • Redirect E3 ligases to PSPC1 • Trigger degradation	• Small size (better PK/PD) • Oral bioavailability potential • Lower complexity than PROTACs • Novel mechanisms	• Difficult to design rationally • Limited to specific E3 ligases • Unpredictable selectivity • Screening intensive	Early research stage	• Phenotypic screening in AML cell lines • Structure-activity relationships • Assess impact on paraspeckle integrity
Small Molecule Inhibitors (Protein-Protein Interaction)	• Disrupt PSPC1-PU.1 interaction • Block PSPC1-mediated transcriptional activation • Preserve protein but inhibit function	• Targets oncogenic function directly • RNA-binding independent • Potentially selective • Oral delivery feasible	• Protein-protein interfaces challenging to target • Requires high-resolution structural data • Selectivity among DBHS family members	Early research stage	• Requires PSPC1-PU.1 co-structure • Fragment-based drug design • High-throughput screening • Validate in primary AML samples
Peptide-based Inhibitors	• Mimetic peptides disrupting PSPC1 protein interactions • Based on CT131 fragment concept	• High specificity • Rational design based on protein structure • Can target multiple interfaces	• Cell permeability • Proteolytic stability • Production costs • Immunogenicity potential	Proof-of-concept (HCC model)	• Cell-penetrating sequences • Stapled peptides for stability • Test dual PSPC1/co-factor targeting • IV administration likely
CRISPR-based Genetic Therapies	• Permanent PSPC1 knockdown in LSCs • Gene editing ex vivo • Targeted to leukemic cells	• Permanent modification • Highly specific • One-time treatment potential • Eliminates resistance	• Delivery to HSCs/LSCs • Off-target editing • Manufacturing complexity • Regulatory hurdles • High cost	Conceptual	• Ex vivo editing of patient HSCs • Ensure normal hematopoiesis unaffected • Long-term safety monitoring • Combination with transplant
Combination Therapies	• PSPC1 inhibition + epigenetic modulators (TET, PRC2 inhibitors) • PSPC1 inhibition + immunotherapy • Multi-targeted approach	• Synergistic effects • Target multiple stemness pathways • Reduce resistance • Lower individual drug doses	• Increased toxicity risk • Complex PK/PD interactions • Optimal sequencing/timing • Regulatory complexity	Preclinical rationale	• Rational combinations based on PSPC1 interactome • Test with standard AML therapies (cytarabine, etc.) • Immune checkpoint inhibitors • Venetoclax combinations

Abbreviations: AML, acute myeloid leukemia; ASO, antisense oligonucleotide; CRBN, cereblon; CT131, C-terminal fragment 131; DBHS, Drosophila behavior/human splicing; HCC, hepatocellular carcinoma; HSC, hematopoietic stem cell; LSC, leukemia stem cell; PK/PD, pharmacokinetics/pharmacodynamics; PRC2, Polycomb repressive complex 2; PROTAC, proteolysis targeting chimera; RISC, RNA-induced silencing complex; siRNA, small interfering RNA; TET, ten-eleven translocation; VHL, von Hippel-Lindau.

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Declaration of interest

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