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Review Article

Paraspeckle Component 1: a multifunctional RNA binding protein

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Abstract: Paraspeckle Component 1 (PSPC1), a Drosophila behavior/human splicing (DBHS) protein family member, represents a pivotal component within paraspeckles. It exerts indispensable functions across a wide array of biological processes, encompassing gene expression, the DNA damage response, the regulation of circadian rhythms, spermatogenesis, cell fate determination, and cancer metastasis. Notably, PSPC1 exhibits overexpression in several types of cancer, including hepatocellular carcinoma, lung cancer, and breast cancer, where it actively contributes to tumorigenesis. This overexpression phenomenon implies that PSPC1 holds the potential to serve as both a biomarker and a therapeutic target for these malignancies. Consequently, a substantial amount of research has been conducted to explore its structure, functions, and role in cancer development and progression. This review article aims to comprehensively summarize the current findings regarding PSPC1.

Keywords: PSPC1, paraspeckle, DNA damage, DNA repair, cancer

Introduction

Paraspeckle Component 1 (PSPC1), alternatively referred to as Paraspeckle Protein 1 (PSP1), is a nucleolar protein that localizes to distinct punctate subnuclear structures known as paraspeckles, which are situated in close proximity to splicing speckles [1, 2]. In transcriptionally active cells, PSPC1 is typically found within these paraspeckles. However, when RNA polymerase II transcription is inhibited or during telophase, it relocates to unique cap-like structures at the nucleolar periphery [1, 3]. Initially identified through proteomic investigations of purified human nucleoli, PSPC1 was observed to aggregate in a novel punctate subnuclear structure within the interchromatin space adjacent to splicing speckles, which led to the naming of these structures as paraspeckles [1, 4]. Paraspeckles are RNA-protein complexes consisting of the long non-coding RNA nuclear paraspeckle assembly transcript 1 (NEAT1) and members of the Drosophila Behavior Human Splicing (DBHS) protein family, such as PSPC1, Splicing Factor proline- and glutamine-rich (SFPQ, formerly known as PSF), and Non-POU-domain-containing octamer binding protein (NONO/p54nrb) [2, 5, 6]. PSPC1 is the first structural protein discovered within paraspeckles, thereby earning the name “Paraspeckle Component 1” [6]. It plays diverse biological roles in the cell nucleus by interacting with both RNA and proteins and is essential for forming and properly functioning paraspeckles [1, 3]. PSPC1 is implicated in crucial cellular processes such as cell fate determination [7] and the regulation of gene expression [8]. Moreover, it functions as a subunit that modulates the activity of related enzymes [9], thereby contributing to the selective expression of specific genes [8, 9].

Structure of the human PSPC1

The human PSPC1 gene, located at the 13q12.11 locus, encodes the PSPC1 protein, which acts as a transcription factor [10]. Like other members of the DBHS protein family, PSPC1 has a well-defined molecular structure with three key functional domains [5]. These are two highly conserved N-terminal RNA recognition motifs (RRM1 and RRM2), a NONA/para-

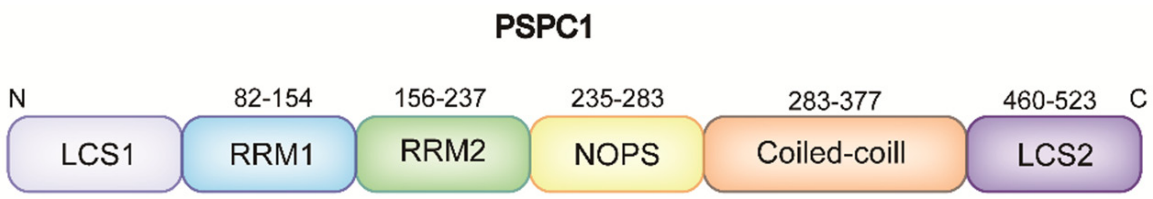

Figure 1. The structure of human PSPC1. Paraspeckle Component 1 (PSPC1) has three key functional domains: two highly conserved N-terminal RNA recognition motifs (RRM1 and RRM2), a NONA/paraspeckle domain (NOPS), and a C-terminal CC domain. In addition, it has intrinsically disordered regions at both ends, known as LCS domains.

speckle (NOPS) domain, and a C-terminal coiled-coil (CC) domain [5] (**Figure 1**).

RRMs are among the most common and well-studied nucleic acid-binding domains, found in 0.5-1.0% of human genes [11]. The RRM domains in PSPC1 mainly recognize and bind specific RNA sequences or structures. They have a typical αβ - fold structure, made up of four antiparallel β - strands and two α - helices [5, 12]. Conserved aromatic and charged residues on these domains, exposed to the solvent, are crucial for RNA binding [13]. However, RRM2 differs from RRM1 as it lacks conserved aromatic residues and has extended β - turns in loops 3 and 5, one of which is highly conserved [5]. Between RRM2 and the CC region, the NOPS domain likely binds nucleic acids because of its surface-exposed basic residues [5, 13]. Meanwhile, the C-terminal CC domain is vital for dimerization and oligomerization, allowing PSPC1 to form complexes with other proteins, essential for interacting with paraspeckle components like NONO and SFPQ [1, 13].

Recent research has deepened our understanding of PSPC1's structure. A 2021 study showed that PSPC1 undergoes phase separation, with PSPC1 droplets seen diffusing and fusing inside cells [14]. In 2022, researchers identified a disordered region at the C-terminal of PSPC1, named the LCS domain (LCS2), rich in glycine (G) and proline (P) [15]. At an estimated nuclear concentration of 5 μM, this domain helps form spherical PSPC1 droplets, connecting to dynamic phase separation [15]. LCS2's phase-separation ability boosts the recruitment of other proteins, thus influencing gene expression and transcription [5, 15].

The ability of biomolecules to undergo liquid-liquid phase separation is closely related to various human diseases, including neurodegenerative disorders and cancer [16, 17]. Although we don't fully understand PSPC1's phase-separation properties and their biological significance, ongoing research is expected to reveal more functions and regulatory mechanisms related to this process.

Regulation of PSPC1 expression

PSPC1 is expressed across diverse human tissues, with notably high levels in the bone marrow [16] and testis [10]. Moreover, PSPC1 upregulation has been observed in multiple cancers, such as liver, lung, breast, and nasopharyngeal carcinoma [18-21], piquing the interest of researchers in elucidating its role in tumorigenesis and disease progression [16].

Hypoxia and external factors modulate expression of PSPC1

Studies indicate that intermittent hypoxia (IH) promotes PSPC1 expression, resulting in elevated PSPC1 levels in the blood and monocytes of patients with obstructive sleep apnea (OSA) [22]. Additionally, research has shown that the absence of NONO leads to increased PSPC1 expression, and PSPC1 can compensate for NONO by forming a stable complex with SFPQ [23]. Furthermore, cisplatin has been reported to induce PSPC1 expression [24]. Besides these findings, nuclear receptor 4A1 (NR4A1) regulates PSPC1 by interacting with the NGF1β response element (NBRE) sequence in the PSPC1 gene promoter [25]. Knockdown of NR4A1 has been shown to reduce PSPC1 expression in MDA-MB-231 breast cancer cells, H1299 lung cancer cells, and SNU449 liver cancer cells [25].

Post-translational modifications regulate the activity of PSPC1

Post-translational modifications represent key regulatory mechanisms that govern protein

activity and function, playing crucial roles in signal transduction, cell cycle regulation, protein degradation, cell differentiation, and development [26]. Various factors influence PSPC1's post-translational modifications. For instance, ATM (ataxia telangiectasia mutated) and ATR (ATM and Rad3-related) have been demonstrated to phosphorylate PSPC1 [27]. Additionally, non-receptor protein tyrosine kinase 6 (PTK6) induces PSPC1 phosphorylation at the Y523 site, promoting protein-protein interactions in the nucleus and contributing to tumor suppression [28]. PSPC1 is also regulated through ubiquitination and degradation [17]. TRIM21, an E3 ubiquitin ligase involved in immune responses and the degradation of intracellular pathogens, mediates PSPC1 ubiquitination and degradation [17]. However, S-phase kinase-associated protein 2 (SKP2) can inhibit TRIM21 - mediated ubiquitination, thereby stabilizing and protecting PSPC1 from degradation [17]. Moreover, the long non-coding RNA (lncRNA) LOC105369504 has been found to reduce PSPC1 stability by promoting its ubiquitination and subsequent proteasomal degradation [29].

Nuclear-cytoplasmic distribution

Several studies have also delved into the nuclear-cytoplasmic distribution of PSPC1 [30, 31]. Researchers have discovered that PSPC1 expression promotes adipocyte-specific protein expression and adipogenesis [30]. During adipocyte differentiation, PSPC1 interacts with DDX3X (a DEAD-box RNA helicase that utilizes ATP to bind or remodel RNA and ribonucleoprotein complexes, playing roles in various regulatory pathways within cells) [30]. As differentiation progresses, PSPC1 translocates from the nucleus to the cytoplasm [30]. Confocal immunofluorescence analysis has revealed that in pre-adipocytes, PSPC1 is entirely localized in the nucleus, whereas in mature adipocytes, PSPC1 staining significantly shifts to the cytoplasm [30]. Additionally, studies have disclosed that PSPC1 shuttles between the nucleus and cytoplasm by binding to importin α2 and traversing the nuclear pore complex (NPC) [31]. Overexpression of importin α2 increases PSPC1 accumulation in paraspeckles, while its impairment or knockdown diminishes PSPC1 localization in paraspeckles [31, 32].

In summary, based on the structural characteristics of PSPC1, it functions predominantly by interacting with other proteins [5]. It also plays a vital role in the paraspeckle formation, acting as a membrane-less nuclear organelle [33]. The subsequent sections will explore the functional roles of PSPC1 and its significance in various diseases.

Functions of the human PSPC1

PSPC1 exerts a pivotal influence across multiple facets of gene regulation, including the repair of DNA double-strand breaks [24], the modification of mRNA [9], the activation of transcription [34], and the termination of transcription [8]. Moreover, it is indispensable for diverse biological processes such as cell differentiation [30], cell fate determination [7], innate immune responses [35], and spermatogenesis [10, 34]. While some of these functions are contingent upon the presence of paraspeckles [7, 8, 35] (**Figure 2**), others transpire independently of paraspeckle formation [9, 24, 30, 36, 37] (**Figure 3**).

The paraspeckle-dependent function of PSPC1

Paraspeckles are membrane-less organelles nestled within the cell nucleus, scaffolded by Neat1-2. This non-coding RNA recruits proteins like PSPC1, SFPQ, and NONO to form their intricate structure [5]. Paraspeckles are implicated in a gamut of physiological processes, including gene expression [8], RNA processing [5, 30], cell differentiation [30], hypoxia adaptation [38], viral infection, and metabolism [35]. As a major constituent of paraspeckles, PSPC1 assumes a critical role in orchestrating these functions (**Figure 2**).

Roles in early embryonic development: As previously alluded, PSPC1 plays a vital role in early embryonic development, and paraspeckles are equally crucial for cell fate determination and differentiation during this phase [7]. The embryo commences its division from a single fertilized egg, progressing through the 2-cell, 4-cell stages, and gradually differentiating into distinct cell types [39]. A 2007 study unearthed molecular disparities between blastomeres at the 4-cell stage, notably in histone modification levels, intimating that the first cell fate decision occurs at this juncture [40]. One of the earliest-identified regulators in this process is CARM1 (Coactivator-associated arginine methyltransferase 1), an enzyme that catalyzes the

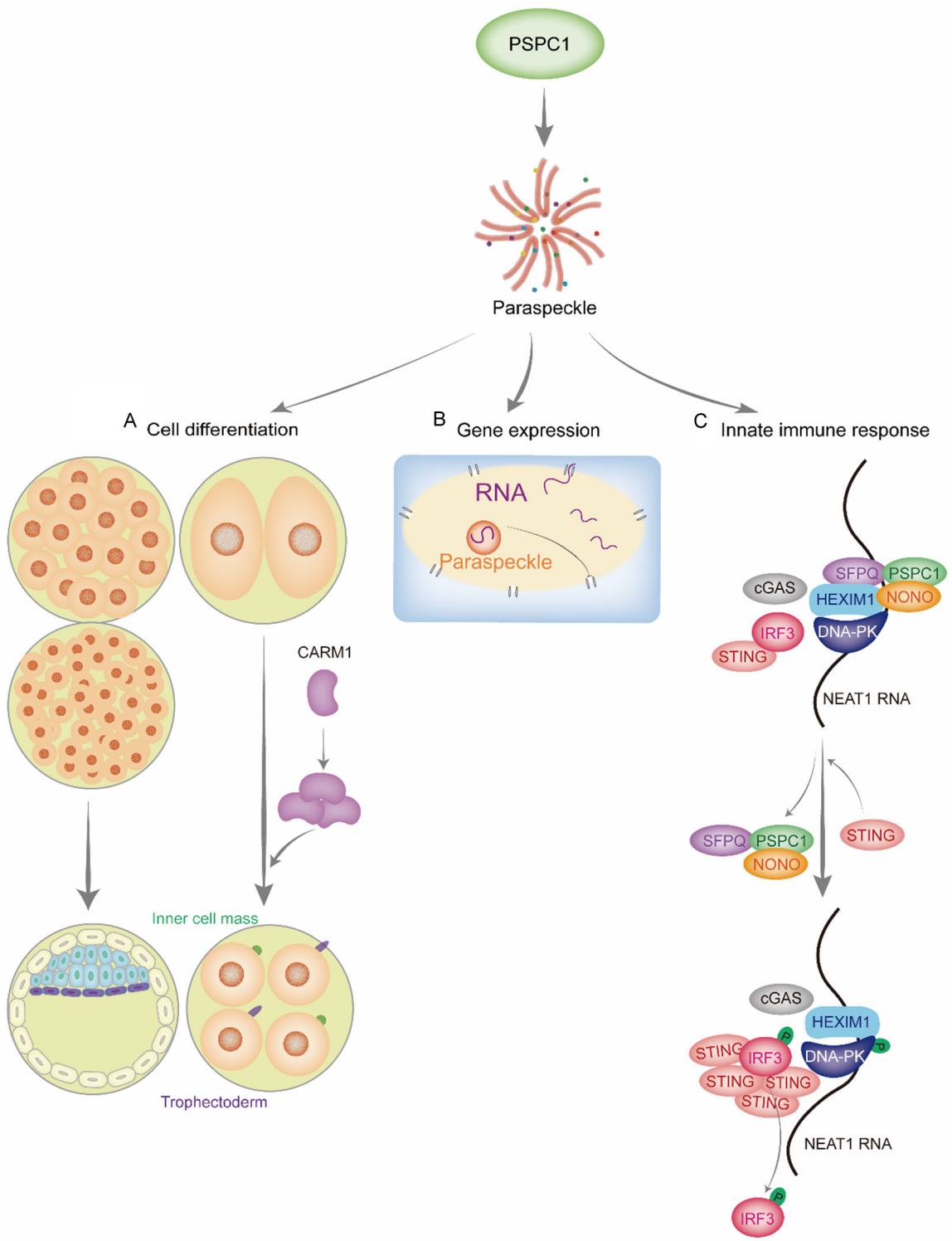

Figure 2. The paraspeckle-dependent function of PSPC1. PSPC1 functions by forming paraspeckles in the following three ways: A. PSPC1 promotes the expression, nuclear localization, and function of CARM1, thereby influencing the fate determination of blastomere cells. In the absence of paraspeckles, embryonic development arrests at the 16- to 32-cell stage, impacting cell fate determination and differentiation. B. By affecting the nuclear retention of mRNAs containing inverted repeated Alu elements (IRAlus), PSPC1 regulates the expression of specific genes. C. PSPC1 participates in forming an RNP complex (HDP-RNP) with HEXIM1, Neat1, DNA-PK, and paraspeckle factors. HDP-RNP can activate the DNA-mediated innate immune response through the cGAS-STING pathway.

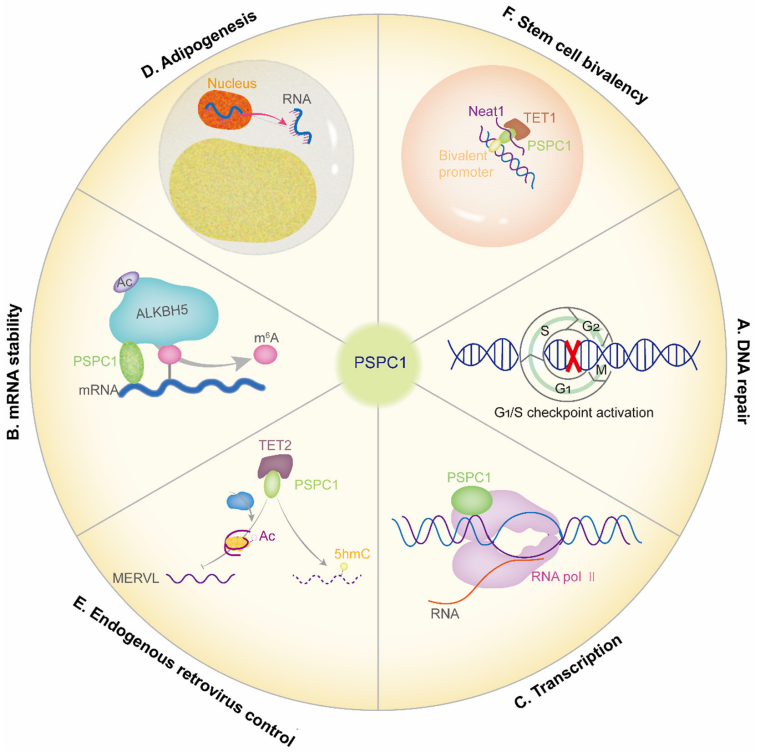

Figure 3. The paraspeckle-independent functions of PSPC1. The paraspeckle-independent functions of PSPC1 primarily include the following aspects: A. Activating the G1/S checkpoint to promote DNA repair. B. PSPC1 tends to bind with ALKBH5 modified by K235 acetylation, forming a complex that enhances ALKBH5's N6-methyladenosine (m6A) demethylation activity. This promotes ALKBH5 recruitment and recognition of RNA m6A, facilitating the removal of RNA m6A modifications and tumorigenesis. C. PSPC1 can inhibit RNA-induced premature release of RNA polymerase II (Pol II). Through interactions with RNA, it stabilizes the binding of Pol II to the template DNA, enhancing gene expression and the transcription process. D. PSPC1 promotes the export of fat-specific RNAs from the nucleus to the cytoplasm, thereby increasing protein expression. E. PSPC1 binds with TET2 and suppresses MERVL expression by regulating the 5-hydroxymethylation of MERVL RNA. Additionally, it inhibits MERVL transcription by removing acetyl groups from histones via HDAC1/2. F. PSPC1 can form a molecular axis with TET1 and Neat1 to control the bivalency of stem cells.

methylation of arginine 26 on histone H3 (H3R-26me) [40]. During early embryonic development, blastomeres with high H3R26me expression are predisposed to become part of the inner cell mass (ICM). In contrast, those with low expression are more likely to develop into trophoblast cells (TE) [40]. By modulating chromatin activity across different genomic regions, CARM1 influences cell function, differentiation, and gene expression. In essence, CARM1 plays a pivotal role in cell development and gene expression regulation, directly steering cell fate determination (**Figure 2A**). In 2018, research from Magdalena Zernicka-Goetz's laboratory revealed that paraspeckles act as upstream regulators of CARM1 during early mouse embryogenesis, governing its expression, nuclear localization, and function, thereby swaying blastomere fate decisions [7]. Knocking down SFPQ led to a significant reduction in CARM1 expression and H3R26me2 levels, and a similar effect was observed upon Neat1 knockdown, underscoring the robust connection between paraspeckles and CARM1 regulation. Further investigations disclosed that knocking out Neat1 or SFPQ culminated in embryonic arrest at the 16-to 32-cell stage, accompanied by an upsurge in Cdx2 expression, which favored TE formation [7]. Intriguingly, CARM1-knockout embryos could still form blastocysts, suggesting that paraspeckles not only regulate CARM1 but also contribute to cell fate determination through additional, as-yet-undiscovered mechanisms [7]. Although this study did not specifically evaluate the impact of PSPC1 knockdown, it is reasonable to surmise that PSPC1, as a key paraspeckle component, also plays a crucial role in cell fate determination (**Figure 2A**). In 2024, further research demonstrated that disrupting paraspeckles promotes exon - skipping splicing (ESS) of CARM1 precursor mRNA (pre-mRNA), contributing to its heterogeneity and control over the first cell fate decision [41]. Notably, LincGET, rather than Neat1, was found to be essential for paraspeckle assembly in embryos [41]. LincGET recruits paraspeckles to the CARM1 gene locus, where it inhibits ESS via heterogeneous nuclear ribonucleoprotein U (HNRNPU), further buttressing their role in cell fate determination [41]. Given its central role in paraspeckle function, PSPC1 will likely to be a linchpin in early embryonic differentiation and lineage specification.

In summary, as a core component of paraspeckles, PSPC1 interacts with long non-cod-

ing RNA Neat1 and other DBHS family members (such as NONO and SFPQ) to regulate cell fate determination, gene expression regulation, and immune responses [17, 28-30].

Roles in gene expression: The regulation of gene expression by paraspeckles is of utmost importance, mainly through the mechanism of RNA nuclear retention [8]. This mechanism is especially pertinent for genes harboring double-stranded RNA regions that undergo adenosine-to-inosine (A - to - I) editing. This editing process influences the nuclear retention of mRNAs with inverted repeated Alu elements (IRAlus), thereby regulating the expression of certain genes [8] (**Figure 2B**). Studies have also unearthed a role for PSPC1 in the transcriptional regulation of herpes simplex virus 1 (HSV-1) genes [42]. HSV-1 infection instigates a redistribution of nuclear speckles and paraspeckles, leading to interactions between the speckle protein SRSF2 (Serine/arginine-rich splicing factor 2) and the paraspeckle components Neat1, PSPC1, and P54nrb [42]. PSPC1 contributes to viral gene transcription by binding to the HSV-1 gene promoter [42]. Additionally, Neat1 and SRSF2 regulate histone modifications near viral genes by associating with the Enhancer of Zeste Homolog 2 (EZH2) and the P300/CBP complex, thereby influencing chromatin structure and transcriptional activation [42]. These findings suggest that PSPC1, in concert with other nuclear body components, facilitates HSV-1 replication by modulating the host cell's transcriptional machinery [42].

Roles in immunity: In immune function, PSPC1 forms a ribonucleoprotein (RNP) complex designated as HDP-RNP, which comprises HEXIM1, Neat1, DNA-PK, and paraspeckle-associated factors [35]. HDP-RNP serves as a crucial nuclear regulator that activates DNA-mediated innate immune responses through the cGAS-STING pathway [35] (**Figure 2C**). Consequently, during viral infection, PSPC1, as part of the paraspeckle complex, contributes to modulate the host immune response [35].

The paraspeckle-independent functions of PSPC1

Roles in DNA double-strand break repair: PSPC1, SFPQ, and NONO, all members of the DBHS protein family, assume distinct roles in DNA double-strand break (DSB) repair [5]. Homologous recombination (HR) and non-homologous end joining (NHEJ) stand as the two primary pathways for DSB repair [43]. Research has demonstrated that NONO and SFPQ collaborate to expedite DSB repair [44]. In NONO-deficient cells, the upregulation of PSPC1 expression implies a certain degree of functional redundancy between PSPC1 and NONO in DNA repair [23]. Moreover, PSPC1 can form a complex with SFPQ to partake in the repair process [23]. PSPC1 seems to be involved in the late-stage DSB repair. Its increased expression in NONO-deficient cells occurs without significantly affecting the expression of other genes associated with NHEJ and HR. This suggests that PSPC1 may influence DNA repair through direct interaction with repair substrates rather than by regulating the expression of repair-related genes [23]. Furthermore, investigations have shown that exposure to cisplatin induces PSPC1 expression in HeLa cells, indicating a potential role of PSPC1 in the DNA damage response (DDR) [24]. However, PSPC1 does not directly engage in DNA repair pathways mediated by γH2AX, 53BP1, or Rad51. When cisplatin induces G1/S phase arrest in HeLa cells, the knockdown of PSPC1 enables cells to bypass the G1/S checkpoint, prematurely enter mitosis, and undergo increased cell death. This emphasizes the crucial role of PSPC1 in safeguarding genomic integrity during DDR [24] (**Figure 3A**).

Function of PSPC1 dimerization: PSPC1's capacity to dimerize has been previously noted [5], yet what are the functional ramifications of this dimerization? Firstly, in terms of RNA binding, PSPC1 can bind to specific single - stranded RNA sequences. Research indicates that PSPC1-DBHS exhibits a high affinity for U-rich single-stranded RNA [45]. Secondly, regarding protein complex formation, PSPC1 forms heterodimers with other DBHS proteins, such as NONO, which impacts their localization and function within the nucleus [45]. Thirdly, regarding structural flexibility, the heterodimerization of PSPC1 and NONO enhances the structural adaptability. This allows the dimer to adjust its conformation to accommodate various binding partners, thereby influencing protein-protein interactions and cellular functions [46]. Finally, concerning protein stability, PSPC1 dimerization maintains protein stability, preventing aggregation and precipitation within

the cell. This is essential for the proper function of the protein and nuclear organization [45].

Roles in mRNA stability: ALKBH5, an RNA demethylase, removes methyl modifications from mRNA to prevent degradation, thereby stabilizing mRNA [46] (**Figure 3B**). As an RNA-binding protein, PSPC1 acts as a regulatory subunit of ALKBH5 [9]. It binds to K235-acetylated ALKBH5, forming a complex that enhances ALKBH5's N6-methyladenosine (m6A) demethylation activity [9]. This interaction facilitates the recruitment of ALKBH5 to m6A-modified RNA, promoting the removal of m6A and contributing to tumorigenesis [9]. Further studies have revealed that mitotic signals stimulate the acetylation of ALKBH5 at K235, strengthening its interaction with PSPC1 and subsequently reducing m6A levels in RNA [9] (**Figure 3B**). Importantly, PSPC1 itself does not directly alter m6A levels; instead, it serves as an RNA-binding platform that enhances the enzymatic activity of ALKBH5, the catalytic core enzyme [9].

Beyond its role in m6A regulation, PSPC1's RNA-binding and phase-separation capabilities impact RNA polymerase II (Pol II) activity both within and outside the nucleus [15]. Pol II drives transcription through various mechanisms, and genome-wide studies have shown that in most metazoan genes, Pol II is bound at their promoter-proximal regions [47, 48]. The pausing and releasing of Pol II at the proximal region downstream of the transcription start site is a critical step in gene transcription and expression regulation [15]. The largest subunit of Pol II contains an intrinsically disordered C-terminal domain (CTD), and the phosphorylation state of this domain determines whether Pol II enters the elongation phase [15]. PSPC1 can prevent the premature release of Pol II by stabilizing the interaction between Pol II and template DNA through RNA binding [15] (**Figure 3C**). Furthermore, PSPC1's phase-separation activity encapsulates the intrinsically disordered CTD of Pol II within droplets, promoting its phosphorylation and release, ultimately enhancing gene expression and transcription [15].

Roles in adipogenesis: PSPC1 plays a pivotal role in adipogenesis [30] (**Figure 3D**). Peroxisome proliferator-activated receptor gamma (PPARγ), the primary transcriptional regulator of adipocyte differentiation, is indispensable for adipocyte development [49]. PSPC1 is a direct target of PPARγ and is induced during adipogenesis. PSPC1 promotes protein expression by binding to adipocyte-specific RNA and facilitating its export to the cytoplasm [30]. The loss of PSPC1 disrupts adipogenesis, alters adipocyte gene expression, and affects obesity and insulin resistance induced by a high-fat diet [30]. Further studies have shown that mutating the RNA recognition motif (RRM) domain of PSPC1 almost completely abolishes its promoting adipogenic function, highlighting the essential role of its two RRM domains in adipocyte differentiation [30]. During adipocyte maturation, PSPC1 binds to the RNA export factor DEAD-box RNA helicase 3 (DDX3X) and translocates from the nucleus to the cytoplasm, promoting the export of target RNAs [30]. In conclusion, PSPC1 plays a key role in adipogenesis and adipose tissue function by regulating adipocyte RNA maturation and processing.

Inhibition of endogenous retroviral (ERVs) transcription: The TET family consists of a group of dioxygenases mainly involved in DNA demethylation, playing a crucial role in gene expression regulation [50]. This family includes TET1, TET2, and TET3, which catalyze the conversion of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), a key step in epigenetic modification and DNA demethylation [51]. Besides DNA, TET proteins have been shown to mediate the oxidation of RNA 5-mC to 5-hmC, expanding their role beyond genomic regulation [51]. Although TET proteins have been extensively studied in the context of DNA modification, their role in regulating endogenous retroviruses (ERVs), which account for 8-10% of the genomes of mice and humans, remains poorly understood [37]. Recent research in pluripotent mouse embryonic stem cells (derived from the inner cell mass of pre-implantation blastocysts) has revealed that PSPC1 recruits TET2 to chromatin in an RNA-dependent manner, relying on its RNA-binding function [37]. PSPC1 interacts with TET2 to suppress the expression of MERVL, a subtype of endogenous retroviruses that is highly expressed in two-cell-stage mouse embryos [37]. The underlying mechanism involves regulating MERVL RNA hydroxy-

methylation, leading to RNA instability [37]. Additionally, the PSPC1-TET2 complex recruits HDAC1/2 (histone deacetylases), which remove acetyl groups from histones, resulting in chromatin compaction and transcriptional repression of MERVL [37] (**Figure 3E**). In summary, PSPC1 facilitates the recruitment of TET2 to chromatin, influencing MERVL RNA stability through HDAC1/2-mediated repression and 5-hmC-driven degradation, thereby inhibiting ERV transcription [37]. Moreover, PSPC1 and TET2 cooperate to regulate the expression of other ERV families [37], reinforcing PSPC1's transcriptional and post-transcriptional regulatory functions.

Regulating stem cell bivalency: In addition to interacting with TET2, PSPC1 also interacts with TET1, which is critical for embryonic stem cells (ESCs) and early development [52]. Studies have shown that PSPC1 and TET1 suppress the expression of bivalent genes, while the long non-coding RNA (lncRNA) Neat1 activates their expression [36]. Polycomb Repressive Complex 2 (PRC2), a member of the Polycomb protein family, has histone methyltransferase activity and acts as a transcriptional repressor [36] (**Figure 3F**). PRC2 primarily regulates the expression of key transcription factors involved in cell differentiation and embryonic development, helping to maintain stem cell identity and control differentiation pathways [52]. In ESCs, PSPC1 binds to TET1, while Neat1 preferentially interacts with PSPC1 at bivalent gene promoters, facilitating the recruitment of PRC2 and repressing bivalent gene expression [36]. During the transition from ESCs to epiblast-like cells (EpiLCs), the PSPC1-TET1 interaction plays a crucial role in recruiting PRC2 to bivalent gene promoters, thereby inhibiting their activation [36]. In contrast, Neat1 promotes the activation of specific bivalent genes by facilitating PRC2 binding to their mRNA transcripts [36]. PSPC1 is vital for maintaining PRC2 chromatin occupancy, thereby ensuring its regulatory function [36]. In summary, TET1, PSPC1, and Neat1 form a molecular axis that regulates stem cell bivalency by modulating PRC2's binding to bivalent gene promoters and their mRNA transcripts. Notably, TET1 regulates bivalent genes independently of its catalytic activity [52], instead relying on PSPC1 to mediate its regulatory effects.

PSPC1 and human diseases and cancer

Roles in cancer

PSPC1 is significant in numerous diseases, especially cancer, where its expression is upregulated [16]. In diverse cancer types, PSPC1 exerts its functions through various of mechanisms. The following summarizes the known mechanisms by which PSPC1 acts in different diseases (**Table 1**).

Promote tumor metastasis and progression: In many cancer types, the upregulation of PSPC1 expression is linked to a poor prognosis [20]. TGF-β has pleiotropic functions in cancer progression [53, 54], acting differently at various stages. In the early stages of cancer, TGF-β inhibits tumor growth by inducing cell differentiation and apoptosis, thus preventing uncontrolled proliferation and transformation [53, 54]. However, in the late stages of cancer, TGF-β promotes epithelial-mesenchymal transition (EMT) and stemness, leading to tumor metastasis and advancing tumor progression [55-57]. PSPC1 interacts with activated nuclear Smad2/3, enhancing TGF-β1 expression and the TGF-β1-Smad pathway in an autocrine manner. By interacting with Smad2/3, PSPC1 modifies their binding preferences, targeting the promoters of TGF-β1, EMT transcription factors, and stem cell transcription factors [20]. This promotes tumor growth, EMT, and the acquisition of stem cell characteristics [20]. Therefore, PSPC1 enhances EMT, stemness, and metastatic capacity by promoting TGF-β1 autocrine signaling and modifying the Smad2/3 signaling pathways [20]. This understanding offers novel potential drug targets for future cancer treatments.

Moreover, PSPC1 enhances cell adhesion and motility by upregulating the expression of insulin-like growth factor 1 receptor (IGF1R) [58]. PSPC1 promotes cytoskeletal reorganization, stress fiber formation, and focal adhesion complex assembly, activating the FAK/Src signaling pathways to facilitate cell migration toward the extracellular matrix (ECM) [58]. Additionally, PSPC1 interacts with paraspeckle components, including NONO, FUS, and the lncRNA Neat1, to regulate IGF1R expression [58]. Given its role in enhancing IGF1R signaling, PSPC1 may be a potential biomarker for IGF1R-targeted cancer therapy.

Table 1. The functions of PSPC1 in different diseases

Disease	Role of PSPC1
Acute Myeloid Leukemia (AML)	Paraspeckle Component 1 (PSPC1) promotes leukemogenesis by maintaining a leukemic transcriptional program in cooperation with PU.1, enhancing AML cell survival and proliferation [16].
Glioblastoma Multiforme (GBM)	PSPC1 interacts with NONO to regulate pre-mRNA splicing, particularly affecting GPX1, which is crucial for redox homeostasis, thus promoting GBM progression [60].
Breast and Ovarian Cancers	PSPC1 inhibition enhances the effects of poly ADP-ribose polymerase (PARP) inhibitors (e.g., olaparib) by preventing DNA repair, increasing DNA damage, and leading to mitotic catastrophe [61].
Pancreatic Ductal Adenocarcinoma (PDAC)	PSPC1 is stabilized by S-phase kinase-associated protein 2 (SKP2), promoting PDAC cell migration and metastasis; inhibition of SKP2 disrupts this process [17].
Hepatocellular Carcinoma (HCC)	PSPC1 regulates protein tyrosine kinase 6 (PTK6) and β-catenin translocation, enhancing Epithelial-mesenchymal transition (EMT), cancer stemness, and metastasis via the Wnt signaling pathway [18].
Hypoxia-Related Diseases	PSPC1, along with Neat1 and paraspeckle components, regulates IRES-dependent translation under hypoxic conditions, influencing cellular adaptation and angiogenesis [38].
Herpes Simplex Virus 1 (HSV-1) Infection	PSPC1 coordinates with SRSF2 and nuclear paraspeckle assembly transcript 1 (NEAT1) to regulate HSV-1 gene transcription by modifying chromatin structure and enhancing viral replication [42].
Obstructive Sleep Apnea (OSA)	PSPC1 is upregulated in response to intermittent hypoxia, promoting Transforming growth factor-beta (TGF-β) signaling and potentially enhancing tumor aggressiveness [65].
Neurodegenerative Diseases (ALS, etc.)	PSPC1 is not mislocalized in ALS but may still impact paraspeckle integrity and protein complex balance [62].
Male Infertility (Obesity-Induced)	PSPC1 is downregulated in the testes of obese mice, affecting androgen receptor signaling and spermatogenesis [34].

Pancreatic ductal adenocarcinoma: As previously mentioned, TRIM21-mediated ubiquitination can promote PSPC1 degradation [17]. SKP2 protects PSPC1 by inhibiting TRIM21-mediated ubiquitination [17]. By stabilizing PSPC1, SKP2 enhances the growth and migratory capabilities of Pancreatic Ductal Adenocarcinoma (PDAC) cells, thereby promoting PDAC metastasis. The traditional SKP2 inhibitor, SMIP004, can disrupt the SKP2/PSPC1 axis, impairing PDAC cell migration [17]. This finding provides new therapeutic insights, potentially opening the door to novel strategies for PDAC treatment.

Hepatocellular carcinoma: In normal hepatocytes, PSPC1 can bind to PTK6 and sequester it in the nucleus, inhibiting metastasis [29]. However, when PSPC1 is upregulated or undergoes the PSPC1-Y523F mutation, phosphorylated PTK6 (p-PTK6) translocates from the nucleus to the cytoplasm, and β-catenin translocates to the nucleus [29]. This promotes EMT, stemness, and metastasis. Nuclear β-catenin interacts with PSPC1, activating the β-catenin-mediated Wnt signaling pathway and promoting tumor progression via the Wnt3a/β-catenin pathway. Furthermore, expressing the C-terminal interaction domain of PSPC1 (PSPC1-CT131) can reverse the aberrant nuclear-cytoplasmic shuttling of p-PTK6/β-catenin, thereby extending the survival of mice with orthotopic liver cancer [28]. This suggests that PSPC1-CT131 may one day be utilized in Hepatocellular carcinoma (HCC) treatment to improve the survival prognosis.

Acute myeloid leukemia: PSPC1 (Paraspeckle Component 1) plays a crucial oncogenic role in acute myeloid leukemia (AML) by maintaining a leukemic transcriptional program in cooperation with PU.1, a key hematopoietic transcription factor [16]. It is highly overexpressed in AML [59], particularly in leukemia stem cells (LSCs), and its elevated expression correlates with a poor prognosis [16]. Unlike normal hematopoiesis, which remains largely unaffected by its depletion, PSPC1 is essential for AML cell survival, proliferation, and differentiation blockage [16]. Mechanistically, PSPC1 functions as a transcriptional cofactor, binding to chromatin with PU.1 to regulate the expression of tumor-promoting genes, including NDC1, a key regulator of cell cycle progression and AML maintenance [16]. Loss of PSPC1 induces differentiation, suppresses AML cell proliferation, and significantly impairs leukemogenesis in both in vitro and in vivo models [16]. Given its crucial role in AML pathogenesis and the dependency of leukemic cells on its function, PSPC1 represents a promising therapeutic target for AML treatment.

Glioblastoma multiforme: As noted above, PSPC1 is a member of the DBHS protein family and plays a key role in RNA processing and cancer progression [8, 19, 20, 28]. PSPC1 was found to play an oncogenic role in glioblastoma multiforme (GBM) through its interaction with the splicing factor NONO [60]. The study demonstrates that PSPC1 interacts with NONO to regulate the splicing of key pre-mRNAs, particularly Glutathione peroxidase 1 (GPX1), essential for maintaining redox homeostasis in GBM cells [60]. Knockdown of PSPC1 impairs NONO's ability to mediate proper splicing, leading to intron retention and disrupted gene expression, ultimately inhibiting GBM growth and invasion [60]. Given its crucial role in RNA splicing and tumor progression, PSPC1 represents a potential therapeutic target for GBM treatment.

Breast and ovarian cancers: Previously, it has been mentioned that PSPC1 promotes DNA damage repair [24], and it has been shown that the inhibition of PSPC1 leads to an enhanced formation of γH2AX foci, a DNA double-strand break marker, by preventing DNA repair mechanisms, thereby increasing DNA damage [24]. Furthermore, suppressing PSPC1 impairs the activation of key proteins involved in the DNA damage response, ATM and DNA-PKcs, thereby forcing cancer cells into mitosis with unresolved DNA damage, ultimately triggering mitotic catastrophe and apoptosis [27]. In BRCA1/2-mutated breast and ovarian cancers, the inhibition of PSPC1 has synergistic effects with poly ADP-ribose polymerase (PARP) inhibitors such as olaparib to enhance anticancer efficacy [61]. PSPC1 was identified as a synthetic lethal chaperone of BRCA1/2, meaning that the inhibition of PSPC1 enhances the efficacy of PARP inhibitors, which are commonly used to treat BRCA-mutated cancers [61]. It was shown that PSPC1 knockdown significantly enhanced the antitumor effect of olaparib, leading to more significant tumor regression and apoptosis in both in vitro and in vivo models [61]. In addition, high PSPC1 expression is associated with a poor prognosis in breast and ovarian cancer patients, suggesting that PSPC1 can be used as a therapeutic target and prognostic biomarker in BRCA-mutated cancers.

Neurodegenerative diseases

Neurodegenerative diseases not only have a high incidence but also present with severe symptoms, thus attracting widespread attention [62]. In sporadic Amyotrophic Lateral Sclerosis (ALS), two paraspeckle component proteins, SFPQ and FUS, exhibit nuclear loss [62, 63], whereas two other component proteins, NONO and PSPC1, are not mislocalized in ALS patients [64]. Although NONO and PSPC1 are not displaced from the nucleus in ALS, the nuclear loss of SFPQ affects the dimerization of DBHS proteins [64]. Additionally, their enrichment in subnuclear bodies may impact ALS, including effects on the structural integrity of subnuclear bodies, the balance of protein complexes, and the regulation of gene expression [64].

Obstructive sleep apnea

As previously mentioned, PSPC1 expression is influenced by intermittent hypoxia [22]. Obstructive sleep apnea (OSA)-induced intermittent hypoxia can elevate PSPC1 levels in the serum [65]. This upregulation of PSPC1 can promote TGF-β expression, which enhances EMT and stemness to increase tumor invasiveness and boosts tumor cells' immune evasion capabilities [21, 65]. This indicates that different diseases are interconnected and may even have mutually reinforcing effects, with PSPC1 playing an indispensable role in both obstructive sleep apnea and melanoma [65].

Discussion

As previously elaborated, the RNA recognition motif (RRM) domain of PSPC1 is pivotal for its role in promoting adipogenesis [30]. However, the role of the paraspeckle complex in adipocytes remains poorly understood. Whether PSPC1's function in promoting adipogenesis is contingent upon the paraspeckle structure is an open question that demands further experimental verification. Given the high structural homology among PSPC1, NONO, and SFPQ, all possess two RRM domains identical to those of PSPC1 [5], exploring whether these proteins can contribute to adipogenesis is intriguing. Moreover, in the absence of PSPC1, can NONO or SFPQ partially substitute for its function, analogous to the partial compensation of NONO by PSPC1 in DNA double-strand break repair? Additionally, the functional dependence of SFPQ and NONO on their RRM domains raises whether PSPC1 exhibits similar characteristics, necessitating in-depth exploration and validation.

In sporadic amyotrophic lateral sclerosis (ALS), PSPC1 and NONO do not display nuclear loss, unlike SFPQ and FUS [64]. This suggests that the paraspeckle complex may experience partial disassembly in sporadic ALS, although the underlying mechanism remains elusive. The specific role of PSPC1 and its regulatory mechanism in this process has yet to be elucidated and requires further investigation. Furthermore, exploring whether PSPC1 undergoes similar alterations in other neurodegenerative diseases and whether it plays a functional role in those settings is essential. Answering these questions will enhance our understanding of PSPC1's role in disease and provide novel insights and potential therapeutic targets.

In numerous cancer types, PSPC1 promotes epithelial-mesenchymal transition (EMT) and stemness and drives tumor metastasis via the TGF-β1 and Smad2/3 signaling pathways [20]. Thus, the question of whether inhibiting PSPC1 can effectively impede cancer metastasis is worthy of exploration. Studies have indicated that high PSPC1 expression is closely associated with a poor patient prognosis, suggesting its potential as a promising biomarker and therapeutic target [20]. With the progress of research, PSPC1 is anticipated to become a crucial target for developing anti-metastatic drugs [20]. Current evidence demonstrates that PSPC1 significantly promotes metastasis in various cancers, including breast, lung, liver, and prostate cancers [20]. Therefore, if specific targeted drugs against PSPC1 can be developed, they could have broad applications in treating multiple cancer types and substantially improve patient outcomes, representing a significant breakthrough in cancer treatment. This discovery may offer new directions for future cancer treatment strategies, especially in inhibiting tumor metastasis.

Conclusion

This article systematically summarizes the intricate functions and molecular mechanisms of PSPC1 in gene expression regulation [30], cell fate determination [7], innate immune responses [35], and tumor progression [20]. As a core member of the DBHS protein family, PSPC1 localizes within paraspeckles, membrane-less nuclear organelles, and serves as a key regulatory factor in various RNA-protein interaction networks [5]. PSPC1 plays a vital role in gene transcription regulation, RNA processing, and DNA damage repair through RNA binding, phase separation, and protein complex assembly [5]. Research shows that PSPC1's structural features include two RNA recognition motifs (RRM), a NOPS domain, and a C-terminal CC domain. These not only endow it with the ability to recognize specific RNA sequences but also enable the formation of dynamic regulatory networks through dimerization and phase separation with other proteins [5]. These characteristics allow PSPC1 to assemble complex RNA-protein complexes within the nucleus, regulating the intricate gene expression processes and transcription elongation.

In disease processes, aberrant PSPC1 expression is closely linked to various cancers' occurrence and development [16, 17]. PSPC1 is significantly upregulated in several tumors, such as hepatocellular carcinoma, lung cancer, and breast cancer, directly driving malignant progression by promoting EMT and enhancing the invasiveness and stemness of tumor cells [20]. Moreover, PSPC1 interacts with the TGF-β/Smad signaling axis, altering the binding preferences of the Smad complex to target and regulate the expression of various genes related to tumor metastasis, thereby promoting tumor growth and metastasis [20]. These findings reveal PSPC1 as a core driver in tumor progression and establish its potential as a diagnostic biomarker and therapeutic target.

Despite the extensive exploration of PSPC1's multiple biological functions, its specific regulatory mechanisms in different cellular contexts and disease states still require further investigation. Notably, PSPC1's phase-separation characteristics influence gene transcription and protein function regulation in dynamic environments, and structural redundancies and differences with other DBHS family members offer rich research directions for the future. Additionally, the precise mechanisms of PSPC1 in adipogenesis, neurodegenerative diseases, and embryonic development and how it mediates cell fate determination under pathological conditions remain to be explored.

Future studies on PSPC1 should focus on the following key aspects: First, deciphering the dynamic structural changes of PSPC1 during phase separation and RNA binding will facilitate the elucidation of its molecular mecha-

nisms in the formation and function of nuclear membrane-less organelles. Second, by employing single-cell transcriptomics and spatial multi-omics technologies, a systematic mapping of PSPC1 expression profiles and regulatory networks in different cell types and pathological states could uncover its specific functions in the tumor microenvironment and other complex diseases. Moreover, using CRISPR-Cas9 and other gene-editing technologies to create PSPC1 loss-of-function or overexpression models in vitro and in vivo could precisely assess its pathological mechanisms in disease progression and potential as a therapeutic target. Finally, developing small-molecule inhibitors targeting PSPC1 or compounds that block its protein-protein interactions may offer new strategies for PSPC1-targeted therapy, especially in preventing tumor metastasis, enhancing anti-tumor immune responses, and treating metabolic diseases.

In conclusion, as a highly dynamic and functionally complex nuclear protein, PSPC1 influences multiple key biological processes in cells through multilayered regulatory mechanisms. Systematic future research on PSPC1, especially its pathogenic mechanisms in tumors, its network relationships with other regulatory factors, and its regulatory patterns in different pathological states, will further unveil the full spectrum of PSPC1's functions and provide theoretical foundations for developing novel diagnostic and therapeutic strategies for related diseases. These research advancements are expected to deepen our understanding of nuclear regulatory mechanisms and drive clinical interventions and innovative drug development in several major disease areas.

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Disclosure of conflict of interest

None.

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References

[1] Ingram HB and Fox AH. Unveiling the intricacies of paraspeckle formation and function. Curr Opin Cell Biol 2024; 90: 102399.

[2] Hirose T, Ninomiya K, Nakagawa S and Yamazaki T. A guide to membraneless organelles and their various roles in gene regulation. Nat Rev Mol Cell Biol 2023; 24: 288-304.

[3] Hirose T, Virnicchi G, Tanigawa A, Naganuma T, Li R, Kimura H, Yokoi T, Nakagawa S, Benard M, Fox AH and Pierron G. NEAT1 long noncoding RNA regulates transcription via protein sequestration within subnuclear bodies. Mol Biol Cell 2014; 25: 169-183.

[4] Andersen JS, Lyon CE, Fox AH, Leung AK, Lam YW, Steen H, Mann M and Lamond AI. Directed proteomic analysis of the human nucleolus. Curr Biol 2002; 12: 1-11.

[5] Knott GJ, Bond CS and Fox AH. The DBHS proteins SFPQ, NONO and PSPC1: a multipurpose molecular scaffold. Nucleic Acids Res 2016; 44: 3989-4004.

[6] Wang Y and Chen LL. Organization and function of paraspeckles. Essays Biochem 2020; 64: 875-882.

[7] Hupalowska A, Jedrusik A, Zhu M, Bedford MT, Glover DM and Zernicka-Goetz M. CARM1 and paraspeckles regulate pre-implantation mouse embryo development. Cell 2018; 175: 1902-1916, e1913.

[8] Chen LL and Carmichael GG. Altered nuclear retention of mRNAs containing inverted repeats in human embryonic stem cells: functional role of a nuclear noncoding RNA. Mol Cell 2009; 35: 467-478.

[9] Zhang XL, Chen XH, Xu B, Chen M, Zhu S, Meng N, Wang JZ, Zhu H, Chen D, Liu JB and Yan GR. K235 acetylation couples with PSPC1 to regulate the m(6)A demethylation activity of ALKBH5 and tumorigenesis. Nat Commun 2023; 14: 3815.

[10] Kuwahara S, Ikei A, Taguchi Y, Tabuchi Y, Fujimoto N, Obinata M, Uesugi S and Kurihara Y. PSPC1, NONO, and SFPQ are expressed in mouse Sertoli cells and may function as coregulators of androgen receptor-mediated transcription. Biol Reprod 2006; 75: 352-359.

[11] Schmeing S and Hart P. Challenges in therapeutically targeting the RNA-recognition motif. Wiley Interdiscip Rev RNA 2024; 15: e1877.

[12] Maris C, Dominguez C and Allain FH. The RNA recognition motif, a plastic RNA-binding platform to regulate post-transcriptional gene expression. FEBS J 2005; 272: 2118-2131.

[13] Koning HJ, Lai JY, Marshall AC, Stroeher E, Monahan G, Pullakhandam A, Knott GJ, Ryan TM, Fox AH, Whitten A, Lee M and Bond CS. Structural plasticity of the coiled-coil interactions in

human SFPQ. Nucleic Acids Res 2025; 53: gkae1198.
[14] Li J, Cui P, Sun Q, Du Z, Chen Z, Li Z, Liu C, Cao Y, Yang Z, Liu R and Luo M. PSPC1 regulates CHK1 phosphorylation through phase separation and participates in mouse oocyte maturation. Acta Biochim Biophys Sin (Shanghai) 2021; 53: 1527-1537.
[15] Shao W, Bi X, Pan Y, Gao B, Wu J, Yin Y, Liu Z, Peng M, Zhang W, Jiang X, Ren W, Xu Y, Wu Z, Wang K, Zhan G, Lu JY, Han X, Li T, Wang J, Li G, Deng H, Li B and Shen X. Phase separation of RNA-binding protein promotes polymerase binding and transcription. Nat Chem Biol 2022; 18: 70-80.
[16] Hong J, Sui P, Li Y, Xu KY, Lee JH, Wang J, Chen S, Zhang P, Wingate N, Noor A, Yuan Y, Hromas R, Zhou H, Hamamoto K, Su R, Yin CC, Ye F, Quesada AE, Chen J, Huang S, Zhou D, You MJ, Yang FC, Wang J and Xu M. PSPC1 exerts an oncogenic role in AML by regulating a leukemic transcription program in cooperation with PU.1. Cell Stem Cell 2025; 32: 463-478, e6.
[17] Yuan J, Zhu Z, Zhang P, Ashrafizadeh M, Abd El-Aty AM, Hacımuftuoglu A, Linnebacher CS, Linnebacher M, Sethi G, Gong P and Zhang X. SKP2 promotes the metastasis of pancreatic ductal adenocarcinoma by suppressing TRIM21-mediated PSPC1 degradation. Cancer Lett 2024; 587: 216733.
[18] Kessler SM, Hosseini K, Hussein UK, Kim KM, List M, Schultheiss CS, Schulz MH, Laggai S, Jang KY and Kiemer AK. Hepatocellular carcinoma and nuclear paraspeckles: induction in chemoresistance and prediction for poor survival. Cell Physiol Biochem 2019; 52: 787-801.
[19] Takeiwa T, Ikeda K, Suzuki T, Sato W, Iino K, Mitobe Y, Kawabata H, Horie K and Inoue S. PSPC1 is a potential prognostic marker for hormone-dependent breast cancer patients and modulates RNA processing of ESR1 and SCFD2. Sci Rep 2022; 12: 9495.
[20] Yeh HW, Hsu EC, Lee SS, Lang YD, Lin YC, Chang CY, Lee SY, Gu DL, Shih JH, Ho CM, Chen CF, Chen CT, Tu PH, Cheng CF, Chen RH, Yang RB and Jou YS. PSPC1 mediates TGF-beta1 autocrine signalling and Smad2/3 target switching to promote EMT, stemness and metastasis. Nat Cell Biol 2018; 20: 479-491.
[21] He H, Zhang L, Lin K, Huang Z, Zhou Y, Lin S, Su Y and Pan J. The prognosis value of PSPC1 expression in nasopharyngeal cancer. Cancer Manag Res 2021; 13: 3281-3291.
[22] Diaz-Garcia E, Garcia-Tovar S, Casitas R, Jaureguizar A, Zamarron E, Sanchez-Sanchez B, Sastre-Perona A, Lopez-Collazo E, Garcia-Rio F and Cubillos-Zapata C. Intermittent hypoxia mediates paraspeckle protein-1 upregulation in sleep apnea. Cancers (Basel) 2021; 13: 3888.
[23] Li S, Li Z, Shu FJ, Xiong H, Phillips AC and Dynan WS. Double-strand break repair deficiency in NONO knockout murine embryonic fibroblasts and compensation by spontaneous upregulation of the PSPC1 paralog. Nucleic Acids Res 2014; 42: 9771-9780.
[24] Gao X, Kong L, Lu X, Zhang G, Chi L, Jiang Y, Wu Y, Yan C, Duerksen-Hughes P, Zhu X and Yang J. Paraspeckle protein 1 (PSPC1) is involved in the cisplatin induced DNA damage response--role in G1/S checkpoint. PLoS One 2014; 9: e97174.
[25] Mohankumar K, Shrestha R and Safe S. Nuclear receptor 4A1 (NR4A1) antagonists target paraspeckle component 1 (PSPC1) in cancer cells. Mol Carcinog 2022; 61: 73-84.
[26] Pan S and Chen R. Pathological implication of protein post-translational modifications in cancer. Mol Aspects Med 2022; 86: 101097.
[27] Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER 3rd, Hurov KE, Luo J, Bakalarski CE, Zhao Z, Solimini N, Lerenthal Y, Shiloh Y, Gygi SP and Elledge SJ. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science 2007; 316: 1160-1166.
[28] Lang YD, Chen HY, Ho CM, Shih JH, Hsu EC, Shen R, Lee YC, Chen JW, Wu CY, Yeh HW, Chen RH and Jou YS. PSPC1-interchanged interactions with PTK6 and beta-catenin synergize oncogenic subcellular translocations and tumor progression. Nat Commun 2019; 10: 5716.
[29] Zhan T, Cheng X, Zhu Q, Han Z, Zhu K, Tan J, Liu M, Chen W, Chen X, Chen X, Tian X and Huang X. LncRNA LOC105369504 inhibits tumor proliferation and metastasis in colorectal cancer by regulating PSPC1. Cell Death Discov 2023; 9: 89.
[30] Wang J, Rajbhandari P, Damianov A, Han A, Sallam T, Waki H, Villanueva CJ, Lee SD, Nielsen R, Mandrup S, Reue K, Young SG, Whitelegge J, Saez E, Black DL and Tontonoz P. RNA-binding protein PSPC1 promotes the differentiation-dependent nuclear export of adipocyte RNAs. J Clin Invest 2017; 127: 987-1004.
[31] Major AT, Hogarth CA, Miyamoto Y, Sarraj MA, Smith CL, Koopman P, Kurihara Y, Jans DA and Loveland KL. Specific interaction with the nuclear transporter importin alpha2 can modulate paraspeckle protein 1 delivery to nuclear paraspeckles. Mol Biol Cell 2015; 26: 1543-1558.
[32] Major AT, Miyamoto Y, Lo CY, Jans DA and Loveland KL. Development of a pipeline for automated, high-throughput analysis of paraspeckle proteins reveals specific roles for importin alpha proteins. Sci Rep 2017; 7: 43323.

[33] Fox AH, Lam YW, Leung AK, Lyon CE, Andersen J, Mann M and Lamond AI. Paraspeckles: a novel nuclear domain. Curr Biol 2002; 12: 13-25.
[34] Myojin R, Kuwahara S, Yasaki T, Matsunaga T, Sakurai T, Kimura M, Uesugi S and Kurihara Y. Expression and functional significance of mouse paraspeckle protein 1 on spermatogenesis. Biol Reprod 2004; 71: 926-932.
[35] Morchikh M, Cribier A, Raffel R, Amraoui S, Cau J, Severac D, Dubois E, Schwartz O, Bennasser Y and Benkirane M. HEXIM1 and NEAT1 long non-coding RNA form a multi-subunit complex that regulates DNA-mediated innate immune response. Mol Cell 2017; 67: 387-399, e385.
[36] Huang X, Bashkenova N, Hong Y, Lyu C, Guallar D, Hu Z, Malik V, Li D, Wang H, Shen X, Zhou H and Wang J. A TET1-PSPC1-Neat1 molecular axis modulates PRC2 functions in controlling stem cell bivalency. Cell Rep 2022; 39: 110928.
[37] Guallar D, Bi X, Pardavila JA, Huang X, Saenz C, Shi X, Zhou H, Faiola F, Ding J, Haruehanroengra P, Yang F, Li D, Sanchez-Priego C, Saunders A, Pan F, Valdes VJ, Kelley K, Blanco MG, Chen L, Wang H, Sheng J, Xu M, Fidalgo M, Shen X and Wang J. RNA-dependent chromatin targeting of TET2 for endogenous retrovirus control in pluripotent stem cells. Nat Genet 2018; 50: 443-451.
[38] Godet AC, Roussel E, David F, Hantelys F, Morfoisse F, Alves J, Pujol F, Ader I, Bertrand E, Burlet-Schiltz O, Froment C, Henras AK, Vitali P, Lacazette E, Tatin F, Garmy-Susini B and Prats AC. Long non-coding RNA Neat1 and paraspeckle components are translational regulators in hypoxia. Elife 2022; 11: e69162.
[39] Shahbazi MN and Pasque V. Early human development and stem cell-based human embryo models. Cell Stem Cell 2024; 31: 1398-1418.
[40] Torres-Padilla ME, Parfitt DE, Kouzarides T and Zernicka-Goetz M. Histone arginine methylation regulates pluripotency in the early mouse embryo. Nature 2007; 445: 214-218.
[41] Wang J, Zhang Y, Gao J, Feng G, Liu C, Li X, Li P, Liu Z, Lu F, Wang L, Li W, Zhou Q and Liu Y. Alternative splicing of CARM1 regulated by Linc-GET-guided paraspeckles biases the first cell fate in mammalian early embryos. Nat Struct Mol Biol 2024; 31: 1341-1354.
[42] Li K and Wang Z. Speckles and paraspeckles coordinate to regulate HSV-1 genes transcription. Commun Biol 2021; 4: 1207.
[43] Gelot C, Kovacs MT, Miron S, Mylne E, Haan A, Boeffard-Dosierre L, Ghouil R, Popova T, Dingli F, Loew D, Guirouilh-Barbat J, Del Nery E, Zinn-Justin S and Ceccaldi R. Poltheta is phosphorylated by PLK1 to repair double-strand breaks in mitosis. Nature 2023; 621: 415-422.
[44] Bladen CL, Udayakumar D, Takeda Y and Dynan WS. Identification of the polypyrimidine tract binding protein-associated splicing factor. p54(nrb) complex as a candidate DNA double-strand break rejoining factor. J Biol Chem 2005; 280: 5205-5210.
[45] Knott GJ, Chong YS, Passon DM, Liang XH, Deplazes E, Conte MR, Marshall AC, Lee M, Fox AH and Bond CS. Structural basis of dimerization and nucleic acid binding of human DBHS proteins NONO and PSPC1. Nucleic Acids Res 2022; 50: 522-535.
[46] Qu J, Yan H, Hou Y, Cao W, Liu Y, Zhang E, He J and Cai Z. RNA demethylase ALKBH5 in cancer: from mechanisms to therapeutic potential. J Hematol Oncol 2022; 15: 8.
[47] Guenther MG, Levine SS, Boyer LA, Jaenisch R and Young RA. A chromatin landmark and transcription initiation at most promoters in human cells. Cell 2007; 130: 77-88.
[48] Core LJ, Waterfall JJ and Lis JT. Nascent RNA sequencing reveals widespread pausing and divergent initiation at human promoters. Science 2008; 322: 1845-1848.
[49] Qiu Y, Gan M, Wang X, Liao T, Chen Q, Lei Y, Chen L, Wang J, Zhao Y, Niu L, Wang Y, Zhang S, Zhu L and Shen L. The global perspective on peroxisome proliferator-activated receptor gamma (PPARgamma) in ectopic fat deposition: a review. Int J Biol Macromol 2023; 253: 127042.
[50] Zhang X, Zhang Y, Wang C and Wang X. TET (Ten-eleven translocation) family proteins: structure, biological functions and applications. Signal Transduct Target Ther 2023; 8: 297.
[51] Liu D, Li G and Zuo Y. Function determinants of TET proteins: the arrangements of sequence motifs with specific codes. Brief Bioinform 2019; 20: 1826-1835.
[52] Chrysanthou S, Tang Q, Lee J, Taylor SJ, Zhao Y, Steidl U, Zheng D and Dawlaty MM. The DNA dioxygenase Tet1 regulates H3K27 modification and embryonic stem cell biology independent of its catalytic activity. Nucleic Acids Res 2022; 50: 3169-3189.
[53] Peng D, Fu M, Wang M, Wei Y and Wei X. Targeting TGF-beta signal transduction for fibrosis and cancer therapy. Mol Cancer 2022; 21: 104.
[54] Gough NR, Xiang X and Mishra L. TGF-beta signaling in liver, pancreas, and gastrointestinal diseases and cancer. Gastroenterology 2021; 161: 434-452, e415.
[55] Massague J. TGFbeta signalling in context. Nat Rev Mol Cell Biol 2012; 13: 616-630.

[56] Feng XH and Derynck R. Specificity and versatility in tgf-beta signaling through Smads. Annu Rev Cell Dev Biol 2005; 21: 659-693.
[57] Lee JH and Massague J. TGF-beta in developmental and fibrogenic EMTs. Semin Cancer Biol 2022; 86: 136-145.
[58] Jen HW, Gu DL, Lang YD and Jou YS. PSPC1 potentiates IGF1R expression to augment cell adhesion and motility. Cells 2020; 9: 1490.
[59] Hoffmeister LM, Suttorp J, Walter C, Antoniou E, Behrens YL, Gohring G, Awada A, von Neuhoff N, Reinhardt D and Schneider M. Panel-based RNA fusion sequencing improves diagnostics of pediatric acute myeloid leukemia. Leukemia 2024; 38: 538-544.
[60] Wang X, Han M, Wang S, Sun Y, Zhao W, Xue Z, Liang X, Huang B, Li G, Chen A, Li X and Wang J. Targeting the splicing factor NONO inhibits GBM progression through GPX1 intron retention. Theranostics 2022; 12: 5451-5469.
[61] Ghosh M, Kang MS, Katuwal NB, Hong SD, Jeong YG, Park SM, Kim SG and Moon YW. PSPC1 inhibition synergizes with Poly(ADP-ribose) polymerase inhibitors in a preclinical model of BRCA-mutated breast/ovarian cancer. Int J Mol Sci 2023; 24: 17086.
[62] Luisier R, Tyzack GE, Hall CE, Mitchell JS, Devine H, Taha DM, Malik B, Meyer I, Greensmith L, Newcombe J, Ule J, Luscombe NM and Patani R. Intron retention and nuclear loss of SFPQ are molecular hallmarks of ALS. Nat Commun 2018; 9: 2010.
[63] Tyzack GE, Luisier R, Taha DM, Neeves J, Modic M, Mitchell JS, Meyer I, Greensmith L, Newcombe J, Ule J, Luscombe NM and Patani R. Widespread FUS mislocalization is a molecular hallmark of amyotrophic lateral sclerosis. Brain 2019; 142: 2572-2580.
[64] Tyzack GE, Manferrari G, Newcombe J, Luscombe NM, Luisier R and Patani R. Paraspeckle components NONO and PSPC1 are not mislocalized from motor neuron nuclei in sporadic ALS. Brain 2020; 143: e66.
[65] Cubillos-Zapata C, Martinez-Garcia MA, Diaz-Garcia E, Garcia-Tovar S, Campos-Rodriguez F, Sanchez-de-la-Torre M, Nagore E, Martorell-Calatayud A, Blasco LH, Pastor E, Abad-Capa J, Montserrat JM, Cabriada-Nuno V, Cano-Pumarega I, Corral-Penafiel J, Arias E, Mediano O, Somoza-Gonzalez M, Dalmau-Arias J, Almendros I, Farre R, Gozal D and Garcia-Rio F; Spanish Sleep Network. Obstructive sleep apnoea is related to melanoma aggressiveness through paraspeckle protein-1 upregulation. Eur Respir J 2023; 61: 2200707.