

## The building process of the functional paraspeckle with long non-coding RNAs

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### 1. ABSTRACT

Nuclei of mammalian cells are highly organized and composed of distinct subnuclear structures termed nuclear bodies. Paraspeckles are subnuclear structures that form around the long non-coding RNA (lncRNA) nuclear paraspeckle assembly transcript 1 (NEAT1) together with numerous RNA-binding proteins, many of which contain an RNA-binding domain and a prion-like domain and are related to specific neurodegenerative diseases. Paraspeckle formation proceeds in conjunction with NEAT1 lncRNA biogenesis and involves the cooperation of multiple paraspeckle-localized RNA-binding proteins. NEAT1 lncRNA likely sequesters

these RNA-binding proteins in paraspeckle structures, which act as molecular sponges at which the nucleoplasmic activities of the sequestered proteins are modulated. This review presents, firstly, current knowledge regarding factors involved in the formation and function of paraspeckles. Secondly, the intracellular functions of all identified paraspeckle proteins, which are potentially controlled through their sequestration in paraspeckles, are categorized. Thirdly, recently identified nuclear bodies containing putative architectural lncRNAs are described and similarities among the architectures of lncRNA-dependent nuclear bodies are discussed.

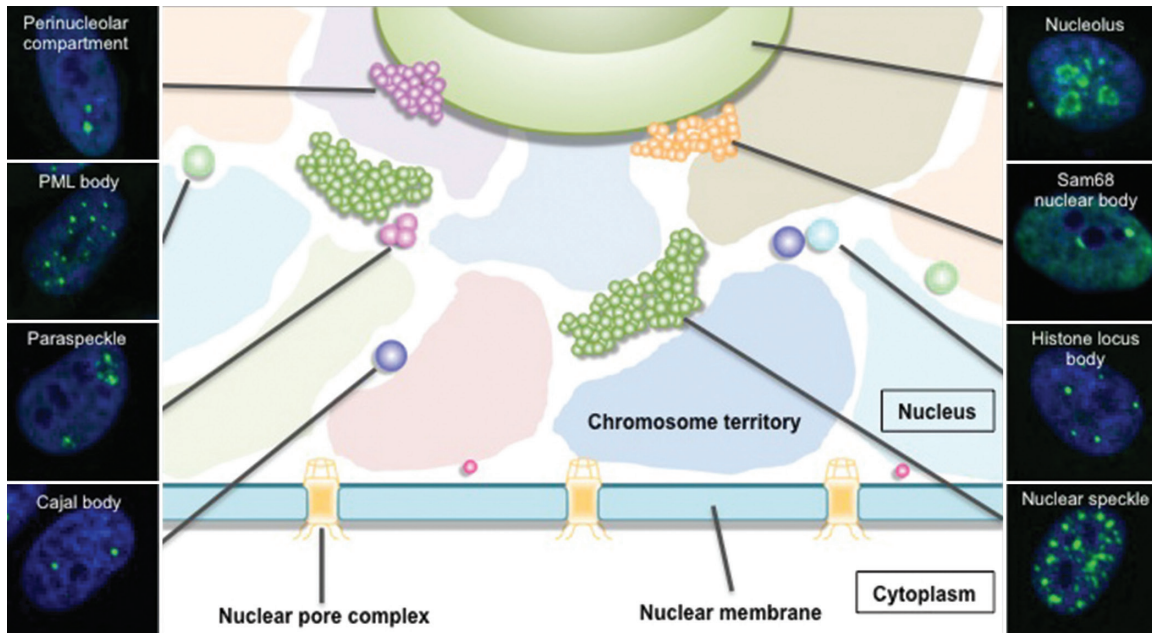
## 2. INTRODUCTION

Genome-wide transcriptome analyses, including high-throughput RNA sequencing and tiling arrays, indicate that more than 90% of the human genome is transcribed into protein-coding RNAs and non-coding RNAs (ncRNAs) (1-6). ncRNAs include a variety of classical ncRNAs, such as rRNA, tRNA, snRNA, small nucleolar RNA (snoRNA), microRNA, and piRNA (7, 8). In addition, a large proportion of ncRNAs are long non-coding RNAs (lncRNAs), which seem to have no protein-coding potential and are longer than 200 nucleotides (9). Several recent studies estimated there to be about 10,000 lncRNAs in humans (10, 11). lncRNAs are usually transcribed by RNA polymerase II from genic, intergenic, and intronic regions and they are transcribed in the antisense direction (9). A limited number of lncRNAs have been functionally characterized and they are involved in diverse cellular processes. However, the functions of most lncRNAs remain largely unknown.

Several studies showed that a large number of lncRNAs predominantly localize in the nucleus, suggesting that they function in nuclear events such as epigenetic regulation or the regulation of pre-mRNA processing (6, 12-18). One well-characterized lncRNA is XIST, which is essential for X-chromosome inactivation via dosage compensation and was discovered more than 20 years ago. XIST is exclusively expressed from the X-chromosome (Xq13.2.), which is inactivated and recruits silencing factors, including the PRC2 complex (19, 20). The HOTAIR lncRNA is a regulator of a HOX gene cluster and recruits the PRC2 complex to specific chromosomal loci (21). The lncRNA Gomafu (also known as MIAT and RNCR2), which is abundantly expressed in a subset of neurons in the central nervous system and forms distinct foci in the nucleus (22, 23), is proposed to regulate splicing by modulating the availabilities of splicing factors (24, 25). The lncRNA MALAT1 (also known as Multiple Endocrine Neoplasia (MEN) alpha and NEAT2), which is abundantly expressed as ~8-kilobase transcripts that localize in nuclear speckles (also known as interchromatin granule clusters) (26), regulates alternative splicing by modulating the phosphorylation of serine/arginine-rich (SR) splicing factors (27, 28). While MALAT1 is dispensable in mouse development, it reportedly contributes to lung cancer metastasis (28-30).

In eukaryotic cells, the nucleus is a highly structured compartment that plays important roles in coordinating the spatiotemporal regulation of various nuclear processes. Nuclear bodies are non-membranous, subnuclear structures in which multiple nuclear regulatory factors, such as transcription factors and RNA processing factors, are enriched, and which have vital roles in cells (31, 32) (Figure 1). For example, the nucleolus is the most characterized nuclear compartment and consists of three distinct domains, namely, the fibrillar centers, the dense fibrillar components, and the granular compartment (33, 34). The main function of the nucleolus is in ribosome biogenesis, including pre-rRNA transcription by RNA polymerase I, pre-rRNA processing and modification, and ribosomal protein assembly, and these processes proceed through the tripartite organization of this structure. The perinucleolar compartment is a subnuclear domain located at the periphery of the nucleolus and contains multiple RNA-binding proteins and RNA polymerase III-transcribed ncRNAs, such as RNase mitochondrial processing RNA, RNase P, hY RNA, Alu RNA, and SRP RNA (35) (Table 1). The perinucleolar compartment is associated with malignancy and positively correlates with metastatic capacity (35). The nuclear speckle is another nuclear structure, which is usually observed as 20–50 irregularly shaped granules, contains multiple splicing factors, and likely plays roles in splicing regulation (36, 37). The histone locus body is a nuclear body associated with histone gene loci, indicating it plays roles in the biogenesis of histone mRNAs (38, 39). The promyelocytic leukemia (PML) body is a distinct nuclear body that ranges from 0.1. to 1 micrometers in diameter and contains various proteins, including the multifunctional PML protein. The PML body has diverse functions, including the sequestration, post-translational modification, and degradation of specific proteins (40). The Cajal body is a nuclear body found in many eukaryotes and contains U snRNAs, scaRNAs, and telomerase RNA, suggesting it functions in their biogenesis (38, 39, 41). Gem is a nuclear body that is often observed adjacent to the Cajal body and contains the SMN complex, which functions in snRNP biogenesis (42-44). The Sam68 (Src-associated in mitosis, 68 kDa) nuclear body (SNB) is a nuclear structure that is observed as 2-5 foci occasionally located adjacent to the nucleolus or Cajal bodies (45). Some nuclear

## Annotation of paraspeckle components



**Figure 1.** Nuclear bodies in vertebrate cells. A schematic of nuclear structures, including representative nuclear bodies, is shown (center). Images of marker proteins (green signals) corresponding to nuclear bodies in the middle panel are shown in the left and right panels. The nuclear body markers are as described. Perinucleolar compartment: PTBP1; promyelocytic leukemia (PML) body: PML; paraspeckle: PSPC1; Cajal body: Coilin; Nucleolus: Nucleolin; Sam68 nuclear body: Sam68; Histone locus body: NPAT; nuclear speckle: SC35. Blue signals indicate nuclear DAPI staining (left and right panels).

bodies are stress-inducible, suggesting that they function in stress responses. One such example is nuclear stress bodies (nSBs), which form on specific pericentromeric regions in response to heat shock and several chemical stresses (46).

Electron microscopic studies showed that a subset of nuclear bodies contain a granular core, which is typical of the presence of ribonucleoproteins (RNPs) (47). Many nuclear bodies contain RNAs, especially ncRNAs, suggesting that these RNAs play a role in the functions of nuclear bodies (Table 1). Among them, some lncRNAs are essential for the formation and/or maintenance of nuclear bodies, including paraspeckles (48). Nuclear paraspeckle assembly transcript 1 (NEAT1) is an architectural component of paraspeckles. This discovery gave rise to the concept that RNAs have an architectural role in nuclear bodies. Here, we review the current understanding of such architectural RNAs, with a focus on recent advances, especially with regards to the NEAT1 lncRNA as the core of the paraspeckle.

### 3. PARASPECKLES

In 2002, the paraspeckle was identified as a subnuclear body that is found in interchromosomal regions adjacent to nuclear speckles (49). Paraspeckles are normally observed as 2–20 discrete nuclear foci with a mean diameter of 0.36 micrometers (49–51). Paraspeckles were confirmed to be equivalent to the interchromatin granule-associated zone (IGAZ), which is an electron-dense structure when viewed by electron microscopy (52, 53). Importantly, paraspeckles are RNase-sensitive structures whose formation depends on transcription by RNA polymerase II (49, 54), suggesting that paraspeckles require RNAs for their maintenance. In 2009, four different groups independently discovered that the NEAT1 lncRNA is an essential architectural component of paraspeckles using different approaches (48, 55–58). All four groups showed that knockdown of NEAT1 results in the disintegration of paraspeckles. In addition, experiments using a reversible RNA polymerase II inhibitor showed that reassembly of paraspeckles is inhibited by knockdown of NEAT1 (58). Taken together, these

## Annotation of paraspeckle components

**Table 1.** Nuclear bodies and their RNA components

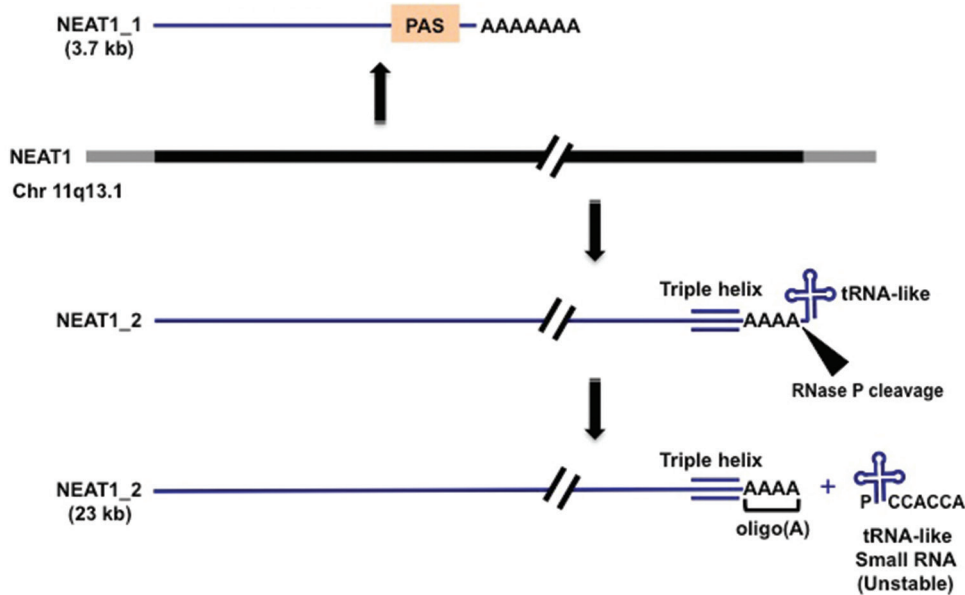
Name	RNA	Marker protein	Associated genomic locus	Description	References
Paraspeckle	NEAT1, CTN-RNA, U1 snRNA	PSPC1, NONO	NEAT1	NEAT1 is essential for the integrity and retention of IR-containing RNAs	48, 49, 51
Nuclear speckle	MALAT-1/NEAT2 Poly (A)+ RNA	SRSF1(SF2/ASF), SRSF2 (SC35)	n/d	Involved in the storage/assembly/ modification of splicing factors, MALAT-1 is not required for nuclear speckle integrity	28, 29, 37
Nucleolus	Pre-rRNA, snoRNA	Nucleolin	rRNA	Ribosome biogenesis	33, 34
Perinucleolar compartment	MRP, Alu RNA, hY RNA, RNase P RNA, SRP RNA	PTBP1, CUG-BP	n/d	Regulation of RNA polymerase III transcripts	35, 308
PML body	n/d	PML	MHC class I	DNA repair, protection against viral infection	40
Cajal body	snRNA, snoRNA, scaRNA, telomerase RNA	Coilin	U snRNA genes	Biogenesis and modification of snRNAs	39
Gem	n/d	SMN	n/d	Biogenesis and/or recycling of nuclear snRNPs?	42-44
Histone locus body	U7 snRNA, Histone pre-mRNA	NPAT	Histone genes	Histone mRNA biogenesis	39
Sam68 nuclear body	Undetermined RNAs	Sam68	n/d	The formation of this body depends on the activity of transcription	45, 288
Cleavage body	n/d	CstF64	n/d	Cleavage factors are enriched, mainly detected during S phase	45, 309-311
Nuclear stress body	Satellite III ncRNA	HSF1, HAP	Pericentromeric	Stress-inducible nuclear body, regulation of transcription and splicing in stress conditions	46, 312
Polycomb group body	TUG1 ncRNA	Bmi, Pc2	Some associate with pericentromeric heterochromatin	Transcriptional regulation?	45, 313, 314
OPT domain	Undetermined RNAs	Oct1, PTF	n/d	Mainly detected during late G1 phase, formation depends on the activity of transcription	45, 315
Clastosome	n/d	19S, 20S core proteasome	n/d	The formation depends on high proteasome activity	45, 316
Nucleolar detention center	Ribosomal intergenic spacer long ncRNAs	VHL, HSP70, MDM2	n/d	Stress-inducible nuclear body	284-286

HAP: heterogenous nuclear ribonucleoprotein A1-associated protein; IR: inverted repeat; n/d: not determined; ncRNA: non-coding RNA; NEAT1: nuclear paraspeckle assembly transcript 1; NONO1: non-POU domain-containing octamer-binding 1; PML: promyelocytic leukemia; PSPC1: paraspeckle component 1; snoRNA: small nucleolar RNA; VHL: von Hippel-Lindau.

data suggest that NEAT1 is essential for the formation and maintenance of paraspeckles. In this section, we summarize the current understanding of

paraspeckle components, how paraspeckles form around NEAT1 lncRNAs together with paraspeckle proteins, and how paraspeckles exert their functions.

## Annotation of paraspeckle components



**Figure 2.** Structures of NEAT1\_1 and NEAT1\_2 long non-coding RNAs. The nuclear paraspeckle assembly transcript 1 (NEAT1) gene is located in chromosome 11q13.1. in humans. Two isoforms of NEAT1, namely, NEAT1\_1 (3.7. kilobases) and NEAT1\_2 (23 kilobases), are transcribed from the same locus. NEAT1\_1 utilizes a canonical polyadenylation signal (PAS) for 3' end processing. In the case of 3' end processing of NEAT1\_2, RNase P cleaves the 3' end of NEAT1\_2 by recognizing a tRNA-like structure. NEAT1\_2 possesses a genomically encoded oligo(A) sequence and a unique triple helical structure at the 3' end. Cleaved tRNA-like small RNA is unstable and rapidly degraded.

### 3.1. NEAT1 lncRNA is an architectural RNA of paraspeckles

NEAT1 lncRNAs are comprised of two isoforms, NEAT1\_1 and NEAT1\_2 (also known as MEN epsilon and MEN beta, respectively, virus-inducible ncRNA, trophoblast stat utron, and trophoblast non-coding RNA) (26, 59-62) (Figure 2). NEAT1 is transcribed by RNA polymerase II from chromosome 11q13 in humans and from chromosome 19qA in mice (59). Human NEAT1\_1 and NEAT1\_2 are transcribed as 3.7.-kb and 23-kb transcripts, respectively, and mouse NEAT1\_1 and NEAT1\_2 are transcribed as 3.2.-kb and 20-kb transcripts, respectively. In addition to human and mouse, there are counterparts of NEAT1 in other mammalian species, including *Macaca mulatta*, *Rattus norvegicus*, *Canis familiaris*, *Equus caballus*, *Bos Taurus*, and *Ornithorhynchus anatinus* (63). The two NEAT1 isoforms do not contain an intron and are not exported to the cytoplasm, but are retained in the nucleus (26, 55-58). Thus, it would be interesting to investigate how NEAT1 avoids nuclear export via the canonical mRNA biogenesis pathway. The NEAT1\_1 and NEAT1\_2 isoforms share the same promoter and 5' region (50, 51, 55, 58, 64). The 3' end of the NEAT1\_1 isoform is processed through

a polyadenylation site (PAS) by canonical cleavage and a polyadenylation system that produces a poly(A) tail (65, 66) (Figure 2). On the other hand, the 3' end of NEAT1\_2 isoform lacks a canonical poly(A) tail; instead, it is non-canonically processed by RNase P, which targets tRNA-like structures located immediately downstream of the 3' end (58) (Figure 2). The NEAT1\_2 isoform possesses a genomically encoded oligo(A) sequence with a characteristic triple helical structure, which is also found at the 3' ends of a subset of other lncRNAs, such as MALAT1 and Kaposi's sarcoma-associated herpesvirus-encoding ncRNAs (67-70) (Figure 2). This triple helical structure stabilizes NEAT1\_2 by protecting its 3' end from degradation (67-70). The tRNA-like molecule formed when NEAT1\_2 is cleaved by RNase P is further processed by RNase Z and then is rapidly degraded by the addition of CCACCA to the 3' end, which is a marker for degradation via a rapid tRNA decay pathway (71). In normal cell culture conditions, both mouse NEAT1 isoforms are highly unstable and their half-lives are approximately 30–60 minutes, which is exceptionally short compared to those of other lncRNAs, suggesting the dynamic nature of paraspeckles (72). On the other hand, human NEAT1 is relatively stable,

## Annotation of paraspeckle components

with a half-life of more than 5 hours; however, the functional consequence of this difference is unclear. NEAT1\_1 is degraded in a poly(A)-binding protein nuclear 1 (PABPN1)-dependent manner (73, 74). This PABPN1-dependent pathway also degrades other lncRNAs, including SHG60 (SNORD60 Host Gene) and TUG1, and mRNAs. In this process, RNA substrates are polyadenylated, which is a marker for degradation via the nuclear exosome (73, 74). Thus, knockdown of PABPN1 and nuclear exosome components results in the accumulation of NEAT1 lncRNAs by increasing their stability. At present, it is unclear whether these factors control paraspeckle formation via regulating the level of each NEAT1 isoform.

High resolution *in situ* hybridization using electron microscopy elucidated the geometry of NEAT1 lncRNAs in paraspeckles (53). The 5' ends of NEAT1\_1/1\_2 and the 3' end of NEAT1\_2 are found at the peripheries of paraspeckles, whereas the central part of NEAT1\_2 is located inside paraspeckles. It is possible that NEAT1\_1 is localized near to the paraspeckle surface and NEAT1\_2 adopts a hairpin-like shape in which the 5' and 3' termini are near to the surface and the central part is located inside the paraspeckle. The IGAZ, which is equivalent to the paraspeckle, is found in close proximity to interchromatin granules corresponding to nuclear speckles in electron microscopy observations (52, 53). U1 snRNA, but not U2 snRNA, is present in the IGAZ (52, 53). In addition, a recent study showed that U1 snRNA relocates to perinucleolar caps upon transcriptional inhibition, similar to paraspeckle proteins, whereas U1-specific proteins do not relocate (75). At present, the roles of U1 snRNA in paraspeckles are unclear. In addition to U1 snRNA, CTN-RNA localizes to paraspeckles (76) (see section 3.4.), but is not required for paraspeckle formation. Thus, to date, only NEAT1 has been found to play an architectural role in paraspeckles.

In many cancer cell lines and primary cells, NEAT1 isoforms are expressed and paraspeckles form. However, in mice, NEAT1\_1 and NEAT1\_2 are expressed in a subpopulation of cells in adult organs, including the stomach and intestines (77). The subpopulation of cells that highly express NEAT1\_2 correlates with the cells that contain paraspeckles (77). Although both mouse and human NEAT1 are essential components of paraspeckles, *Neat1*-knockout mice are viable and show no apparent phenotype in normal laboratory conditions (77). At

the cellular level, *Neat1*-knockout mouse embryonic fibroblasts lack paraspeckles, as expected. In these cells, expression of *Neat1\_2*, but not of *Neat1\_1*, can rescue paraspeckle formation (77). Overexpression of NEAT1\_1 in cells expressing endogenous NEAT1 reportedly increases the number of paraspeckles, suggesting that NEAT1\_1 facilitates paraspeckle formation (57, 65). Thus, NEAT1\_2 is necessary for *de novo* formation of paraspeckles, which is consistent with the observation that NEAT1\_2 localizes inside paraspeckles (53).

## 3.2. Identification of new paraspeckle proteins

Initial studies of paraspeckles identified paraspeckle protein components, including DBHS (*Drosophila melanogaster* behavior, human splicing) proteins (PSPC1 (paraspeckle component 1), NONO (non-POU domain-containing octamer-binding), and SFPQ (splicing factor, proline- and glutamine-rich, also known as PSF (PTB-associated splicing factor)), RNA-binding motif (RBM)14, and CPSF6 (49, 50, 76, 78). Our group performed genome-wide screening to identify paraspeckle proteins by expressing Venus (a fluorescent protein)-tagged proteins from a full-length human cDNA library that contains the open reading frames of 18,467 protein-coding genes in HeLa cells (65). We selected clones that exhibited typical paraspeckle-like localization patterns. Then, we compared their localization with those of the endogenous paraspeckle protein SFPQ and markers of other nuclear bodies, including the Cajal body, nucleolus, and nuclear speckles, and selected clones that specifically co-localized with paraspeckles. Finally, 34 clones were identified as new paraspeckle components (Table 2). The localizations of these new paraspeckle proteins were further validated by examining the co-localization of the corresponding endogenous proteins with NEAT1. These paraspeckle proteins commonly relocate to perinucleolar caps upon transcriptional inhibition, which is a characteristic of known paraspeckle components, whereas NEAT1 lncRNAs are diffusely present in the nucleoplasm (55, 58). It is noteworthy that many paraspeckle proteins are likely distributed throughout the nucleoplasm, as well as being concentrated in paraspeckles (51, 65). In addition, several recent studies expanded the list of paraspeckle proteins (79, 80) (Table 2). Here, we overview the similarities between identified paraspeckle proteins as well as their functions.

## Annotation of paraspeckle components

**Table 2.** Paraspeckle components

RNAs		Aliases	Known functions		References
NEAT1 (NEAT1_1 and NEAT1_2)		MEN epsilon/beta	Essential for paraspeckle formation		55-58
CTN-RNA		mCAT2	Nuclear-retained mRNA		76
U1 snRNA			Unknown in paraspeckles		52, 53
Proteins	Aliases	Category	Structures and functions	Neurodegenerative diseases	References
HNRNPK	CSBP, TUNP	1A	Essential for paraspeckle integrity	n/d	65
NONO	p54nrb, NMT55, PPP1R114	1A	DBHS, Essential for paraspeckle integrity	n/d	49, 54, 55
RBM14	PSP2, CoAA, SIP, SYTIP1, TMEM137	1A	PLD (+), Essential for paraspeckle integrity	n/d	49, 91
SFPQ	PSF, POMP100	1A	DBHS, PLD (+), Essential for paraspeckle integrity, Involved in ADARB2 regulation	FTD and AD	54, 55, 76, 91, 267
DAZAP1		1B	PLD (+), Essential for paraspeckle integrity	n/d	65
FUS	TLS, hnRNPP2, ALS6, POMP75, ETM41	1B	FET family protein, PLD (+), Essential for paraspeckle integrity	ALS and FTD	65
HNRNPH 3	2H9	1B	PLD (+), Essential for paraspeckle integrity	n/d	65
CPSF7	CFIm59	2	Important for paraspeckle integrity	n/d	65
FAM98A		2	Important for paraspeckle integrity	n/d	65
FAM113A	PCED1A, C20orf81	2	Important for paraspeckle integrity	n/d	65
FIGN		2	Important for paraspeckle integrity	n/d	65
FUSIP1	SRSF10, SRp38, NSSR1, TASR	2	Important for paraspeckle integrity	n/d	65
HNRNPA1	ALS19, IBMRFD3	2	PLD (+), Important for paraspeckle integrity	ALS and MSP	65
HNRNPR		2	Important for paraspeckle integrity	n/d	65
HNRNPUL1	E1B-AP5	2	PLD (+), Important for paraspeckle integrity	n/d	65
RBM12	SWAN	2	Important for paraspeckle integrity	n/d	65
TDP-43	TARDBP, ALS10	2	PLD (+), Important for paraspeckle integrity	ALS and FTD	65
CPSF6	CFIm68, HPBRII-4	3A	No effect on paraspeckle formation and slight reduction of NEAT1 expression upon knockdown	n/d	78
NUDT21	CFIm25, CPSF5	3A	No effect on paraspeckle formation and slight reduction of NEAT1 expression upon knockdown	n/d	65
UBAP2L	NICE-4	3A	No effect on paraspeckle formation and slight reduction of NEAT1 expression upon knockdown	n/d	65
AHDC1	MRD25	3B	No effect on paraspeckle formation upon knockdown	n/d	65
AKAP8L	HAP95, HA95, NAKAP95, NAKAP	3B	No effect on paraspeckle formation upon knockdown	n/d	65

Contd...

## Annotation of paraspeckle components

**Table 2.** Contd...

Proteins	Aliases	Category	Structures and functions	Neurodegenerative diseases	References
CIRBP	CIRP	3B	No effect on paraspeckle formation upon knockdown	n/d	65
EWSR1	EWS	3B	FET family protein, PLD (+), No effect on paraspeckle formation upon knockdown	ALS and FTD	65
PSPC1	PSP1	3B	DBHS, PLD (+), No effect on paraspeckle formation upon knockdown	n/d	49, 91
RBM3	RNPL	3B	No effect on paraspeckle formation upon knockdown	n/d	65
RBM4B	RBM30, ZCCHC15, ZCCHC21B, ZCRB3B	3B	No effect on paraspeckle formation upon knockdown	n/d	65
RBM7		3B	No effect on paraspeckle formation upon knockdown	n/d	65
RBMX	hnRNPG	3B	No effect on paraspeckle formation upon knockdown	n/d	65
RUNX3	AML2, CBFA3, PEBP2aC	3B	No effect on paraspeckle formation upon knockdown	n/d	65
TAF15	TAFII68, RBP56	3B	FET family protein, PLD (+), No effect on paraspeckle formation upon knockdown	ALS and FTD	65
ZC3H6	ZC3HDC6	3B	No effect on paraspeckle formation upon knockdown	n/d	65
ZNF335	NIF1, MCPH 10	3B	No effect on paraspeckle formation upon knockdown	n/d	65
ENOX1	CNOX, PIG38	n/d	Involved in paraspeckle formation	n/d	79
FAM53B	KIAA0140	n/d	Involved in paraspeckle formation	n/d	79
HECTD3		n/d	Involved in paraspeckle formation	n/d	79
ZNF24	ZNF191, KOX17, RSG-A, ZSCAN3, Zfp191	n/d	Involved in paraspeckle formation	n/d	79
RNA polymerase II		n/d	Inhibition of RNA polymerase II causes redistribution of paraspeckle components	n/d	215
Annexin A10	ANXA10, ANX14	n/d	Overexpression reduces paraspeckle number	n/d	80
CYBA	p22-PHOX	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
FAM53A	DNTNP	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
GATA1	ERYF1, NF-E1, GF-1, XLANP, XLTDA, XLTT	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
KIAA1683		n/d	No effect on paraspeckle formation upon knockdown	n/d	79

Contd...



## Annotation of paraspeckle components

**Table 2.** Contd...

Proteins	Aliases	Category	Structures and functions	Neurodegenerative diseases	References
KLF4	EZF, GKLF	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
LMNB2	LAMB2, LMN2	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
SCYL1	HT019, GKLP, NKTL, NTKL, P105, TAPK, TEIF, TRAP	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
SH2B1	PSM	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
SRSF11	SRp54, p54, NET2	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
XIAP	BIRC4, IAP-3ILP1, MIHA, XLP2	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
ZNF444	EZF-2, ZSCAN17	n/d	No effect on paraspeckle formation upon knockdown	n/d	79
BCL6	ZNF51, ZBTB27, BCL6A, BCL5, LAZ3	n/d	n/d	n/d	196
BCL11A	BCL11A-XL, CTIP1, ZNF856, EVI9, HBFQTL5	n/d	n/d	n/d	196
CELF6	BRUNOL6	n/d	n/d	n/d	65
CHMP6	VPS20	n/d	n/d	n/d	79
DLX3	AI4, TDO	n/d	n/d	n/d	65
HNRNPA1L2		n/d	PLD (+)	n/d	65
HNRNPF		n/d	n/d	n/d	65
HNRNPH 1		n/d	PLD (+), Involved in ADARB2 regulation	n/d	65, 91, 267
HNRNPM	CEAR4, HTGR1, NAGR1	n/d	n/d	n/d	151
KIAA1530	UVSSA, UVSS3	n/d	n/d	n/d	79
MEX3C	BM-013, RKHD2, RNF194	n/d	n/d	n/d	65
SOX9	SRA1, CMPD1, CMD1	n/d	n/d	n/d	212
SS18L1	CREST	n/d	PLD (+)	ALS	65
v-FOS		n/d	n/d	n/d	79
WTX	AMER1, FAM123B, OSCS	n/d	n/d	n/d	241
WT1 (+KTS) <sup>1</sup>	WAGR, AWT1, GUD, NPHS4, WIT-2, WT33	n/d	n/d	n/d	240

<sup>1</sup>Its DNA-binding domain is disrupted by the insertion of three amino acids. AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; FTD: frontotemporal dementia; HNRNP: heterogeneous nuclear ribonucleoprotein; KLF4: Kruppel-like factor 4; MEN: multiple endocrine neoplasia; MSP: multisystem proteinopathy; NEAT: nuclear paraspeckle assembly transcript 1; PLD: prion-like domain; PLD (+): RNA-binding protein with a prion-like domain; PSF: PTB-associated splicing factor; SFPQ: splicing factor, proline- and glutamine-rich; SOX9: sex-determining region Y-box 9; XIAP: X-linked inhibitor of apoptosis protein

## Annotation of paraspeckle components

Many paraspeckle proteins are likely RNA-binding proteins that contain an RNA recognition motif (RRM), a KH domain, a RGG box, or a zinc finger motif as canonical RNA-binding domains. These include 32 paraspeckle proteins, namely, NONO, SFPQ, RBM14, heterogeneous nuclear ribonucleoprotein (HNRNP)K, DAZAP1, FUS, HNRNPH3, CPSF7, HNRNPA1, HNRNPR, HNRNPUL1, RBM12, FUSIP, TDP-43, CPSF6, NUDT21, PSPC1, CIRBP, EWSR1, RBM3, RBM4B, RBM7, RBMX, TAF15, CELF6, HNRNPA1L2, HNRNPF, HNRNPH1, MEX3C, HNRNPM, SRSF11, and ENOX1. Multiple paraspeckle proteins are disease-related. The genes encoding 13 paraspeckle proteins (NONO, SFPQ, CPSF6, EWSR1, FUS, TAF15, DAZAP1, RBM3, SS18L1, WT1, BCL6, BCL11A, ZNF444, and HNRNPH1) are located at breakpoints of chromosomal translocation that produce abnormal fusion proteins responsible for various types of cancers (81-86). Several proteins (TDP-43, FUS, EWSR1, TAF15, HNRNPA1, SS18L1, and SFPQ) involved in neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), have also been identified as paraspeckle proteins, suggesting a relationship between paraspeckles and these diseases (87-91) (Table 2). Proteins containing a prion-like domain (PLD), which have similarities to yeast prion proteins and are prone to aggregation, are enriched among paraspeckle proteins (87, 91) (see section 3.5.). In addition, a set of paraspeckle proteins (FUS, EWSR1, TAF15, TDP-43, HNRNPA1, HNRNPM, CPSF6, DAZAP1, RBM4B, and ENOX1) aggregate and cause toxicity when overexpressed in *Saccharomyces cerevisiae* (92). Various paraspeckle proteins (e.g. NONO, SFPQ, PSPC1, RBM14, HNRNPK, FUS, TAF15, EWSR1, HNRNPUL1, RBMX, RUNX3, KIAA1530 and RNA polymerase II) are shown to be involved in DNA damage response (93-112). Some paraspeckle proteins (e.g., NONO, SFPQ, RBM14, EWSR1, FUS, TAF15, and TDP-43) are RNA-binding proteins, which mediate transcription and RNA processing (113). Several proteins (e.g., CPSF6, CPSF7, and NUDT21) are involved in 3' end processing of mRNAs and lncRNAs (65, 114, 115). NUDT21 (nucleoside diphosphate linked moiety X (Nudix)-type motif 21) possesses a NUDIX hydrolase domain that acts as an authentic RNA-binding domain. The mechanisms underlying the involvement of these proteins in the production of NEAT1 are described in section 3.4. (65).

## 3.3. Annotated functions of each paraspeckle protein

Paraspeckle proteins are present diffusely throughout the nucleoplasm as well as being concentrated in paraspeckles. Some paraspeckle proteins interact dynamically with paraspeckles, which raises the intriguing possibility that the function of each paraspeckle protein is regulated by its shuttling between these nuclear compartments and that paraspeckle dynamics may affect the nucleoplasmic functions of these proteins. Thus, in this section, we overview the known functions of each paraspeckle protein according to their classifications.

### 3.3.1. DBHS proteins

DBHS proteins have similar conserved domains, including two RRM and a coiled-coil domain. They form all possible combinations of heterodimers (54, 55, 116). Crystal structural analysis revealed that NONO and PSPC1 form a heterodimer via their coiled-coil domains, which is critical for the formation of paraspeckles (117). Mutational analysis showed that the RRM and coiled-coil domain of PSPC1 are both required for its targeting to paraspeckles, while the coiled-coil domain of PSPC1 is necessary for its targeting to the nucleolar cap upon transcriptional inhibition (54). The second RRM of SFPQ is sufficient for its targeting to paraspeckles (118). Interestingly, NONO and SFPQ are reportedly involved in various nuclear events including transcription, pre-mRNA splicing/processing, post-transcriptional regulation, and DNA damage. NONO and SFPQ both interact with the C-terminal domain of RNA polymerase II (119, 120). NONO and SFPQ, together with Matrin 3, are involved in the nuclear retention of hyper-edited mRNA (121). All DBHS proteins are involved in the DNA damage response (93-95).

### 3.3.2. FET/TET family proteins

FET/TET family proteins (FUS/TLS, EWSR1 and TAF15) that localize in paraspeckles contain a RRM, a zinc finger domain, and a PLD (87, 91). FET family members are multifunctional proteins involved in various gene expression processes, such as transcription, splicing, and mRNA transport (81). The N-terminal PLD of FET family members fuses with many partner proteins in various types of sarcoma and leukemia (81, 86). In addition, these proteins are reportedly involved in several neurodegenerative diseases including ALS and FTD (90, 91, 122). All FET family members are involved in the DNA damage response (96-102). FUS (also known as

## Annotation of paraspeckle components

TLS and HNRNP P2) is an essential paraspeckle protein encoded by an ALS-causing gene and forms cytoplasmic aggregates in motor neurons from ALS patients carrying a FUS mutation (123, 124). FUS is a multifunctional protein involving in a variety of cellular processes, including transcription, RNA processing and transport, and cellular body formation (125). FUS interacts with various gene expression machineries, such as basal transcription factors (TFIID and TFIIB), RNA polymerase II, and U1 snRNP (81, 126). Consistent with this, knockdown of FUS changes the distribution of serine-2-phosphorylated RNA polymerase II (127). FUS binds to a specific lncRNA(s) to regulate the transcription of the *CCND1* gene (128). A recent study showed that FUS interacts with the SMN complex and is required for the formation of Gem, a nuclear body that contains the SMN complex (126). FUS binds to thousands of RNA targets *in vivo*, and shows specificities in terms of its binding motifs and patterns (129-134). Interestingly, FUS reportedly has a SUMO1 E3 ligase activity that regulates the sumoylation and thus the anti-proliferative activity of Ebp1 (135). EWSR1 (Ewing sarcoma RNA-binding protein 1) has been extensively investigated in the context of Ewing sarcoma (136, 137). EWSR1 interacts with basal transcription factors and RNA polymerase II, suggesting it functions in transcriptional regulation (138). EWSR1 was recently implicated in ALS and FTD (90, 91, 122). The TAF15 protein (also known as TAFII68) associates with a distinct population of TFIID complexes (139). TAF15 interacts with U1 snRNAs, but not with canonical U1 snRNP proteins, and with several Sm proteins (75). This U1-TAF15 complex tightly associates with chromatin and relocalizes to nucleolar caps upon transcriptional inhibition (75). Analysis of the *in vivo* RNA-binding site of TAF15 revealed its important role in the pre-mRNA splicing of a set of neuronal transcripts (140). Mutations in *TAF15* genes have been identified in multiple ALS patients (92).

### 3.3.3. HNRNP proteins

Multiple HNRNPs, including HNRNPA1, A1L2, F, G, H1, H3, K, M, P2, R, and UL1, have been identified as paraspeckle proteins and are involved in a range of RNA metabolism processes, including the packaging of nascent pre-mRNA transcripts, pre-mRNA splicing and processing, and translational regulation (141, 142). HNRNPs are RNA-binding proteins that commonly contain two or three RNA-binding domains, including a RRM or a KH domain. HNRNPA1 is involved in a variety of RNA processing events, including

alternative splicing, and shuttles between the nucleus and cytoplasm (143). Recently, mutations in the *HNRNPA1* gene were identified in ALS and multisystem proteinopathy (MSP); the mutations are found in the PLD of HNRNPA1 and increase the aggregation of this protein (144). HNRNPF regulates mRNA processing by recognizing G-tract RNA sequences (145). HNRNPH1 also binds G-rich sequences, including G runs/G triplets (146, 147), and regulates alternative polyadenylation and cleavage as well as alternative splicing (148). HNRNPH3 is as an essential paraspeckle protein that functions as a splicing factor and participates in early heat shock-induced splicing arrest via transiently leaving HNRNP complexes (149). HNRNPK is a multifunctional essential paraspeckle protein that is involved in multiple gene expression processes, including transcriptional regulation, pre-mRNA splicing, mRNA stability, and translation (150). The critical role of HNRNPK in paraspeckle formation is described below. HNRNPM associates with the spliceosome and influences the splicing patterns of specific genes (151). HNRNPM reportedly interacts with two paraspeckle core proteins, namely, SFPQ and NONO, and localizes in paraspeckles (151). HNRNPR reportedly interacts with SMN (152, 153) and is required for the localization of beta-actin mRNA in spinal motor neurons (154). HNRNPR is involved in the reinitiation of *c-fos* gene expression in cooperation with the Mediator complex (155). HNRNPUL1 is responsible for U7 snRNP-dependent transcriptional repression of replication-dependent histone genes (156).

### 3.3.4. RBM family proteins

Multiple RBM family members (RBM3, RBM4B, RBM7, RBM12, RBM14, and RBMX) have been identified as paraspeckle proteins. RBM7 functions in pre-mRNA splicing (157) and is a component of the nuclear exosome targeting complex, which is specifically required for the degradation of promoter-upstream transcripts by the nuclear exosome (158). RBM14 (also known as PSP2 and CoAA) is an essential paraspeckle protein that stabilizes NEAT1 lncRNAs. It acts as a co-activator activator by associating with thyroid hormone receptor-binding protein, which functions as a nuclear receptor co-activator (159). RBM14 also acts as a splicing modulator (160) and is a SYT-interacting protein. SYT (also known as synovial sarcoma translocation and SS18) is a proto-oncogene and a subunit of the BAF chromatin-remodeling complex (161). The paraspeckle protein SS18L1 (also known as CREST) is a paralog of

## Annotation of paraspeckle components

SYT and a calcium-responsive component of the neuron-specific BAF chromatin-remodeling complex (162). SS18L1 was recently identified as a causative gene of ALS (89). RBMX (RNA-binding motif protein X-chromosome, also known as HNRNPG) is an ubiquitously expressed splicing regulator that is recruited to nascent transcripts (163). RBMX is also a chromosomal protein that regulates sister chromatid cohesion and the DNA damage response (164) and is reportedly required for brain development (165).

### 3.3.5. Other canonical RNA-binding proteins

TDP-43, which is encoded by the ALS-causing gene *TARDBP*, contains a PLD and RRM, which are required for its targeting to paraspeckles (88). TDP-43 was identified as a major component of ubiquitin-positive aggregates found in the motor neurons of ALS and FTD patients (166-170). C-terminal fragments of TDP-43 are usually found in these patients (166-170). Subsequently, multiple mutations in the *TARDBP* gene were identified in ALS patients. TDP-43 is reportedly required for the formation of a distinct nuclear body, Gem (126, 171, 172). DAZAP1 (Deleted in Azoospermia-Associated Protein 1) is as an essential paraspeckle protein that regulates splicing and translation and is required for normal development and spermatogenesis (173-177). The subcellular localization of DAZAP1 is dynamically regulated in response to signals and during spermatogenesis (177-181). CELF6/BRUNOL6 is involved in alternative splicing (182). *Celf6*-knockout mice show autism-related behaviors (183). Two SR protein family members (SRSF10, also known as SRp38, FUSIP1, and TRA2B, as well as SRSF11/SRp54) have been identified as paraspeckle proteins. SRSF10 acts as a splicing repressor in response to heat shock (184) and modulates alternative splicing via GA-rich binding motifs (184-187). Expression of SRSF10 is reportedly reduced in human obesity and contributes to the metabolic phenotypes associated with alteration of the splicing of target genes (188). SRSF11 functions in both constitutive and alternative splicing, and interacts with U2AF65, which associates with 3' splice sites (189). CIRBP and RBM3 are two major cold-inducible RNA-binding proteins, are highly homologous, and are induced by moderate cold shock and other stresses including hypoxia and ultraviolet (UV) radiation (190, 191). A recent study identified CIRBP and RBM3 as important regulators of circadian gene expression (192). PAR-CLIP analysis revealed that both proteins bind 3' UTRs near to PAS and their knockdown shortens

the 3' UTRs, while their up-regulation upon low temperature exposure lengthens the 3' UTRs. The 3' UTRs to which these proteins bind shows circadian oscillation, suggesting that these cold-inducible proteins function in circadian gene expression via alternative polyadenylation (192).

### 3.3.6. Transcription factors

Multiple transcription factors (AHDC1, DLX3, ZNF335, RUNX3, ZNF24, KLF4, GATA1, BCL6, BCL11A, SOX9 (sex-determining region Y-box 9), WT1, ZNF444, and SCYL1) are paraspeckle proteins. Many of these (AHDC1, DLX3, ZNF335, BCL11A, BCL6, GATA1, WT1, SOX9, ZNF444, and RUNX3) are involved in malignancy and various genetic diseases such as Xia-Gibbs syndrome, Tricho-Dento-Osseous syndrome, and the neurodevelopmental disorder microcephaly-10 (84, 193-206). The transcription factor KLF4 (Kruppel-like factor 4) is a so-called "Yamanaka factor" necessary for the induction of induced pluripotent stem cells (207). This is consistent with the finding that paraspeckles are undetectable in pluripotent embryonic stem (ES) cells, meaning KLF4 is free to function in the nucleoplasm. ZNF24 inhibits angiogenesis by repressing vascular endothelial growth factor transcription during development and tumor growth (208). ZNF24 is a DNA replication factor (209). Knockdown of ZNF24 reduces the number of paraspeckles and NEAT1 expression (79). SOX9 is a transcription factor that plays essential roles in chondrocyte differentiation and the development of several organs, including the liver and pancreas (210, 211). The paraspeckle protein NONO mediates SOX9-dependent *Col2a1* expression (212). Overexpression of mutant NONO lacking a RRM causes morphological changes in paraspeckles and inhibits the maturation of *Col2a1* mRNA and chondrocyte differentiation *in vitro* and *in vivo*, suggesting the importance of paraspeckles during chondrogenesis (212). SCYL1 is predominantly expressed in neurons and its loss-of-function mutation causes a recessive form of spinocerebellar neurodegeneration in mouse (213). An early onset progressive motor neuron disorder in *Scyl1*-deficient mice is associated with the mislocalization of TDP-43 (214). In addition to transcription factors, immunofluorescence analysis showed that RNA polymerase II localizes in paraspeckles (215). However, paraspeckles are not considered to be active transcriptional sites because neither the active form of RNA polymerase II nor newly synthesized RNAs have been detected in these structures (215). It is noteworthy that active

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transcription may occur in the peripheries of paraspeckles, suggesting the transient involvement of paraspeckles in transcription (215).

### 3.3.7. Proteins involved in the ubiquitin-proteasome pathway

Several paraspeckle proteins are involved in the ubiquitin-proteasome pathway. MEX3C is an RNA-binding E3 ubiquitin ligase, and HECTD3 and XIAP (X-linked inhibitor of apoptosis) are E3 ubiquitin ligases (216-220). UBAP2L (ubiquitin-associated protein 2-like, also known as NICE4) is thought to be involved in the ubiquitin-proteasome pathway and aggregates in the presence of a proteasome inhibitor (221, 222). Interestingly, UBAP2L is an RNA-binding protein (223-225). MEX3C belongs to an evolutionarily conserved family that possesses KH domains and RING domains and is involved in mRNA degradation and chromosomal stabilization (220, 226, 227). *Mex3c*-mutant mice display reduced adipose deposition, increased energy expenditure, and growth retardation (228). HECTD3 ubiquitinates several target proteins such as Tara, MALT1, caspase-8, and Syntaxin 8 (229, 230-232). Depletion of HECTD3 results in defects in chromosome segregation (230). Knockdown of HECTD3 reduces the number of paraspeckle foci and NEAT1 expression (79). XIAP is known as a regulator of cell migration and development as well as an inhibitor of apoptosis (218, 219, 233). Loss-of-function mutations in human XIAP cause X-linked lymphoproliferative syndrome type 2 (234). Knockdown of XIAP (X-linked inhibitor of apoptosis protein) leads to reductions in the number paraspeckle foci and the level of NEAT1 (79). As described below, paraspeckles are markedly enlarged by proteasome inhibition and thus it would be interesting to investigate whether these E3 ligases contribute to the regulation of paraspeckle functions upon proteasome inhibition.

### 3.3.8. Other proteins

Several proteins (e.g., FAM98A, FAM113A, FAM123B, FAM53A, and FAM53B) in the FAM (Family with sequence similarity) family have been identified as paraspeckle proteins, although their functions are mostly unknown. FAM98A is an RNA-binding protein (223-225). FAM113A (also known as PCED1A (PC-esterase domain-containing 1A)) is a putative hydrolytic enzyme with esterase and lipase activities (235, 236). *WTX* (also known as FAM123B) is a suppressor gene of Wilms tumors and is linked to osteopathia striata with cranial sclerosis (237-239). *WTX* interacts with WT1,

another Wilms tumor suppressor protein that has been identified as a paraspeckle protein (240, 241). AKAP8L (also known as NAKAP95 and HAP95) is an RNA-binding protein (223-225). AKAP8L binds to RNA helicase A and activates constitutive transport element-mediated RNA export (242, 243). FIGN (also known as fidgetin) is a member of the AAA (ATPases associated with diverse cellular activities) protein family. Mutations in the mouse FIGN homolog were identified by positional cloning of *fidgetin*-mutant mice, which exhibit defective development (244). FIGN and AKAP8L interact with each other and this is critical for palatogenesis (245). SH2B1 is a Src homology 2 (SH2) domain-containing adaptor protein that modulates a variety of receptor-mediated signaling events (246, 247). Loss-of-function mutations in human SH2B1 are associated with defects in adaptive behaviors and obesity (248). *LMNB2* encodes lamin B2, an ubiquitously expressed intermediate filament protein, and mutations in the *LMNB2* gene are associated with acquired partial lipodystrophy (also known as Barraquer-Simons syndrome) (249-253). *CYBA* encodes cytochrome b-245, alpha polypeptide (also known as p22-phox) that is an essential subunit of NADPH oxidase (NOX), which plays an important role in the immune system, including phagocytes (254). Many mutations in the *CYBA* gene cause autosomal recessive chronic granulomatous disease (CGD) (254). ENOX1 (ecto-NOX disulfide-thiol exchanger 1), which contains an RRM, is an NADH oxidase in the plasma membrane electron transport pathway (255). This pathway is distinct from the well-known mitochondrial electron transport pathway and is important for many cellular processes, including cellular defense, intracellular redox homeostasis, and cell growth and survival (255). KIAA1530 (also known as UVSSA) reportedly participates in transcription-coupled repair together with CSA (Cockayne syndrome complementation group protein A) (103-106). Annexin A10 belongs to an annexin family of calcium- and phospholipid-binding proteins and is a tumor suppressor (80).

## 3.4. The mechanism underlying paraspeckle formation

Paraspeckles contain NEAT1 lncRNAs, along with numerous proteins as described above; therefore, they are considered to be huge RNP complexes. Electron microscopic analyses indicated that paraspeckles have a mean diameter of 0.36 micrometers (53), which is more than 1,500-fold larger than ribosomes, a classical RNP complex. As described above, NEAT1 lncRNAs are essential components of paraspeckles. In this section, we

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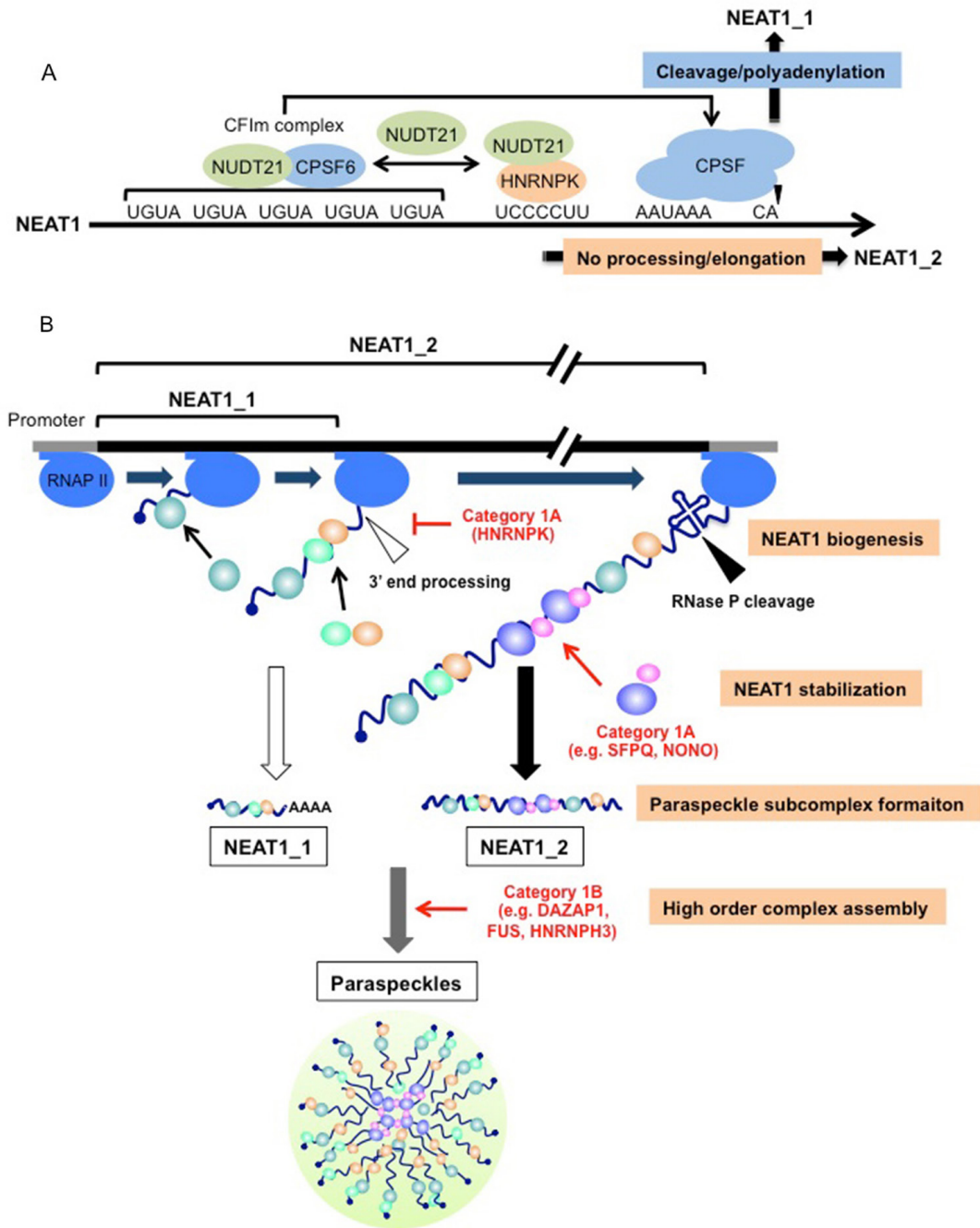
review the current understanding of how such huge paraspeckles form around NEAT1 lncRNAs. DNA and RNA fluorescence *in situ* hybridization (FISH) analyses showed that a subpopulation of NEAT1 lncRNAs co-localize with NEAT1 genomic loci, suggesting that paraspeckles initially form in close proximity to NEAT1 genomic loci (57). Spector and colleagues showed that transcription of NEAT1 lncRNAs from genomic loci can induce *de novo* paraspeckle formation at the transcription sites (256). They used an artificially integrated *NEAT1* gene, which produces NEAT1 lncRNA tagged with multiple MS2-binding stem-loops that can be visualized with bound EYFP-MS2 protein. In this condition, paraspeckles formed on the integrated *NEAT1* gene locus. On the other hand, paraspeckles were not detected when NEAT1 lncRNAs were artificially tethered at the distinct genomic locus. Taken together, paraspeckles co-transcriptionally formed with nascent NEAT1 lncRNAs at NEAT1 genomic loci. In addition, tethering of paraspeckle proteins, rather than NEAT1, cannot induce *de novo* paraspeckle formation, and rapid assembly and disassembly of paraspeckles is induced by global transcriptional induction and repression, respectively. Therefore, paraspeckle formation is proposed to fit a two-step model, in which initial non-random seeding events are followed by self-assembly steps (256, 257). NEAT1 appears to act as a seeding molecule for paraspeckles. Paraspeckle formation proceeds by the nucleation of NEAT1 with core paraspeckle proteins, followed by high-order assembly steps (Figure 3B). It should be noted that the majority of paraspeckles are located distant to NEAT1 genomic loci, suggesting that assembled paraspeckles are released from NEAT1 genomic loci and relocate to the nucleoplasm via unknown mechanisms.

After we identified new paraspeckle proteins as described above, we investigated how these components function in paraspeckle formation (65). We categorized paraspeckle proteins into three groups, with a few subgroups, based on their importance to paraspeckle formation and NEAT1 expression (Table 2). Paraspeckle proteins in category 1 (NONO, SFPQ, RBM14, HNRNPK, DAZAP1, FUS, and HNRNPH3) are essential for paraspeckle formation. Knockdown of any category 1 protein results in paraspeckle disintegration (65). Category 1 proteins were further divided into two subgroups, 1A (NONO, SFPQ, RBM14, and HNRNPK) and 1B (DAZAP1, FUS, and HNRNPH3) according to their importance to NEAT1 expression. Category 1A proteins are required for

paraspeckle formation and NEAT1 expression, while category 1B proteins are required for paraspeckle formation but not for NEAT1 expression (65). The existence of category 1B suggests that there is a distinct step of paraspeckle formation during which NEAT1 RNP sub-complexes assemble into intact paraspeckles (Figure 3B). Interestingly, all proteins in category 1B are RNA-binding proteins that contain PLDs (87, 91). Thus, it is conceivable that the PLDs of these proteins play a pivotal role in paraspeckle formation in light of recent findings linking PLDs with RNA granule formation (258, 259) (see section 3.5.). A recent study supports this model. Fong *et al.* identified a subset of paraspeckle proteins and showed that knockdown of several of these proteins (HECTD3, ZNF24, and XIAP) reduces the number of paraspeckle foci without affecting the level of NEAT1 (79). Another set of paraspeckle proteins was classified into category 2. Knockdown of proteins in category 2 reduces the number of paraspeckles, substantially changes paraspeckle morphology, and slightly changes NEAT1 expression (65). Paraspeckle proteins in category 3 do not affect paraspeckle formation (65). Proteins in category 3A increase the level of NEAT1\_1, although knockdown of proteins in category 3B has no effect on NEAT1 expression. However, it is possible that these non-essential paraspeckle proteins play regulatory roles in paraspeckles in particular conditions such as in specific developmental stages, cell types, and diseases.

Among category 1A proteins, the DBHS proteins SFPQ and NONO directly bind NEAT1, and knockdown of either protein causes paraspeckle disintegration accompanied by a specific reduction in the level of NEAT1\_2 (55, 65). The category 1A protein HNRNPK is involved in alternative 3' end processing for the production of two NEAT1 isoforms (Figure 3A). Knockdown of HNRNPK increases the level of NEAT1\_1 (by more than 2-fold) and reduces the level of NEAT1\_2, suggesting that HNRNPK switches NEAT1 expression from the NEAT1\_1 isoform to the NEAT1\_2 isoform by arresting 3' end processing of NEAT1\_1 (65). SELEX (Systematic Evolution of Ligands by EXponential enrichment) analysis showed that HNRNPK preferentially binds CU-rich sequences (260). Immediately upstream of the PAS of NEAT1\_1, there is a putative HNRNPK-binding site, UCCCCUU, which perfectly matches a SELEX-derived sequence and is conserved in rodents, suggesting that binding of HNRNPK to this motif regulates NEAT1\_1 synthesis. Mutational analysis of this conserved motif revealed that

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**Figure 3.** Model for the biogenesis of paraspeckles. A. Model for the synthesis of nuclear paraspeckle assembly transcript 1 (NEAT1) long non-coding RNA isoforms through modulation of the polyadenylation of the NEAT1<sub>1</sub> isoform. The Cleavage factor Im (CFIm) complex (NUDT21-CPSF6) binds to the cluster of UGUA sequences upstream of the polyadenylation site (AAUAAA) to recruit the CPSF complex for polyadenylation to this site. HNRNPK binds to the UCCCCUU sequence and competes with NUDT21 for binding to CPSF6. B. Current model for paraspeckle formation. Paraspeckle formation is divided into four main steps, namely, NEAT1 synthesis, NEAT1 stabilization, paraspeckle subcomplex formation, and high-order complex assembly. Paraspeckle proteins essential for paraspeckle formation are classified as category 1A or 1B (see text for details) and are thought to function in the early steps of paraspeckle formation. HNRNPK inhibits 3' end processing of NEAT1<sub>1</sub> by competing with the CFIm complex as shown in Figure 3A. SFPQ and NONO are required for the stabilization of NEAT1<sub>2</sub>. Category 1B proteins play a role in the subsequent assembly step to build high-order structures.

## Annotation of paraspeckle components

HNRNPK suppresses usage of the PAS of NEAT1\_1 through binding to this site, which facilitates the production of NEAT1\_2 (65). Two category 3A proteins, CPSF6 and NUDT21, which counteract HNRNPK, form a heterodimer called Cleavage factor Im (CFIm) complex to facilitate 3' end processing of alternatively processed mRNAs (114). Knockdown of either protein eliminates the expression of NEAT1\_1 and increases the level of NEAT1\_2, which is opposite to the effects of HNRNPK (65). Intact paraspeckles remain detectable even when expression of NEAT1\_1 is diminished, which further supports the idea that NEAT1\_1 is dispensable for paraspeckle formation (65). In terms of its underlying mechanism, the CFIm complex binds to the UGUA sequence, of which there are five clustered upstream of the PAS of NEAT1\_1, to promote production of NEAT1\_1 (65). An *in vitro* study analyzing the mechanism underlying the 3' end processing of NEAT1\_1 by HNRNPK and the CFIm complex indicated that HNRNPK competes with CPSF6 for binding to NUDT21 to form the CFIm complex (65). Taken together, HNRNPK facilitates the production of NEAT1\_2 by arresting CFIm-dependent NEAT1\_1 polyadenylation (65) (Figure 3A).

### 3.5. PLD-containing paraspeckle proteins and their implications in the mechanism underlying paraspeckle formation

About 1 percent of human proteins harbor a PLD, which is also recognized as a low complexity (LC) domain, in which the composition of amino acids is biased (87, 91). PLDs are prone to aggregation and are enriched in uncharged polar amino acids (asparagine, glutamine, tyrosine, and serine) and glycine. PLD-containing proteins are linked to several aggregate-associated diseases including neurodegenerative diseases (87, 90, 91). PLDs are enriched in RNA-binding proteins. Approximately 20 percent of PLD-containing proteins bind RNA (91) (Table 2). As described in section 3.3., many paraspeckle proteins (e.g., SFPQ, RBM14, DAZAP1, EWSR1, FUS, HNRNPA1, HNRNPA1L2, HNRNPH1, HNRNPH3, HNRNPUL1, SS18L1, TAF15, TARDBP, and PSPC1) contain PLDs (91) (Table 2). Most essential category 1 proteins contain PLDs and thus PLDs likely play a pivotal role in the formation and/or functions of paraspeckles. In fact, the PLD of FUS is required for its targeting to paraspeckles (261). Next, we describe how non-membranous cellular bodies containing PLD-containing proteins form and discuss how PLDs contribute to paraspeckle formation.

Several reports suggest the importance of PLDs in the assembly of cellular bodies. The PLD of TIA1 protein is suggested to be involved in the assembly of stress granules (SGs), which are discrete cytoplasmic foci formed in response to various stresses and which contain stalled translation complexes (262). Expression of TIA1 lacking a PLD results in impaired SG assembly, and this is rescued by expression of TIA1 in which the PLD has been substituted with a domain of yeast prion Sup35. Another report using *S. cerevisiae* suggests that the PLD of LSM4 contributes to the assembly of yeast processing bodies (P bodies), which are cytoplasmic RNA granules that contain untranslated mRNAs with translation repressors and mRNA decay factors (263).

A remarkable advance has recently been made in the research field of RNA granules. McNight and colleagues serendipitously found that biotinylated isoxazole (b-isox) chemical precipitates RNA-protein complexes from cell and tissue lysates and induces hydrogel formation (258, 259). These precipitates contain numerous RNAs and RNA-binding proteins, many of which possess LC domains (258, 259). A significant number of proteins in the precipitates are components of cellular bodies, especially SGs (258). In addition, many of the core precipitated proteins are paraspeckle proteins, including DAZAP1, EWSR1, FAM98A, FUS, HNRNPA1, HNRNPF, RBM3/HNRNPG, HNRNPH1, HNRNPK, HNRNPR, RBM3, TAF15, TARDBP, and UBAP2L (65, 258, 259). X-ray analysis of b-isox indicated that it forms small crystals that recruit PLD-containing proteins to their surfaces (258). Furthermore, X-ray diffraction and electron microscopy studies revealed that these hydrogels are comprised of uniformly polymerized amyloid-like fibers, and the formation of the hydrogels was reversible, unlike that of amyloid, reflecting the formation of cellular bodies (258). Thus, it is thought that this experimental system could be used as *in vitro* model of cellular body formation. In addition, only high concentrations of purified PLD-containing, RNA-binding proteins can form hydrogels *in vitro* without b-isox (258). The PLD-containing, RNA-binding protein FUS is abundant among the proteins in b-isox precipitates (258). FUS is an essential paraspeckle component and can form hydrogels *in vitro* at high concentrations (~10–50 mg/ml), suggesting that PLDs can undergo a concentration-dependent phase transition to a hydrogel-like state in the absence of b-isox (258). When FUS is mislocalized in the cytoplasm owing to mutation or deletion of its nuclear localization signal, which is found in a



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subpopulation of ALS patients, it is incorporated into SGs (125, 264). Introduction of mutations into the PLD of FUS to disrupt its prion-like properties inhibits *in vitro* hydrogel formation and the incorporation of FUS into SGs in cells (258). Another interesting feature of these hydrogels is the co-polymerization of specific proteins. The PLDs of FUS or HNRNPA2, another PLD-containing, RNA-binding protein, co-polymerize with RBM3, HNRNPA1, or CIRBP, which are all paraspeckle proteins (258). A hydrogel-binding assay to examine whether proteins can be trapped by the hydrogel *in vitro* indicated that the intrinsic properties of PLDs determine which proteins they co-polymerize with (258). These data suggest that PLDs contribute to the specific recruitment of proteins to cellular bodies. Taken together, these findings shed light on the roles of PLDs in the formation of non-membranous cellular bodies.

More recent work from the McNight laboratory identified proteins in b-isox precipitates from nuclear extracts, rather than from total cell lysates (225). In this case, polymeric fibers of PLDs from the FET family member proteins FUS/TLS, EWSR1 and TAF15, which are all paraspeckle proteins, and RNA-binding proteins containing PLDs specifically interacted with RNA polymerase II, whose interactions are regulated by phosphorylation of its C-terminal domain. Among the list of proteins in b-isox precipitates from nuclear extracts, there were multiple paraspeckle proteins (e.g., TAF15, RNA polymerase II, RBM14, EWSR1, HNRNPUL1, RBMX, FUS, HNRNPM, SFPQ, HNRNPK, NONO, HNRNPH1, HNRNPA1, HNRNPF, UBAP2L, DAZAP1, SRSF10, AKAP8, SRSF11, TARDBP, HNRNPH3, CPSF6, CIRBP, RBM4B, and HNRNPR), suggesting that paraspeckle proteins are prone to aggregate in the nucleus, consistent with the existence of PLDs. Furthermore, Cech and colleagues showed that RNAs promote formation of high-order FUS assemblies *in vitro* (265). These assemblies had characteristics of beta-zipper structures and a LC domain was required for the assembly process, suggesting that RNAs nucleate these high-order FUS assemblies. Interestingly, FUS forms high-order fibers of 30–50 nm in diameter with RNAs *in vitro*. These data suggest that PLDs contribute to cellular body formation with seed RNAs. In the case of paraspeckles, as mentioned above, most category 1A and 1B proteins contain PLDs and thus PLDs likely contribute to the formation of high-order paraspeckle structures with NEAT1 as the seed RNA. Recently, Crooke and colleagues reported that transfected 20-mer phosphorothioate-modified

antisense oligonucleotides can recruit paraspeckle proteins to form morphologically normal and apparently functional paraspeckle-like structures lacking NEAT1 RNA (266). Future studies will reveal the precise roles of PLDs and RNA sequences in paraspeckle formation.

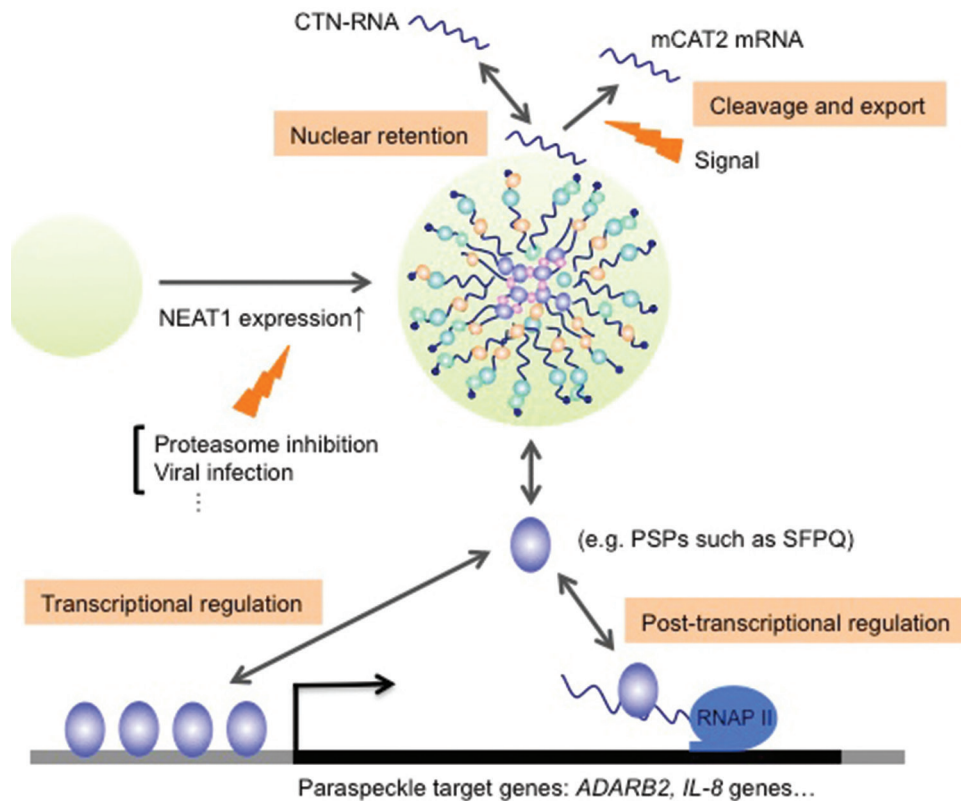
## 3.6. Paraspeckle functions

### 3.6.1. Mechanistic insights into paraspeckle functions

Although the physiological functions of paraspeckles remain only partly understood, one known function of paraspeckles is in the regulation of the expression of specific transcripts via their retention in paraspeckles. One representative RNA is CTN-RNA (cationic amino acid transporter 2 transcribed nuclear RNA), which is transcribed as ~8-kb transcripts from the protein-coding mouse cationic amino acid transporter 2 (*mCAT2*) gene (76) (Figure 4). CTN-RNA contains the entire open reading frame of the *mCAT2* gene and possesses extended 5' and 3' UTRs. The 3' UTR of CTN-RNA contains three inverted repeats (IRs) derived from short interspersed nucleotide element repeats, which can form an imperfect stem loop, and it is A-to-I edited by adenosine deaminase acting on RNA (ADAR) RNA-editing enzymes (76). These IRs in the 3' UTR could be required for nuclear retention. Under stress conditions, such as interferon-gamma and lipopolysaccharide treatment, CTN-RNA is post-transcriptionally cleaved and released as ~4.2-kb *mCAT2* mRNAs to the cytoplasm for translation (76). In addition to CTN-RNA, paraspeckles are reportedly required for the nuclear retention of several mRNAs that contain IRs in their 3' UTRs. One of these is Lin28 mRNA, which is expressed and exported into the cytoplasm for translation in human ES cells (56). In these cells, NEAT1 is barely expressed and paraspeckles are not detected. After the differentiation of ES cells into trophoblast cells, NEAT1 is highly expressed. Thereafter, paraspeckles form and Lin28 mRNA is retained in the nucleus, suggesting a general mechanism in which mRNAs containing IRs are regulated via their nuclear retention. The expression level of NEAT1 is regulated in several conditions, including various stress conditions and differentiation processes, as described below, and thus nuclear retention of IR-containing mRNAs is likely controlled under these conditions.

In addition to their functions in the nuclear retention of mRNAs, our recent collaborative study revealed another function of paraspeckles (267). This study identified NEAT1 target genes by microarray analysis and showed that NEAT1 transcriptionally

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**Figure 4.** Models for paraspeckle functions. The paraspeckle retains mCTN-RNA in the nucleus. mCTN-RNA is released by endonucleolytic cleavage upon certain stress signals (top). Nuclear paraspeckle assembly transcript 1 (NEAT1) expression is induced by several conditions, including proteasome inhibition and viral infection, resulting in paraspeckle enlargement (middle). Paraspeckle proteins, such as SFPQ, are sequestered in paraspeckles depending on the paraspeckle size. This reduces the levels of freely available paraspeckle proteins in the nucleoplasm. Consequently, gene expression of paraspeckle target genes can be regulated transcriptionally and/or post-transcriptionally. PSPs: paraspeckle proteins.

regulates its target genes by sequestering proteins from the promoters of the target genes in paraspeckles (Figure 4). Some NEAT1 target genes are regulated by the paraspeckle proteins SFPQ and HNRNPH1 (267). Thus, both NEAT1 lncRNA and paraspeckle proteins are required for this regulation. RNA-specific adenosine deaminase B2 (ADARB2) is a prominent target of NEAT1 (267). ADARB2 gene expression is up-regulated in NEAT1-knockdown cells. Dramatically enlarged paraspeckles, which form as a result of transcriptional up-regulation of NEAT1 induced by proteasome inhibition upon MG132 or bortezomib treatment, cause down-regulation of ADARB2 and several other target genes (267). This down-regulation is accompanied by the dissociation of SFPQ from the ADARB2 promoter, suggesting that SFPQ positively regulates ADARB2 expression and that the dissociation of SFPQ from the promoters of target genes leads to their reduced expression in the

presence of a proteasome inhibitor (267). In addition, paraspeckle enlargement is biologically important because embryonic fibroblasts (MEFs) from *Neat1*-knockout mice are more sensitive to proteasome inhibition than wild type MEFs (267). Taken together, these data suggest a model in which paraspeckles act as a sponge to sequester specific transcription factors and/or RNA-binding proteins. In this way, specific target genes can be regulated by changing the size of paraspeckles, which may contribute to cellular responses (Figure 4).

### 3.6.2. Possible functions of paraspeckles during virus infection

NEAT1 expression is induced, maybe through the Toll-like receptor 3 pathway, by infection of influenza virus or herpes simplex virus or by poly I:C treatment, leading to the enlargement of paraspeckles (268). These enlarged paraspeckles

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sequester SFPQ from the nucleoplasm and reduce the occupancy of SFPQ on the promoter of the *IL-8* gene. In this context, unlike proteasome inhibition, SFPQ acts as a transcriptional repressor, resulting in transcriptional activation of the *IL-8* gene. These results suggest that NEAT1 functions in the innate immune response via activating antiviral genes. In virus-infected cells, translation is strongly repressed and thus the lncRNA-mediated response mechanism, which does not require translation, will be important. In addition to the influenza and herpes simplex viruses, NEAT1 is induced by the Japanese encephalitis virus, by the rabies virus, and in HIV-infected cells (62, 269). Furthermore, NEAT1 is also induced by hypoxia, which represses translation, in human breast cancer cell lines, although it has not been determined whether paraspeckles are enlarged in these conditions (270).

### 3.6.3. Paraspeckle functions in development and diseases

NEAT1 is up-regulated in developmental processes and certain disease conditions. As described above, NEAT1 is up-regulated in myotube differentiation from C2C12 cells (58). NEAT1 expression is also increased in placentas with intrauterine growth restriction, which is a fetal disease characterized by an inability of the fetus to reach its growth potential (271). NEAT1 is highly expressed and TDP-43 abundantly binds NEAT1 in the brains of patients with FTD, which is the second most common form of dementia after Alzheimer's disease and is characterized by degeneration of the frontal lobe of the brain (172, 272). Interestingly, the paraspeckle protein SFPQ is mislocalized in the cytoplasm in astrocytes from the brains of FTD patients and Alzheimer's disease patients (273, 274). Paraspeckle formation was not examined in these conditions and thus it will be interesting to investigate whether paraspeckles are disintegrated in these conditions and whether this contributes to disease pathogenesis. Recently, our collaborative work showed that NEAT1\_2 is up-regulated in early-stage motor neurons from the spinal cords of ALS patients (88). Consistent with this, paraspeckle formation is induced in motor neurons of ALS patients, whereas paraspeckles are not observed in healthy control motor neurons, suggesting that paraspeckles have protective or damaging roles in ALS.

## 4. OTHER lncRNA-CONTAINING NUCLEAR BODIES

In addition to paraspeckles, several lncRNA-containing nuclear bodies form under

normal and stress conditions. These bodies are important to gene expression changes in response to stress. In this section, we summarize these other nuclear bodies, which contain lncRNAs as structural components.

### 4.1. Nuclear stress bodies

Nuclear stress bodies (nSBs) are formed as transient RNase-sensitive nuclear structures, with a diameter of 0.3–3 micrometers, in response to heat shock and several chemical stress conditions (46, 275–280). nSBs are present in humans and monkeys, but not in rodents. Their formation is initiated by the transcription of satellite III (Sat III) ncRNAs from pericentromeric regions (primarily 9q12 in human), which are heterochromatic in non-stressed condition (46, 276, 277, 279, 280). Sat III ncRNAs, which are strongly induced in stress conditions, are polyadenylated RNAs containing repetitive sequences with multiple GGAAT or GGAGT repeats (46, 278, 281). nSBs contain several transcription factors, including HSF1 (heat shock factor 1), HSF2 (heat shock factor 2), TonEBP (tonicity enhancer-binding protein), Sam68, and several splicing factors, including SAFB, SRSF1, SRSF7, and SRSF9, as protein components (46, 277, 278). The formation of nSBs is initiated through a direct interaction between HSF1 and Sat III ncRNA (46). In stress conditions, nSBs are thought to globally influence gene expression via sequestering transcription factors and splicing factors, and then contribute to recovery from these conditions (46, 278). When Sat III ncRNAs are knocked down, SRSF1 and SAFB cannot localize to nSBs, although HSF1 still localizes in nSBs, suggesting that Sat III ncRNAs can act as scaffolds for RNA-binding proteins (279). Consistently, the RRM2 of SRSF1 is required for its targeting to nSBs, suggesting splicing factors are recruited to Sat III ncRNAs via direct RNA binding (282). Furthermore, artificial tethering experiments showed that Sat III ncRNAs can initiate *de novo* formation of nSBs, indicating the architectural role of Sat III ncRNAs (283).

### 4.2. Nucleolar detention center

In 2012, Audas *et al.* reported that loci of the nucleolar intergenic spacer (IGS), where heterochromatin normally forms and which is thus transcriptionally silent, produces ribosomal IGS ncRNAs in response to several stresses, including acidosis (284–286). In stress conditions, IGS ncRNAs form a large subnucleolar structure

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called the detention center and play a role in the sequestration of key cellular proteins in the nucleolus (287). For instance, the stress-responsive transcription factor HIF1A is degraded by the ubiquitin E3 ligase von Hippel-Lindau (VHL) in normal conditions. However, in oxidative stress conditions, IGS<sub>28</sub> ncRNA, which is produced from a region ~28 kilobases downstream of rRNA gene loci, is induced and sequesters VHL in the nucleolus. Knockdown of IGS<sub>28</sub> prevents the localization of VHL to the nucleolus in oxidative stress conditions. Fluorescence Recovery after Photobleaching (FRAP) analysis showed that VHL is stably localized in the nucleolus (284). In addition to IGS<sub>28</sub> RNA, several IGS RNAs, including IGS<sub>16</sub>, IGS<sub>22</sub>, and IGS<sub>20</sub>, which are transcribed from regions ~16, 22, and 20 kilobases downstream of the rRNA gene loci, respectively, are induced in several stress conditions. In the heat shock condition, HSP70 is sequestered in the nucleolus in an IGS<sub>16</sub>- and IGS<sub>22</sub>-dependent manner. In addition, MDM2 is sequestered in the nucleolus by IGS<sub>20</sub> under transcriptional stress (284). Similar to Sat III and IGS ncRNAs, stress-responsive ncRNAs could exist in heterochromatic regions of the genome and spatially sequester specific proteins from their functional sites. This mechanism could contribute to cellular stress responses.

### 4.3. Miscellaneous

As mentioned above, RNA-containing nuclear bodies and lncRNAs that localize in specific nuclear bodies have been reported (Table 1). However, it remains to be investigated whether all these nuclear bodies require RNAs to maintain their structures. Here, we summarize the nuclear bodies that potentially contain architectural RNAs. Electron microscopic analyses identified RNA-containing nuclear bodies. One is the SNB (Figure 1), which is a distinct nuclear foci located at the periphery of the nucleolus (45, 288). SNBs are electron-dense structures, suggesting they contain RNAs (45, 288). However, the RNA(s) present in this nuclear body remains to be identified and whether RNAs are required for the maintenance of SNBs remains to be determined. Another report showed that an RNA-containing nuclear structure is found in UVC-induced apoptotic human umbilical vein endothelial cells (289).

Meanwhile, several studies suggested the existence of nuclear bodies that depend on specific ncRNAs to maintain their structures. Sno-lncRNA is a class of nuclear-enriched lncRNAs derived

from excised introns, which possess snoRNA-like structures at both ends (290). Among them, five abundant sno-lncRNAs transcribed from human chromosome 15q11-q13 are specifically deleted in Prader-Willi syndrome (PWS) (291). These sno-lncRNAs localize in distinct nuclear foci, although snoRNAs are usually concentrated in Cajal bodies or nucleoli (290). Double DNA and RNA FISH analysis showed that sno-lncRNAs in the PWS region accumulate at or near processing sites (290). These PWS region sno-lncRNAs sequester the alternative splicing regulator FOX2 (also known as RBM9) in a specific nuclear region via the multiple FOX2-binding sites on sno-lncRNAs, leading to alteration of FOX2-dependent splicing (290). Therefore, FOX2 proteins may be uniformly distributed in PWS patients, in which PWS region sno-lncRNAs are not expressed, and altered alternative splicing in many tissues during embryonic development and adulthood may lead to multisystemic dysfunctions in PWS.

Aside from the nucleus, the mitotic spindle is an RNase-sensitive structure that several RNAs, including rRNAs, associate with (292-294). In *Xenopus* oocytes, proper organization of the cytoskeleton requires two RNAs, namely, short interspersed repeat transcripts (Xsirts ncRNA) and mRNA of T-box factor from the vegetally localized transcript (295, 296). In addition, spreading initiation centers are foci that form during the early stage of cell spreading and contain numerous RNA-binding proteins, including FUS, HNRNPK, and HNRNPE1, and RNAs, including rRNAs (297). Thus, investigation of the molecular features of these RNA-containing cellular structures would expand our understanding of architectural RNAs.

## 5. SUMMARY AND PERSPECTIVES

The paraspeckle is a subnuclear structure that contains NEAT1 lncRNA as an architectural component. This nuclear body retains specific mRNAs or sequesters specific proteins to regulate gene expression. It is also plausible that paraspeckles sequester RNA-binding proteins that function in post-transcriptional regulation (Figure 4). It is important to elucidate the precise mechanism underlying how the interactions between NEAT1 and paraspeckle proteins are regulated to control gene expression, particularly in stress conditions. It is also intriguing to pursue the importance of NEAT1 and paraspeckles *in vivo* under various stress conditions using *Neat1*-knockout mice. Numerous paraspeckle

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proteins have been identified; therefore, it would be interesting to investigate whether gene regulation or post-translational modification of these components influences the formation or functions of paraspeckles. As described in section 3.5., many paraspeckle proteins appeared to be RNA-binding proteins that have PLDs. Thus, another important question is how PLDs function in the formation of paraspeckles and other cellular bodies.

In addition to endogenous nuclear bodies, disease-linked RNA repeats form nuclear foci and have critical roles in disease pathogenesis (298-302). Basically, these RNA foci contain proteins, especially RNA-binding proteins, to form RNP complexes. One such well-known disease is myotonic dystrophy, which is a genetic disorder with multisystemic symptoms. This disease is caused by extended repeats of CTG or CCTG in the genomes of patients with myotonic dystrophy type 1 or type 2, respectively. Nuclear foci containing CUG or CCUG RNA repeats transcribed from these loci are thought to cause this disease, suggesting the toxic RNA hypothesis. These repeat RNAs form nuclear foci, which sequester the RNA splicing factor muscleblind-like (MBNL), resulting in the disturbance of gene expression, including splicing (298-302). Knockout of MBNL in mice leads to similar phenotypes as the human disease, suggesting the importance of sequestration of MBNL in repeat-containing RNA granules (303, 304). Another example of an RNA repeat-associated disease is X-associated tremor ataxia syndrome, which is a common genetic disorder of the central nervous system (298-302). In this disease, CGG repeats in the *fragile X syndrome* gene are expressed and form nuclear foci, which sequester several RNA-binding proteins, including Sam68, HNRNPG, and MBNL (305). Another such disease is ALS with GGGGCC-repeat expansion in the *C9ORF72* gene (90, 306, 307). Although several underlying mechanisms have been proposed, GGGGCC repeats form nuclear foci and sequester various RNA-binding proteins, which are potentially related to the pathogenesis of this disease (90). At present, these diseases are not curable. Investigation of lncRNA-containing nuclear bodies will help to understand how these disease-associated RNA repeats form nuclear foci and contribute to the diseases.

As described above, recent studies indicated the presence of lncRNA-containing nuclear bodies and the importance of lncRNAs

in the integrity of nuclear bodies. Thus, the paraspeckle would be a useful model system in which to investigate the architectural roles of lncRNAs. For example, one of the most important questions concerning the mechanism underlying the formation of lncRNA-containing nuclear bodies is which lncRNA elements are required for protein interactions and how they form high-order assemblies. To understand this, detail analyses of the binding sites of RNA-binding proteins by HITS-CLIP (high-throughput sequencing of RNA isolated by crosslinking immunoprecipitation) and related methods would be powerful tools. In the near future, it will be precisely revealed how lncRNAs and proteins form nuclear bodies by identifying the architectural RNA elements of lncRNAs and the functional domains of the protein components.

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