[Frontiers in Bioscience, Elite, 7, 1-47, January 1, 2015]

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

Tomohiro Yamazaki[1], Tetsuro Hirose[1]

[1]*Institute for Genetic Medicine, Hokkaido University, Sapporo 060-0815, Japan*

TABLE OF CONTENTS

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

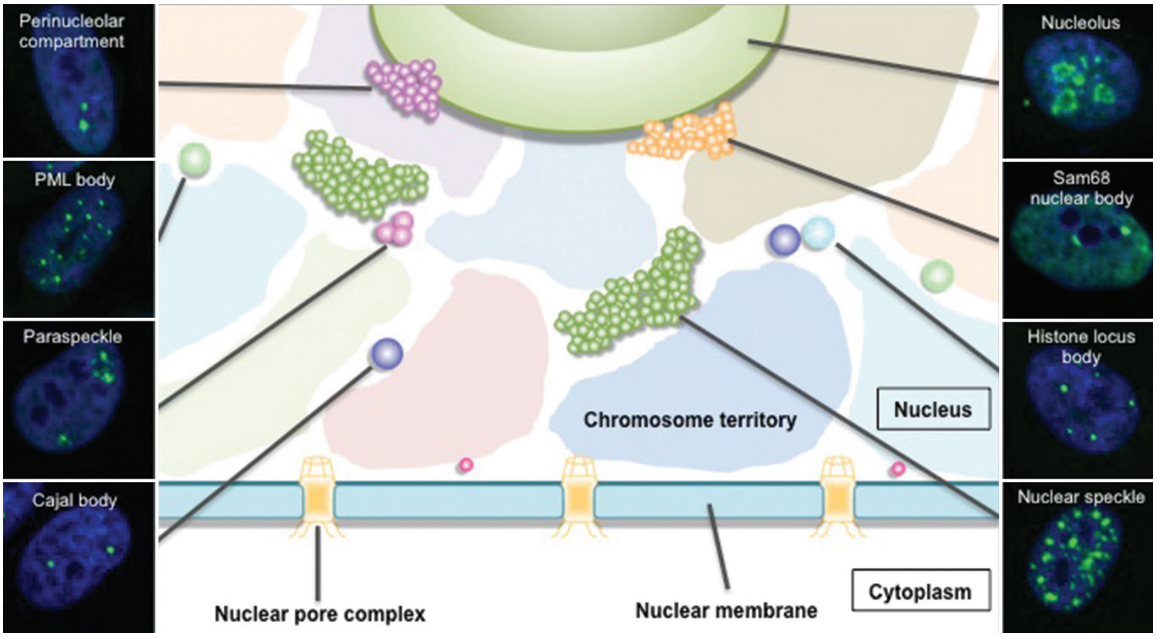

Figure 1. Nuclear bodies in vertebrate cells. A schematic of nuclear structures, including representative nuclear bodies, is shown (center). Images of marker proteins (green signals) corresponding to nuclear bodies in the middle panel are shown in the left and right panels. The nuclear body markers are 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

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.

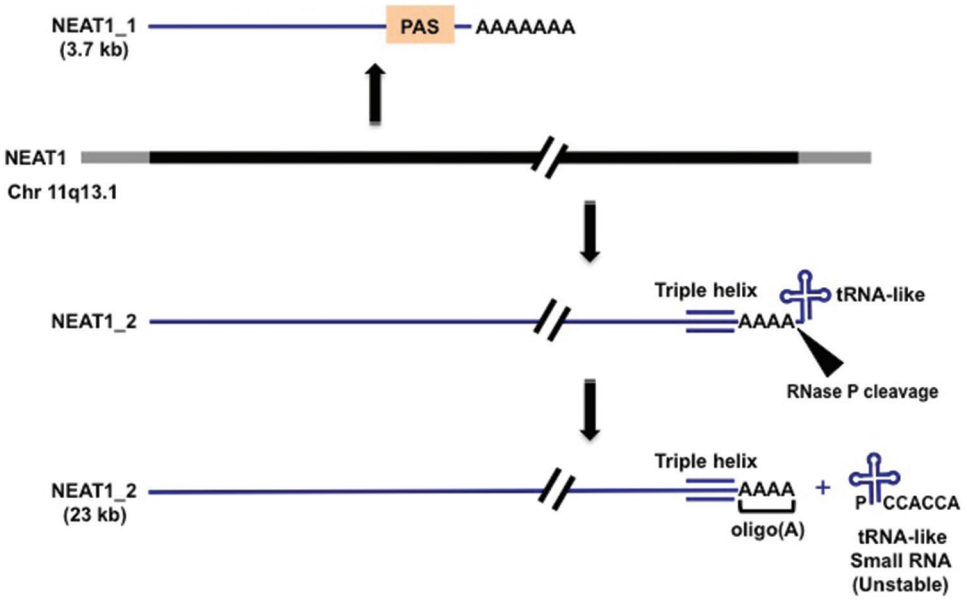

Figure 2. Structures of NEAT1_1 and NEAT1_2 long non-coding RNAs. The nuclear paraspeckle assembly transcript 1 (NEAT1) gene is located in chromosome 11q13.1. in humans. Two isoforms of NEAT1, namely, NEAT1_1 (3.7. kilobases) and NEAT1_2 (23 kilobases), are transcribed from the same locus. NEAT1_1 utilizes 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,

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 relocalize 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.

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...

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...

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)[1]	WAGR, AWT1, GUD, NPHS4, WIT-2, WT33	n/d	n/d	n/d	240

[1]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

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 RRMs 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

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

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 RRMs, 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

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-medicated 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

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

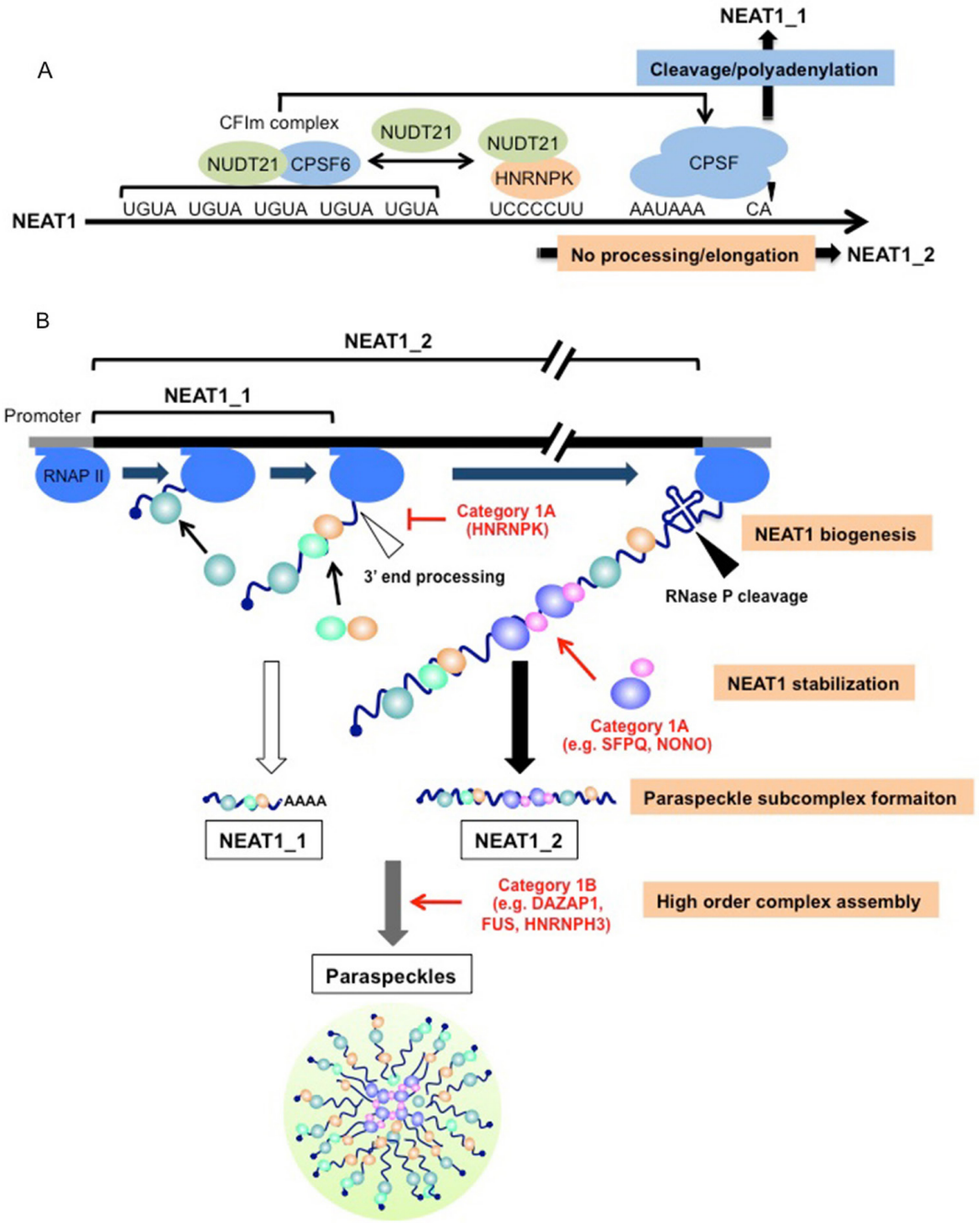

Figure 3. Model for the biogenesis of paraspeckles. A. Model for the synthesis of nuclear paraspeckle assembly transcript 1 (NEAT1) long non-coding RNA isoforms through modulation of the polyadenylation of the NEAT1_1 isoform. The Cleavage factor Im (CFIm) complex (NUDT21-CPSF6) binds to the cluster of UGUA sequences upstream of the polyadenylation site (AAUAAA) to recruit the CPSF complex for polyadenylation to this site. HNRNAPK 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_1 by competing with the CFIm complex as shown in Figure 3A. SFPQ and NONO are required for the stabilization of NEAT1_2. Category 1B proteins play a role in the subsequent assembly step to build high-order structures.

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 a 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, RBMX/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

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

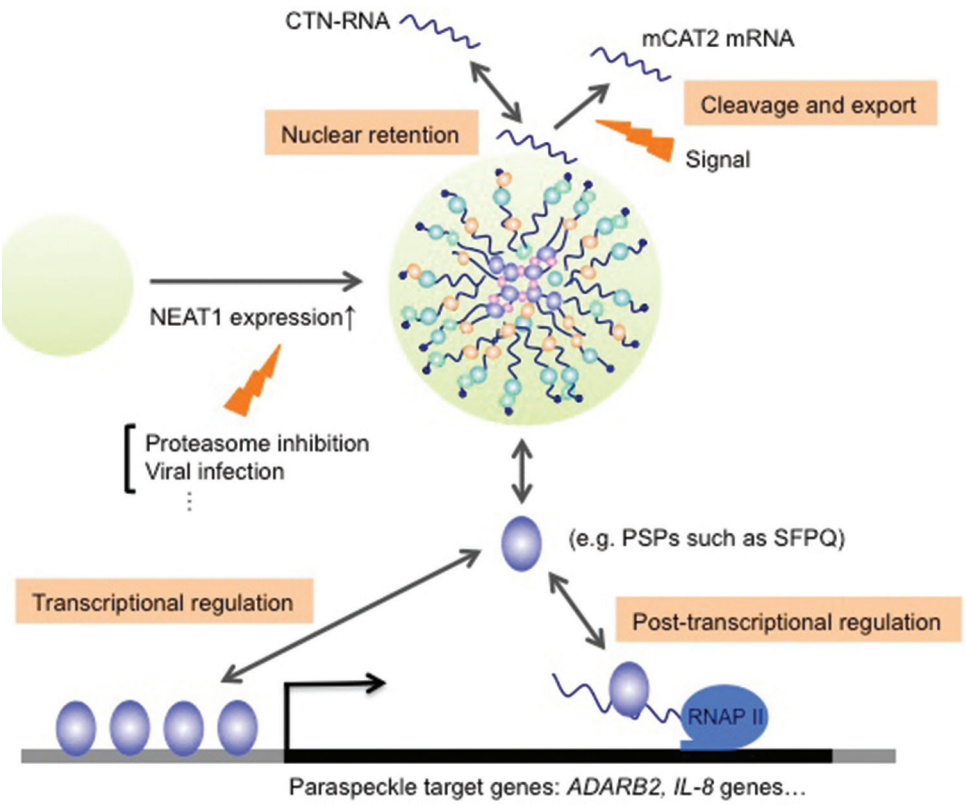

Figure 4. Models for paraspeckle functions.The paraspeckle retains mCTN-RNA in the nucleus. mCTN-RNA is released by endonucleolytic cleavage upon certain stress signals (top). Nuclear paraspeckle assembly transcript 1 (NEAT1) expression is induced by several conditions, including proteasome inhibition 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

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

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_{28} 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_{28} 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_{28} RNA, several IGS RNAs, including IGS_{16}, IGS_{22}, and IGS_{20}, 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_{16}- and IGS_{22}-dependent manner. In addition, MDM2 is sequestered in the nucleolus by IGS_{20} 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 cytokeratin cytoskeleton requires two RNAs, namely, short interspersed repeat transcripts (Xlsirts 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

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.

6. ACKNOWLEDGEMENTS

This research was supported by the Funding Program for Next Generation World-Leading Researchers (NEXT Program) of the Japan Society for the Promotion of Science (JSPS), by grants from the New Energy and Industrial Technology Development Organization (NEDO), Ministry of Education, Culture, Sports, Science, and Technology of Japan (MEXT), the Mitsubishi Foundation, the Sumitomo Foundation, the Naito Foundation, and the Mochida Memorial Foundation for Medical and Pharmaceutical Research (to T.H.).

7. REFERENCES

1. P. Bertone, V. Stolc, T. E. Royce, J. S. Rozowsky, A. E. Urban, X. Zhu, J. L. Rinn, W. Tongprasit, M. Samanta, S. Weissman, M. Gerstein and M. Snyder: Global identification of human transcribed sequences with genome tiling arrays. Science, 306(5705), 2242-6 (2004) DOI: 10.1126/science.1103388

2. P. Carninci, T. Kasukawa, S. Katayama, J. Gough, M. C. Frith, N. Maeda, R. Oyama, T. Ravasi, B. Lenhard, C. Wells, R. Kodzius, K. Shimokawa, V. B. Bajic, S. E. Brenner, S. Batalov, A. R. Forrest, M. Zavolan, M. J. Davis, L. G. Wilming, V. Aidinis, J. E. Allen, A. Ambesi-Impiombato, R. Apweiler, R. N. Aturaliya, T. L. Bailey, M. Bansal, L. Baxter, K. W. Beisel, T. Bersano, H. Bono,

A. M. Chalk, K. P. Chiu, V. Choudhary, A. Christoffels, D. R. Clutterbuck, M. L. Crowe, E. Dalla, B. P. Dalrymple, B. de Bono, G. Della Gatta, D. di Bernardo, T. Down, P. Engstrom, M. Fagiolini, G. Faulkner, C. F. Fletcher, T. Fukushima, M. Furuno, S. Futaki, M. Gariboldi, P. Georgii-Hemming, T. R. Gingeras, T. Gojobori, R. E. Green, S. Gustincich, M. Harbers, Y. Hayashi, T. K. Hensch, N. Hirokawa, D. Hill, L. Huminiecki, M. Iacono, K. Ikeo, A. Iwama, T. Ishikawa, M. Jakt, A. Kanapin, M. Katoh, Y. Kawasawa, J. Kelso, H. Kitamura, H. Kitano, G. Kollias, S. P. Krishnan, A. Kruger, S. K. Kummerfeld, I. V. Kurochkin, L. F. Lareau, D. Lazarevic, L. Lipovich, J. Liu, S. Liuni, S. McWilliam, M. Madan Babu, M. Madera, L. Marchionni, H. Matsuda, S. Matsuzawa, H. Miki, F. Mignone, S. Miyake, K. Morris, S. Mottagui-Tabar, N. Mulder, N. Nakano, H. Nakauchi, P. Ng, R. Nilsson, S. Nishiguchi, S. Nishikawa, F. Nori, O. Ohara, Y. Okazaki, V. Orlando, K. C. Pang, W. J. Pavan, G. Pavesi, G. Pesole, N. Petrovsky, S. Piazza, J. Reed, J. F. Reid, B. Z. Ring, M. Ringwald, B. Rost, Y. Ruan, S. L. Salzberg, A. Sandelin, C. Schneider, C. Schönbach, K. Sekiguchi, C. A. Semple, S. Seno, L. Sessa, Y. Sheng, Y. Shibata, H. Shimada, K. Shimada, D. Silva, B. Sinclair, S. Sperling, E. Stupka, K. Sugiura, R. Sultana, Y. Takenaka, K. Taki, K. Tammoja, S. L. Tan, S. Tang, M. S. Taylor, J. Tegner, S. A. Teichmann, H. R. Ueda, E. van Nimwegen, R. Verardo, C. L. Wei, K. Yagi, H. Yamanishi, E. Zabarovsky, S. Zhu, A. Zimmer, W. Hide, C. Bult, S. M. Grimmond, R. D. Teasdale, E. T. Liu, V. Brusic, J. Quackenbush, C. Wahlestedt, J. S. Mattick, D. A. Hume, C. Kai, D. Sasaki, Y. Tomaru, S. Fukuda, M. Kanamori-Katayama, M. Suzuki, J. Aoki, T. Arakawa, J. Iida, K. Imamura, M. Itoh, T. Kato, H. Kawaji, N. Kawagashira, T. Kawashima, M. Kojima, S. Kondo, H. Konno, K. Nakano, N. Ninomiya, T. Nishio, M. Okada, C. Plessy, K. Shibata, T. Shiraki, S. Suzuki, M. Tagami, K. Waki, A. Watahiki, Y. Okamura-Oho, H. Suzuki, J. Kawai, Y. Hayashizaki, F. Consortium and R. G. E. R. G. a. G. S. G. G. N. P. C. Group): The transcriptional landscape of the mammalian genome. Science, 309(5740), 1559-63 (2005)
DOI: 10.1126/science.1112014

3. Z. Cheng, M. Ventura, X. She, P. Khaitovich, T. Graves, K. Osoegawa, D. Church, P. DeJong, R. K. Wilson, S. Pääbo, M. Rocchi and E. E. Eichler: A genome-wide comparison of recent chimpanzee and human segmental duplications. Nature, 437(7055), 88-93 (2005)
DOI: 10.1038/nature04000

4. S. Katayama, Y. Tomaru, T. Kasukawa, K. Waki, M. Nakanishi, M. Nakamura, H. Nishida, C. C. Yap, M. Suzuki, J. Kawai, H. Suzuki, P. Carninci, Y. Hayashizaki, C. Wells, M. Frith, T. Ravasi, K. C. Pang, J. Hallinan, J. Mattick, D. A. Hume, L. Lipovich, S. Batalov, P. G. Engström, Y. Mizuno, M. A. Faghihi, A. Sandelin, A. M. Chalk, S. Mottagui-Tabar, Z. Liang, B. Lenhard, C. Wahlestedt, R. G. E. R. Group, G. S. G. G. N. P. C. Group) and F. Consortium: Antisense transcription in the mammalian transcriptome. Science, 309(5740), 1564-6 (2005)
DOI: 10.1126/science.1112009

5. E. Birney, J. A. Stamatoyannopoulos, A. Dutta, R. Guigó, T. R. Gingeras, E. H. Margulies, Z. Weng, M. Snyder, E. T. Dermitzakis, R. E. Thurman, M. S. Kuehn, C. M. Taylor, S. Neph, C. M. Koch, S. Asthana, A. Malhotra, I. Adzhubei, J. A. Greenbaum, R. M. Andrews, P. Flicek, P. J. Boyle, H. Cao, N. P. Carter, G. K. Clelland, S. Davis, N. Day, P. Dhami, S. C. Dillon, M. O. Dorschner, H. Fiegler, P. G. Giresi, J. Goldy, M. Hawrylycz, A. Haydock, R. Humbert, K. D. James, B. E. Johnson, E. M. Johnson, T. T. Frum, E. R. Rosenzweig, N. Karnani, K. Lee, G. C. Lefebvre, P. A. Navas, F. Neri, S. C. Parker, P. J. Sabo, R. Sandstrom, A. Shafer, D. Vetrie, M. Weaver, S. Wilcox,

M. Yu, F. S. Collins, J. Dekker, J. D. Lieb, T. D. Tullius, G. E. Crawford, S. Sunyaev, W. S. Noble, I. Dunham, F. Denoeud, A. Reymond, P. Kapranov, J. Rozowsky, D. Zheng, R. Castelo, A. Frankish, J. Harrow, S. Ghosh, A. Sandelin, I. L. Hofacker, R. Baertsch, D. Keefe, S. Dike, J. Cheng, H. A. Hirsch, E. A. Sekinger, J. Lagarde, J. F. Abril, A. Shahab, C. Flamm, C. Fried, J. Hackermüller, J. Hertel, M. Lindemeyer, K. Missal, A. Tanzer, S. Washietl, J. Korbel, O. Emanuelsson, J. S. Pedersen, N. Holroyd, R. Taylor, D. Swarbreck, N. Matthews, M. C. Dickson, D. J. Thomas, M. T. Weirauch, J. Gilbert, J. Drenkow, I. Bell, X. Zhao, K. G. Srinivasan, W. K. Sung, H. S. Ooi, K. P. Chiu, S. Foissac, T. Alioto, M. Brent, L. Pachter, M. L. Tress, A. Valencia, S. W. Choo, C. Y. Choo, C. Ucla, C. Manzano, C. Wyss, E. Cheung, T. G. Clark, J. B. Brown, M. Ganesh, S. Patel, H. Tammana, J. Chrast, C. N. Henrichsen, C. Kai, J. Kawai, U. Nagalakshmi, J. Wu, Z. Lian, J. Lian, P. Newburger, X. Zhang, P. Bickel, J. S. Mattick, P. Carninci, Y. Hayashizaki, S. Weissman, T. Hubbard, R. M. Myers, J. Rogers, P. F. Stadler, T. M. Lowe, C. L. Wei, Y. Ruan, K. Struhl, M. Gerstein, S. E. Antonarakis, Y. Fu, E. D. Green, U. Karaöz, A. Siepel, J. Taylor, L. A. Liefer, K. A. Wetterstrand, P. J. Good, E. A. Feingold, M. S. Guyer, G. M. Cooper, G. Asimenos, C. N. Dewey, M. Hou, S. Nikolaev, J. I. Montoya-Burgos, A. Löytynoja, S. Whelan, F. Pardi, T. Massingham, H. Huang, N. R. Zhang, I. Holmes, J. C. Mullikin, A. Ureta-Vidal, B. Paten, M. Seringhaus, D. Church, K. Rosenbloom, W. J. Kent, E. A. Stone, S. Batzoglou, N. Goldman, R. C. Hardison, D. Haussler, W. Miller, A. Sidow, N. D. Trinklein, Z. D. Zhang, L. Barrera, R. Stuart, D. C. King, A. Ameur, S. Enroth, M. C. Bieda, J. Kim, A. A. Bhinge, N. Jiang, J. Liu, F. Yao, V. B. Vega, C. W. Lee, P. Ng, A. Yang, Z. Moqtaderi, Z. Zhu, X. Xu, S. Squazzo, M. J. Oberley, D. Inman, M. A. Singer, T. A. Richmond, K. J. Munn, A. Rada-Iglesias, O. Wallerman, J. Komorowski, J. C. Fowler, P. Couttet, A. W. Bruce, O. M. Dovey, P. D. Ellis, C. F. Langford, D. A. Nix, G. Euskirchen, S. Hartman, A. E. Urban, P. Kraus, S. Van Calcar, N. Heintzman, T. H. Kim, K. Wang, C. Qu, G. Hon, R. Luna, C. K. Glass, M. G. Rosenfeld, S. F. Aldred, S. J. Cooper, A. Halees, J. M. Lin, H. P. Shulha, M. Xu, J. N. Haidar, Y. Yu, V. R. Iyer, R. D. Green, C. Wadelius, P. J. Farnham, B. Ren, R. A. Harte, A. S. Hinrichs, H. Trumbower, H. Clawson, J. Hillman-Jackson, A. S. Zweig, K. Smith, A. Thakkapallayil, G. Barber, R. M. Kuhn, D. Karolchik, L. Armengol, C. P. Bird, P. I. de Bakker, A. D. Kern, N. Lopez-Bigas, J. D. Martin, B. E. Stranger, A. Woodroffe, E. Davydov, A. Dimas, E. Eyras, I. B. Hallgrímsdóttir, J. Huppert, M. C. Zody, G. R. Abecasis, X. Estivill, G. G. Bouffard, X. Guan, N. F. Hansen, J. R. Idol, V. V. Maduro, B. Maskeri, J. C. McDowell, M. Park, P. J. Thomas, A. C. Young, R. W. Blakesley, D. M. Muzny, E. Sodergren, D. A. Wheeler, K. C. Worley, H. Jiang, G. M. Weinstock, R. A. Gibbs, T. Graves, R. Fulton, E. R. Mardis, R. K. Wilson, M. Clamp, J. Cuff, S. Gnerre, D. B. Jaffe, J. L. Chang, K. Lindblad-Toh, E. S. Lander, M. Koriabine, M. Nefedov, K. Osoegawa, Y. Yoshinaga, B. Zhu, P. J. de Jong, E. P. Consortium, N. C. S. Program, B. C. o. M. H. G. S. Center, W. U. G. S. Center, B. Institute and C. s. H. O. R. Institute: Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature, 447(7146), 799-816 (2007) DOI: 10.1038/nature05874

6. P. Kapranov, J. Cheng, S. Dike, D. A. Nix, R. Duttagupta, A. T. Willingham, P. F. Stadler, J. Hertel, J. Hackermüller, I. L. Hofacker, I. Bell, E. Cheung, J. Drenkow, E. Dumais, S. Patel, G. Helt, M. Ganesh, S. Ghosh, A. Piccolboni, V. Sementchenko, H. Tammana and T. R. Gingeras: RNA maps reveal new RNA classes and a possible function for pervasive transcription. Science, 316(5830), 1484-8 (2007)

DOI: 10.1126/science.1138341

7. T. Hirose, Y. Mishima and Y. Tomari: Elements and machinery of non-coding RNAs: toward their taxonomy. EMBO Rep, 15(5), 489-507 (2014) DOI: 10.1002/embr.201338390
8. T. R. Cech and J. A. Steitz: The noncoding RNA revolution-trashing old rules to forge new ones. Cell, 157(1), 77-94 (2014) DOI: 10.1016/j.cell.2014.03.008
9. I. Ulitsky and D. P. BarTel: lincRNAs: genomics, evolution, and mechanisms. Cell, 154(1), 26-46 (2013) DOI: 10.1016/j.cell.2013.06.020
10. M. N. Cabili, C. Trapnell, L. Goff, M. Koziol, B. Tazon-Vega, A. Regev and J. L. Rinn: Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev, 25(18), 1915-27 (2011) DOI: 10.1101/gad.17446611
11. T. Derrien, R. Johnson, G. Bussotti, A. Tanzer, S. Djebali, H. Tilgner, G. Guernec, D. Martin, A. Merkel, D. G. Knowles, J. Lagarde, L. Veeravalli, X. Ruan, Y. Ruan, T. Lassmann, P. Carninci, J. B. Brown, L. Lipovich, J. M. Gonzalez, M. Thomas, C. A. Davis, R. Shiekhattar, T. R. Gingeras, T. J. Hubbard, C. Notredame, J. Harrow and R. Guigó: The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res, 22(9), 1775-89 (2012) DOI: 10.1101/gr.132159.111
12. K. V. Prasanth and D. L. Spector: Eukaryotic regulatory RNAs: an answer to the 'genome complexity' conundrum. Genes Dev, 21(1), 11-42 (2007) DOI: 10.1101/gad.1484207
13. O. Yazgan and J. E. Krebs: Noncoding but nonexpendable: transcriptional regulation by large noncoding RNA in eukaryotes. Biochem Cell Biol, 85(4), 484-96 (2007) DOI: 10.1139/O07-061
14. R. Kurokawa, M. G. Rosenfeld and C. K. Glass: Transcriptional regulation through noncoding RNAs and epigenetic modifications. RNA Biol, 6(3), 233-6 (2009) DOI: 10.4161/rna.6.3.8329
15. J. E. Wilusz, H. Sunwoo and D. L. Spector: Long noncoding RNAs: functional surprises from the RNA world. Genes Dev, 23(13), 1494-504 (2009) DOI: 10.1101/gad.1800909
16. L. L. Chen and G. G. Carmichael: Decoding the function of nuclear long non-coding RNAs. Curr Opin Cell Biol, 22(3), 357-64 (2010) DOI: 10.1016/j.ceb.2010.03.003
17. X. Wang, X. Song, C. K. Glass and M. G. Rosenfeld: The long arm of long noncoding RNAs: roles as sensors regulating gene transcriptional programs. Cold Spring Harb Perspect Biol, 3(1), a003756 (2011) DOI: 10.1101/cshperspect.a003756
18. M. B. Clark and J. S. Mattick: Long noncoding RNAs in cell biology. Semin Cell Dev Biol, 22(4), 366-76 (2011) DOI: 10.1016/j.semcdb.2011.01.001
19. J. T. Lee: The X as model for RNA's niche in epigenomic regulation. Cold Spring Harb Perspect Biol, 2(9), a003749 (2010) DOI: 10.1101/cshperspect.a003749
20. J. T. Lee: Epigenetic regulation by long noncoding RNAs. Science, 338(6113), 1435-9 (2012) DOI: 10.1126/science.1231776
21. J. L. Rinn, M. Kertesz, J. K. Wang, S. L. Squazzo, X. Xu, S. A. Brugmann, L. H. Goodnough, J. A. Helms, P. J. Farnham, E. Segal and H. Y. Chang: Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell, 129(7), 1311-23 (2007) DOI: 10.1016/j.cell.2007.05.022
22. M. Sone, T. Hayashi, H. Tarui, K. Agata, M. Takeichi and S. Nakagawa: The mRNA-like noncoding RNA Gomafu constitutes a novel nuclear domain in a subset of neurons. J Cell Sci, 120(Pt 15), 2498-506 (2007) DOI: 10.1242/jcs.009357

23. J. Y. Ip and S. Nakagawa: Long non-coding RNAs in nuclear bodies. Dev Growth Differ, 54(1), 44-54 (2012) DOI: 10.1111/j.1440-169X.2011.01303.x

24. H. Tsuiji, R. Yoshimoto, Y. Hasegawa, M. Furuno, M. Yoshida and S. Nakagawa: Competition between a noncoding exon and introns: Gomafu contains tandem UACUAAC repeats and associates with splicing factor-1. Genes Cells, 16(5), 479-90 (2011) DOI: 10.1111/j.1365-2443.2011.01502.x

25. G. Barry, J. A. Briggs, D. P. Vanichkina, E. M. Poth, N. J. Beveridge, V. S. Ratnu, S. P. Nayler, K. Nones, J. Hu, T. W. Bredy, S. Nakagawa, F. Rigo, R. J. Taft, M. J. Cairns, S. Blackshaw, E. J. Wolvetang and J. S. Mattick: The long non-coding RNA Gomafu is acutely regulated in response to neuronal activation and involved in schizophrenia-associated alternative splicing. Mol Psychiatry, 19(4), 486-94 (2014) DOI: 10.1038/mp.2013.45

26. J. N. Hutchinson, A. W. Ensminger, C. M. Clemson, C. R. Lynch, J. B. Lawrence and A. Chess: A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains. BMC Genomics, 8, 39 (2007) DOI: 10.1186/1471-2164-8-39

27. V. Tripathi, J. D. Ellis, Z. Shen, D. Y. Song, Q. Pan, A. T. Watt, S. M. Freier, C. F. Bennett, A. Sharma, P. A. Bubulya, B. J. Blencowe, S. G. Prasanth and K. V. Prasanth: The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell, 39(6), 925-38 (2010) DOI: 10.1016/j.molcel.2010.08.011

28. B. Zhang, G. Arun, Y. S. Mao, Z. Lazar, G. Hung, G. Bhattacharjee, X. Xiao, C. J. Booth, J. Wu, C. Zhang and D. L. Spector: The lncRNA Malat1 is dispensable for mouse development but its transcription plays a cis-regulatory role in the adult. Cell Rep, 2(1), 111-23 (2012) DOI: 10.1016/j.celrep.2012.06.003

29. S. Nakagawa, J. Y. Ip, G. Shioi, V. Tripathi, X. Zong, T. Hirose and K. V. Prasanth: Malat1 is not an essential component of nuclear speckles in mice. RNA, 18(8), 1487-99 (2012) DOI: 10.1261/rna.033217.112

30. T. Gutschner, M. Hämmerle, M. Eissmann, J. Hsu, Y. Kim, G. Hung, A. Revenko, G. Arun, M. Stentrup, M. Gross, M. Zörnig, A. R. MacLeod, D. L. Spector and S. Diederichs: The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res, 73(3), 1180-9 (2013) DOI: 10.1158/0008-5472.CAN-12-2850

31. M. Dundr and T. Misteli: Biogenesis of nuclear bodies. Cold Spring Harb Perspect Biol, 2(12), a000711 (2010) DOI: 10.1101/cshperspect.a000711

32. Y. S. Mao, B. Zhang and D. L. Spector: Biogenesis and function of nuclear bodies. Trends Genet, 27(8), 295-306 (2011) DOI: 10.1016/j.tig.2011.05.006

33. S. Boulon, B. J. Westman, S. Hutten, F. M. Boisvert and A. I. Lamond: The nucleolus under stress. Mol Cell, 40(2), 216-27 (2010) DOI: 10.1016/j.molcel.2010.09.024

34. T. Pederson: The nucleolus. Cold Spring Harb Perspect Biol, 3(3) (2011) DOI: 10.1101/cshperspect.a000638

35. C. Pollock and S. Huang: The perinucleolar compartment. Cold Spring Harb Perspect Biol, 2(2), a000679 (2010) DOI: 10.1101/cshperspect.a000679

36. A. I. Lamond and D. L. Spector: Nuclear speckles: a model for nuclear organelles. Nat Rev Mol Cell Biol, 4(8), 605-12 (2003) DOI: 10.1038/nrm1172

37. D. L. Spector and A. I. Lamond: Nuclear speckles. Cold Spring Harb Perspect Biol, 3(2) (2011) DOI: 10.1101/cshperspect.a000646

38. W. F. Marzluff, E. J. Wagner and R. J. Duronio: Metabolism and regulation of

canonical histone mRNAs: life without a poly(A) tail. Nat Rev Genet, 9(11), 843-54 (2008)
DOI: 10.1038/nrg2438

39. Z. F. Nizami, S. Deryusheva and J. G. Gall: Cajal bodies and histone locus bodies in Drosophila and Xenopus. Cold Spring Harb Symp Quant Biol, 75, 313-20 (2010)
DOI: 10.1101/sqb.2010.75.005

40. V. Lallemand-Breitenbach and H. de Thé: PML nuclear bodies. Cold Spring Harb Perspect Biol, 2(5), a000661 (2010)
DOI: 10.1101/cshperspect.a000661

41. M. Cioce and A. I. Lamond: Cajal bodies: a long history of discovery. Annu Rev Cell Dev Biol, 21, 105-31 (2005)
DOI: 10.1146/annurev.cellbio.20.010403.103738

42. S. Paushkin, A. K. Gubitz, S. Massenet and G. Dreyfuss: The SMN complex, an assemblyosome of ribonucleoproteins. Curr Opin Cell Biol, 14(3), 305-12 (2002)
DOI: 10.1016/S0955-0674(02)00332-0

43. A. K. Gubitz, W. Feng and G. Dreyfuss: The SMN complex. Exp Cell Res, 296(1), 51-6 (2004)
DOI: 10.1016/j.yexcr.2004.03.022

44. D. J. Battle, M. Kasim, J. Yong, F. Lotti, C. K. Lau, J. Mouaikel, Z. Zhang, K. Han, L. Wan and G. Dreyfuss: The SMN complex: an assembly machine for RNPs. Cold Spring Harb Symp Quant Biol, 71, 313-20 (2006)
DOI: 10.1101/sqb.2006.71.001

45. M. Carmo-Fonseca, M. T. Berciano and M. Lafarga: Orphan nuclear bodies. Cold Spring Harb Perspect Biol, 2(9), a000703 (2010)
DOI: 10.1101/cshperspect.a000703

46. G. Biamonti and C. Vourc'h: Nuclear stress bodies. Cold Spring Harb Perspect Biol, 2(6), a000695 (2010)
DOI: 10.1101/cshperspect.a000695

47. A. M. Dupuy-Coin, S. R. Kalifat and M. Bouteille: Nuclear bodies as proteinaceous structures containing ribonucleoproteins. J Ultrastruct Res, 38(1), 174-87 (1972)
DOI: 10.1016/S0022-5320(72)90091-3

48. T. Kawaguchi and T. Hirose: Architectural roles of long noncoding RNAs in the intranuclear formation of functional paraspeckles. Front Biosci (Landmark Ed), 17, 1729-46 (2012)
DOI: 10.2741/4015

49. A. H. Fox, Y. W. Lam, A. K. Leung, C. E. Lyon, J. Andersen, M. Mann and A. I. Lamond: Paraspeckles: a novel nuclear domain. Curr Biol, 12(1), 13-25 (2002)
DOI: 10.1016/S0960-9822(01)00632-7

50. C. S. Bond and A. H. Fox: Paraspeckles: nuclear bodies built on long noncoding RNA. J Cell Biol, 186(5), 637-44 (2009)
DOI: 10.1083/jcb.200906113

51. A. H. Fox and A. I. Lamond: Paraspeckles. Cold Spring Harb Perspect Biol, 2(7), a000687 (2010)
DOI: 10.1101/cshperspect.a000687

52. N. Visa, F. Puvion-Dutilleul, J. P. Bachellerie and E. Puvion: Intranuclear distribution of U1 and U2 snRNAs visualized by high resolution in situ hybridization: revelation of a novel compartment containing U1 but not U2 snRNA in HeLa cells. Eur J Cell Biol, 60(2), 308-21 (1993)

53. S. Souquere, G. Beauclair, F. Harper, A. Fox and G. Pierron: Highly ordered spatial organization of the structural long noncoding NEAT1 RNAs within paraspeckle nuclear bodies. Mol Biol Cell, 21(22), 4020-7 (2010)
DOI: 10.1091/mbc.E10-08-0690

54. A. H. Fox, C. S. Bond and A. I. Lamond: P54nrb forms a heterodimer with PSP1 that localizes to paraspeckles in an RNA-dependent manner. Mol Biol Cell, 16(11), 5304-15 (2005)
DOI: 10.1091/mbc.E05-06-0587

55. Y. T. Sasaki, T. Ideue, M. Sano, T. Mituyama and T. Hirose: MENepsilon/beta noncoding RNAs are essential for structural integrity of nuclear paraspeckles. Proc Natl Acad Sci U S A, 106(8), 2525-30 (2009)
DOI: 10.1073/pnas.0807899106

56. L. L. Chen and G. G. Carmichael: Altered nuclear retention of mRNAs containing inverted repeats in human embryonic stem cells: functional role of a nuclear noncoding RNA. Mol Cell, 35(4), 467-78 (2009)
DOI: 10.1016/j.molcel.2009.06.027

57. C. M. Clemson, J. N. Hutchinson, S. A. Sara, A. W. Ensminger, A. H. Fox, A. Chess and J. B. Lawrence: An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. Mol Cell, 33(6), 717-26 (2009)
DOI: 10.1016/j.molcel.2009.01.026

58. H. Sunwoo, M. E. Dinger, J. E. Wilusz, P. P. Amaral, J. S. Mattick and D. L. Spector: MEN epsilon/beta nuclear-retained non-coding RNAs are up-regulated upon muscle differentiation and are essential components of paraspeckles. Genome Res, 19(3), 347-59 (2009)
DOI: 10.1101/gr.087775.108

59. S. C. Guru, S. K. Agarwal, P. Manickam, S. E. Olufemi, J. S. Crabtree, J. M. Weisemann, M. B. Kester, Y. S. Kim, Y. Wang, M. R. Emmert-Buck, L. A. Liotta, A. M. Spiegel, M. S. Boguski, B. A. Roe, F. S. Collins, S. J. Marx, L. Burns and S. C. Chandrasekharappa: A transcript map for the 2.8.-Mb region containing the multiple endocrine neoplasia type 1 locus. Genome Res, 7(7), 725-35 (1997)

60. J. A. Peyman: Repression of major histocompatibility complex genes by a human trophoblast ribonucleic acid. Biol Reprod, 60(1), 23-31 (1999)
DOI: 10.1095/biolreprod60.1.23

61. A. Geirsson, R. J. Lynch, I. Paliwal, A. L. Bothwell and G. L. Hammond: Human trophoblast noncoding RNA suppresses CIITA promoter III activity in murine B-lymphocytes. Biochem Biophys Res Commun, 301(3), 718-24 (2003)
DOI: 10.1016/S0006-291X(03)00028-7

62. S. Saha, P. Sugumar, P. Bhandari and P. N. Rangarajan: Identification of Japanese encephalitis virus-inducible genes in mouse brain and characterization of GARG39/IFIT2 as a microtubule-associated protein. J Gen Virol, 87(Pt 11), 3285-9 (2006)
DOI: 10.1099/vir.0.82107-0

63. P. F. Stadler: Evolution of the Long Non-coding RNAs MALAT1 and MENβ/ε. In: Advances in Bioinformatics and Computational Biology, 1-12. Eds: BSB 2010, LNBI6268 (2010)

64. Y. T. Sasaki and T. Hirose: How to build a paraspeckle. Genome Biol, 10(7), 227 (2009)
DOI: 10.1186/gb-2009-10-7-227

65. T. Naganuma, S. Nakagawa, A. Tanigawa, Y. F. Sasaki, N. Goshima and T. Hirose: Alternative 3'-end processing of long noncoding RNA initiates construction of nuclear paraspeckles. EMBO J, 31(20), 4020-34 (2012)
DOI: 10.1038/emboj.2012.251

66. T. Naganuma and T. Hirose: Paraspeckle formation during the biogenesis of long non-coding RNAs. RNA Biol, 10(3), 456-61 (2013)
DOI: 10.4161/rna.23547

67. K. T. Tycowski, M. D. Shu, S. Borah, M. Shi and J. A. Steitz: Conservation of a triple-helix-forming RNA stability element in noncoding and genomic RNAs of diverse viruses. Cell Rep, 2(1), 26-32 (2012)
DOI: 10.1016/j.celrep.2012.05.020

68. J. E. Wilusz, C. K. JnBaptiste, L. Y. Lu, C. D. Kuhn, L. Joshua-Tor and P. A. Sharp: A triple helix stabilizes the 3' ends of long noncoding RNAs that lack poly(A) tails. Genes Dev, 26(21), 2392-407 (2012)
DOI: 10.1101/gad.204438.112

69. J. A. Brown, M. L. Valenstein, T. A. Yario, K. T. Tycowski and J. A. Steitz: Formation of triple-helical structures by the 3'-end sequences of MALAT1 and MENβ noncoding RNAs. Proc Natl Acad Sci U S A, 109(47), 19202-7 (2012)
DOI: 10.1073/pnas.1217338109

70. J. A. Brown, D. Bulkley, J. Wang, M. L. Valenstein, T. A. Yario, T. A. Steitz and J. A. Steitz: Structural insights into the stabilization of MALAT1 noncoding RNA by a bipartite triple helix. Nat Struct Mol Biol, 21(7), 633-40 (2014)
DOI: 10.1038/nsmb.2844

71. J. E. Wilusz, J. M. Whipple, E. M. Phizicky and P. A. Sharp: tRNAs marked with CCACCA are targeted for degradation. Science, 334(6057), 817-21 (2011)
DOI: 10.1126/science.1213671

72. M. B. Clark, R. L. Johnston, M. Inostroza-Ponta, A. H. Fox, E. Fortini, P. Moscato, M. E. Dinger and J. S. Mattick: Genome-wide analysis of long noncoding RNA stability. Genome Res, 22(5), 885-98 (2012)
DOI: 10.1101/gr.131037.111

73. Y. B. Beaulieu, C. L. Kleinman, A. M. Landry-Voyer, J. Majewski and F. Bachand: Polyadenylation-dependent control of long noncoding RNA expression by the poly(A)-binding protein nuclear 1. PLoS Genet, 8(11), e1003078 (2012)
DOI: 10.1371/journal.pgen.1003078

74. S. M. Bresson and N. K. Conrad: The human nuclear poly(a)-binding protein promotes RNA hyperadenylation and decay. PLoS Genet, 9(10), e1003893 (2013)
DOI: 10.1371/journal.pgen.1003893

75. L. Jobert, N. Pinzón, E. Van Herreweghe, B. E. Jády, A. Guialis, T. Kiss and L. Tora: Human U1 snRNA forms a new chromatin-associated snRNP with TAF15. EMBO Rep, 10(5), 494-500 (2009)
DOI: 10.1038/embor.2009.24

76. K. V. Prasanth, S. G. Prasanth, Z. Xuan, S. Hearn, S. M. Freier, C. F. Bennett, M. Q. Zhang and D. L. Spector: Regulating gene expression through RNA nuclear retention. Cell, 123(2), 249-63 (2005)
DOI: 10.1016/j.cell.2005.08.033

77. S. Nakagawa, T. Naganuma, G. Shioi and T. Hirose: Paraspeckles are subpopulation-specific nuclear bodies that are not essential in mice. J Cell Biol, 193(1), 31-9 (2011)
DOI: 10.1083/jcb.201011110

78. S. Dettwiler, C. Aringhieri, S. Cardinale, W. Keller and S. M. Barabino: Distinct sequence motifs within the 68-kDa subunit of cleavage factor Im mediate RNA binding, protein-protein interactions, and subcellular localization. J Biol Chem, 279(34), 35788-97 (2004)
DOI: 10.1074/jbc.M403927200

79. K. W. Fong, Y. Li, W. Wang, W. Ma, K. Li, R. Z. Qi, D. Liu, Z. Songyang and J. Chen: Whole-genome screening identifies proteins localized to distinct nuclear bodies. J Cell Biol, 203(1), 149-64 (2013)
DOI: 10.1083/jcb.201303145

80. N. Quiskamp, M. Poeter, C. A. Raabe, U. M. Hohenester, S. König, V. Gerke and U. Rescher: The tumor suppressor annexin A10 is a novel component of nuclear paraspeckles. Cell Mol Life Sci, 71(2), 311-29 (2014)
DOI: 10.1007/s00018-013-1375-4

81. W. J. Law, K. L. Cann and G. G. Hicks: TLS, EWS and TAF15: a model for transcriptional integration of gene expression. Brief Funct Genomic Proteomic, 5(1), 8-14 (2006)
DOI: 10.1093/bfgp/ell015

82. N. Kim, P. Kim, S. Nam, S. Shin and S. Lee: ChimerDB--a knowledgebase for fusion sequences. Nucleic Acids Res, 34(Database issue), D21-4 (2006)
DOI: 10.1093/nar/gkj019

83. P. Kim, S. Yoon, N. Kim, S. Lee, M. Ko, H. Lee, H. Kang and J. Kim: ChimerDB 2.0.--a knowledgebase for fusion genes updated. Nucleic Acids Res, 38(Database issue), D81-5 (2010)
DOI: 10.1093/nar/gkp982

84. P. Brandal, I. Panagopoulos, B. Bjerkehagen and S. Heim: t(19;22)(q13;q12) Translocation leading to the novel fusion gene EWSR1-ZNF444 in soft tissue myoepithelial carcinoma. Genes

Chromosomes Cancer, 48(12), 1051-6 (2009)
DOI: 10.1002/gcc.20706

85. L. Brandimarte, V. Pierini, D. Di Giacomo, C. Borga, F. Nozza, P. Gorello, M. Giordan, G. Cazzaniga, G. Te Kronnie, R. La Starza and C. Mecucci: New MLLT10 gene recombinations in pediatric T-acute lymphoblastic leukemia. Blood, 121(25), 5064-7 (2013)
DOI: 10.1182/blood-2013-02-487256

86. C. Thomsen, P. Grundevik, P. Elias, A. Ståhlberg and P. Aman: A conserved N-terminal motif is required for complex formation between FUS, EWSR1, TAF15 and their oncogenic fusion proteins. FASEB J, 27(12), 4965-74 (2013)
DOI: 10.1096/fj.13-234435

87. O. D. King, A. D. Gitler and J. Shorter: The tip of the iceberg: RNA-binding proteins with prion-like domains in neurodegenerative disease. Brain Res, 1462, 61-80 (2012)
DOI: 10.1016/j.brainres.2012.01.016

88. Y. Nishimoto, S. Nakagawa, T. Hirose, H. J. Okano, M. Takao, S. Shibata, S. Suyama, K. Kuwako, T. Imai, S. Murayama, N. Suzuki and H. Okano: The long non-coding RNA nuclear-enriched abundant transcript 1_2 induces paraspeckle formation in the motor neuron during the early phase of amyotrophic lateral sclerosis. Mol Brain, 6, 31 (2013)
DOI: 10.1186/1756-6606-6-31

89. A. Chesi, B. T. Staahl, A. Jovičić, J. Couthouis, M. Fasolino, A. R. Raphael, T. Yamazaki, L. Elias, M. Polak, C. Kelly, K. L. Williams, J. A. Fifita, N. J. Maragakis, G. A. Nicholson, O. D. King, R. Reed, G. R. Crabtree, I. P. Blair, J. D. Glass and A. D. Gitler: Exome sequencing to identify de novo mutations in sporadic ALS trios. Nat Neurosci, 16(7), 851-5 (2013)
DOI: 10.1038/nn.3412

90. S. C. Ling, M. Polymenidou and D. W. Cleveland: Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. Neuron, 79(3), 416-38 (2013)
DOI: 10.1016/j.neuron.2013.07.033

91. Y. R. Li, O. D. King, J. Shorter and A. D. Gitler: Stress granules as crucibles of ALS pathogenesis. J Cell Biol, 201(3), 361-72 (2013)
DOI: 10.1083/jcb.201302044

92. J. Couthouis, M. P. Hart, J. Shorter, M. DeJesus-Hernandez, R. Erion, R. Oristano, A. X. Liu, D. Ramos, N. Jethava, D. Hosangadi, J. Epstein, A. Chiang, Z. Diaz, T. Nakaya, F. Ibrahim, H. J. Kim, J. A. Solski, K. L. Williams, J. Mojsilovic-Petrovic, C. Ingre, K. Boylan, N. R. Graff-Radford, D. W. Dickson, D. Clay-Falcone, L. Elman, L. McCluskey, R. Greene, R. G. Kalb, V. M. Lee, J. Q. Trojanowski, A. Ludolph, W. Robberecht, P. M. Andersen, G. A. Nicholson, I. P. Blair, O. D. King, N. M. Bonini, V. Van Deerlin, R. Rademakers, Z. Mourelatos and A. D. Gitler: A yeast functional screen predicts new candidate ALS disease genes. Proc Natl Acad Sci U S A, 108(52), 20881-90 (2011)
DOI: 10.1073/pnas.1109434108

93. M. Salton, Y. Lerenthal, S. Y. Wang, D. J. Chen and Y. Shiloh: Involvement of Matrin 3 and SFPQ/NONO in the DNA damage response. Cell Cycle, 9(8), 1568-76 (2010)
DOI: 10.4161/cc.9.8.11298

94. K. Ha, Y. Takeda and W. S. Dynan: Sequences in PSF/SFPQ mediate radioresistance and recruitment of PSF/SFPQ-containing complexes to DNA damage sites in human cells. DNA Repair (Amst), 10(3), 252-9 (2011)
DOI: 10.1016/j.dnarep.2010.11.009

95. X. Gao, L. Kong, X. Lu, G. Zhang, L. Chi, Y. Jiang, Y. Wu, C. Yan, P. Duerksen-Hughes, X. Zhu and J. Yang: Paraspeckle protein 1 (PSPC1) is involved in the cisplatin induced DNA damage response--role in G1/S checkpoint. PLoS One, 9(5), e97174 (2014)
DOI: 10.1371/journal.pone.0097174

96. M. P. Paronetto, B. Miñana and J. Valcárcel: The Ewing sarcoma protein regulates DNA damage-induced alternative splicing. Mol Cell, 43(3), 353-68 (2011)
DOI: 10.1016/j.molcel.2011.05.035

97. A. S. Mastrocola, S. H. Kim, A. T. Trinh, L. A. Rodenkirch and R. S. Tibbetts: The RNA-binding protein fused in sarcoma (FUS) functions downstream of poly(ADP-ribose) polymerase (PARP) in response to DNA damage. J Biol Chem, 288(34), 24731-41 (2013)
DOI: 10.1074/jbc.M113.497974

98. W. Y. Wang, L. Pan, S. C. Su, E. J. Quinn, M. Sasaki, J. C. Jimenez, I. R. Mackenzie, E. J. Huang and L. H. Tsai: Interaction of FUS and HDAC1 regulates DNA damage response and repair in neurons. Nat Neurosci, 16(10), 1383-91 (2013)
DOI: 10.1038/nn.3514

99. S. Jungmichel, F. Rosenthal, M. Altmeyer, J. Lukas, M. O. Hottiger and M. L. Nielsen: Proteome-wide identification of poly(ADP-Ribosyl)ation targets in different genotoxic stress responses. Mol Cell, 52(2), 272-85 (2013)
DOI: 10.1016/j.molcel.2013.08.026

100. S. Britton, E. Dernoncourt, C. Delteil, C. Froment, O. Schiltz, B. Salles, P. Frit and P. Calsou: DNA damage triggers SAF-A and RNA biogenesis factors exclusion from chromatin coupled to R-loops removal. Nucleic Acids Res (2014)
DOI: 10.1093/nar/gku601

101. H. Qiu, S. Lee, Y. Shang, W. Y. Wang, K. F. Au, S. Kamiya, S. J. Barmada, S. Finkbeiner, H. Lui, C. E. Carlton, A. A. Tang, M. C. Oldham, H. Wang, J. Shorter, A. J. Filiano, E. D. Roberson, W. G. Tourtellotte, B. Chen, L. H. Tsai and E. J. Huang: ALS-associated mutation FUS-R521C causes DNA damage and RNA splicing defects. J Clin Invest, 124(3), 981-99 (2014)
DOI: 10.1172/JCI72723

102. Q. Deng, C. J. Holler, G. Taylor, K. F. Hudson, W. Watkins, M. Gearing, D. Ito, M. E. Murray, D. W. Dickson, N. T. Seyfried and T. Kukar: FUS is phosphorylated by DNA-PK and accumulates in the cytoplasm after DNA damage. J Neurosci, 34(23), 7802-13 (2014)
DOI: 10.1523/JNEUROSCI.0172-14.2014

103. J. Fei and J. Chen: KIAA1530 protein is recruited by Cockayne syndrome complementation group protein A (CSA) to participate in transcription-coupled repair (TCR). J Biol Chem, 287(42), 35118-26 (2012)
DOI: 10.1074/jbc.M112.398131

104. P. Schwertman, A. Lagarou, D. H. Dekkers, A. Raams, A. C. van der Hoek, C. Laffeber, J. H. Hoeijmakers, J. A. Demmers, M. Fousteri, W. Vermeulen and J. A. Marteijn: UV-sensitive syndrome protein UVSSA recruits USP7 to regulate transcription-coupled repair. Nat Genet, 44(5), 598-602 (2012)
DOI: 10.1038/ng.2230

105. X. Zhang, K. Horibata, M. Saijo, C. Ishigami, A. Ukai, S. Kanno, H. Tahara, E. G. Neilan, M. Honma, T. Nohmi, A. Yasui and K. Tanaka: Mutations in UVSSA cause UV-sensitive syndrome and destabilize ERCC6 in transcription-coupled DNA repair. Nat Genet, 44(5), 593-7 (2012)
DOI: 10.1038/ng.2228

106. Y. Nakazawa, K. Sasaki, N. Mitsutake, M. Matsuse, M. Shimada, T. Nardo, Y. Takahashi, K. Ohyama, K. Ito, H. Mishima, M. Nomura, A. Kinoshita, S. Ono, K. Takenaka, R. Masuyama, T. Kudo, H. Slor, A. Utani, S. Tateishi, S. Yamashita, M. Stefanini, A. R. Lehmann, K. Yoshiura and T. Ogi: Mutations in UVSSA cause UV-sensitive syndrome and impair RNA polymerase IIo processing in transcription-coupled nucleotide-excision repair. Nat Genet, 44(5), 586-92 (2012)
DOI: 10.1038/ng.2229

107. M. Yuan, C. G. Eberhart and M. Kai: RNA binding protein RBM14 promotes radio-resistance in glioblastoma by regulating DNA repair and cell differentiation. Oncotarget, 5(9), 2820-2826 (2014)

108. A. Moumen, P. Masterson, M. J. O'Connor and S. P. Jackson: hnRNP K: An HDM2 target and transcriptional coactivator of p53 in response to DNA damage. Cell, 123(6), 1065-1078 (2005) DOI: 10.1016/j.cell.2005.09.032

109. S. E. Polo, A. N. Blackford, J. R. Chapman, L. Baskcomb, S. Gravel, A. Rusch, A. Thomas, R. Blundred, P. Smith, J. Kzhyshkowska, T. Dobner, A. M. R. Taylor, A. S. Turnell, G. S. Stewart, R. J. Grand and S. P. Jackson: Regulation of DNA-End Resection by hnRNPU-like Proteins Promotes DNA Double-Strand Break Signaling and Repair. Molecular Cell, 45(4), 505-516 (2012) DOI: 10.1016/j.molcel.2011.12.035

110. B. Adamson, A. Smogorzewska, F. D. Sigoillot, R. W. King and S. J. Elledge: A genome-wide homologous recombination screen identifies the RNA-binding protein RBMX as a component of the DNA-damage response. Nature Cell Biology, 14(3), 318-328 (2012) DOI: 10.1038/ncb2426

111. T. Ozaki, A. Nakagawara and H. Nagase: RUNX Family Participates in the Regulation of p53-Dependent DNA Damage Response. International Journal of Genomics (2013) DOI: 10.1155/2013/271347

112. P. C. Hanawalt and G. Spivak: Transcription-coupled DNA repair: two decades of progress and surprises. Nature Reviews Molecular Cell Biology, 9(12), 958-970 (2008) DOI: 10.1038/nrm2549

113. D. Auboeuf, D. H. Dowhan, M. Dutertre, N. Martin, S. M. Berget and B. W. O'Malley: A subset of nuclear receptor coregulators act as coupling proteins during synthesis and maturation of RNA transcripts. Mol Cell Biol, 25(13), 5307-16 (2005) DOI: 10.1128/MCB.25.13.5307-5316.2005

114. S. Kim, J. Yamamoto, Y. Chen, M. Aida, T. Wada, H. Handa and Y. Yamaguchi: Evidence that cleavage factor Im is a heterotetrameric protein complex controlling alternative polyadenylation. Genes Cells, 15(9), 1003-13 (2010) DOI: 10.1111/j.1365-2443.2010.01436.x

115. A. R. Gruber, G. Martin, W. Keller and M. Zavolan: Cleavage factor Im is a key regulator of 3' UTR length. RNA Biol, 9(12), 1405-12 (2012) DOI: 10.4161/rna.22570

116. R. Myojin, S. Kuwahara, T. Yasaki, T. Matsunaga, T. Sakurai, M. Kimura, S. Uesugi and Y. Kurihara: Expression and functional significance of mouse paraspeckle protein 1 on spermatogenesis. Biol Reprod, 71(3), 926-32 (2004) DOI: 10.1095/biolreprod.104.028159

117. D. M. Passon, M. Lee, O. Rackham, W. A. Stanley, A. Sadowska, A. Filipovska, A. H. Fox and C. S. Bond: Structure of the heterodimer of human NONO and paraspeckle protein component 1 and analysis of its role in subnuclear body formation. Proc Natl Acad Sci U S A, 109(13), 4846-50 (2012) DOI: 10.1073/pnas.1120792109

118. B. T. Dye and J. G. Patton: An RNA recognition motif (RRM) is required for the localization of PTB-associated splicing factor (PSF) to subnuclear speckles. Exp Cell Res, 263(1), 131-44 (2001) DOI: 10.1006/excr.2000.5097

119. A. Emili, M. Shales, S. McCracken, W. Xie, P. W. Tucker, R. Kobayashi, B. J. Blencowe and C. J. Ingles: Splicing and transcription-associated proteins PSF and p54nrb/nonO bind to the RNA polymerase II CTD. RNA, 8(9), 1102-11 (2002) DOI: 10.1017/S1355838202025037

120. S. Kameoka, P. Duque and M. M. Konarska: p54(nrb) associates with the 5' splice site within large transcription/splicing complexes. EMBO J, 23(8), 1782-91 (2004) DOI: 10.1038/sj.emboj.7600187

121. Z. Zhang and G. G. Carmichael: The

fate of dsRNA in the nucleus: a p54(nrb)-containing complex mediates the nuclear retention of promiscuously A-to-I edited RNAs. Cell, 106(4), 465-75 (2001)
DOI: 10.1016/S0092-8674(01)00466-4

122. I. R. Mackenzie and M. Neumann: FET proteins in frontotemporal dementia and amyotrophic lateral sclerosis. Brain Res, 1462, 40-3 (2012)
DOI: 10.1016/j.brainres.2011.12.010

123. C. Vance, B. Rogelj, T. Hortobágyi, K. J. De Vos, A. L. Nishimura, J. Sreedharan, X. Hu, B. Smith, D. Ruddy, P. Wright, J. Ganesalingam, K. L. Williams, V. Tripathi, S. Al-Saraj, A. Al-Chalabi, P. N. Leigh, I. P. Blair, G. Nicholson, J. de Belleroche, J. M. Gallo, C. C. Miller and C. E. Shaw: Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. Science, 323(5918), 1208-11 (2009)
DOI: 10.1126/science.1165942

124. T. J. Kwiatkowski, D. A. Bosco, A. L. Leclerc, E. Tamrazian, C. R. Vanderburg, C. Russ, A. Davis, J. Gilchrist, E. J. Kasarskis, T. Munsat, P. Valdmanis, G. A. Rouleau, B. A. Hosler, P. Cortelli, P. J. de Jong, Y. Yoshinaga, J. L. Haines, M. A. Pericak-Vance, J. Yan, N. Ticozzi, T. Siddique, D. McKenna-Yasek, P. C. Sapp, H. R. Horvitz, J. E. Landers and R. H. Brown: Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. Science, 323(5918), 1205-8 (2009)
DOI: 10.1126/science.1166066

125. D. Dormann and C. Haass: Fused in sarcoma (FUS): an oncogene goes awry in neurodegeneration. Mol Cell Neurosci, 56, 475-86 (2013)
DOI: 10.1016/j.mcn.2013.03.006

126. T. Yamazaki, S. Chen, Y. Yu, B. Yan, T. C. Haertlein, M. A. Carrasco, J. C. Tapia, B. Zhai, R. Das, M. Lalancette-Hebert, A. Sharma, S. Chandran, G. Sullivan, A. L. Nishimura, C. E. Shaw, S. P. Gygi, N. A. Shneider, T. Maniatis and R. Reed: FUS-SMN protein interactions link the motor neuron diseases ALS and SMA. Cell Rep, 2(4), 799-806 (2012)
DOI: 10.1016/j.celrep.2012.08.025

127. J. C. Schwartz, C. C. Ebmeier, E. R. Podell, J. Heimiller, D. J. Taatjes and T. R. Cech: FUS binds the CTD of RNA polymerase II and regulates its phosphorylation at Ser2. Genes Dev, 26(24), 2690-5 (2012)
DOI: 10.1101/gad.204602.112

128. X. Wang, S. Arai, X. Song, D. Reichart, K. Du, G. Pascual, P. Tempst, M. G. Rosenfeld, C. K. Glass and R. Kurokawa: Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature, 454(7200), 126-30 (2008)
DOI: 10.1038/nature06992

129. J. I. Hoell, E. Larsson, S. Runge, J. D. Nusbaum, S. Duggimpudi, T. A. Farazi, M. Hafner, A. Borkhardt, C. Sander and T. Tuschl: RNA targets of wild-type and mutant FET family proteins. Nat Struct Mol Biol, 18(12), 1428-31 (2011)
DOI: 10.1038/nsmb.2163

130. S. Ishigaki, A. Masuda, Y. Fujioka, Y. Iguchi, M. Katsuno, A. Shibata, F. Urano, G. Sobue and K. Ohno: Position-dependent FUS-RNA interactions regulate alternative splicing events and transcriptions. Sci Rep, 2, 529 (2012)
DOI: 10.1038/srep00529

131. C. Lagier-Tourenne, M. Polymenidou, K. R. Hutt, A. Q. Vu, M. Baughn, S. C. Huelga, K. M. Clutario, S. C. Ling, T. Y. Liang, C. Mazur, E. Wancewicz, A. S. Kim, A. Watt, S. Freier, G. G. Hicks, J. P. Donohue, L. Shiue, C. F. Bennett, J. Ravits, D. W. Cleveland and G. W. Yeo: Divergent roles of ALS-linked proteins FUS/TLS and TDP-43 intersect in processing long pre-mRNAs. Nat Neurosci, 15(11), 1488-97 (2012)
DOI: 10.1038/nn.3230

132. B. Rogelj, L. E. Easton, G. K. Bogu, L. W. Stanton, G. Rot, T. Curk, B. Zupan, Y. Sugimoto, M. Modic, N. Haberman, J. Tollervey, R. Fujii, T. Takumi, C. E. Shaw

and J. Ule: Widespread binding of FUS along nascent RNA regulates alternative splicing in the brain. Sci Rep, 2, 603 (2012)
DOI: 10.1038/srep00603

133. T. Nakaya, P. Alexiou, M. Maragkakis, A. Chang and Z. Mourelatos: FUS regulates genes coding for RNA-binding proteins in neurons by binding to their highly conserved introns. RNA, 19(4), 498-509 (2013)
DOI: 10.1261/rna.037804.112

134. Y. Zhou, S. Liu, G. Liu, A. Oztürk and G. G. Hicks: ALS-associated FUS mutations result in compromised FUS alternative splicing and autoregulation. PLoS Genet, 9(10), e1003895 (2013)
DOI: 10.1371/journal.pgen.1003895

135. S. M. Oh, Z. Liu, M. Okada, S. W. Jang, X. Liu, C. B. Chan, H. Luo and K. Ye: Ebp1 sumoylation, regulated by TLS/FUS E3 ligase, is required for its anti-proliferative activity. Oncogene, 29(7), 1017-30 (2010)
DOI: 10.1038/onc.2009.411

136. E. C. Toomey, J. D. Schiffman and S. L. Lessnick: Recent advances in the molecular pathogenesis of Ewing's sarcoma. Oncogene, 29(32), 4504-16 (2010)
DOI: 10.1038/onc.2010.205

137. M. P. Paronetto: Ewing sarcoma protein: a key player in human cancer. Int J Cell Biol, 2013, 642853 (2013)
DOI: 10.1155/2013/642853

138. A. Bertolotti, T. Melot, J. Acker, M. Vigneron, O. Delattre and L. Tora: EWS, but not EWS-FLI-1, is associated with both TFIID and RNA polymerase II: interactions between two members of the TET family, EWS and hTAFII68, and subunits of TFIID and RNA polymerase II complexes. Mol Cell Biol, 18(3), 1489-97 (1998)
No DOI Found

139. A. Bertolotti, Y. Lutz, D. J. Heard, P. Chambon and L. Tora: hTAF(II)68, a novel RNA/ssDNA-binding protein with homology to the pro-oncoproteins TLS/FUS and EWS is associated with both TFIID and RNA polymerase II. EMBO J, 15(18), 5022-31 (1996)
No DOI Found

140. F. Ibrahim, M. Maragkakis, P. Alexiou, M. A. Maronski, M. A. Dichter and Z. Mourelatos: Identification of in vivo, conserved, TAF15 RNA binding sites reveals the impact of TAF15 on the neuronal transcriptome. Cell Rep, 3(2), 301-8 (2013)
DOI: 10.1016/j.celrep.2013.01.021

141. R. Martinez-Contreras, P. Cloutier, L. Shkreta, J. F. Fisette, T. Revil and B. Chabot: hnRNP proteins and splicing control. Adv Exp Med Biol, 623, 123-47 (2007)
DOI: 10.1007/978-0-387-77374-2_8

142. S. P. Han, Y. H. Tang and R. Smith: Functional diversity of the hnRNPs: past, present and perspectives. Biochem J, 430(3), 379-92 (2010)
DOI: 10.1042/BJ20100396

143. J. Jean-Philippe, S. Paz and M. Caputi: hnRNP A1: the Swiss army knife of gene expression. Int J Mol Sci, 14(9), 18999-9024 (2013)
DOI: 10.3390/ijms140918999

144. H. J. Kim, N. C. Kim, Y. D. Wang, E. A. Scarborough, J. Moore, Z. Diaz, K. S. MacLea, B. Freibaum, S. Li, A. Molliex, A. P. Kanagaraj, R. Carter, K. B. Boylan, A. M. Wojtas, R. Rademakers, J. L. Pinkus, S. A. Greenberg, J. Q. Trojanowski, B. J. Traynor, B. N. Smith, S. Topp, A. S. Gkazi, J. Miller, C. E. Shaw, M. Kottlors, J. Kirschner, A. Pestronk, Y. R. Li, A. F. Ford, A. D. Gitler, M. Benatar, O. D. King, V. E. Kimonis, E. D. Ross, C. C. Weihl, J. Shorter and J. P. Taylor: Mutations in prion-like domains in hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy and ALS. Nature, 495(7442), 467-73 (2013)
DOI: 10.1038/nature11922

145. C. Dominguez, J. F. Fisette, B. Chabot and F. H. Allain: Structural basis of G-tract

recognition and encaging by hnRNP F quasi-RRMs. Nat Struct Mol Biol, 17(7), 853-61 (2010)
DOI: 10.1038/nsmb.1814

146. M. Caputi and A. M. Zahler: Determination of the RNA binding specificity of the heterogeneous nuclear ribonucleoprotein (hnRNP) H/H'/F/2H9 family. J Biol Chem, 276(47), 43850-9 (2001)
DOI: 10.1074/jbc.M102861200

147. S. C. Huelga, A. Q. Vu, J. D. Arnold, T. Y. Liang, P. P. Liu, B. Y. Yan, J. P. Donohue, L. Shiue, S. Hoon, S. Brenner, M. Ares and G. W. Yeo: Integrative genome-wide analysis reveals cooperative regulation of alternative splicing by hnRNP proteins. Cell Rep, 1(2), 167-78 (2012)
DOI: 10.1016/j.celrep.2012.02.001

148. Y. Katz, E. T. Wang, E. M. Airoldi and C. B. Burge: Analysis and design of RNA sequencing experiments for identifying isoform regulation. Nat Methods, 7(12), 1009-15 (2010)
DOI: 10.1038/nmeth.1528

149. D. Mahé, P. Mähl, R. Gattoni, N. Fischer, M. G. Mattei, J. Stévenin and J. P. Fuchs: Cloning of human 2H9 heterogeneous nuclear ribonucleoproteins. Relation with splicing and early heat shock-induced splicing arrest. J Biol Chem, 272(3), 1827-36 (1997)
DOI: 10.1074/jbc.272.3.1827

150. K. Bomsztyk, O. Denisenko and J. Ostrowski: hnRNP K: one protein multiple processes. Bioessays, 26(6), 629-38 (2004)
DOI: 10.1002/bies.20048

151. M. Marko, M. Leichter, M. Patrinou-Georgoula and A. Guialis: hnRNP M interacts with PSF and p54(nrb) and co-localizes within defined nuclear structures. Exp Cell Res, 316(3), 390-400 (2010)
DOI: 10.1016/j.yexcr.2009.10.021

152. Z. Mourelatos, L. Abel, J. Yong, N. Kataoka and G. Dreyfuss: SMN interacts with a novel family of hnRNP and spliceosomal proteins. EMBO J, 20(19), 5443-52 (2001)
DOI: 10.1093/emboj/20.19.5443

153. W. Rossoll, A. K. Kröning, U. M. Ohndorf, C. Steegborn, S. Jablonka and M. Sendtner: Specific interaction of Smn, the spinal muscular atrophy determining gene product, with hnRNP-R and gry-rbp/hnRNP-Q: a role for Smn in RNA processing in motor axons? Hum Mol Genet, 11(1), 93-105 (2002)
DOI: 10.1093/hmg/11.1.93

154. M. Glinka, T. Herrmann, N. Funk, S. Havlicek, W. Rossoll, C. Winkler and M. Sendtner: The heterogeneous nuclear ribonucleoprotein-R is necessary for axonal beta-actin mRNA translocation in spinal motor neurons. Hum Mol Genet, 19(10), 1951-66 (2010)
DOI: 10.1093/hmg/ddq073

155. A. Fukuda, M. Shimada, T. Nakadai, K. Nishimura and K. Hisatake: Heterogeneous nuclear ribonucleoprotein R cooperates with mediator to facilitate transcription reinitiation on the c-Fos gene. PLoS One, 8(8), e72496 (2013)
DOI: 10.1371/journal.pone.0072496

156. T. Ideue, S. Adachi, T. Naganuma, A. Tanigawa, T. Natsume and T. Hirose: U7 small nuclear ribonucleoprotein represses histone gene transcription in cell cycle-arrested cells. Proc Natl Acad Sci U S A, 109(15), 5693-8 (2012)
DOI: 10.1073/pnas.1200523109

157. T. B. Guo, L. G. Boros, K. C. Chan, A. P. Hikim, A. P. Hudson, R. S. Swerdloff, A. P. Mitchell and W. A. Salameh: Spermatogenetic expression of RNA-binding motif protein 7, a protein that interacts with splicing factors. J Androl, 24(2), 204-14 (2003)
No DOI Found

158. M. Lubas, M. S. Christensen, M. S. Kristiansen, M. Domanski, L. G. Falkenby, S. Lykke-Andersen, J. S. Andersen, A. Dziembowski and T. H. Jensen: Interaction profiling identifies the human

nuclear exosome targeting complex. Mol Cell, 43(4), 624-37 (2011)
DOI: 10.1016/j.molcel.2011.06.028

159. T. Iwasaki, W. W. Chin and L. Ko: Identification and characterization of RRM-containing coactivator activator (CoAA) as TRBP-interacting protein, and its splice variant as a coactivator modulator (CoAM). J Biol Chem, 276(36), 33375-83 (2001)
DOI: 10.1074/jbc.M101517200

160. D. Auboeuf, A. Hönig, S. M. Berget and B. W. O'Malley: Coordinate regulation of transcription and splicing by steroid receptor coregulators. Science, 298(5592), 416-9 (2002)
DOI: 10.1126/science.1073734

161. M. Perani, P. Antonson, R. Hamoudi, C. J. Ingram, C. S. Cooper, M. D. Garrett and G. H. Goodwin: The proto-oncoprotein SYT interacts with SYT-interacting protein/co-activator activator (SIP/CoAA), a human nuclear receptor co-activator with similarity to EWS and TLS/FUS family of proteins. J Biol Chem, 280(52), 42863-76 (2005)
DOI: 10.1074/jbc.M502963200

162. J. I. Wu, J. Lessard, I. A. Olave, Z. Qiu, A. Ghosh, I. A. Graef and G. R. Crabtree: Regulation of dendritic development by neuron-specific chromatin remodeling complexes. Neuron, 56(1), 94-108 (2007)
DOI: 10.1016/j.neuron.2007.08.021

163. R. Kanhoush, B. Beenders, C. Perrin, J. Moreau, M. Bellini and M. Penrad-Mobayed: Novel domains in the hnRNP G/RBMX protein with distinct roles in RNA binding and targeting nascent transcripts. Nucleus, 1(1), 109-22 (2010)
No DOI Found

164. S. Matsunaga, H. Takata, A. Morimoto, K. Hayashihara, T. Higashi, K. Akatsuchi, E. Mizusawa, M. Yamakawa, M. Ashida, T. M. Matsunaga, T. Azuma, S. Uchiyama and K. Fukui: RBMX: a regulator for maintenance and centromeric protection of sister chromatid cohesion. Cell Rep, 1(4), 299-308 (2012)
DOI: 10.1016/j.celrep.2012.02.005

165. E. Tsend-Ayush, L. A. O'Sullivan, F. S. Grützner, S. M. Onnebo, R. S. Lewis, M. L. Delbridge, J. A. Marshall Graves and A. C. Ward: RBMX gene is essential for brain development in zebrafish. Dev Dyn, 234(3), 682-8 (2005)
DOI: 10.1002/dvdy.20432

166. M. Neumann, D. M. Sampathu, L. K. Kwong, A. C. Truax, M. C. Micsenyi, T. T. Chou, J. Bruce, T. Schuck, M. Grossman, C. M. Clark, L. F. McCluskey, B. L. Miller, E. Masliah, I. R. Mackenzie, H. Feldman, W. Feiden, H. A. Kretzschmar, J. Q. Trojanowski and V. M. Lee: Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science, 314(5796), 130-3 (2006)
DOI: 10.1126/science.1134108

167. T. Arai, M. Hasegawa, H. Akiyama, K. Ikeda, T. Nonaka, H. Mori, D. Mann, K. Tsuchiya, M. Yoshida, Y. Hashizume and T. Oda: TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun, 351(3), 602-11 (2006)
DOI: 10.1016/j.bbrc.2006.10.093

168. E. Kabashi, P. N. Valdmanis, P. Dion, D. Spiegelman, B. J. McConkey, C. Vande Velde, J. P. Bouchard, L. Lacomblez, K. Pochigaeva, F. Salachas, P. F. Pradat, W. Camu, V. Meininger, N. Dupre and G. A. Rouleau: TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. Nat Genet, 40(5), 572-4 (2008)
DOI: 10.1038/ng.132

169. J. Sreedharan, I. P. Blair, V. B. Tripathi, X. Hu, C. Vance, B. Rogelj, S. Ackerley, J. C. Durnall, K. L. Williams, E. Buratti, F. Baralle, J. de Belleroche, J. D. Mitchell, P. N. Leigh, A. Al-Chalabi, C. C. Miller, G. Nicholson and C. E. Shaw:

TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. Science, 319(5870), 1668-72 (2008)
DOI: 10.1126/science.1154584

170. M. A. Gitcho, R. H. Baloh, S. Chakraverty, K. Mayo, J. B. Norton, D. Levitch, K. J. Hatanpaa, C. L. White, E. H. Bigio, R. Caselli, M. Baker, M. T. Al-Lozi, J. C. Morris, A. Pestronk, R. Rademakers, A. M. Goate and N. J. Cairns: TDP-43 A315T mutation in familial motor neuron disease. Ann Neurol, 63(4), 535-8 (2008)
DOI: 10.1002/ana.21344

171. X. Shan, P. M. Chiang, D. L. Price and P. C. Wong: Altered distributions of Gemini of coiled bodies and mitochondria in motor neurons of TDP-43 transgenic mice. Proc Natl Acad Sci U S A, 107(37), 16325-30 (2010)
DOI: 10.1073/pnas.1003459107

172. H. Tsuiji, Y. Iguchi, A. Furuya, A. Kataoka, H. Hatsuta, N. Atsuta, F. Tanaka, Y. Hashizume, H. Akatsu, S. Murayama, G. Sobue and K. Yamanaka: Spliceosome integrity is defective in the motor neuron diseases ALS and SMA. EMBO Mol Med, 5(2), 221-34 (2013)
DOI: 10.1002/emmm.201202303

173. L. C. Hsu, H. Y. Chen, Y. W. Lin, W. C. Chu, M. J. Lin, Y. T. Yan and P. H. Yen: DAZAP1, an hnRNP protein, is required for normal growth and spermatogenesis in mice. RNA, 14(9), 1814-22 (2008)
DOI: 10.1261/rna.1152808

174. E. Goina, N. Skoko and F. Pagani: Binding of DAZAP1 and hnRNPA1/A2 to an exonic splicing silencer in a natural BRCA1 exon 18 mutant. Mol Cell Biol, 28(11), 3850-60 (2008)
DOI: 10.1128/MCB.02253-07

175. T. Pastor and F. Pagani: Interaction of hnRNPA1/A2 and DAZAP1 with an Alu-derived intronic splicing enhancer regulates ATM aberrant splicing. PLoS One, 6(8), e23349 (2011)
DOI: 10.1371/journal.pone.0023349

176. R. W. Smith, R. C. Anderson, J. W. Smith, M. Brook, W. A. Richardson and N. K. Gray: DAZAP1, an RNA-binding protein required for development and spermatogenesis, can regulate mRNA translation. RNA, 17(7), 1282-95 (2011)
DOI: 10.1261/rna.2717711

177. R. Choudhury, S. G. Roy, Y. S. Tsai, A. Tripathy, L. M. Graves and Z. Wang: The splicing activator DAZAP1 integrates splicing control into MEK/Erk-regulated cell proliferation and migration. Nat Commun, 5, 3078 (2014)
DOI: 10.1038/ncomms4078

178. Y. Vera, T. Dai, A. P. Hikim, Y. Lue, E. C. Salido, R. S. Swerdloff and P. H. Yen: Deleted in azoospermia associated protein 1 shuttles between nucleus and cytoplasm during normal germ cell maturation. J Androl, 23(5), 622-8 (2002)

179. Y. Kurihara, H. Watanabe, A. Kawaguchi, T. Hori, K. Mishiro, M. Ono, H. Sawada and S. Uesugi: Dynamic changes in intranuclear and subcellular localizations of mouse Prrp/DAZAP1 during spermatogenesis: the necessity of the C-terminal proline-rich region for nuclear import and localization. Arch Histol Cytol, 67(4), 325-33 (2004)
DOI: 10.1679/aohc.67.325

180. Y. T. Lin and P. H. Yen: A novel nucleocytoplasmic shuttling sequence of DAZAP1, a testis-abundant RNA-binding protein. RNA, 12(8), 1486-93 (2006)
DOI: 10.1261/rna.42206

181. Y. T. Lin, W. C. Wen and P. H. Yen: Transcription-dependent nuclear localization of DAZAP1 requires an N-terminal signal. Biochem Biophys Res Commun, 428(3), 422-6 (2012)
DOI: 10.1016/j.bbrc.2012.10.076

182. A. N. Ladd, N. H. Nguyen, K. Malhotra and T. A. Cooper: CELF6, a member of the CELF family of RNA-binding proteins, regulates muscle-specific splicing enhancer-dependent alternative splicing. J Biol Chem, 279(17), 17756-64 (2004)
DOI: 10.1074/jbc.M310687200

183. J. D. Dougherty, S. E. Maloney, D. F. Wozniak, M. A. Rieger, L. Sonnenblick, G. Coppola, N. G. Mahieu, J. Zhang, J. Cai, G. J. Patti, B. S. Abrahams, D. H. Geschwind and N. Heintz: The disruption of Celf6, a gene identified by translational profiling of serotonergic neurons, results in autism-related behaviors. J Neurosci, 33(7), 2732-53 (2013)
DOI: 10.1523/JNEUROSCI.4762-12.2013

184. C. Shin, Y. Feng and J. L. Manley: Dephosphorylated SRp38 acts as a splicing repressor in response to heat shock. Nature, 427(6974), 553-8 (2004)
DOI: 10.1038/nature02288

185. Y. Shi and J. L. Manley: A complex signaling pathway regulates SRp38 phosphorylation and pre-mRNA splicing in response to heat shock. Mol Cell, 28(1), 79-90 (2007)
DOI: 10.1016/j.molcel.2007.08.028

186. G. Biamonti and J. F. Caceres: Cellular stress and RNA splicing. Trends Biochem Sci, 34(3), 146-53 (2009)
DOI: 10.1016/j.tibs.2008.11.004

187. X. Zhou, W. Wu, H. Li, Y. Cheng, N. Wei, J. Zong, X. Feng, Z. Xie, D. Chen, J. L. Manley, H. Wang and Y. Feng: Transcriptome analysis of alternative splicing events regulated by SRSF10 reveals position-dependent splicing modulation. Nucleic Acids Res, 42(6), 4019-30 (2014)
DOI: 10.1093/nar/gkt1387

188. J. Pihlajamäki, C. Lerin, P. Itkonen, T. Boes, T. Floss, J. Schroeder, F. Dearie, S. Crunkhorn, F. Burak, J. C. Jimenez-Chillaron, T. Kuulasmaa, P. Miettinen, P. J. Park, I. Nasser, Z. Zhao, Z. Zhang, Y. Xu, W. Wurst, H. Ren, A. J. Morris, S. Stamm, A. B. Goldfine, M. Laakso and M. E. Patti: Expression of the splicing factor gene SFRS10 is reduced in human obesity and contributes to enhanced lipogenesis. Cell Metab, 14(2), 208-18 (2011)
DOI: 10.1016/j.cmet.2011.06.007

189. C. F. Kennedy, A. Krämer and S. M. Berget: A role for SRp54 during intron bridging of small introns with pyrimidine tracts upstream of the branch point. Mol Cell Biol, 18(9), 5425-34 (1998)
No DOI Found

190. S. Wellmann, C. Bührer, E. Moderegger, A. Zelmer, R. Kirschner, P. Koehne, J. Fujita and K. Seeger: Oxygen-regulated expression of the RNA-binding proteins RBM3 and CIRP by a HIF-1-independent mechanism. J Cell Sci, 117(Pt 9), 1785-94 (2004)
DOI: 10.1242/jcs.01026

191. M. E. Lleonart: A new generation of proto-oncogenes: cold-inducible RNA binding proteins. Biochim Biophys Acta, 1805(1), 43-52 (2010)
DOI: 10.1016/j.bbcan.2009.11.001

192. Y. Liu, W. Hu, Y. Murakawa, J. Yin, G. Wang, M. Landthaler and J. Yan: Cold-induced RNA-binding proteins regulate circadian gene expression by controlling alternative polyadenylation. Sci Rep, 3, 2054 (2013)
DOI: 10.1038/srep02054

193. T. Wagner, J. Wirth, J. Meyer, B. Zabel, M. Held, J. Zimmer, J. Pasantes, F. D. Bricarelli, J. Keutel, E. Hustert, U. Wolf, N. Tommerup, W. Schempp and G. Scherer: Autosomal sex reversal and campomelic dysplasia are caused by mutations in and around the SRY-related gene SOX9. Cell, 79(6), 1111-20 (1994)
DOI: 10.1016/0092-8674(94)90041-8

194. J. W. Foster, M. A. Dominguez-Steglich, S. Guioli, C. Kwok, P. A. Weller, M. Stevanović, J. Weissenbach, S. Mansour, I. D. Young and P. N. Goodfellow: Campomelic dysplasia and autosomal sex reversal caused by mutations in an SRY-related gene. Nature, 372(6506), 525-30 (1994)
DOI: 10.1038/372525a0

195. J. A. Price, D. W. Bowden, J. T. Wright, M. J. Pettenati and T. C. Hart: Identification of a mutation in DLX3 associated with tricho-dento-osseous (TDO) syndrome.

Hum Mol Genet, 7(3), 563-9 (1998)
DOI: 10.1093/hmg/7.3.563

196. H. Liu, G. C. Ippolito, J. K. Wall, T. Niu, L. Probst, B. S. Lee, K. Pulford, A. H. Banham, L. Stockwin, A. L. Shaffer, L. M. Staudt, C. Das, M. J. Dyer and P. W. Tucker: Functional studies of BCL11A: characterization of the conserved BCL11A-XL splice variant and its interaction with BCL6 in nuclear paraspeckles of germinal center B cells. Mol Cancer, 5, 18 (2006)
DOI: 10.1186/1476-4598-5-18

197. R. Shimizu, J. D. Engel and M. Yamamoto: GATA1-related leukaemias. Nat Rev Cancer, 8(4), 279-87 (2008)
DOI: 10.1038/nrc2348

198. L. S. Chuang and Y. Ito: RUNX3 is multifunctional in carcinogenesis of multiple solid tumors. Oncogene, 29(18), 2605-15 (2010)
DOI: 10.1038/onc.2010.88

199. Y. J. Yang, A. E. Baltus, R. S. Mathew, E. A. Murphy, G. D. Evrony, D. M. Gonzalez, E. P. Wang, C. A. Marshall-Walker, B. J. Barry, J. Murn, A. Tatarakis, M. A. Mahajan, H. H. Samuels, Y. Shi, J. A. Golden, M. Mahajnah, R. Shenhav and C. A. Walsh: Microcephaly gene links trithorax and REST/NRSF to control neural stem cell proliferation and differentiation. Cell, 151(5), 1097-112 (2012)
DOI: 10.1016/j.cell.2012.10.043

200. C. L. Balduini and A. Savoia: Genetics of familial forms of thrombocytopenia. Hum Genet, 131(12), 1821-32 (2012)
DOI: 10.1007/s00439-012-1215-x

201. V. G. Sankaran, R. Ghazvinian, R. Do, P. Thiru, J. A. Vergilio, A. H. Beggs, C. A. Sieff, S. H. Orkin, D. G. Nathan, E. S. Lander and H. T. Gazda: Exome sequencing identifies GATA1 mutations resulting in Diamond-Blackfan anemia. J Clin Invest, 122(7), 2439-43 (2012)
DOI: 10.1172/JCI63597

202. J. Boultwood and A. Pellagatti: Reduced translation of GATA1 in Diamond-Blackfan anemia. Nat Med, 20(7), 703-4 (2014)
DOI: 10.1038/nm.3630

203. L. S. Ludwig, H. T. Gazda, J. C. Eng, S. W. Eichhorn, P. Thiru, R. Ghazvinian, T. I. George, J. R. Gotlib, A. H. Beggs, C. A. Sieff, H. F. Lodish, E. S. Lander and V. G. Sankaran: Altered translation of GATA1 in Diamond-Blackfan anemia. Nat Med, 20(7), 748-53 (2014)
DOI: 10.1038/nm.3557

204. Y. Y. Chau and N. D. Hastie: The role of Wt1 in regulating mesenchyme in cancer, development, and tissue homeostasis. Trends Genet, 28(10), 515-24 (2012)
DOI: 10.1016/j.tig.2012.04.004

205. A. M. Kaindl: Autosomal recessive primary microcephalies (MCPH). Eur J Paediatr Neurol, 18(4), 547-8 (2014)
DOI: 10.1016/j.ejpn.2014.03.010

206. F. Xia, M. N. Bainbridge, T. Y. Tan, M. F. Wangler, A. E. Scheuerle, E. H. Zackai, M. H. Harr, V. R. Sutton, R. L. Nalam, W. Zhu, M. Nash, M. M. Ryan, J. Yaplito-Lee, J. V. Hunter, M. A. Deardorff, S. J. Penney, A. L. Beaudet, S. E. Plon, E. A. Boerwinkle, J. R. Lupski, C. M. Eng, D. M. Muzny, Y. Yang and R. A. Gibbs: De novo truncating mutations in AHDC1 in individuals with syndromic expressive language delay, hypotonia, and sleep apnea. Am J Hum Genet, 94(5), 784-9 (2014)
DOI: 10.1016/j.ajhg.2014.04.006

207. K. Takahashi and S. Yamanaka: Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell, 126(4), 663-76 (2006)
DOI: 10.1016/j.cell.2006.07.024

208. D. Jia, S. M. Hasso, J. Chan, D. Filingeri, P. A. D'Amore, L. Rice, C. Pampo, D. W. Siemann, D. Zurakowski, S. J. Rodig and M. A. Moses: Transcriptional repression of VEGF by ZNF24: mechanistic studies and vascular consequences in vivo. Blood, 121(4), 707-15 (2013)
DOI: 10.1182/blood-2012-05-433045

209. A. J. Lopez-Contreras, I. Ruppen, M.

Nieto-Soler, M. Murga, S. Rodriguez-Acebes, S. Remeseiro, S. Rodrigo-Perez, A. M. Rojas, J. Mendez, J. Muñoz and O. Fernandez-Capetillo: A proteomic characterization of factors enriched at nascent DNA molecules. Cell Rep, 3(4), 1105-16 (2013)
DOI: 10.1016/j.celrep.2013.03.009

210. H. Akiyama, M. C. Chaboissier, J. F. Martin, A. Schedl and B. de Crombrugghe: The transcription factor Sox9 has essential roles in successive steps of the chondrocyte differentiation pathway and is required for expression of Sox5 and Sox6. Genes Dev, 16(21), 2813-28 (2002)
DOI: 10.1101/gad.1017802

211. Y. Kawaguchi: Sox9 and programming of liver and pancreatic progenitors. J Clin Invest, 123(5), 1881-6 (2013)
DOI: 10.1172/JCI66022

212. K. Hata, R. Nishimura, S. Muramatsu, A. Matsuda, T. Matsubara, K. Amano, F. Ikeda, V. R. Harley and T. Yoneda: Paraspeckle protein p54nrb links Sox9-mediated transcription with RNA processing during chondrogenesis in mice. J Clin Invest, 118(9), 3098-108 (2008)
DOI: 10.1172/JCI31373

213. W. M. Schmidt, C. Kraus, H. Höger, S. Hochmeister, F. Oberndorfer, M. Branka, S. Bingemann, H. Lassmann, M. Müller, L. I. Macedo-Souza, M. Vainzof, M. Zatz, A. Reis and R. E. Bittner: Mutation in the Scyl1 gene encoding amino-terminal kinase-like protein causes a recessive form of spinocerebellar neurodegeneration. EMBO Rep, 8(7), 691-7 (2007)
DOI: 10.1038/sj.embor.7401001

214. S. Pelletier, S. Gingras, S. Howell, P. Vogel and J. N. Ihle: An early onset progressive motor neuron disorder in Scyl1-deficient mice is associated with mislocalization of TDP-43. J Neurosci, 32(47), 16560-73 (2012)
DOI: 10.1523/JNEUROSCI.1787-12.2012

215. S. Q. Xie, S. Martin, P. V. Guillot, D. L. Bentley and A. Pombo: Splicing speckles are not reservoirs of RNA polymerase II, but contain an inactive form, phosphorylated on serine2 residues of the C-terminal domain. Mol Biol Cell, 17(4), 1723-33 (2006)
DOI: 10.1091/mbc.E05-08-0726

216. D. Rotin and S. Kumar: Physiological functions of the HECT family of ubiquitin ligases. Nat Rev Mol Cell Biol, 10(6), 398-409 (2009)
DOI: 10.1038/nrm2690

217. S. Galbán and C. S. Duckett: XIAP as a ubiquitin ligase in cellular signaling. Cell Death Differ, 17(1), 54-60 (2010)
DOI: 10.1038/cdd.2009.81

218. M. B. Metzger, V. A. Hristova and A. M. Weissman: HECT and RING finger families of E3 ubiquitin ligases at a glance. J Cell Sci, 125(Pt 3), 531-7 (2012)
DOI: 10.1242/jcs.091777

219. T. K. Oberoi-Khanuja, A. Murali and K. Rajalingam: IAPs on the move: role of inhibitors of apoptosis proteins in cell migration. Cell Death Dis, 4, e784 (2013)
DOI: 10.1038/cddis.2013.311

220. B. Pereira, M. Le Borgne, N. T. Chartier, M. Billaud and R. Almeida: MEX-3 proteins: recent insights on novel post-transcriptional regulators. Trends Biochem Sci, 38(10), 477-9 (2013)
DOI: 10.1016/j.tibs.2013.08.004

221. I. B. Wilde, M. Brack, J. M. Winget and T. Mayor: Proteomic characterization of aggregating proteins after the inhibition of the ubiquitin proteasome system. J Proteome Res, 10(3), 1062-72 (2011)
DOI: 10.1021/pr1008543

222. D. Li and Y. Huang: Knockdown of ubiquitin associated protein 2-like inhibits the growth and migration of prostate cancer cells. Oncol Rep (2014)
DOI: 10.3892/or.2014.3360

223. A. Castello, B. Fischer, K. Eichelbaum, R. Horos, B. M. Beckmann, C. Strein, N. E. Davey, D. T. Humphreys, T. Preiss, L. M. Steinmetz, J. Krijgsveld and M. W.

Hentze: Insights into RNA biology from an atlas of mammalian mRNA-binding proteins. Cell, 149(6), 1393-406 (2012) DOI: 10.1016/j.cell.2012.04.031

224. A. G. Baltz, M. Munschauer, B. Schwanhäusser, A. Vasile, Y. Murakawa, M. Schueler, N. Youngs, D. Penfold-Brown, K. Drew, M. Milek, E. Wyler, R. Bonneau, M. Selbach, C. Dieterich and M. Landthaler: The mRNA-bound proteome and its global occupancy profile on protein-coding transcripts. Mol Cell, 46(5), 674-90 (2012) DOI: 10.1016/j.molcel.2012.05.021

225. I. Kwon, M. Kato, S. Xiang, L. Wu, P. Theodoropoulos, H. Mirzaei, T. Han, S. Xie, J. L. Corden and S. L. McKnight: Phosphorylation-regulated binding of RNA polymerase II to fibrous polymers of low-complexity domains. Cell, 155(5), 1049-60 (2013) DOI: 10.1016/j.cell.2013.10.033

226. F. Cano, H. Bye, L. M. Duncan, K. Buchet-Poyau, M. Billaud, M. R. Wills and P. J. Lehner: The RNA-binding E3 ubiquitin ligase MEX-3C links ubiquitination with MHC-I mRNA degradation. EMBO J, 31(17), 3596-606 (2012) DOI: 10.1038/emboj.2012.218

227. R. A. Burrell, S. E. McClelland, D. Endesfelder, P. Groth, M. C. Weller, N. Shaikh, E. Domingo, N. Kanu, S. M. Dewhurst, E. Gronroos, S. K. Chew, A. J. Rowan, A. Schenk, M. Sheffer, M. Howell, M. Kschischo, A. Behrens, T. Helleday, J. Bartek, I. P. Tomlinson and C. Swanton: Replication stress links structural and numerical cancer chromosomal instability. Nature, 494(7438), 492-6 (2013) DOI: 10.1038/nature11935

228. Y. Jiao, S. K. George, Q. Zhao, M. W. Hulver, S. M. Hutson, C. E. Bishop and B. Lu: Mex3c mutation reduces adiposity and increases energy expenditure. Mol Cell Biol, 32(21), 4350-62 (2012) DOI: 10.1128/MCB.00452-12

229. L. Zhang, L. Kang, W. Bond and N. Zhang: Interaction between syntaxin 8 and HECTd3, a HECT domain ligase. Cell Mol Neurobiol, 29(1), 115-21 (2009) DOI: 10.1007/s10571-008-9303-0

230. Y. Zhu, C. Wang, J. Lan, J. Yu, C. Jin and H. Huang: Phosphorylation of Tara by Plk1 is essential for faithful chromosome segregation in mitosis. Exp Cell Res, 318(18), 2344-52 (2012) DOI: 10.1016/j.yexcr.2012.07.001

231. Y. Li, Y. Kong, Z. Zhou, H. Chen, Z. Wang, Y. C. Hsieh, D. Zhao, X. Zhi, J. Huang, J. Zhang, H. Li and C. Chen: The HECTD3 E3 ubiquitin ligase facilitates cancer cell survival by promoting K63-linked polyubiquitination of caspase-8. Cell Death Dis, 4, e935 (2013) DOI: 10.1038/cddis.2013.464

232. Y. Li, X. Chen, Z. Wang, D. Zhao, H. Chen, W. Chen, Z. Zhou, J. Zhang, H. Li and C. Chen: The HECTD3 E3 ubiquitin ligase suppresses cisplatin-induced apoptosis via stabilizing MALT1. Neoplasia, 15(1), 39-48 (2013) No DOI Found

233. N. S. Kenneth and C. S. Duckett: IAP proteins: regulators of cell migration and development. Curr Opin Cell Biol, 24(6), 871-5 (2012) DOI: 10.1016/j.ceb.2012.11.004

234. S. Rigaud, M. C. Fondanèche, N. Lambert, B. Pasquier, V. Mateo, P. Soulas, L. Galicier, F. Le Deist, F. Rieux-Laucat, P. Revy, A. Fischer, G. de Saint Basile and S. Latour: XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. Nature, 444(7115), 110-4 (2006) DOI: 10.1038/nature05257

235. C. C. Akoh, G. C. Lee, Y. C. Liaw, T. H. Huang and J. F. Shaw: GDSL family of serine esterases/lipases. Prog Lipid Res, 43(6), 534-52 (2004) DOI: 10.1016/j.plipres.2004.09.002

236. V. Anantharaman and L. Aravind: Novel eukaryotic enzymes modifying cell-surface biopolymers. Biol Direct, 5, 1 (2010)

DOI: 10.1186/1745-6150-5-1

237. Z. A. Jenkins, M. van Kogelenberg, T. Morgan, A. Jeffs, R. Fukuzawa, E. Pearl, C. Thaller, A. V. Hing, M. E. Porteous, S. Garcia-Miñaur, A. Bohring, D. Lacombe, F. Stewart, T. Fiskerstrand, L. Bindoff, S. Berland, L. C. Adès, M. Tchan, A. David, L. C. Wilson, R. C. Hennekam, D. Donnai, S. Mansour, V. Cormier-Daire and S. P. Robertson: Germline mutations in WTX cause a sclerosing skeletal dysplasia but do not predispose to tumorigenesis. Nat Genet, 41(1), 95-100 (2009)
DOI: 10.1038/ng.270

238. S. B. Herman, S. K. Holman, S. P. Robertson, L. Davidson, B. Taragin and J. Samanich: Severe osteopathia striata with cranial sclerosis in a female case with whole WTX gene deletion. Am J Med Genet A, 161A(3), 594-9 (2013)
DOI: 10.1002/ajmg.a.35716

239. A. Fujita, N. Ochi, H. Fujimaki, H. Muramatsu, Y. Takahashi, J. Natsume, S. Kojima, M. Nakashima, Y. Tsurusaki, H. Saitsu, N. Matsumoto and N. Miyake: A novel WTX mutation in a female patient with osteopathia striata with cranial sclerosis and hepatoblastoma. Am J Med Genet A, 164A(4), 998-1002 (2014)
DOI: 10.1002/ajmg.a.36369

240. J. R. Dutton, D. Lahiri and A. Ward: Different isoforms of the Wilms' tumour protein WT1 have distinct patterns of distribution and trafficking within the nucleus. Cell Prolif, 39(6), 519-35 (2006)
DOI: 10.1111/j.1365-2184.2006.00409.x

241. M. N. Rivera, W. J. Kim, J. Wells, A. Stone, A. Burger, E. J. Coffman, J. Zhang and D. A. Haber: The tumor suppressor WTX shuttles to the nucleus and modulates WT1 activity. Proc Natl Acad Sci U S A, 106(20), 8338-43 (2009)
DOI: 10.1073/pnas.0811349106

242. C. Westberg, J. P. Yang, H. Tang, T. R. Reddy and F. Wong-Staal: A novel shuttle protein binds to RNA helicase A and activates the retroviral constitutive transport element. J Biol Chem, 275(28), 21396-401 (2000)
DOI: 10.1074/jbc.M909887199

243. J. P. Yang, H. Tang, T. R. Reddy and F. Wong-Staal: Mapping the functional domains of HAP95, a protein that binds RNA helicase A and activates the constitutive transport element of type D retroviruses. J Biol Chem, 276(33), 30694-700 (2001)
DOI: 10.1074/jbc.M102809200

244. Y. Yang, C. L. Mahaffey, N. Bérubé, A. Nystuen and W. N. Frankel: Functional characterization of fidgetin, an AAA-family protein mutated in fidget mice. Exp Cell Res, 304(1), 50-8 (2005)
DOI: 10.1016/j.yexcr.2004.11.014

245. Y. Yang, C. L. Mahaffey, N. Bérubé and W. N. Frankel: Interaction between fidgetin and protein kinase A-anchoring protein AKAP95 is critical for palatogenesis in the mouse. J Biol Chem, 281(31), 22352-9 (2006)
DOI: 10.1074/jbc.M603626200

246. T. J. Maures, J. H. Kurzer and C. Carter-Su: SH2B1 (SH2-B) and JAK2: a multifunctional adaptor protein and kinase made for each other. Trends Endocrinol Metab, 18(1), 38-45 (2007)
DOI: 10.1016/j.tem.2006.11.007

247. B. Desbuquois, N. Carré and A. F. Burnol: Regulation of insulin and type 1 insulin-like growth factor signaling and action by the Grb10/14 and SH2B1/B2 adaptor proteins. FEBS J, 280(3), 794-816 (2013)
DOI: 10.1111/febs.12080

248. M. E. Doche, E. G. Bochukova, H. W. Su, L. R. Pearce, J. M. Keogh, E. Henning, J. M. Cline, S. Saeed, A. Dale, T. Cheetham, I. Barroso, L. S. Argetsinger, S. O'Rahilly, L. Rui, C. Carter-Su and I. S. Farooqi: Human SH2B1 mutations are associated with maladaptive behaviors and obesity. J Clin Invest, 122(12), 4732-6 (2012)
DOI: 10.1172/JCI62696

249. R. A. Hegele, H. Cao, D. M. Liu, G. A. Costain, V. Charlton-Menys, N. W.

Rodger and P. N. Durrington: Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy. Am J Hum Genet, 79(2), 383-9 (2006)
DOI: 10.1086/505885

250. H. J. Worman and G. Bonne: "Laminopathies": a wide spectrum of human diseases. Exp Cell Res, 313(10), 2121-33 (2007)
DOI: 10.1016/j.yexcr.2007.03.028

251. H. J. Worman, L. G. Fong, A. Muchir and S. G. Young: Laminopathies and the long strange trip from basic cell biology to therapy. J Clin Invest, 119(7), 1825-36 (2009)
DOI: 10.1172/JCI37679

252. N. M. Maraldi, C. Capanni, V. Cenni, M. Fini and G. Lattanzi: Laminopathies and lamin-associated signaling pathways. J Cell Biochem, 112(4), 979-92 (2011)
DOI: 10.1002/jcb.22992

253. P. O. Simsek-Kiper, E. Roach, G. E. Utine and K. Boduroglu: Barraquer-Simons syndrome: a rare clinical entity. Am J Med Genet A, 164(7), 1756-60 (2014)
DOI: 10.1002/ajmg.a.36491

254. D. Roos, D. B. Kuhns, A. Maddalena, J. Bustamante, C. Kannengiesser, M. de Boer, K. van Leeuwen, M. Y. Köker, B. Wolach, J. Roesler, H. L. Malech, S. M. Holland, J. I. Gallin and M. J. Stasia: Hematologically important mutations: the autosomal recessive forms of chronic granulomatous disease (second update). Blood Cells Mol Dis, 44(4), 291-9 (2010)
DOI: 10.1016/j.bcmd.2010.01.009

255. D. J. Scarlett, P. M. Herst and M. V. Berridge: Multiple proteins with single activities or a single protein with multiple activities: the conundrum of cell surface NADH oxidoreductases. Biochim Biophys Acta, 1708(1), 108-19 (2005)
DOI: 10.1016/j.bbabio.2005.03.006

256. Y. S. Mao, H. Sunwoo, B. Zhang and D. L. Spector: Direct visualization of the co-transcriptional assembly of a nuclear body by noncoding RNAs. Nat Cell Biol, 13(1), 95-101 (2011)
DOI: 10.1038/ncb2140

257. M. Dundr: Seed and grow: a two-step model for nuclear body biogenesis. J Cell Biol, 193(4), 605-6 (2011)
DOI: 10.1083/jcb.201104087

258. M. Kato, T. W. Han, S. Xie, K. Shi, X. Du, L. C. Wu, H. Mirzaei, E. J. Goldsmith, J. Longgood, J. Pei, N. V. Grishin, D. E. Frantz, J. W. Schneider, S. Chen, L. Li, M. R. Sawaya, D. Eisenberg, R. Tycko and S. L. McKnight: Cell-free formation of RNA granules: low complexity sequence domains form dynamic fibers within hydrogels. Cell, 149(4), 753-67 (2012)
DOI: 10.1016/j.cell.2012.04.017

259. T. W. Han, M. Kato, S. Xie, L. C. Wu, H. Mirzaei, J. Pei, M. Chen, Y. Xie, J. Allen, G. Xiao and S. L. McKnight: Cell-free formation of RNA granules: bound RNAs identify features and components of cellular assemblies. Cell, 149(4), 768-79 (2012)
DOI: 10.1016/j.cell.2012.04.016

260. T. Thisted, D. L. Lyakhov and S. A. Liebhaber: Optimized RNA targets of two closely related triple KH domain proteins, heterogeneous nuclear ribonucleoprotein K and alphaCP-2KL, suggest Distinct modes of RNA recognition. J Biol Chem, 276(20), 17484-96 (2001)
DOI: 10.1074/jbc.M010594200

261. T. A. Shelkovnikova, H. K. Robinson, C. Troakes, N. Ninkina and V. L. Buchman: Compromised paraspeckle formation as a pathogenic factor in FUSopathies. Hum Mol Genet, 23(9), 2298-312 (2014)
DOI: 10.1093/hmg/ddt622

262. N. Gilks, N. Kedersha, M. Ayodele, L. Shen, G. Stoecklin, L. M. Dember and P. Anderson: Stress granule assembly is mediated by prion-like aggregation of TIA-1. Mol Biol Cell, 15(12), 5383-98 (2004)
DOI: 10.1091/mbc.E04-08-0715

263. C. J. Decker, D. Teixeira and R. Parker: Edc3p and a glutamine/asparagine-rich

domain of Lsm4p function in processing body assembly in Saccharomyces cerevisiae. J Cell Biol, 179(3), 437-49 (2007)
DOI: 10.1083/jcb.200704147

264. D. Dormann, R. Rodde, D. Edbauer, E. Bentmann, I. Fischer, A. Hruscha, M. E. Than, I. R. Mackenzie, A. Capell, B. Schmid, M. Neumann and C. Haass: ALS-associated fused in sarcoma (FUS) mutations disrupt Transportin-mediated nuclear import. EMBO J, 29(16), 2841-57 (2010)
DOI: 10.1038/emboj.2010.143

265. J. C. Schwartz, X. Wang, E. R. Podell and T. R. Cech: RNA seeds higher-order assembly of FUS protein. Cell Rep, 5(4), 918-25 (2013)
DOI: 10.1016/j.celrep.2013.11.017

266. W. Shen, X. H. Liang and S. T. Crooke: Phosphorothioate oligonucleotides can displace NEAT1 RNA and form nuclear paraspeckle-like structures. Nucleic Acids Res, 42(13), 8648-62 (2014)
DOI: 10.1093/nar/gku579

267. T. Hirose, G. Virnicchi, A. Tanigawa, T. Naganuma, R. Li, H. Kimura, T. Yokoi, S. Nakagawa, M. Bénard, A. H. Fox and G. Pierron: NEAT1 long noncoding RNA regulates transcription via protein sequestration within subnuclear bodies. Mol Biol Cell, 25(1), 169-83 (2014)
DOI: 10.1091/mbc.E13-09-0558

268. K. Imamura, N. Imamachi, G. Akizuki, M. Kumakura, A. Kawaguchi, K. Nagata, A. Kato, Y. Kawaguchi, H. Sato, M. Yoneda, C. Kai, T. Yada, Y. Suzuki, T. Yamada, T. Ozawa, K. Kaneki, T. Inoue, M. Kobayashi, T. Kodama, Y. Wada, K. Sekimizu and N. Akimitsu: Long noncoding RNA NEAT1-dependent SFPQ relocation from promoter region to paraspeckle mediates IL8 expression upon immune stimuli. Mol Cell, 53(3), 393-406 (2014)
DOI: 10.1016/j.molcel.2014.01.009

269. Q. Zhang, C. Y. Chen, V. S. Yedavalli and K. T. Jeang: NEAT1 long noncoding RNA and paraspeckle bodies modulate HIV-1 posttranscriptional expression. MBio, 4(1), e00596-12 (2013)
DOI: 10.1128/mBio.00596-12

270. H. Choudhry, J. Schödel, S. Oikonomopoulos, C. Camps, S. Grampp, A. L. Harris, P. J. Ratcliffe, J. Ragoussis and D. R. Mole: Extensive regulation of the non-coding transcriptome by hypoxia: role of HIF in releasing paused RNApol2. EMBO Rep, 15(1), 70-6 (2014)
DOI: 10.1002/embr.201337642

271. S. Gremlich, F. Damnon, D. Reymondin, O. Braissant, J. C. Schittny, D. Baud, S. Gerber and M. Roth-Kleiner: The long non-coding RNA NEAT1 is increased in IUGR placentas, leading to potential new hypotheses of IUGR origin/development. Placenta, 35(1), 44-9 (2014)
DOI: 10.1016/j.placenta.2013.11.003

272. J. R. Tollervey, T. Curk, B. Rogelj, M. Briese, M. Cereda, M. Kayikci, J. König, T. Hortobágyi, A. L. Nishimura, V. Zupunski, R. Patani, S. Chandran, G. Rot, B. Zupan, C. E. Shaw and J. Ule: Characterizing the RNA targets and position-dependent splicing regulation by TDP-43. Nat Neurosci, 14(4), 452-8 (2011)
DOI: 10.1038/nn.2778

273. Y. D. Ke, Y. Ke, J. Dramiga, U. Schütz, J. J. Kril, L. M. Ittner, H. Schröder and J. Götz: Tau-mediated nuclear depletion and cytoplasmic accumulation of SFPQ in Alzheimer's and Pick's disease. PLoS One, 7(4), e35678 (2012)
DOI: 10.1371/journal.pone.0035678

274. N. T. Seyfried, Y. M. Gozal, L. E. Donovan, J. H. Herskowitz, E. B. Dammer, Q. Xia, L. Ku, J. Chang, D. M. Duong, H. D. Rees, D. S. Cooper, J. D. Glass, M. Gearing, M. G. Tansey, J. J. Lah, Y. Feng, A. I. Levey and J. Peng: Quantitative analysis of the detergent-insoluble brain proteome in frontotemporal lobar degeneration using SILAC internal standards. J Proteome Res, 11(5), 2721-38 (2012)
DOI: 10.1021/pr2010814

275. J. Cotto, S. Fox and R. Morimoto: HSF1 granules: a novel stress-induced nuclear compartment of human cells. J Cell Sci, 110 (Pt 23), 2925-34 (1997)
No DOI Found

276. I. Chiodi, M. Biggiogera, M. Denegri, M. Corioni, F. Weighardt, F. Cobianchi, S. Riva and G. Biamonti: Structure and dynamics of hnRNP-labelled nuclear bodies induced by stress treatments. J Cell Sci, 113 (Pt 22), 4043-53 (2000)
No DOI Found

277. M. Denegri, D. Moralli, M. Rocchi, M. Biggiogera, E. Raimondi, F. Cobianchi, L. De Carli, S. Riva and G. Biamonti: Human chromosomes 9, 12, and 15 contain the nucleation sites of stress-induced nuclear bodies. Mol Biol Cell, 13(6), 2069-79 (2002)
DOI: 10.1091/mbc.01-12-0569

278. G. Biamonti: Nuclear stress bodies: a heterochromatin affair? Nat Rev Mol Cell Biol, 5(6), 493-8 (2004)
DOI: 10.1038/nrm1405

279. R. Valgardsdottir, I. Chiodi, M. Giordano, F. Cobianchi, S. Riva and G. Biamonti: Structural and functional characterization of noncoding repetitive RNAs transcribed in stressed human cells. Mol Biol Cell, 16(6), 2597-604 (2005)
DOI: 10.1091/mbc.E04-12-1078

280. C. Jolly and S. C. Lakhotia: Human sat III and Drosophila hsr omega transcripts: a common paradigm for regulation of nuclear RNA processing in stressed cells. Nucleic Acids Res, 34(19), 5508-14 (2006)
DOI: 10.1093/nar/gkl711

281. K. H. Choo, E. Earle and C. McQuillan: A homologous subfamily of satellite III DNA on human chromosomes 14 and 22. Nucleic Acids Res, 18(19), 5641-8 (1990)
DOI: 10.1093/nar/18.19.5641

282. I. Chiodi, M. Corioni, M. Giordano, R. Valgardsdottir, C. Ghigna, F. Cobianchi, R. M. Xu, S. Riva and G. Biamonti: RNA recognition motif 2 directs the recruitment of SF2/ASF to nuclear stress bodies. Nucleic Acids Res, 32(14), 4127-36 (2004)
DOI: 10.1093/nar/gkh759

283. S. P. Shevtsov and M. Dundr: Nucleation of nuclear bodies by RNA. Nat Cell Biol, 13(2), 167-73 (2011)
DOI: 10.1038/ncb2157

284. T. E. Audas, M. D. Jacob and S. Lee: Immobilization of proteins in the nucleolus by ribosomal intergenic spacer noncoding RNA. Mol Cell, 45(2), 147-57 (2012)
DOI: 10.1016/j.molcel.2011.12.012

285. T. E. Audas, M. D. Jacob and S. Lee: The nucleolar detention pathway: A cellular strategy for regulating molecular networks. Cell Cycle, 11(11), 2059-62 (2012)
DOI: 10.4161/cc.20140

286. M. D. Jacob, T. E. Audas, S. T. Mullineux and S. Lee: Where no RNA polymerase has gone before: novel functional transcripts derived from the ribosomal intergenic spacer. Nucleus, 3(4), 315-9 (2012)
DOI: 10.4161/nucl.20585

287. M. D. Jacob, T. E. Audas, J. Uniacke, L. Trinkle-Mulcahy and S. Lee: Environmental cues induce a long noncoding RNA-dependent remodeling of the nucleolus. Mol Biol Cell, 24(18), 2943-53 (2013)
DOI: 10.1091/mbc.E13-04-0223

288. T. Chen, F. M. Boisvert, D. P. Bazett-Jones and S. Richard: A role for the GSG domain in localizing Sam68 to novel nuclear structures in cancer cell lines. Mol Biol Cell, 10(9), 3015-33 (1999)
DOI: 10.1091/mbc.10.9.3015

289. M. A. Karreman, A. V. Agronskaia, A. J. Verkleij, F. F. Cremers, H. C. Gerritsen and B. M. Humbel: Discovery of a new RNA-containing nuclear structure in UVC-induced apoptotic cells by integrated laser electron microscopy. Biol Cell, 101(5), 287-99 (2009)
DOI: 10.1042/BC20080076

290. Q. F. Yin, L. Yang, Y. Zhang, J. F. Xiang, Y. W. Wu, G. G. Carmichael and L. L. Chen: Long noncoding RNAs with snoRNA ends. Mol Cell, 48(2), 219-30 (2012) DOI: 10.1016/j.molcel.2012.07.033

291. S. B. Cassidy, S. Schwartz, J. L. Miller and D. J. Driscoll: Prader-Willi syndrome. Genet Med, 14(1), 10-26 (2012) DOI: 10.1038/gim.0b013e31822bead0

292. M. D. Blower, M. Nachury, R. Heald and K. Weis: A Rae1-containing ribonucleoprotein complex is required for mitotic spindle assembly. Cell, 121(2), 223-34 (2005) DOI: 10.1016/j.cell.2005.02.016

293. M. D. Blower, E. Feric, K. Weis and R. Heald: Genome-wide analysis demonstrates conserved localization of messenger RNAs to mitotic microtubules. J Cell Biol, 179(7), 1365-73 (2007) DOI: 10.1083/jcb.200705163

294. A. Jambhekar, A. B. Emerman, C. T. Schweidenback and M. D. Blower: RNA stimulates Aurora B kinase activity during mitosis. PLoS One, 9(6), e100748 (2014) DOI: 10.1371/journal.pone.0100748

295. M. Kloc, K. Wilk, D. Vargas, Y. Shirato, S. Bilinski and L. D. Etkin: Potential structural role of non-coding and coding RNAs in the organization of the cytoskeleton at the vegetal cortex of Xenopus oocytes. Development, 132(15), 3445-57 (2005) DOI: 10.1242/dev.01919

296. M. Kloc, S. Bilinski and M. T. Dougherty: Organization of cytokeratin cytoskeleton and germ plasm in the vegetal cortex of Xenopus laevis oocytes depends on coding and non-coding RNAs: three-dimensional and ultrastructural analysis. Exp Cell Res, 313(8), 1639-51 (2007) DOI: 10.1016/j.yexcr.2007.02.018

297. C. L. de Hoog, L. J. Foster and M. Mann: RNA and RNA binding proteins participate in early stages of cell spreading through spreading initiation centers. Cell, 117(5), 649-62 (2004) DOI: 10.1016/S0092-8674(04)00456-8

298. M. Wojciechowska and W. J. Krzyzosiak: Cellular toxicity of expanded RNA repeats: focus on RNA foci. Hum Mol Genet, 20(19), 3811-21 (2011) DOI: 10.1093/hmg/ddr299

299. M. Ramaswami, J. P. Taylor and R. Parker: Altered ribostasis: RNA-protein granules in degenerative disorders. Cell, 154(4), 727-36 (2013) DOI: 10.1016/j.cell.2013.07.038

300. V. V. Belzil, T. F. Gendron and L. Petrucelli: RNA-mediated toxicity in neurodegenerative disease. Mol Cell Neurosci, 56, 406-19 (2013) DOI: 10.1016/j.mcn.2012.12.006

301. D. L. Nelson, H. T. Orr and S. T. Warren: The unstable repeats--three evolving faces of neurological disease. Neuron, 77(5), 825-43 (2013) DOI: 10.1016/j.neuron.2013.02.022

302. A. Mohan, M. Goodwin and M. S. Swanson: RNA-protein interactions in unstable microsatellite diseases. Brain Res (2014) DOI: 10.1016/j.brainres.2014.03.039

303. R. N. Kanadia, K. A. Johnstone, A. Mankodi, C. Lungu, C. A. Thornton, D. Esson, A. M. Timmers, W. W. Hauswirth and M. S. Swanson: A muscleblind knockout model for myotonic dystrophy. Science, 302(5652), 1978-80 (2003) DOI: 10.1126/science.1088583

304. R. N. Kanadia, J. Shin, Y. Yuan, S. G. Beattie, T. M. Wheeler, C. A. Thornton and M. S. Swanson: Reversal of RNA missplicing and myotonia after muscleblind overexpression in a mouse poly(CUG) model for myotonic dystrophy. Proc Natl Acad Sci U S A, 103(31), 11748-53 (2006) DOI: 10.1073/pnas.0604970103

305. C. Sellier, F. Rau, Y. Liu, F. Tassone, R. K. Hukema, R. Gattoni, A. Schneider, S. Richard, R. Willemsen, D. J. Elliott, P. J. Hagerman and N. Charlet-Berguerand: Sam68 sequestration and partial loss of function are associated with splicing

alterations in FXTAS patients. EMBO J, 29(7), 1248-61 (2010)
DOI: 10.1038/emboj.2010.21

306. A. E. Renton, E. Majounie, A. Waite, J. Simón-Sánchez, S. Rollinson, J. R. Gibbs, J. C. Schymick, H. Laaksovirta, J. C. van Swieten, L. Myllykangas, H. Kalimo, A. Paetau, Y. Abramzon, A. M. Remes, A. Kaganovich, S. W. Scholz, J. Duckworth, J. Ding, D. W. Harmer, D. G. Hernandez, J. O. Johnson, K. Mok, M. Ryten, D. Trabzuni, R. J. Guerreiro, R. W. Orrell, J. Neal, A. Murray, J. Pearson, I. E. Jansen, D. Sondervan, H. Seelaar, D. Blake, K. Young, N. Halliwell, J. B. Callister, G. Toulson, A. Richardson, A. Gerhard, J. Snowden, D. Mann, D. Neary, M. A. Nalls, T. Peuralinna, L. Jansson, V. M. Isoviita, A. L. Kaivorinne, M. Hölttä-Vuori, E. Ikonen, R. Sulkava, M. Benatar, J. Wuu, A. Chiò, G. Restagno, G. Borghero, M. Sabatelli, D. Heckerman, E. Rogaeva, L. Zinman, J. D. Rothstein, M. Sendtner, C. Drepper, E. E. Eichler, C. Alkan, Z. Abdullaev, S. D. Pack, A. Dutra, E. Pak, J. Hardy, A. Singleton, N. M. Williams, P. Heutink, S. Pickering-Brown, H. R. Morris, P. J. Tienari, B. J. Traynor and I. Consortium: A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron, 72(2), 257-68 (2011)
DOI: 10.1016/j.neuron.2011.09.010

307. M. DeJesus-Hernandez, I. R. Mackenzie, B. F. Boeve, A. L. Boxer, M. Baker, N. J. Rutherford, A. M. Nicholson, N. A. Finch, H. Flynn, J. Adamson, N. Kouri, A. Wojtas, P. Sengdy, G. Y. Hsiung, A. Karydas, W. W. Seeley, K. A. Josephs, G. Coppola, D. H. Geschwind, Z. K. Wszolek, H. Feldman, D. S. Knopman, R. C. Petersen, B. L. Miller, D. W. Dickson, K. B. Boylan, N. R. Graff-Radford and R. Rademakers: Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron, 72(2), 245-56 (2011)
DOI: 10.1016/j.neuron.2011.09.011

308. A. Ghetti, S. Piñol-Roma, W. M. Michael, C. Morandi and G. Dreyfuss: hnRNP I, the polypyrimidine tract-binding protein: distinct nuclear localization and association with hnRNAs. Nucleic Acids Res, 20(14), 3671-8 (1992)
DOI: 10.1093/nar/20.14.3671

309. W. Schul, B. Groenhout, K. Koberna, Y. Takagaki, A. Jenny, E. M. Manders, I. Raska, R. van Driel and L. de Jong: The RNA 3' cleavage factors CstF 64 kDa and CPSF 100 kDa are concentrated in nuclear domains closely associated with coiled bodies and newly synthesized RNA. EMBO J, 15(11), 2883-92 (1996)
No DOI Found

310. S. Bléoo, X. Sun, M. J. Hendzel, J. M. Rowe, M. Packer and R. Godbout: Association of human DEAD box protein DDX1 with a cleavage stimulation factor involved in 3'-end processing of pre-MRNA. Mol Biol Cell, 12(10), 3046-59 (2001)
DOI: 10.1091/mbc.12.10.3046

311. L. Li, K. Roy, S. Katyal, X. Sun, S. Bléoo and R. Godbout: Dynamic nature of cleavage bodies and their spatial relationship to DDX1 bodies, Cajal bodies, and gems. Mol Biol Cell, 17(3), 1126-40 (2006)
DOI: 10.1091/mbc.E05-08-0768

312. P. Mähl, Y. Lutz, E. Puvion and J. P. Fuchs: Rapid effect of heat shock on two heterogeneous nuclear ribonucleoprotein-associated antigens in HeLa cells. J Cell Biol, 109(5), 1921-35 (1989)
DOI: 10.1083/jcb.109.5.1921

313. P. Buchenau, J. Hodgson, H. Strutt and D. J. Arndt-Jovin: The distribution of polycomb-group proteins during cell division and development in Drosophila embryos: impact on models for silencing. J Cell Biol, 141(2), 469-81 (1998)
DOI: 10.1083/jcb.141.2.469

314. A. J. Saurin, C. Shiels, J. Williamson, D. P. Satijn, A. P. Otte, D. Sheer and P. S. Freemont: The human polycomb group complex associates with pericentromeric

heterochromatin to form a novel nuclear domain. J Cell Biol, 142(4), 887-98 (1998) DOI: 10.1083/jcb.142.4.887

315. A. Pombo, P. Cuello, W. Schul, J. B. Yoon, R. G. Roeder, P. R. Cook and S. Murphy: Regional and temporal specialization in the nucleus: a transcriptionally-active nuclear domain rich in PTF, Oct1 and PIKA antigens associates with specific chromosomes early in the cell cycle. EMBO J, 17(6), 1768-78 (1998) DOI: 10.1093/emboj/17.6.1768

316. M. Lafarga, M. T. Berciano, E. Pena, I. Mayo, J. G. Castaño, D. Bohmann, J. P. Rodrigues, J. P. Tavanez and M. Carmo-Fonseca: Clastosome: a subtype of nuclear body enriched in 19S and 20S proteasomes, ubiquitin, and protein substrates of proteasome. Mol Biol Cell, 13(8), 2771-82 (2002) DOI: 10.1091/mbc.E02-03-0122

Key Words: Long noncoding RNA, Paraspeckle, NEAT1 lncRNA, Nuclear body, Prion-like domain, Neurodegenerative diseases, Review

Send correspondence to: Tetsuro Hirose, Institute for Genetic Medicine, Hokkaido University, Kita 15, Nishi 7, Kita-ku, Sapporo 060-0815, Japan, Tel: 81-11-706-5071, Fax: 81-11-706-7540, E-mail: hirose@igm.hokudai.ac.jp1. P. Bertone, V. Stolc, T. E. Royce, J. S. Rozowsky, A. E. Urban, X. Zhu, J. L. Rinn, W. Tongprasit, M. Samanta, S. Weissman, M. Gerstein and M. Snyder: Global identification of human transcribed sequences with genome tiling arrays. Science, 306(5705), 2242-6 (2004)