Nuclear paraspeckles function in mediating gene regulatory and apoptotic pathways

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ABSTRACT

The nucleus is an essential hub for the regulation of gene expression in both spatial and temporal contexts. The complexity required to manage such a feat has resulted in the evolution of multiple sub-structures in the nucleus such as the nucleolus, small Cajal bodies and nuclear stress bodies. The paraspeckle is another membraneless structure composed of RNA elements, primarily the long non-coding RNA (lncRNA) Nuclear Enriched Abundant Transcript 1 (NEAT1), associated with RNA binding proteins (RBPs). The paraspeckle is showing signs of being involved in various aspects of gene regulation and its role in many pathologies from cancer to viral infection is beginning to be addressed. Research into paraspeckle-directed gene regulation highlights the increase in the appreciation of the biological significance of non-coding RNA (ncRNA). This review will thus cover the basis of how a structure as large as a paraspeckle forms along with its functions. It will also explore how it effects pathological conditions and can be used in clinical intervention, with special emphasis on the multitude of methods utilised by paraspeckles for apoptotic regulation.

1. Introduction

Paraspeckles were first discovered in HeLa cells in 2002 but are found across multiple mammalian tissues associated with splicing speckles [4]. Despite their discovery almost 20 years ago, very little is as yet known about the specific roles fulfilled by these structures in both normal cell biology and more so in diseases, particularly cancer and neurodegenerative diseases. With the data presently available only part of the structural characteristics of the paraspeckles have been elucidated and the understanding of the paraspeckle functions is still at the beginning.

1.1. Paraspeckle structure and formation

The paraspeckle is composed of RNA elements, with the major one being the long non-coding RNA (lncRNA) Nuclear Enriched Abundant Transcript 1 (NEAT1), as well as RNA binding proteins (RBPs). NEAT1, also known as Nuclear Paraspeckle Assembly Transcript 1 is composed of 3 general domains (Fig. 1), required for its pivotal role in paraspeckle formation: domain A which stabilises the transcript, domain B which allows for the production of 2 separate isoforms of NEAT1, and domain C which allows for the formation of the paraspeckle [1]. NEAT1 forms 2 transcripts, NEAT1_1 and NEAT1_2 with the transcripts arising via alternative 3’ untranslated region (UTR) processing. NEAT1_2 is the longer transcript and is essential for paraspeckle formation whilst NEAT1_1 is the shorter transcript and not essential, although it does tend to associate with paraspeckles, serving a currently unknown function [2,3,5]. A total of 37 RBPs have so far been discovered to interact with the paraspeckle [4]. Seven of these proteins are essential for paraspeckle formation, namely non-POU domain-containing octamer-binding protein (NONO or P54nrb), splicing factor proline- and glutamine-rich (SFPQ), RNA Binding Motif Protein 14 (RBM14), heterogeneous nuclear ribonucleoprotein K (HNRNPK), fused in sarcoma (FUS), DAZ-associated protein 1, and heterogeneous nuclear ribonucleoprotein H3 (HNRNPH3) and Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodelling complexes [4].

The NEAT1 transcript is essential for paraspeckle formation, adopting a U-shape in the core of the paraspeckle, with its 3’ and 5’ ends at the periphery [8]. NEAT1 is also crucial for the regulation of paraspeckle formation as evidenced by the fact that paraspeckles form independent of expression of certain paraspeckle proteins such as Splicing Factor Proline And Glutamine Rich (SFPQ) or Paraspeckle Protein 1α (PSP1α), but correlate directly with NEAT1 expression. This suggests that NEAT1 acts as a bottleneck for the production of paraspeckles [9]. However NEAT1 transcripts mediate gene regulation through other paraspeckle independent mechanisms, such as acting as a miRNA
like domains, recruiting more proteins to form a large structure aided by the recruiting FUS, SPFQ and NONO with the latter 2 forming a coiled coil domain three and is involved in the binding to proteins to build the paraspeckle by the NEAT1_1 transcript thus leading to the production of the NEAT1_2 transcript. HNRNPK which has been shown to prevent polyadenylation of NEAT1 to form the NEAT1_1 transcript thus leading to the production of the NEAT1_2 transcript by repressing Cleavage and polyadenylation specificity factor subunit 6 (CPSF6) [76]. Lastly the C domain which can then be further subdivided into three and is involved in the binding to proteins to build the paraspeckle by recruiting FUS, SPFQ and NONO with the latter 2 forming a coiled coil domain that can bind to other proteins such as RMB14, which like FUS contain prion-like domains, recruiting more proteins to form a large structure aided by the interaction of (SWI/SNF) remodelling complexes.

The formation of the paraspeckle begins with NONO forming a heterodimer with SPFQ, which then binds to the C region of NEAT1 [1]. From there, protein-protein interactions through the coiled coil (CC) domain result in the polymerisation across the NEAT1 transcript. This was shown through the ability of SPFQ to coat DNA in a polymer through the CC domain [8]. Further proteins are then included which contain the prion-like domain (PLD), most likely due to further protein recruitment by NEAT1. These domains then interact through weak electrostatic forces to form a giant structure denser than the nucleoplasm around it, which induces a liquid-liquid phase separation. Supporting this is the ability of FUS and RNA Binding Motif Protein 14 (RBM14) to form a hydrogel in vitro, as well as being critical components for Paraspeckle formation [7]. This also appears to be aided by the remodelling complexes SWI/SNF which appear to both help in the recruitment of PLD proteins as well as helping them to create a network of protein interactions to form a large structure [74,75]. Recent evidence has also brought to light the importance of RNA-RNA interactions, as repeated regions present in RNAs can undergo multiple base pairing and interact to form stable large granules such as the paraspeckle. This is supported by the fact that the concentration of NEAT1 in the paraspeckle is high enough to create the relevant RNA-RNA multivalent interactions to stabilise the paraspeckle [8]. Furthermore when NONO, a protein essential for paraspeckle assembly was forced to dissociate from the paraspeckle via 1,6-hexanediol, this resulted in the disassembly of the paraspeckle but also the formation of NEAT1 foci. This demonstrates the ability of NEAT1 to engage in RNA-RNA interactions to form relatively large structures although its significance, whether this is important to the paraspeckle stability or serves some other regulatory role is currently unknown.

2. Paraspeckle function

The function of the paraspeckle was previously considered non-essential due to the observation that NEAT1 knock-out mice had adequate health and fertility [16]. It was later found that NEAT1 was required for corpus luteum formation and can affect fertility in certain sub-populations, as well as mammary gland development and lactation in mice [17]. Multiple functions for paraspeckles in pathology have been described and these will be explored in the subsequent sections through the analysis of paraspeckle mediated gene regulation.

2.1. Regulation of genes through A-1 editing and nuclear retention

In cells, primary RNA transcripts are being edited by changing their base sequence. A common modification is the conversion of adenosine to inosine by the protein adenosine deaminase RNA specific (ADAR) [18]. This process is known as A-I RNA-editing. These transcripts are then bound to the paraspeckle proteins, p54nrb (NONO), SPFQ, and matrin 3 as a complex [21]. This allows for the retention of the mRNA transcripts in the nucleus, further supported by the presence of hyper-edited RNA in the paraspeckle [19]. This is especially effective in mRNAs with inverted ALU repeats in their non-coding 3' UTR, as shown by the fact that mRNAs containing these elements are less able to leave the nucleus to undergo translation (although there are exceptions) indicating that other unknown factors must play a role in the cytoplasmic shuttling of these mRNAs [25]. The details of this mechanism and its importance are exemplified thanks to a study looking at the expression pattern of Cationic amino acid transporter 2 (CAT-2) [20]. The study found that under non-stressful conditions only some CAT-2 mRNA is present. Most of it is found in the nucleus as CAT-2 RNA transcribed using an alternative promoter (CTN-RNA) which has a 3' UTR that is substantially edited and thus included into the paraspeckle preventing its translation. Upon cellular stress however, the 3' UTR is cleaved, resulting in its release from the paraspeckles, effectively providing a rapid means of increasing the concentration of a protein. This is important not only to display the mechanisms in mRNA retention and release, but also
because the protein product of CAT-2 RNA is a plasma membrane receptor responsible for the uptake of L-arginine in the metabolic production of nitric oxide as a part of the stress response defence mechanism [21]. This forms part of the inflammatory pathway [22] and also a component of carcinogenesis [23], thus linking paraspeckles to inflammation and in turn the creation and maintenance of tumours. Thus increasing paraspeckle formation and retention could be an approach to inhibit the inflammatory pathway which causes and maintains a variety of cancers. In addition to the previous mechanism were the mRNA was separated from the paraspeckle due to splicing out of the edited section of the mRNA it should also be noted that alternative polyadenylation can result in transcripts lacking the 3’ UTR that is modified to bind to paraspeckles, including the removal of the highly edited inverted ALU elements [24].

Another factor in mRNA nuclear retention are post-translational modifications. For example, coactivator-associated arginine methyltransferase 1 (CARM1) can methylate the CC domain of NONO, which decreases its affinity to edited transcripts [71]. Another notable modification involves the methylation of SPFPQ and its citrullination which works as an antagonistic modification to methylation. This methylation is likely mediated by Protein Arginine Methyltransferase 1 (PRMT1) and unlike the methylation of NONO, was shown to increase RNA affinity. Furthermore the ability of NONO-SPFPQ aggregates to form in paraspeckles seems to be effected by post-translational modifications [72], signifying their importance and the need to gain more information about how these modifications effect both paraspeckle formation and nuclear retention.

This mode of gene regulation has an added advantage over other methods, such as histone modification, because it allows rapid mobilisation of a large number of transcripts. In hypoxic conditions, NEAT1 is expressed and induces paraspeckle formation due to Hypoxia Inducible Factor 2 α (HIF-2α) [46]. This then cause the nuclear retention of the F11 receptor (F11R) transcript by interactions with P54nrb [47]. This does not alter the cytoplasmic concentration significantly but when paraspeckles are no longer present due to a return of oxygen, this transcript is released in bulk from the paraspeckles, leading to a rapid increase in F11R, which can act as both a receptor for reoviruses and integrin Lymphocyte function-associated antigen 1 (LFA1) [48], which thus makes cells previously exposed to hypoxic conditions more sensitive to stress pathways immediately after the return of normal oxygen concentrations (Fig. 2).

The importance of this mechanism can be further solidified in stem cells. Human embryonic stem cells (hESCs) do not form paraspeckles due to gene repression of NEAT1, thus RNA normally retained within the nucleus can enter the cytoplasm for translation [25]. An example is the LIN28a protein, shown to reprogram somatic cells to pluripotent ones [26] whilst also effecting the microRNA pathways to assist in the maintenance of the pluripotent state [25,27–30]. It should also be noted that this mechanism is not just for endogenous RNA but viral RNA (such as HIV-1 mRNA) is also supressed by paraspeckle retention [31].

2.2. Protein sequestration in paraspeckle-mediated gene expression

In addition to the various RNA transcripts mediated by paraspeckle, the very formation results in the sequestering of various proteins (such as SFPQ [13] and NONO [32]) which on their own can regulate genes. The recruitment of these paraspeckle components affects their ability to interact with their normal genes. This can be shown by the fact that NONO is shown to affect circadian rhythm [33], which is dysregulated in neurodegenerative disorders [34], which in turn have been shown to contain abnormal amounts of paraspeckles [35], indicating abnormal regulation of NONO as a contributor of neurodegenerative disease.

SPFPQ also interacts with a variety of other factors including a mitochondrial iron transporter Uncharacterised protein FP15737, a translation activator Eukaryotic Translation Initiation Factor 4 Gamma 3 (ef4G3), a cellular Src (sarcoma) kinase (SRC) substrate that plays a crucial role in the formation of invadopodia (cellular extensions of the cytoplasm that break down the extracellular matrix, used by cancer cells to leave their tissue of origin and become invasive) in carcinogenesis: the SH3 And PX Domains 2 (SH3PXD2A) protein, and a zinc finger homeobox protein, Teashirt Zinc Finger Homeobox 2 (OVCl0-2) [36]. Another interesting target of this pathway is RNA-editing deaminase-2 (ADARB2), that is activated by SPFPQ [36]. This protein unlike others in the adenine deaminase family does not display catalytic activity and is thus seen as a competitor to inhibit other ADAR proteins [37]. The fact that the paraspeckles can inhibit a suppressor of the RNA-editing pathway shows another degree of control in the A-1 RNA-editing pathway mediated by the paraspeckles.

As further elaborated in the next section, FUS mutations are a major cause of amyotrophic lateral sclerosis (ALS) and although a lot of focus has been placed on the accumulation of cytoplasmic FUS, a study has demonstrated that FUS mutations in ALS resulted in dysfunctional paraspeckles [55]. This leads to alternate levels of FUS recruitment in paraspeckles, which changes them in such a way that it alters NONO levels in the paraspeckles leading to dysregulation of NONO pathways, including the previously mentioned circadian rhythm, as well as cellular pH and cellular proliferation [56].

Furthermore, paraspeckles sequestering nuclear proteins seem to play a role in modulating the response to hypoxia. It has been noted that various changes in gene expression in response to hypoxia do not have upstream Hypoxia-Inducible Factor (HIF) binding sites (HIF proteins refer to the protein family primarily responsible for executing the response to hypoxia). However, paraspeckle formation occurs in response to hypoxic conditions due to an interaction between HIF-2 and NEAT1 [46], meaning that paraspeckles could mediate a variety of hypoxic responses, especially those involved in protein downregulation [58,59]. The fact that NEAT1 serves as a mediator for the hypoxic response which makes cancer more aggressive [60] indicates it as a potential prognostic marker and therapeutic target.

Association of proteins to paraspeckles also plays a role in ensuring proper differentiation of cells. This can be seen in the development of luteal cells forming the corpus luteum [17]. Half of NEAT1 knockout female mice fail to develop a proper corpus luteum along with diminished progesterone levels. It has been known that SPFPQ is a repressor of proteins involved in steroidogenesis [69]. Also, in NEAT1 knockouts, nuclear concentration of SPFPQ is up by 20% [17]. This might not be
significant enough to play a primary role in corpus luteum development, but it can become important in specific disease conditions, which have not yet been discovered. Furthermore NEAT1 has been shown to be involved in the process of de-differentiation of vascular smooth muscle. This was first demonstrated when NEAT1 knockout mice were shown to form less scar tissue on vascular tears. This is due to paraspeckles sequestering a subunit of the histone-methylating complex containing WD repeats, the protein WD Repeat Domain 5 (WDR5), which activates a set of specialised smooth muscle genes. Hence their repression leads to de-differentiation [70] (Fig. 3).

Despite this sequestration, it should be mentioned that the proteins retain the ability to bind and influence promoter regions after being sequestered to paraspeckles, meaning that this sequestration is not analogous to a loss of function. This is exemplified by Herpes simplex virus type 1 (HSV-1) infection, were the paraspeckle protein Paraspeckle Component 1 (PSPC1) can mediate the Signal transducer and activator of transcription 3 (STAT3)-based promoter activation of viral genes through STAT3 recruitment. PSPC1, NEAT1 and P54nrb are capable of interacting with HSV-1 genes localising them to the paraspeckle. Conversely SFPQ has been shown to act as a competitive inhibitor of STAT3-promoter interaction to inhibit viral replication. However, overall paraspeckle inhibition has been shown to inhibit viral replication [40] (even though paraspeckles are the target of HSV-1 infection. Of note is that it is more common that they act as anti-viral structures, as was the case for the retention of HIV transcripts described in the previous section (further details into the anti-viral aspects of cancer check are provided in Ref. [42] and section 3.2.1). Whilst this is true for viral genes, it opens the possibility that paraspeckles can bind to other genes and influence transcription through the proteins they recruit, which could be rather relevant to gene regulation considering the presence of remodelling complexes in the paraspeckle [41].

2.3. microRNA (miRNA) formation in paraspeckles

miRNA biogenesis is a complex process including many different proteins involved in different pathways. Recent research has discovered that paraspeckles form a part of this pathway. This was demonstrated using DiGeorge syndrome chromosomal region 8 (DGCR8), a subunit of the microprocessor complex involved in processing miRNA. Under specific conditions it is localised into the paraspeckle [43]. In addition, DGCR8 can weakly bind to NEAT1 [44]. NEAT1 also forms hairpin loops a secondary structure that the microprocessor binds to, facilitating interactions with the paraspeckle and miRNA [43]. However, the previously mentioned study about viable NEAT1 knockout mice suggests that this role is redundant in normal conditions. This role may also help to explain the association of paraspeckles with splicing speckles, since approximately 80% of miRNA originates from spliced intron regions [45]. Spliced out introns from the splicing speckles can immediately associate with paraspeckles to be processed.

Human NEAT1_2 can also recruit miRNA processors by containing the miRNA miR-612 in its 3’ region in the form of a pseudo RNA which when processed to its mature form [43] could help to recruit the microprocessor complex. However, deletions of the miRNA using CRISPR-CAS9 had no effect on the paraspeckle and furthermore this region is absent in mice [76]. Thus more information will have to be gathered before the role that this pseudo-RNA plays can be addressed clinically.

3. Paraspeckles in apoptosis

Paraspeckles are heavily involved in apoptotic pathways through
the previous example there are instances of paraspeckles and by extension NEAT1 of acting as an important tumour suppressor. For example, NEAT1 has been revealed to be a key tumour suppressor acting in conjunction with p53 [61] and furthermore it has been even shown to attenuate the cell cycle [62]. Despite this, NEAT1 also functions as part of a negative feedback loop to deactivate p53 pathways and thus mediates carcinogenesis through p53 inactivation [38]. Therefore the role and effects of NEAT1 in cancer p53 modulation and apoptosis should be of primary concern to mediate apoptosis in cancer cells and allow for p53 mediated tumour supression.

3.2. Apoptosis, paraspeckles and neurodegenerative disorder

However, aside from cancer apoptosis being a paraspeckle-mediated process, it is also highly important from a neurodegenerative standpoint. Mutations in the TAR DNA Binding Protein (TARDBP) gene is a highly important factor considered to be responsible for up to 95% of sporadic Amyotrophic Lateral Sclerosis (ALS) [63]. The protein product of this gene helps to co-ordinate miRNA and its loss of function results in global miRNA decrease. This feature however is not limited to ALS and is common to many disorders of this nature [64]. This global decrease in miRNA then leads to apoptosis. This is due to the interferon stimulated gene (ISG) pathway used to kill cells that have been infected by viruses. This occurs when double stranded RNA (dsRNA) response is lessened due a modification to a protein involved in dsRNA breakdown pathway such as the poly-ADP-ribosylation of the RNA-induced silencing complex (RISC) as is the case in viral infection. This weakened dsRNA response then weakens the ability of miRNAs to repress genes leading to the translation of apoptotic ISGs, which are then expressed. This effect could either be brought about by the previously mentioned weakened dsRNA response or a decrease in miRNA levels which would still lead to the translation of the ISG transcripts. However, upon over expression of miRNA, the dsRNA apoptotic pathway detects this increase resulting in apoptosis [65,66] (Fig. 4). Paraspeckle generation has thus been shown to be favoured in the case of abnormal miRNA expression (both over and under expression), and results in increased cell survival in order to mitigate apoptosis to increase neuronal survival. This increased cell survival is seen across multiple neurodegenerative disorders such as Huntington's Disease were NEAT1 upregulation has been shown to increase cellular viability [67]. This opens the possibility for drugs capable of increasing neuronal survival across a broad spectrum of disorders which although cannot cure the disease, can work in conjunction with other drugs to improve prognosis and survivability.

4. Conclusion

In summary, paraspeckles are involved in multiple aspects of gene regulation, RNA retention through A-I RNA-editing, and sequestering of important nuclear proteins and miRNA factors, leading it to be involved in various pathologies such as cancer, viral infection and neurodegenerative disease. This takes place through multiple mechanisms of altering the balance between survival and apoptosis in response to cellular stress, further highlighting the importance of nuclear sub-structures in a medical context.

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