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Emerging role of RNA●DNA hybrids in *C9orf72*-linked neurodegeneration

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Abbreviations: ALS, amyotrophic lateral sclerosis; AOA2, ataxia with oculomotor apraxia type 2; *C9orf72*, chromosome 9 open reading frame 72; CpG island, cytosine-phosphate-guanine island; FTD, frontotemporal dementia; HRE, hexanucleotide repeat expansion.

RNA plays an active role in structural polymorphism of the genome through the formation of stable RNA●DNA hybrids (R-loops). R-loops can modulate normal physiological processes and are also associated with pathological conditions, such as those related to nucleotide repeat expansions. A guanine-rich hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9orf72*) has been linked to a spectrum of neurological conditions including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Here we discuss the possible roles, both locally and genome-wide, of R-loops that may arise from the *C9orf72* hexanucleotide repeat. R-loops have the potential to influence the pathological processes identified in many repeat expansion diseases, such as repeat instability, transcriptional dysregulation, epigenetic modification, and antisense-mediated gene regulation. We propose that, given the wide-ranging consequences of R-loops in the cell, these structures could underlie multiple pathological processes in *C9orf72*-linked neurodegeneration.

Introduction

Hybrids formed between RNA and DNA occur naturally in both prokaryotes and eukaryotes. As necessary steps in the flow of genetic information, RNA●DNA duplexes are produced during transcription, reverse transcription (viral and telomeric), DNA replication (RNA primer), and by co- and post-transcriptional rehybridization. These hybrids are generally thought to be small in size and quickly resolved by the appropriate cellular mechanisms. Nevertheless, stable and long-lasting RNA●DNA hybrids with important functions have been observed (see reviews[1-3]).

RNA●DNA hybridization, in the context of duplex DNA, occurs when RNA displaces a strand of the original DNA duplex, forming an RNA●DNA hybrid/single-stranded DNA structure referred to as an R-loop (**Fig. 1**).[4] R-loop formation is enhanced by high guanine (G) content[5] and transcription-linked negative DNA supercoiling.[6] One possible explanation for the increased formation of R-loops in regions with high guanine content is that G-rich single-stranded DNA is prone to forming stable secondary structures. These structures can include hairpins and stacks of Hoogsteen base pair-stabilized guanine tetrads known as G-quadruplexes. The ability of the displaced single-stranded DNA to form these stable structures is thought to increase the probability of RNA●DNA hybrid formation. Transcription-linked negative supercoiling promotes unwinding of the DNA duplex, increasing accessibility of the DNA strands for RNA binding and promoting formation of strand-stabilizing G-quadruplex formation.[7] Once formed, RNA●DNA duplexes can be highly stable,[8,9] and the guanine-cytosine hydrogen bonds of Watson-Crick base pairing in the G-rich sequences further promote the stabilization of the RNA●DNA duplexes. In addition to Watson-Crick base pairing in hybrid helices, intermolecular G-quadruplexes between RNA and DNA have been proposed to further stabilize G-rich hybrids.[10,11]

R-loops have been identified across species and, at least in the budding yeast, are associated with all the RNA polymerases including Pol I, II, III, and even mitochondrial polymerase.[12] R-loops are naturally occuring structures that are associated with transcription but can also be formed by the post-transcriptional rehybridization of single-stranded RNA with cDNA.[13] Diverse biological functions of R-loops have been proposed, including roles in transcriptional regulation, DNA replication, telomere elongation, and genome editing.[1-3] Not surprisingly, the cell has evolved specialized mechanisms for regulating the formation and dissolution of R-loops. For example, the RecA/Rad51 family protein, which facilitates strand exchange in homologous recombination[14], has been found to promote R-loop formation in bacteria and yeasts.[13,15,16] In the flowering plant *Arabidopsis*, a homeodomain protein AtNDX was observed to bind to the single-stranded DNA and stabilize R-loops.[17] Conversely, several proteins are known to prevent the accumulation of R-loops, including the helicase senataxin[18] and the RNA●DNA hybrid-specific endonucleases RNase H1 and H2.[19] In addition, perturbation at multiple steps in RNA processing, including transcription, splicing,

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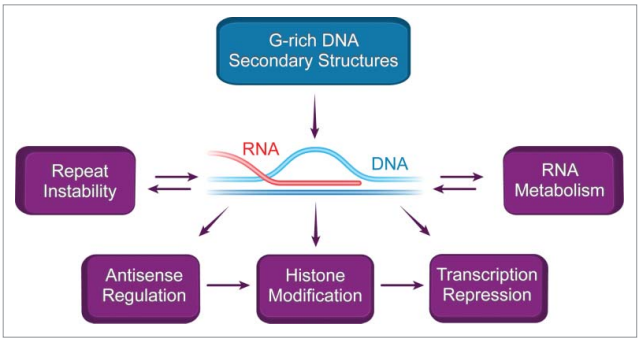

Figure 1. A proposed model for the emerging roles of RNA DNA hybrids in *C9orf72* repeat-expansion-associated diseases. Repeat-containing RNAs (red) invade DNA duplexes (blue) and form RNA•DNA hybrids, R-loops. The R-loops promote repeat instability and may in turn be influenced by variable repeat lengths. These R-loops can initiate transcriptional repression through several regulatory mechanisms, including polymerase pausing/termination, antisense transcription, and histone/DNA methylation. The formation of R-loops is closely tied to multiple aspects of RNA metabolism, including transcription, splicing, degradation, and nuclear transport. Transcripts containing the *C9orf72* repeats could act locally upon the *C9orf72* gene or globally at other genomic sites. Thus, R-loops may contribute to disease through reduced expression of *C9orf72* gene products as well as acquired nucleic acid-based toxicity.

degradation, and nuclear transport, leads to increased R-loop formation,[20-22] suggesting that a balance in R-loop equilibrium is closely tied to RNA homeostasis.

Optimal regulation of R-loops is thought to be necessary for cellular health and proper function. Accordingly, perturbation of R loop-associated factors has been linked to cancer and neurodegenerative diseases. Here we briefly summarize recent advances in R-loop biology and its potential mechanistic link to *C9orf72* hexanucleotide repeat expansion (HRE) diseases, with the aim of providing a current perspective and initiating a discussion on the potentially important connection between R-loop dysregulation and this form of neurodegeneration.

C9orf72 repeat expansion diseases

An expanded hexanucleotide repeat in *C9orf72*, (GGGGCC)n, is the most common genetic mutation identified to date in the motor neuron degenerative disease amyotrophic lateral sclerosis (ALS).[23,24] The *C9orf72* HRE also represents the most common genetic cause of frontotemporal dementia (FTD), which is characterized by degeneration of the frontal and temporal lobes of the brain and is the second most common type of dementia in people younger than 65.[25] Furthermore, the *C9orf72* HRE is linked to rare cases of other neurological conditions, including Alzheimer's disease,[26-29] Huntington's disease,[30] multiple system atrophy,[31] depressive pseudodementia,[32] bipolar disorder,[33-35] and schizophrenia.[36] Given these wide-ranging implications, understanding the molecular mechanisms of *C9orf72* HRE-associated diseases has become a significant challenge in the study of neurodegeneration. Currently, the proposed mechanisms for *C9orf72* HRE-linked pathogenesis include the a loss of function of the *C9orf72* gene products and a gained toxicity of the transcribed HRE, with the latter including RNA toxicity and unconventional poly dipeptide products translated from the repeats.[37-41] However, these pathogenic mechanisms are not mutually exclusive, and studies of their molecular bases are currently underway.

Recently, the *C9orf72* HRE was shown to be capable of readily forming R-loops in vitro.[42,43] The properties of (GGGGCC)n repeats are highly conducive to R-loop formation at the *C9orf72* HRE. The DNA (GGGGCC)n repeats can form stable secondary structures, including hairpins and G-quadruplexes,[42,44,45] which are thought to stabilize the displaced DNA strand and therefore increase stability of the RNA•DNA hybrid duplex. Once formed, the GGGGCC•CCCCGG RNA•DNA hybrid is predicted to be highly stable, given its complete GC content. *C9orf72* HRE repeat length is highly unstable and there is increasing evidence that the expansion leads to reduced gene expression, epigenetic modification, and bidirectional transcription. As we describe below, these cellular processes have been shown in other instances to involve R-loops. Therefore, we propose that R-loop formation as a consequence of the *C9orf72* HRE may underly multiple processes in *C9orf72*-linked neurodegeneration (**Fig. 1**).

Repeat instability

An important step in understanding *C9orf72*-linked diseases is elucidating the origin of the repeat expansion. The typical human *C9orf72* allele contains 2-25 units of the GGGGCC repeat[46]. ALS and FTD-linked alleles have been found to contain up to thousands of repeat units. Interestingly, genetic analysis of the *C9orf72* HRE mutations has identified a common haplotype, but the lengths of the *C9orf72* HRE vary among carriers. This observation suggests a scenario of either unstable repeats from a single founder[47] or a predisposing haplotype shared by different founders.[48] Genetic anticipation, which describes earlier symptom onset in subsequent generations, has been observed in other repeat expansion diseases, but it has yet to be established for the *C9orf72* syndrome. It has been suggested that in individual patients carrying the *C9orf72* HRE, cells from different tissues or different regions of the brain exhibit varying lengths of repeats.[48-50] Irrespective of the neuronal or glial origins of these brain cells, the repeat instability could arise during somatic cell division, post-mitotic stages, or both, as seen in other repeat expansion diseases.

Short-repeat (microsatellite) expansions are responsible for nearly 40 different types of genetic disorders, primarily neurological and neuromuscular disorders.[51-54] Most of these diseases are associated with repeat instability, showing either an expansion or contraction of the repeat region. The instability has been linked to atypical DNA secondary structures that are prone to erroneous replication or repair.[55,56] Also, the formation of R-loops enhances the instability of the (CAG)n repeat,[57] although it remains unclear how R-loops promote repeat instability. A recent study by Reddy et al. suggests that R-loops play a role in repeat instability that is dependent on their processing by certain cellular factors.[43] This study showed that incubating transcriptionally generated R-loops with mammalian cell lysates in a cell-free system could induce a high frequency of repeat length variations on

the R-loop-bearing DNA template. Interestingly, double R-loops generated by bidirectional transcription in vitro were much more susceptible to repeat instability than were single R-loops of either direction. Of note, the *C9orf72* HRE, (GGGGCC)n appeared to be more prone to such R-loop-dependent repeat instability than was the (CAG)n used in the study.[43]

Much remains to be learned about the genesis and mechanism of *C9orf72* hexanucleotide repeat instability in native settings. The occurance of repeat instability depends on cell types, model organisms, developmental stages, and aging, suggesting that a number of cellular factors exist to regulate the instability. Studying these factors in both in vitro and in vivo models, as well as characterizing the instability in patients, will deepen our understanding of the intergenerational and somatic repeat instability observed for patients.

Transcription

R-loops have increasingly been shown to mediate transcriptional pausing or stalling,[58,59] which may contribute to a reduction in the *C9orf72* gene expression in patients' cells carrying the repeat expansion. The *C9orf72* gene uses alternative start and splicing to produce at least 3 transcript variants. V2 (NM_018325.3) and V3 (NM_001256054.1) encode a long isoform of the protein, and V1 (NM_145005.5) encodes a short isoform.[24] According to common annotation, the *C9orf72* HRE, (GGGGCC)n, is located either in intron 1, as for transcripts V1 and V3, or at a promoter region, as for transcript V2. However, the presence of the expanded repeat apparently complicates regulation of *C9orf72* gene expression. For example, there is a reported increase in the usage of alternative transcriptional start sites upstream of the expanded repeat.[60] In addition, most studies report a reduction in individual or all variants of *C9orf72*,[24,37,42,61-68] with a consensus for markedly reduced levels of V2, which is the predominant variant among the 3 transcripts. There is increasing evidence that R-loops can repress transcription, suggesting that this mechanism of repression may contribute to the observed reduction in *C9orf72* gene expression in patients' cells.

R-loops have been shown to negatively regulate transcription at the steps of initiation, elongation, and termination in vitro and in vivo.[69] R-loop-mediated transcriptional regulation has been observed in both normal genes and expanded repeat loci. For instance, the (GAA)n repeat in Friedreich's ataxia has been shown to form R-loops[70,71] and directly inhibit polymerase processitivity.[72-75] Consistent with reduced *C9orf72* gene expression in patients' cells, the (GGGGCC)n repeat exhibits trancriptional stalling in vitro in a length-dependent manner, which may be mediated, in part, by R-loops formed on the repeat sequences.[42] In additon to their direct impact on RNA polymerases, R-loops are also proposed to mediate other mechanisms of transcriptional repression, such as histone methylation.

Histone and DNA methylations

Multiple lines of evidence suggest that R-loops mediate transcriptional silencing through histone methylation.[58,59,76] A (CGG)n expansion, linked to Fragile X syndrome, is positioned within the 5' untranslated region of transcripts from the fragile X mental retardation 1 (FMR1) gene and leads to silencing of the FMR1 gene. R-loops were recently shown to form at this (CGG)n expansion in patients' cells.[58,76,77] Using a human embryonic stem cell-derived neuronal culture system, Colak et al. demonstrated that the formation of RNA•DNA hybrids coincided with the initiation of transcriptional silencing of FMR1.[76] Moreover, this formation of RNA•DNA hybrids was associated with histone H3 dimethylated on lysine 9 (H3K9me2) marks, which have been implicated in R-loop-mediated transcriptional regulation.[58,59,76] Silencing of the FMR1 gene by the expanded repeats depended on neuronal differentiation,[76] and it still remains to be determined how R-loops are regulated during development and other cellular processes.

In another recent study by Groh et al., R-loops were found to form in vivo on (GAA)n repeats in the cells of patients with Friedreich's ataxia.[58] These (GAA)n R-loops were transcription-dependent and colocalized with the repressive histone modification H3K9me2. Furthermore, R-loop formation appeared to precede H3K9 dimethylation.[58] Trimethylation of H3K9, H3K27, and H4K20 has been associated with reduced *C9orf72* gene expression in ALS/FTD patient brain tissues and fibroblasts carrying the expanded repeat.[64] Additionally, H3S10 phosphorylation is thought to influence the modification of surrounding residues and modulate gene expression through activation or repression.[78] Repressive H3S10 phosphorylation was found to be associated with R-loops,[79] and it will be interesting to determine whether these marks are present at the expanded *C9orf72* locus. In brief, repressive histone modifications at the *C9orf72* HRE locus may be initiated as a result of the formation of R-loops, but future studies will be needed to assess this connection.

In addition to histone modification, DNA methylation has been associated with the expanded *C9orf72* repeats in the cells of ALS and FTD patients.[62,68,80-82] There are 2 cytosine-phosphate-guanine (CpG) islands flanking the *C9orf72* repeat locus. The CpG island upstream of the repeat has been found to have increased methylation in a subset of expanded repeat carriers,[62,68,81] while the CpG island downstream of the repeat is unmethylated. The expanded repeat itself is not apparently hypermethylated.[68] Interestingly, R-loops are often found at CpG islands and are proposed to suppress DNA methylation.[5] Understanding the relationship between R-loops and DNA/histone modification at the *C9orf72* locus, as well as the contributions of these factors to disease, will be an important task in future investigation.

Antisense transcript-mediated gene regulation

Production of both sense and antisense transcripts from the expanded *C9orf72* hexanucleotide repeats has been observed in patients' cells.[39,83-86] A genome-wide study in yeast found that RNA•DNA hybrids are enriched in genes that produce antisense transcripts and that the expression of these genes is regulated by the hybrids.[87] A recent study by Skourti-Stathaki et al. reported that R-loops induce antisense transcription, which leads to RNA interference-dependent repressive histone marks over mammalian gene terminators.[59] R-loops were previously found to be

enriched at G-rich RNA polymerase II transcription terminators[18] and, consistent with a role of R-loops in mediating repressive histone marks,[58,76] the R-loops at terminators promoted H3K9me2 marks and heterochromatin structures.[59] Interestingly, this process was mediated by R-loop-dependent antisense transcription, which led to the formation of double-stranded RNAs and the recruitment of DICER, Argonautes, G9a histone lysine methyltransferase, and heterochromatin protein 1γ.[59] Given that the *C9orf72* hexanucleotide repeats have been found to produce antisense transcripts and also display histone methylation, it is possible that R-loop-dependent transcriptional silencing of the *C9orf72* gene is influenced by a mechanism involving these antisense transcripts.

Genome-wide trans-acting RNA●DNA hybrids

Thus far, we have mainly discussed R-loops formed in *cis*, with the RNA moiety either transcriptionally coupled or rehybridized to its DNA template. RNAs can also act in *trans* and form RNA●DNA hybrids at distant genomic sites.[13] This possibility would be increased for repeat-containing RNAs if their cDNA sequences occur at genomic sites other than the original gene. For example, based on alignment searches in the National Center for Biotechnology Information databases, the *C9orf72* (GGGGCC)n repeat, ranging from 3 to 8 units, occurs tens of times in the human genome, a frequency much higher than would be expected by chance based on the size of the genome. In addition, the repetitive nature of the repeat RNAs may facilitate the formation of intermolecular RNA●DNA hybrids in *trans* via non-Watson-Crick hydrogen bonds. It is likely that hybrid secondary structures such as hairpins or G-quadruplexes can be formed between GC-rich RNAs and DNAs even if their sequences are not completely complementary. Irrespective of their specific conformations, genome-wide *trans*-acting RNA●DNA hybrids constitute a possible mechanism for gain-of-function RNA toxicity in the pathogenesis of repeat expansion diseases.

RNA●DNA hybrids in relation to ALS genes

There are several clues that suggest a critical link between R-loops and the genes implicated in ALS and other neurological conditions. The best characterized case is senataxin, an RNA helicase that has an established function in resolving R-loops.[18,88,89] Mutations in senataxin have been linked to ataxia with oculomotor apraxia type 2 (AOA2) and juvenile amyotrophic lateral sclerosis type 4(ALS4).[90] Although the mechanisms of these diseases and the full spectrum of senataxin's functions remain to be elucidated, the R-loop-related transcription and DNA repair functions suggest specific avenues of investigation.

In another instance of R-loop connections to neurodegeneration, a recent study by Salvi et al. showed that the yeast homolog of ataxin-2, Pbp1, functions to inhibit formation of RNA●DNA hybrids.[91] A trinucleotide repeat (CAG)n expansion that encodes a polyglutamine stretch in the ataxin-2 gene is linked to the neurodegenerative disease spinocerebellar ataxia type 2,[92-94] and intermediate-length repeat expansions in ataxin-2 increase the risk for ALS.[95]. Recently, the intermediate-length repeat in ataxin-2 was observed to be a potential disease modifier in *C9orf72* expansion carriers and there is a co-occurrence of the 2 expansion mutations in ALS/FTD patients.[96,97] Human ataxin-2 has been implicated in multiple RNA-processing functions; however, its potential function in modulating R-loops, if confirmed, could provide a mechanistic link among these neurodegenerative diseases.

Finally, RNA●DNA hybrid-specific nuclease, RNase H2, is linked to a severe neurological disease Aicardi-Goutières syndrome.[98] Mutations in 3 components of an RNase H2 enzyme complex have been linked to the disease.[99] The immunological symptoms of the disease suggest that increased endogenous RNA●DNA hybrids can inadvertently trigger innate immune responses.[99] Immune activation, in particular inflammation, is also an important aspect of the pathogenesis of neurodegenerative diseases such as ALS/FTD,[100] suggesting another potential link between R-loop formation and neurodegeneration.

Perspectives

Neurodegenerative disorders that arise as a consequence of the *C9orf72* hexanucleotide repeat expansion are fundamentally nucleic acid diseases. R-loop formation, a seemingly robust feature of the *C9orf72* repeat, may mediate both loss-of-function and gain-of-function pathogenic mechanisms. The *C9orf72* repeat provides exciting new opportunites for future in vitro and in vivo studies that will expand our understanding of RNA●DNA hybrid structures in health and disease..Furthermore, despite a common genetic cause, there is significant variation in disease pathology and symptoms linked to the *C9orf72* HRE. Formation of RNA●DNA hybrid structures at the *C9orf72* locus may trigger multiple divergent pathogenic cascades that contribute to the diversity of *C9orf72* syndrome. Given the upstream position in pathogenic cascades, the *C9orf72* RNA●DNA hybrid may also prove to be a valuable therapeutic target.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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