**RNA-loops (DNA/RNA hybrids) mechanisms, genomic and cellular roles-A review with emphasis on neuropsychiatric diseases**

**Abstract**

RNAs adopt heterogenous folded structures that are essential for function and thus play critical roles in cellular biology. An example of this is the ribosome, a complex, three-dimensionally folded macromolecular machine that coordinates protein synthesis. Advances in RNA biochemistry, structural and molecular biology, and bioinformatics have unveiled other non-coding RNAs whose functions are dictated by their structure. It is not surprising that aberrantly folded RNA structures enable disease.

R-loops are nucleic acid structures encompassing an RNA-DNA hybrid and a displaced single-stranded DNA (ssDNA) (Hegazyet al., 2019). Once thought to be uncommon transcriptional byproducts, but reclassified as prevalent and functionally significant in a variety of eukaryotic and prokaryotic species. During transcription, R-loops naturally form when the developing RNA hybridizes with the DNA template strands; displacing the non-template strand and creating a three-stranded structure. RNA loops are fundamental secondary structural elements that play crucial roles in RNA function and interaction within cells. Recent developments in immunoprecipitation techniques (e.g., DRIP-seq) and high-throughput sequencing have made it possible to profile R-loops throughout the genome, demonstrating their occurrence in both coding and non-coding areas. The RNA loops are involved in a wide range of biological processes spanning genome regulation, physiology and repair. Mounting evidence also supports R-loop deregulation as a frequent, initiating, event during the development of several human pathologies, such as cancer and neurological disorder. Several applications of RNAloop in biomedical research, clinical and diagnostics underscores their application potential. With this background, we update the current available literature nd review diverse aspects of RNAloops traversing from their roles in cell biology and physiology, genome regulation and instability, the cellular mechanisms and methods of detection. Finally, we in detail curate literature of their roles in Human diseases with emphasis on neurodegenerative diseases.

**1.Introduction**

A variety of topological, structural and hybridization events occur during DNA replication and gene transcription. Unwinding of the DNA double helix provides access for polymerase to a template strand, and creates torsional stress that can manifest anomalous formation of “non-traditional” moieties. One such structure is known as an R-loop (Allison and Wang 2019). As RNA polymerase progresses along the DNA double helix, newly transcribed RNA threads back to hybridize with the transiently accessible template strand and displace the non-template strand (Cooper and Hausman 2013). Structurally, the hybrid adopts an intermediate conformation between B-form double-stranded (ds) DNA and A-form dsRNA. This form carries more stability than dsDNA and must be enzymatically resolved in order to restore the native double helix. The presence of RNA-Loop has biological relevances in regulating gene expression and specialized rearrangement events (Crossley et al., 2019). Misregulation of R-loop homeostasis promotes genomic instability is associated with progressive neurodegenerative disorders.Figure-1 represents the dual nature of RNAloop in cells.

Over the course of almost 50 years, R-loop research has developed from a structural curiosity to a crucial component of genomic biology. In RNA paired regions form stems, and the unpaired segments connecting them are called loops. R-loops are three-stranded nucleic acid structures made up of displaced single-stranded DNA (ssDNA) and an RNA:DNA hybrid. There are various types of loops, including: Hairpin loops: Formed when a single strand of RNA folds back on itself, creating a stem and a loop at the end.Internal loops: Occur within a double-stranded RNA region where non-complementary sequences are looped out.Bulge loops: A type of internal loop where only one side of the stem has looped-out bases. Multibranch loops: Formed when three or more stems converge (scitable). These loops, along with other structural motifs, contribute to the complex three-dimensional structures of RNA molecules, which are essential for their stability and function. Hydrogen bonding between nucleobases plays a crucial role in the formation of RNA secondary and tertiary structures (Kornienko et al., 2024); only 60–70% of bases in structured RNA form classic Watson-Crick contacts. Non-canonical Hoogsteen and wobble pairs are common in RNA and contribute to the diversity of folding and function (Olson et al., 2019).

R-loops are now understood to be dynamic structures with crucial roles in gene regulation, replication, genomic stability, and illness, despite previously being believed to be uncommon transcriptional byproducts or artifacts of *in vitro* research (Zhu et al., 2024). R-loops were initially discovered in 1970s when Thomas, White, and Davis (1976) used electron microscopy to visualize these unusual three-stranded nucleic acid structures. In their groundbreaking discovery, they found that mRNA transcripts displaced one DNA strand, creating a loop of single-stranded DNA, when they hybridized back to their DNA templates. These hybrid structures—consisting of a DNA: RNA duplex and a displaced ssDNA—were coined “R-loops” due to the prominent looping of the DNA strand. These findings opened new avenues for exploring nucleic acid interactions beyond classical Watson-Crick pairing and laid the groundwork for later studies on the interplay between transcription and genome structure. Around 2010 witnessed a dramatic transformation in R-loop research with the advent of genome-wide mapping technologies. A key development was the introduction of DRIP-seq (DNA: RNA Immunoprecipitation followed by sequencing) by Ginno et al., 2012, which enabled researchers to detect R-loops at high resolution across the genome. Their study revealed that R-loops are abundant at unmethylated CpG island promoters, especially in human embryonic stem cells, suggesting a regulatory role in gene expression. Subsequent research revealed that R-loops influence DNA methylation patterns, chromatin accessibility, and RNA polymerase II pausing. They are also enriched at transcription termination sites (Skourti-Stathaki et al., 2011; Chen et al., 2015). Normally, mRNP biogenesis machinery targets nascent RNA and processes and prepares the strand for nuclear export. Thus a homeostasis exists between formation and removal of R-loops across the genome.

Topoisomerases and Helicases aid in preventing R-loop formation by reducing exposure times of ssDNA during transcription (Davletgildeeva et al., 2025). RNase H removes R-loops by specifically digesting RNA in helical formation. Together these processes reduce R-loop accumulation during transcription. Factors that lead to pausing of RNA polymerase render conditions favorable for R-loop formation (replication stress, DNA damage, fork collisions, etc)( Saxena and Lee Zou 2022). R-loops nucleate from G-clusters. The loop then extends along GC rich sequences within the gene during elongation (Roy and Lieber 2009). The balance between removal and formation creates equilibrium at nucleation sites across the genome. In general, R loops may interfere with DNA replication, repair and transcription, thus compromising genome integrity and function. Therefore, cells have developed different mechanisms to either prevent or resolve such DNA-RNA hybrids. When any of these mechanisms fail, R loops become a threat to genome integrity and cell proliferation, becoming a potential source of cellular pathologies (García-Muse and Tatiana et al., Cell, 2019). Features that can apply to the displaced ssDNA of an R loop, accumulated evidence suggests that R-loop-mediated replication fork (RF) stalling is a major feature of transcription-replication conflicts and R-loop-induced DNA damage. Apart from the fact that an ssDNA may be highly accessible to metabolites, reactive oxygen species (ROS), DNA modifying enzymes, or nucleases that would increase the incidence of DNA damage (Lindahl, 1993).Figure-2 illustrates the role of R‐loops in genome stability.

Topoisomerase I suppresses genomic instability by preventing interference between replication and transcription (Yadav et al., 2016 ). In order to understand the impact of R loops in cell fate and proliferation, we need to answer questions such as what differentiates physiological from unscheduled pathological R loops, how often unscheduled R loops form along genomes, how cells protect themselves from pathological R loops, or how R loops can affect chromatin structure and compromise genome integrity. (García-Muse and Tatiana et al., 2019). Genome-wide analyses have unveiled R loops are present in normal/wild-type cells at more DNA regions than anticipated. Genome coverage data oscillate from 8% in yeast to 10% in Arabidopsis or 5% in human cells (Wahba et al., 2016; Xu et al., 2017; Sanz et al., 2016). Altogether the data indicate that DNA-RNA hybrids accumulate preferentially at highly transcribed genes, including the rRNA and tRNA loci, as well as in some transposable elements (Ty in yeast), centromeres and telomeres, antisense-RNAs or ncRNAs regions (Chan et al., 2014; Chen et al., 2017). In yeast, the R-loop-prone open reading frames (ORFs) are generally highly transcribed and have high GC content, but the proportion of ORFs observed fluctuates from 20% to more than 65% depending on the study (El Hage et al., 2014). In the case of mammalian cells, R loops are also detected mainly at active genes, and they also accumulate at promoter and terminator regions in which they play a role in gene expression regulation (Rinaldi et al., 2021).

**2.Biological roles of RNA-Loop**

**2.1.Genomic roles of R-Loops**

The myriad roles of RNA loops at genomic, cell biology and physiology levels are summarized briefly in the section.

**Transcription Regulation**

R-loops are now recognized as epigenetic markers and regulators of transcription. R-loops naturally occur during transcription and depending on the context, can either stimulate or suppress gene expression (Li et al., 2023). In their genome-wide R-loop mapping study of human cells, Brian and Luke 2020 report that unmethylated CpG island promoters are enriched in R-loops. Since, these structures identify the 5' ends of active genes, it is possible that they aid in defining transcription start sites and support open chromatin conditions. By either stalling RNA polymerase II or aiding in the recruitment of chromatin modifiers, R-loops could be a component of a regulatory mechanism that modifies transcription. Conversely, in some contexts, R-loops can act as physical barriers, impeding polymerase progression and repressing transcription (Sollier and Cimprich 2015). R-loop involvement in gene regulation is reported in plants (Sun et al., 2013). In *Arabidopsis thaliana*, antisense transcripts, named *COOLAIR*, is found to promote transcriptional silencing of *FLOWERING LOCUS C* (*FLC*) during cold exposure (Csorba et al., 2014). *FLC* is a gene that encodes the floral repressor, FLC, whose epigenetic silencing occurs as a result of effective vernalization, a process of prolonged cold exposure that accelerates flowering. R-loop formation and stabilization at the *COOLAIR* promoter region was found to reduce the expression of these antisense transcripts (Sun et al., 2013). In yeast R-loop formation is found to be responsible for transcriptional blocks in rDNA repeats in the absence of topoisomerase I (Hage et al., 2010).

**2.1.Genome organization, RNA processing and DNA damage.**

Aberrant or excessive R-loop formation can lead to genomic instability (Hegazy et al., 2020). R-loops serve important physiological roles; their dysregulation can threaten the genomic integrity. Unscheduled R-loops can stall replication forks leading to double-strand DNA breaks and rearrangements of chromosomes (Kemiha et al., 2021). R-loop formation is facilitated by factors such as impaired RNA processing, RNA-binding protein dysfunction and histone modification defects. Coordination with RNA processing machinery is necessary to minimize detrimental genomic instability caused by transcription-coupled R-loop creation (Santos-Pereira and Aguilera, 2015). RNA-binding proteins like FUS and TDP-43 along with the components of the THO/TREX complex aid in the resolution of R-loops by encouraging effective RNA export and splicing (Groh and Gromak 2014). Deficits or mutations in these proteins may result in the buildup of R-loops and related genomic stress.

**Class Switch Recombination in Immune cells**

R-loops play a crucial role in promoting immunoglobulin class switch recombination (CSR) in activated B cells (Pavri 2017). They develop at the switch (S) regions of the IgH locus, where they supply ssDNA substrates for AID, an enzyme that triggers DNA breaks and recombination events. The immune system's capacity to react to infections and the production of a variety of antibodies depend on this process.

**Telomere maintenance and TERRA Regulation**

TERRA (telomeric repeat-containing RNA) is a lengthy non-coding RNA that is produced by transcription of telomeres, the protective caps at the ends of chromosomes (Chebly et al., 2022). It has been demonstrated that TERRA controls telomere stability by forming R-loops by hybridization with telomeric DNA. In ALT (alternative lengthening of telomeres) cancer cells, Arora et al., 2014, demonstrated that TERRA-derived R-loops are regulated by RNase H1, an enzyme that breaks down RNA in RNA-DNA hybrids. For telomerase-negative cells, these R-loops may help in homologous recombination-based telomere elongation. They are also necessary for appropriate telomere maintenance.

**2.3.Cellular and Biological Roles**

R-loops play critical roles across various cellular processes, including DNA replication, repair, gene regulation, DNA and histone modifications. These roles have significant implications for stem cell biology and disease pathogenesis, immunogenesis. Additional roles include gene silencing maintenance of genome stability and the formation of epigenome signatures (Chen et al., 2025; Ivanov et al., 2024). They do play essential positive functions required for important biological processes they can also contribute to DNA damage and genome instability. Research evidences suggests that dysregulation of R-loops are involved in a number of human diseases, including neurological disorders, cancer, and autoimmune diseases (Richard and Manley 2017).

R-loop is crucial for maintaining the normal cellular functions. In mouse ESCs, R-loops at polycomb target genes modulate gene repression by influencing the recruitment of PRC1 and PRC2. Removing R-loops decreases these complexes' recruitment, leading to Pol II activation and gene derepression, while stable removal of PRC2 affects only R-loop-negative genes (Skourti-Stathaki et al., 2019). R-loops are emerging as pivotal regulators of stem cell biology. R-loop structures can compromise genomic stability by obstructing DNA replication and transcription processes, leading to replication stress and potential DSBs (Chen et al., 2025).

A significant cause of replication stress is persistent R-loops. They prevent fork advancement, which can result in genomic instability and the buildup of DNA breaks (Chang and Stirling 2017). By using helicases like *Senataxin* and *RNase H* enzymes to unwind RNA-DNA hybrids the cell reduces this danger (Yang et al., 2023). Increased mutagenesis and genomic fragility are linked to deficiencies in these processes. According to Chédin 2017, Histone modifications and higher-order genome structure can be influenced by R-loop interactions with chromatin-modifying complexes. R-loops, for example, have been demonstrated to interact with H3K4me3 and H3K27ac histone marks or recruit polycomb repressive complexes, influencing transcriptional outcomes at particular loci(Kim and Wang 2021). This interaction highlights R-loops capacity to function as dynamic epigenetic regulators.

**2.4.Genome stability**

In addition, R-loops may transiently form in response to double-strand breaks in order to stabilize the damaged location and attract repair components, which will aid homologous recombination (Alonso and Noordermeer 2021). Aberrant R-loop emergence during repair, however, can potentially result in harmful chromosomal rearrangements and translocations (Fang Li, et al., 2023). The R-loop formation efficiency is greatly influenced by DNA end structures, which can range from 2.8% to 73%, and notably higher on sticky ends with 3′ or 5′ single-stranded overhangs compared to blunt ends without any overhangs (Lim et al., 2023). The R-loops can interfere with ongoing-round transcription by extending unidirectionally upstream from the DSB sites and reaching the transcription start site. R-loops have been shown to be linked to histone modifications like histone H3 Ser-10 phosphorylation (H3S10P), which is a known mark of chromatin compaction (Castellano-Pozo et al., 2013). Moreover, the extended R-loops have the ability to endure and maintain their structures, which effectively hinders the efficient initiation of further transcription rounds (Belotserkovskii, et al., 2018). R-loops may also play important role in DNA modification. The DNA methyltransferase DNMT3B1 binds DNA:RNA hybrids less efficiently than dsDNA (Fernandez, et al., 2023). Therefore, R-loop formation in promoter regions can promote gene expression by blocking DNA methylation.

R-loops have been regarded as a threat to genome stability due to the vulnerability of the exposed single-stranded DNA regions to modifications or damages (Anindya R., 2020). Furthermore, replication stress results from the accumulation of R-loops (Promonet et al., 2020). Therefore, R-loops are regarded as detrimental byproducts of transcription, and their formation should be suppressed by topoisomerases and eliminated by helicases and ribonucleases.

**4.Detection methods**

Different methodologies have been developed to detect DNA RNA hybrids *in vivo* that include the isolation and physical analysis of nucleic acids resistant to ribonuclease (RNase) A and sensitive to RNase H (Huertas and Aguilera, 2003); electron microscopy (EM) (Backert, 2002) or chromatin immunoprecipitation (ChIP) and/or immunofluorescence (IF) using an inactivated RNaseH (Chen et al.,2017) and the RNaseH1 hybrid-binding domain (HB) fused to the green fluorescent protein (GFP) (Bhatia et al., 2014). Nevertheless, the most commonly used methods rely on the S9.6 anti-10 nucleotide DNA-RNA hybrid monoclonal antibody (Boguslawski et al., 1986). This antibody has been extensively used for DNA-RNA hybrid immunoprecipitation (DRIP) followed by either qPCR at specific DNA regions or by sequencing for genome wide studies, as well as for IF. These analyses have enabled a relatively precise idea on the distribution of hybrids along the different regions of eukaryotic genomes. Technically, DRIP and IF assays, treatment with RNaseH1, which specifically degrades the RNA moiety of the hybrid, is required because the S9.6 antibody is also able to recognize double-stranded RNAs (dsRNAs) present at high concentration at specific sites (Hartono et al., 2018). Several techniques using next-generation sequencing now exist to map the positions of R loops and answer questions about how their distribution changes between cell types or growth conditions. In footprinting, bisulfite treatment converts cytosine in the displaced ssDNA of the R-loop to uracil, which is read as thymine during sequencing. As with many R-loop driven phenotypes, exogenous RNase H treatment is used to ensure this signal depends on an RNA-DNA hybrid (Yu et al., 2003). Most widely adopted method for R-loop mapping is DRIP-seq, which uses next generation sequencing to map R-loops isolated by S9.6 immunoprecipitation (Mukhopadhyay et al., 2025). In DRIP-seq, nucleic acids are extracted from unfixed cells and gently fragmented using restriction enzymes. After immunoprecipitation, sequencing libraries are created using a standard dsDNA approach. Alternatively, the material can be used for targeted, higher precision quantification by qPCR. Additional methods include, DRIP-RNA-seq (Chan, et al., 2014), RDIP-seq (Nadel et al., 2015) and DRIPc-seq (Sanz et al., 2021) which address both strand-specificity and resolution by sequencing the RNA component of the hybrid instead of the DNA. Finally, bis-DRIP-seq combines in situ ssDNA bisulfite footprinting with S9.6 hybrid pulldown, theoretically improving the specificity by targeting both. Interestingly, there are some differences in where hybrids map depending on the method used bis-DRIP-seq and R-ChIP-seq both involve an *in situ* step and show R-loops to be highly concentrated at gene promoters and almost entirely absent from the 3’ end of genes(Khan and Danckwardt 2022).

**5.RNA-loop cellular regulation mechanisms**

The process of R-loop formation is the result of several factors working together rather than the result of a single factor acting alone. The DNA-RNA hybrid structure is robust and resistant to dissociation because of the three hydrogen bond connections between the C and G bases (Fakharzadeh et al., 2023). Numerous enzymes are essential for DNA-associated physiological processes, and one of the main causes of R-loop formation is the lack of pertinent helicases or RNases (Rinaldi et al., 2020).Certain binding proteins may act as catalysts for the development of R-loops. The production and accumulation may also be impacted by variations in the relative protein content. Replication protein A (RPA), which is widely distributed in eukaryotic cells and is thought to be the protective protein of ssDNA, is one of the proteins that are present after ssDNA formation in eukaryotic cells and keep the DNA in the single-stranded state (Nasheuer et al., 2024). RPA has a high binding affinity for both DNA and RNA during the transcription process. Additionally, RNase H1, an enzyme that binds tightly to DNA-RNA hybrids and eliminates the RNA strand within them, is aided by RPA (Bento, et al., 2019). According to Zacco et al.,2018 TDP-43 has highly conserved RNA recognition motifs (RRMs) that firmly attach to RNA strands. Because of its capacity to bind RNA, the TDP-43 (TAR DNA-binding protein) can encourage the shedding of RNA from the template strand and stop it from cross-linking with ssDNA (Prasad et al., 2019). The stability of R-loops is also aided by certain secondary DNA structures. According to Sato and Knipscheer et al. (2020), G-quadruplex (G4) structures are mostly produced on single strand DNA (ssDNA) and are made up of four guanine bases using the Hoogsteen base pairing principle. According to studies, G4 structures and R-loops at telomeres are formed in part by the loss of ATRX (Yang et al., 2021). Additionally, the G4 structures directly impede transcription and DNA replication, leading to genomic instability (Valton et al., 2016). By causing cells to produce G4 structures, reactive oxygen species (ROS) may also encourage the formation of R-loops, which might then be further boosted by ligands (Wang et al., 2020). The creation of R-loops can be influenced by the DNA sequence. According to recent scientific studies, DNA sequences with a high GC content are more likely to form the R-loop, particularly when GC-rich DNA sequences are transcribed to create GC-rich transcripts (Palmer et al., 2025). In addition, Pol II-transcribed RNA from the telomere terminal region typically contains UUAGGG repeats; this type of RNA is known as telomeric repeat-containing RNA/TERRA. The R-loop is formed when a nascent RNA invades dsDNA, according to the sequence features of TERRA (Gong and Liu.et al. 2023). As an unmethylated promoter sequence often found in the human genome, CpG islands (CGI: C-G and G-C rich sequences) manifests a significant strand asymmetry in the distribution of guanines and cytosines, a property known as GC skew (Angeloni and Bogdanovic 2021). Such a property also makes it a hotspot for R-loop formation.

Transcription-replication collision (TRC).Possible route for excessive R-loop accumulation is TRCs, a crucial pathogenic mechanism that is intimately linked to cell viability and genomic stability (Yea-Lih and Philippe et al., 2021). Inappropriate regulatory systems may produce TRCs, which can halt both transcription and replication and cause additional genome damage when they occur concurrently in the same genomic areas (Hamperl et al., 2017). The negative impacts are more severe and the accumulation of R-loops is likely to occur in head-on collisions, where transcription and replication proceed in opposite directions (Milano. et al., 2024). When transcription and the replication fork are moving in the same direction, co-directional collision takes place, the transcriptome follows the replication fork, and significantly fewer R-loops are generated (Merrikh et al., 2012). Inhibiting BRD4 expression can increase the formation of R-loops and facilitate TRC, DNA damage, and cell death mediated by replication stress and fork slowing.

Splicing factor and relevant RNase SRSF1 (Serine/Arginine-rich Splicing Factor 1)- splicing regulatory factor that can excise longer pre-mRNA transcripts, generating shorter mature mRNA molecules (Kretova et al., 2023).This process accelerates the dissociation of mRNA from the DNA template, thereby facilitating the renaturation of the double stranded DNA. However, some of the longer pre-mRNA transcripts fail to be properly spliced into multiple shorter mature mRNA molecules when SRSF1 is mutated. These unspliced pre-mRNA transcripts often contain enriched G-cluster sequences, which prevent the mRNA from dissociating from the template strand, leading to the formation of R-loop structures (Han, et al., 2023). Additionally, Top I recruitment was impacted by a mutant SRSF1, which resulted in highly twisted dsDNA and ultimately double-strand breaks (DSBs). According to Sorrells et al. (2018), mutations in splicing factors, such as SF3B1, can cause dsDNA breakage and neuronal cell death, which is followed by a continuous buildup of R-loops. As a result, splicing irregularities impact many cellular processes and are intimately linked to genome instability (Shkreta and Chabot. et al., 2015).

**6.R-loops as important risk factors for human diseases**

Numerous biological processes, such as transcription, DNA replication, and epigenetic control, depend on R-loops. As scientific knowledge has evolved over the past ten years, the pathogenic roles of R-loops in human disease have grown in significance. Their significance in physiological cell processes and illness is highlighted by this duality. Cells with abnormalities in regulatory function are more likely to exhibit pathological states (Lloyd et al., 2013). R-loop accumulation results in the formation of transcription arrest complexes, which impede DNA replication and regular transcription processes (Brickner et al., 2022). This exacerbates the disease phenotype and amplifies the pathological state of the defective cells (Zeman and Cimprich, 2014). Disease development is aided by pathological R-loops, which trigger innate immunity (Crossley et al., 2023). The last characteristic shared by many human diseases, including cancer, severe hereditary disorders, aging-related disorders, myelodysplastic syndromes, childhood cancers, Ewing's sarcoma, and neurodegenerative diseases, is the large number of pathological R-loops caused by imbalances in cellular physiological functions (Richard and Manley, 2017). Table 1 provides a summary of the human illnesses linked to the R-loop and the causal agents.   
Briefly the role of RNA loop and mechanisms with associated pathology is described in the following paragraphs.

Cancer-According to Hanahan and Weinberg (2011), cancer cells have high levels of DNA damage and mutagenesis and depend on hyperactive growth factor signaling. R-loops created during transcription damage DNA, which may be a connection between the characteristics of cancer. R-loops have been shown to accumulate and cause DNA damage at estrogen-induced genes in breast cancer cells exposed to high levels of estrogen signaling (Stork et al., 2016). Oncogenic mutations in HRAS also result in R-loop accumulation, DNA damage, and replication stress (Kotsantis et al., 2016). Carcinogenic aldehyde-treated cells break down BRCA2, which leads to the accumulation of R-loops that damage DNA (Tan et al., 2017). R-loop accumulation at halted transcription complexes is another effect of BRCA1 mutations (Zhang et al., 2017). R-loops created during oncogenesis may degrade DNA and apply selection pressure to cancer cells. Several seemingly unrelated splicing factor mutations were discovered to all cause R-loop formation in a study of pre-leukemic myelodysplastic syndromes, indicating a shared mechanism of action (Chen et al., 2018). According to recent research, innate immune and pro-inflammatory reactions are triggered by genomic instability and DNA damage, namely through the activation of the cGAS-STING axis (Li and Chen. et al., 2018).   
Autoimmune Diseases-Mutations in enzymes that break down nucleic acids cause Aicardi Goutieres Syndrome (AGS), a rare inflammatory condition that affects the brain, skin, and immune system. DNA fragments produced from stalled replication forks and cytoplasmic DNA in micronuclei has been directly associated with cGAS-STING activation in AGS cells (Coquel et al., 2018). The genome of AGS cells contains high RNA-DNA hybrids and novel locations where RNA-DNA hybrids occurance overlap with locations where DNA methylation is lower (Lim et al., 2015). The lack of the WAS protein, WASp, results in R-loop accumulation, abnormalities in the splicing of certain genes, and R-loop-mediated DSBs in T helper cells in Wiskott-Aldrich syndrome (WAS) childhood leukemia (Sarkar et al., 2018).   
Blood diseases, Acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), adult T-cell leukemia, and B-cell lymphoma are all linked to R-loop abundance (Lee et al., 2023; Chen et al., 2018). One of the crucial mechanisms for the advancement of R-loop-induced illness is the activation of DDX41-inflammation pathways. In addition to unwinding DNA-RNA hybrids, the helicase dead-box helicase 41 (DDX41) in blood diseases stimulates the cGAMP synthase (cGAS)-Stimulator of Interferon Genes (STING) pathway (Winstone et al., 2024). Furthermore, abnormally high levels of R-loops in blood disorders can result from aberrant expression of transcriptional regulators like SRSF2 and U2 small nuclear RNA auxiliary factor 1 (U2AF1), epigenetic factors like m6A methylation (Hwang et al., 2024), and lncRNAs like HOTTIP (Luo et al., 2022).Figure-4 illustrates R-loops and their by-products in immune functions.

**5.1.Role of R-loops in human neurodegenerative diseases**

Neurodegenerative diseases are associated with the progressive loss of neurons. Whilst R-loops are important regulators of cellular processes, they are also associated with the pathologies of multiple disorders, including repeat expansion, motor neuron, inflammatory, and aging diseases. Decades of research from basic to clinical studies have unveiled key genetic factors and biochemical pathways implicated in NDDs. Eight major hallmarks of NDDs have emerged from these studies: protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death (Wilson III et al., 2023). These hallmarks are highly interconnected, suggesting that neuronal vulnerability stems from a combination of these pathological features. Most of the pathology of NDDs is associated with non-dividing neuronal cells, highlighting the importance of transcriptional processes in underlying disease mechanisms (Firdaus et al., 2024). Recent evidence suggests that R-loops contribute to the pathology of several NDDs.Figure-5 depicts virus mediated RNA loop origin and pathology in the CNS. An increasing body of research associates R-loop dysregulation and mutations in R-loop factors with various NDDs. The vast area is summarized and organized briefly under the subsections.

1.R-loop-associated processes in neurodegeneration—R-loops and transcription— The misregulation of R-loops can trigger a range of transcriptional changes that contribute to neurodegeneration. Most R-loops are formed co-transcriptionally, and these structures can constitute a roadblock to RNA polymerase (Pol) progression (Khan et al., 2022). In conditions including Friedreich ataxia (FRDA), fragile X syndrome (FXS), and C9orf72-associated amyotrophic lateral sclerosis (ALS), it has been demonstrated that R-loops accumulate across enlarged repeats (Cooper-Knock et al., 2015). Given that Pol II kinetics have an impact on splice site selection, R-loops may have an impact on splicing (Yustis et al., 2024). The retention of their host intron in impacted patient cells and brain tissue is caused by CG-rich repeat expansions in myotonic dystrophy type 2 and ALS/frontotemporal dementia (FTD) (Sznajder, et al., 2018). R-loops have the ability to start epigenetic gene silencing as well. The RNA/DNA hybrid that FMR1 mRNA creates in FXS encourages H3K9 dimethylation and FMR1 promoter inactivation. The deposition of repressive chromatin marks and the ensuing silence of the FXN gene are driven by FRDA, R-loop development across the FXN expansion.RNA/DNA helicase senataxin (SETX), mutated in ALS4 and ataxia with oculomotor apraxia type 2 (AOA2), is recruited to R- loops that promote Pol II transcription termination(Richard et al., 2020). Loss of SETX is associated with global R-loop accumulation and elevated Pol II stalling in AOA2 patient cells(Kannan et al., 2024). Finally, R-loops act as promoters for antisense transcription; hence, they highlight a role for these structures in driving the antisense and bidirectional transcription observed at expanded repeats.

2.Repeat instability and R-loops Repeat expansion causes earlier disease onset in subsequent generations and accelerates the course of disease. While transcription through enlarged repeats also encourages instability, DNA replication is a key factor in repeat growth. The formation of R-loops during transcription of these regions has been shown to increase with repeat tract length (Reddy et al., 2011). They promote repeat instability, driving either repeat expansions or contractions and contributing to neurodegeneration (Freudenreich 2019).R-loop formation occurs during transcription, independently of DNA replication, R- loop-mediated instability may be particularly relevant to neuronal cells (Westover et al., 2024). ssDNA exposed by R-loops are targets for cytosine deamination, oxidative stress, and processing by nucleases. Nucleases generate DNA nicks, and subsequent misaligned repair can result in expansions or contractions of repeat regions(R Iyer et al., 2015).Base excision repair (BER) enzymes have also been implicated in processing R-loops, resulting in repeat deletion (Laverde, et al., 2020). xeroderma pigmentosum transcription-coupled nucleotide excision repair (TC-NER) factors, complementation group F and group G (XPF and XPG) flap endonucleases can process R-loops and affect repeat instability (Sollier et al., 2014).

3.R-loops as a cause of genome instability and DNA damage—R-loops are a serious danger to the stability of the genome. Cells have countered this by developing systems that control the development and resolution of R-loops, preventing damage to DNA (Patel, et al., 2022). For instance, helicases like SETX or RNase H can resolve R-loop(Yang et al., 2023). By eliminating the negative torsional tension behind Pol II, which otherwise encourages the annealing of the nascent RNA with the DNA template, Topoisomerase I (Top1) inhibits the creation of R-loops. Furthermore, by attaching to the RNA as it leaves the polymerase, additional RNA processing factors help prevent the development of R-loops(Shafiq et al., 2017). Increased R-loop-related DNA damage in NDDs is associated with mutations in a number of R-loop regulators, such as SETX, RNase H2, fused in sarcoma (FUS), and TAR DNA-binding protein 43 (TDP-43)(). R-loops cause DNA damage in a number of ways. DNA breakage and transcriptional stress can be brought on by R-loop accumulation, altered Pol II kinetics, and Pol II stalling (Zhao et al., 2022). Because neurons consume large amounts of oxygen, they are especially vulnerable to the accumulation of transcriptional double-strand breaks (DSBs) (Zhao et al., 2023). These DSBs can trap transcription-blocking topoisomerase cleavage complexes (Top1ccs) by producing reactive oxygen species (ROS) (Cristini, et al., 202o). A number of NDDs, including ALS/FTD and spinocerebellar ataxia with axonal neuropathy type 1 (SCAN1), show transcriptional DSBs, R-loop misregulation, and impaired Top1cc elimination(Yeo, et al., 2014).The exposed ssDNA that R-loops release is vulnerable to DNA damage and mutagenesis due to the activity of nucleases and enzymes that change DNA (Chatzidoukaki et al., 2021). In TC-NER, scheduled R-loops can be converted into DSBs via XPG and XPF (Lin and Pasero 2014). A mechanism related to multiple NDDs, mutations in TC-NER factors cause R-loop accumulation and DSBs. Loops are known to have an impact on DNA repair mechanisms and to be a possible cause of DNA damage. DDR factors can be recruited via RNA/DNA hybrids created by de novo transcription or hybridization of pre-existing nascent RNA at DSBs (Stirling and Hieter 2016).

4.R-loops, cell death, and neuroinflammation. R-loops are becoming more widely acknowledged as inflammatory mediators. Early studies showed that synthetic RNA/DNA hybrids directly bind to the DNA-sensing receptor cyclic GMP-AMP synthase (cGAS), triggering its activation (Mosallanejad, et al., 2022). Additionally, Toll-like receptor 9 (TLR9) and NLR family pyrin domain-containing 3 (NLRP3) have been implicated in immune responses to viral and bacterial RNA/DNA hybrids (Vanaja, et al., 2014). Misregulation of R-loop homeostasis in cells results in the formation and cytoplasmic release of R-loop by-products, such as RNA/DNA hybrids or ssDNA, which directly trigger inflammation in neurodegeneration (Zhang et al., 2025). Autoimmune disorder AGS with RNase H2 mutations results in the accumulation of R-loops, which are processed by XPG and XPF, as well as micronuclei formation, initiating cGAS/STING and NLRP3 inflammasome signaling (Bradley and Savage 2023). XPF and XPG process enhanced nuclear R-loops in SETX-mutated AOA2 patient cells to produce RNA/DNA hybrids, which are then actively trafficked into the cytoplasm (García-Muse, Andrés Aguilera 2019). When cGAS and TLR3 recognize these hybrids, interferon regulatory factor 3 is activated, which results in immunological reactions and cell death. When transposable elements (TEs) in neural progenitors are abnormally mobilized in Alzheimer's disease, cytoplasmic RNA/DNA hybrids build up and activate the cGAS–STING pathway and apoptotic signaling.

5.Protein aggregation R-loops: Proteins must be disrupted to go from liquid-like droplets to aggregates in order for cells to function normally; an imbalance can result in the creation of protein aggregates in NDDs. Intrinsically disordered regions (IDRs), which promote liquid–liquid phase separation (LLPS) and condensate production, are frequently found in proteins linked to NDDs. IDR-containing proteins, which can create membrane-less R-loop foci via LLPS and are crucial for coordinating R-loop-related events, are more abundant in the R-loop proteome (Basha et al., 2025). The primary R-loop binding site, for instance, is located in the C-terminal IDR of fragile X mental retardation protein (FMRP), which may alter R-loop processing and encourage LLPS (Dettori et al., 2021).

6. Protein aggregates may occur as a result of mutations in R-loop regulators. Mutations in FUS linked to ALS impair poly (ADP-ribose) polymerase (PARP)-dependent DDR signaling, increasing DNA damage and causing FUS to mislocalize, which encourages protein aggregation (Naumann et al., 2018). Protein aggregation may be directly influenced by R-loops. Furthermore, elevated transcriptional activity in ATM-mutant cells and brain tissue activates PARP enzymes by increasing ROS, RNA/DNA hybrids, and ssDNA breaks (Woolley, et al., 2023). RNase H1 overexpression was demonstrated to reduce aggregation formation in these SETX-depleted cells, indicating once more a reliance on R-loops. NDDs with R-loop misregulation are also found to exhibit altered autophagy and proteolysis (Barmaki et al., 2023). For instance, models of C9orf72-related illness with elevated R-loops showed accumulation of p62, a protein that mediates the effective autophagic clearance of protein aggregates.

7. R-loops, reactive oxygen species, and mitochondrial dysfunction— Given the high metabolic demand of neuronal cells, mitochondrial dysfunction is a common hallmark of NDDs (Xu et al., 2024). Mitochondrial dysfunction can lead to deleterious levels of ROS, a source of DNA damage (Nissanka et al., 2016). R-loops can be both damaged and induced by ROS. Due to the presence of exposed ssDNA, R-loops are highly susceptible to ROS-induced damage, most frequently 8-oxoguanine (8-oxoG) formation (Poetsch 2019). The accumulation of this damage has been suggested to alter R-loop processing. 8-oxoG adducts impair the recruitment of the R-loop processing enzyme RNase H1 to R-loops in mitochondrial DNA (mtDNA), eliciting R-loop accumulation (Renaudin et al., 2021).

**Applications of RNA loop**

Recent advances of biological drugs have broadened the scope of therapeutic targets for a variety of human diseases. Recent shift in RNA-based therapeutics several RNA variants including RNAloop are under clinical investigation for diseases ranging from genetic disorders to HIV infection to various cancers (Zhu et al., 2022). RNA loops, particularly in the form of aptamers or RNA nanoparticles, are being explored as targeted drug delivery agents due to their ability to bind specific molecules and facilitate cellular uptake. Advantages of the method include delivery to targeted cells, precise therapeutic payloads and improved treatment efficacy and reduction of off-target effects (Xin Li et al., 2022). RNA loops are employed in RNA-derived oligonucleotides as tools for (antisense/small interfering RNA) are currently designed for a number of human diseases (Ertural et al., 2025).

In the diagnosis of cancer RNAloops represent a potential biomarker for determining the prognostic outcomes in the XLT-WAS(X-linked thrombocytopenia (XLT)) clinical spectrum (Struve et al., 2021). R-loops have been identified to correlate with MM’s (Multiple myeloma) progression (Bruno et al., 2022). Unravelling the origin of genetic alterations from point mutations to chromosomal rearrangements is greatly enhanced by the discovery of RNA-DNA hybrids (R-loops) that behave as hotspots of genomic instability (Boros-Oláh, 2019). Embryonal tumours with multilayered rosettes (ETMRs) targeting with R-loops with topoisomerase and PARP inhibitors is now suggested as an effective treatment strategy for this deadly disease (Lambo et al., 2019). Finally, manipulating R-loop dynamics has potential in several areas of stem cells viz., therapeutics, stem-cell stability and differentiation efficiency. In some diseases, mutations can disrupt R-loop formation, leading to genomic instability and disease progression. By correcting these R-loop abnormalities, researchers could potentially develop new therapeutic strategies (Chen, et al., 2025).

**Conclusion**

R-loops are DNA–RNA hybrids that play multifunctional roles in gene regulation, including replication, transcription, transcription–replication collision, epigenetics, and preserving the integrity of the genome. The aberrant formation and accumulation of unscheduled R-loops can disrupt gene expression and damage DNA, thereby causing genome instability. Recent links between unscheduled R-loop accumulation and the abundance of proteins that modulate R-loop biogenesis have been associated with numerous human diseases, including various cancers. Although R-loops are not necessarily causative for all disease entities described to date, they can perpetuate and even exacerbate the initially disease-eliciting pathophysiology, making them structures of interest for molecular diagnostics. They have emerged as swiss-army knife to cells with broad functional spectrum functions in genome organization, gene regulation, and genome integrity. Additional and precise insights into the mechanisms, and proteins involved will foster basic and application in clinical diagnosis. The abundance of R-loop-binding proteins and can also be exploited as a potential biomarker for diseases.

From a diagnostic point of view scope for further technical improvements are required for example, it would be desirable to acquire techniques that can differentiate between scheduled and unscheduled R-loops, techniques that permit the detection of R-loops from circulating cells, or techniques that allow for detection from widely available clinical (paraffin-embedded) material. It seems possible that perturbations of R-loop biology could also confer detrimental effects during early (human) development. Such effects are not normally searched for, e.g., in human fetal tissue, and hence the further evolution of technologies used to detect R-loops could provide novel insights into the biology and consequences of scheduled and unscheduled R-loops. While several experimental methods are now available to detect, quantify, and study R-loop dynamics, the structural and functional characterization of an R-loop still remains a major challenge. Along these lines, studies that structurally characterize and target R-loops with the help of systematic prediction and detection pipelines will enable development of new clinically relevant therapeutic probes.

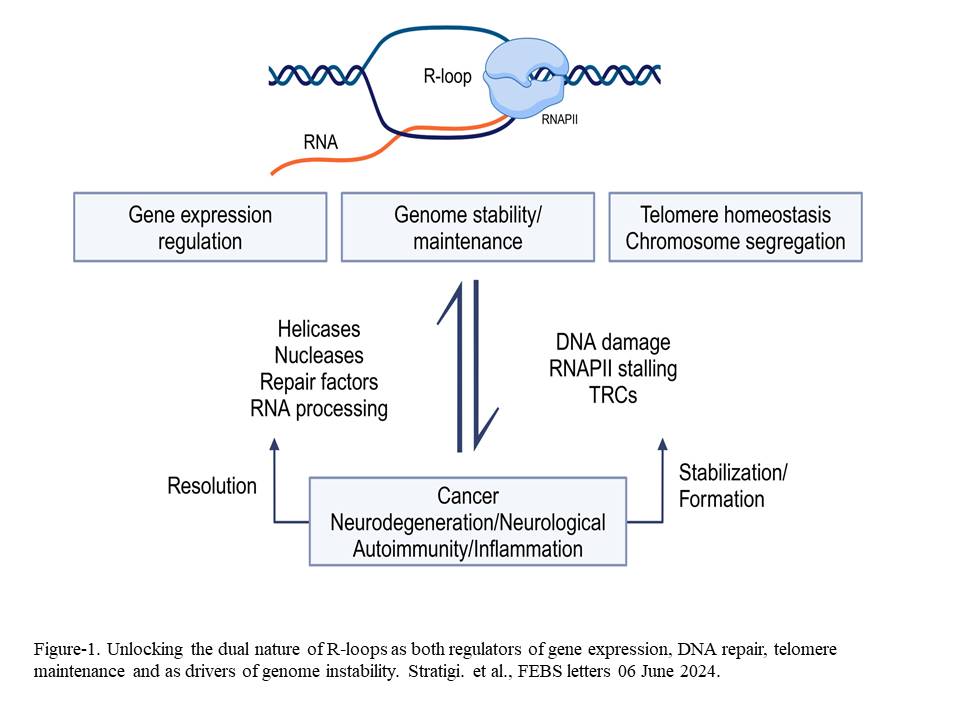
The review has not covered perturbations of R-loops exhaustively or the detection methods. Our major focus was to infer cellular and genomic insights into pathology and disease biology of neurodegenerative diseases. Considerable progress has been made in understanding the complexity and regulation of R-loops and their resulting biological functions. With burgeoning genome sequencing of genomes across tree of life and availability of data it could be expected it will fuel basic and clinical research on RNA loop.

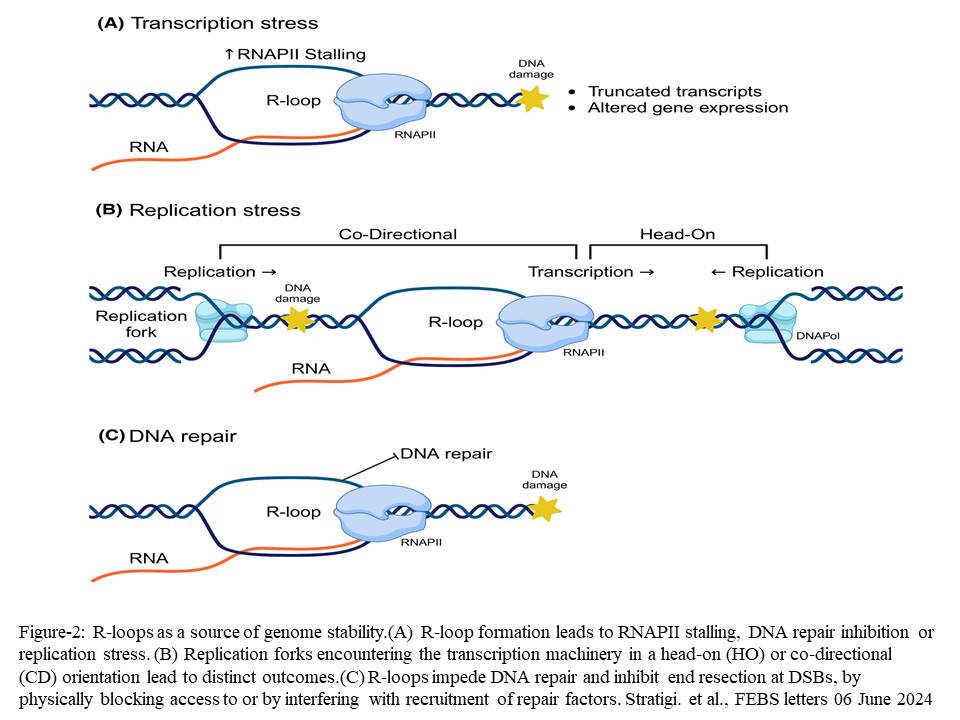
**Ethics-Declaration:** No Human or animal study was conducted hence no ethics required.

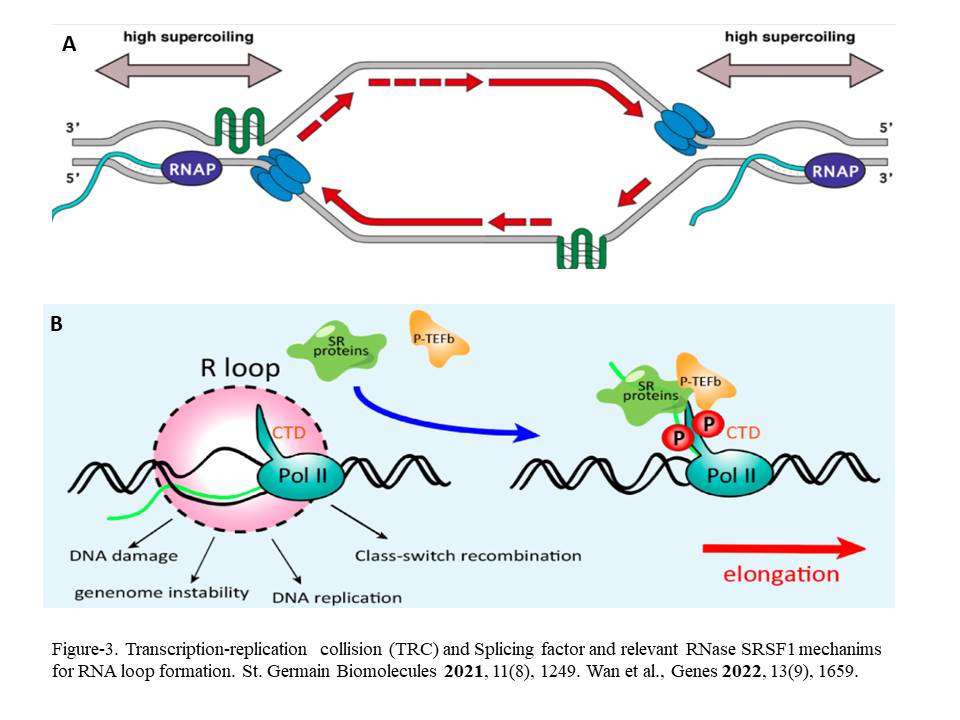
**Tables and figures.**

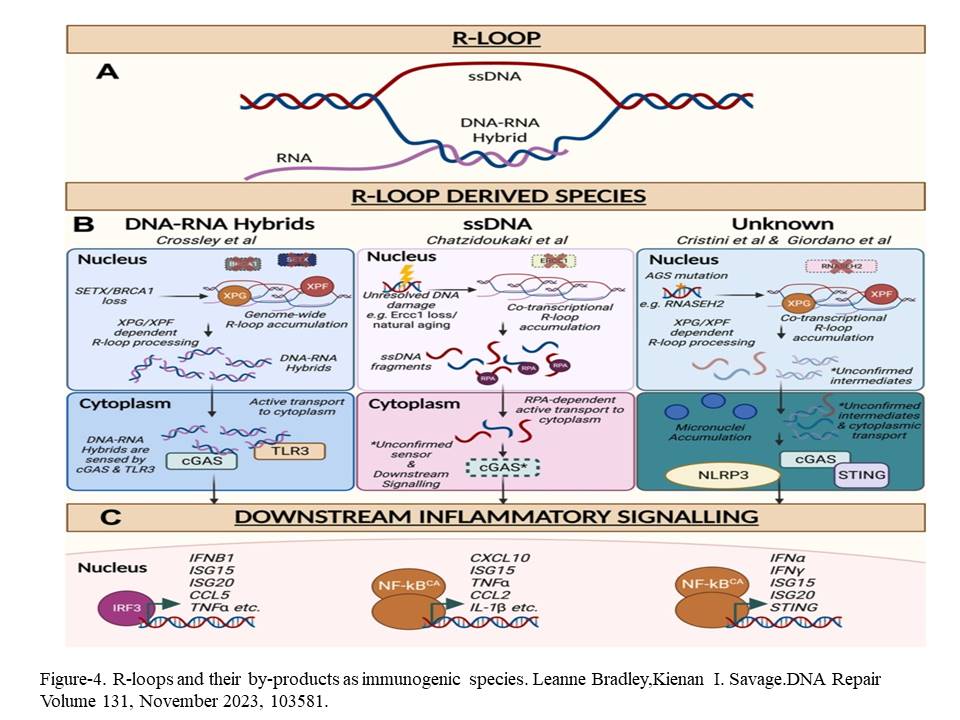
**Table.1-Brief list of Human diseases associated with RNA-loop.**

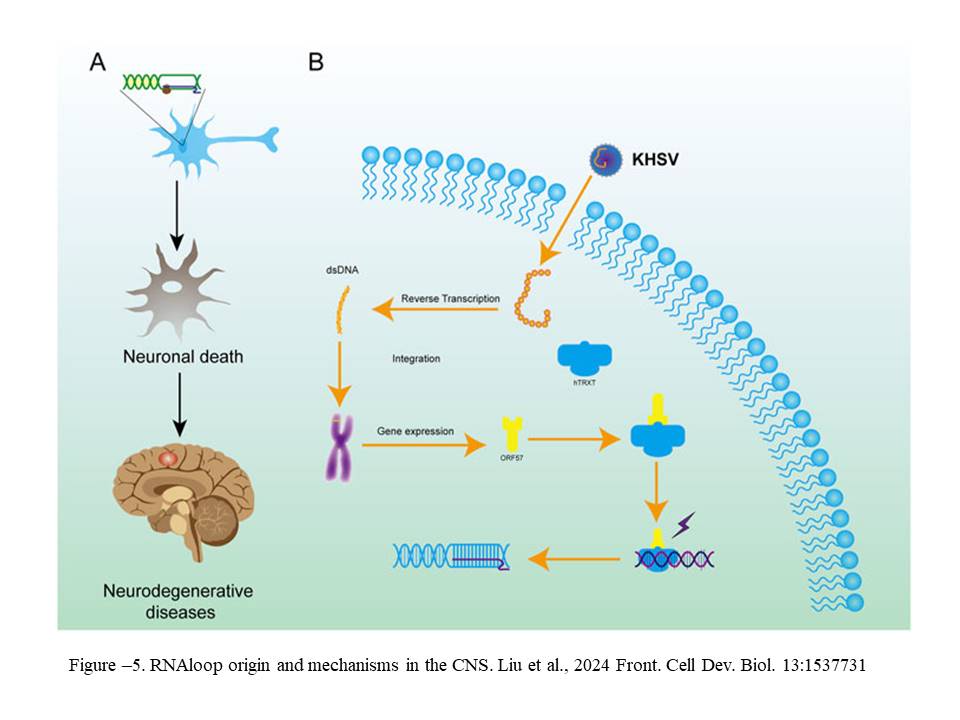
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| --- | --- | --- | --- |
| Sl.no | Disease/Phenotype | RNA-loop factor/Mechanism | Reference |
| 1. | ALS and FTD | C9ORF72/repeat expansion induce aberrant transcriptional interference, leading to DNA damage | Chiara Beghѐ et al., 2025  Tatiana Garcı´a-Muse1 and Andre´s Aguilera 2019 |
| 2. | AOA2 | SETX/ Recessive mutations reduce helicase activity, leading to elevated levels in AOA2 cells |
| 3. | FXS | (CGG)n > 200 expansion  FMR1 silencing and repeat contraction. Global accumulation of R-loops and DSBs |
| 4. | SCAN1 | TDP1 elevated Top1cc levels and DSBs |
| 5. | BRCA1 | BRCA1  Insufficient processing and accumulation of co-transcribed DNA damage. |
| 6. | BRCA2 | BRCA2  Interferes with the regulation of RNAPII, and exacerbates genome instability. mRNAexport, leading to genome damage. |
| 7. | SRSF1 | The downregulation leads to the accumulation of R-ring dysregulation |
| 8. | AML and MDS | DDX41/replication stress, DSB, and remodeling of inflammatory signaling pathways |
| 9. | Xeroderma pigmentosum | XP/Processes R-loops to limit their levels. |
| 10. | Immunodeficiency centromere instability, and facial anomalies syndrome (ICF) | ICF/ RNA: DNA hybrids promote damage and instability at telomeric regions in ICF. |

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