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G-Quadruplexes in RNA Biology: Current Developments and Prospects

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Abstract

Four-stranded structures called RNA G-quadruplexes (RG4s) are known to regulate DNA-related activities and gene expression mechanisms ranging from transcription to protein synthesis. Targeting these structures for therapeutic purposes is an appealing option because of their potential to shape cellular processes related to disease development through their influence on RNA biology. Here, we provide an overview of the state of the art regarding RG4s, emphasizing the most recent findings that lend credence to the idea of transient structures that dynamically fluctuate in cellulo, their interactions with RNA modifications, their function in cell compartmentalization, and their dysregulation affecting the host immune response. We highlight RG4-binding proteins as effectors of their biological functions and determinants of their transient conformation.

Keywords: RNA Biology; G-Quadruplexes; DNA

Introduction

According to the central dogma, "DNA encodes RNA, RNA encodes protein," RNA is a necessary molecule for the transmission of genetic information within cells. In addition to acting as a link between DNA and protein, RNA is vital to a cell's ability to control this information in both qualitative and quantitative ways, making it a crucial hub for process control within the cell. The unintended consequence of RNA's primary function is that it is prone to vulnerability, which makes it a potential source or accomplice in a number of dysfunctions that result in human diseases [1,2].

Methodology

Non-canonical structures known as RNA G-quadruplexes (RG4s) are becoming more and more significant in the fields of RNA biology and disease. Stacks of guanine tetrads (G-quartets) bound together by Hoogsteen hydrogen bonds form these stable four-stranded conformations. The first factor driving this growing interest is the abundance of these structures, which number in the thousands in mammalian transcriptomes. This, along with their enrichment in specific RNA regions (untranslated regions, in particular or classes (mRNAs, non-coding RNAs has added to the growing body of evidence suggesting that RG4s are ubiquitous and may even have biological significance. A second explanation is that RG4s are tunable, meaning that ligands and cations can regulate how they fold.

Their identification and characterization as important regulators of cellular physiology in the context of health and disease has been made possible by this, and it has also created opportunities for their use as targetable molecular switches for therapeutic purposes. Research conducted on individual mRNAs or at the transcriptome level has generally agreed that RG4s are crucial regulators of every post-transcriptional step. There, they can alter the genome's coding capacity and regulate when, where, and how much protein needs to be synthesized. A number of diseases are linked to disruptions in cellular processes caused by misregulation of RG4-mediated RNA biology [3].

These structures have gained prominence in newly developing fields, frequently straddling several disciplines, and have the potential to significantly influence RNA research in the coming ten years. RG4 research has been coordinated with other novel directions in RNA biology due to the resurgence of interest in determining the RNA protein partners. The development of new technologies that capture RBPs at the system-wide level has undoubtedly been the driving force behind the prominence of these factors. From transcription to protein synthesis, RG4s are able to control every stage of gene expression, including pre-mRNA maturation [which includes 3′-end processing, which adds a poly-A tail and removes introns (shown in red) through splicing], export of mature transcripts into the cytoplasm, mRNA transport, translation, and stability of localization. These regulatory mechanisms might be dependent on RG4s present in non-coding RNAs like miRNAs (miR) as well as mRNAs. In addition to controlling transcription (nuclear and mitochondrial), RG4s can influence other DNA-related processes like telomere elongation, DNA replication, and recombination when they are found in telomeric repeat-containing RNA (TERRA) or at DNA/RNA hybrid structures (R-loops). The primary RG4 partners are RNA-binding proteins (RBPs), which support them in all cellular processes and control the balance between their structured and unstructured forms [4-7].

RG4s, in turn, have the ability to control RBP activity through sequestration mechanisms. According to recent findings, RG4s play a significant role in the biology of mitochondrial RNA, in phase separation-mediated condensate formation, and in RNA modifications that are essential for gene expression pathways. RG4-mediated regulation can impact multiple cellular processes (blue box) and consequently have an impact on pathological conditions linked to human diseases (purple box), potentially in a synergistic or competitive manner with RBPs. Abbreviations: FXS (fragile X syndrome); FTD (frontotemporal dementia); ALS (amyotrophic lateral sclerosis).

Dynamics of RG4 folding

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All in all, these investigations indicate that RNA structures, RG4s or otherwise, have the capacity to form secondary structures when given the chance. However, in vivo, cellular components present a challenge to mRNAs because they need to unfold in order to perform their messenger function. These components can change mRNAs into an alternate Watson-Crick base pair structure or a linear form. RBPs became prominent candidates to control RG4 folding in cellule due to their abundance and capacity to control all post-transcriptional gene expression steps. This allowed for a number of studies to characterize the RG4-binding protein machinery using unbiased RNA affinity proteomic-wide approaches (also known as RNA purification coupled with mass spectrometry, or RP-MS [8].

These investigations supported the idea that some RBPs are involved in moving RG4s toward an unfolded state while also providing evidence of transient RG4 folding. These findings were corroborated by more recent in cellulo RG4-capturing techniques and live-cell imaging of RG4 folding and unfolding. Using the RP-MS method, these were recently discovered to be RNAs in which 7-deaza-guanines inhibited RG4 structuration. The RG4 is first unwound by the RNA helicase DHX36, which is followed by the binding of hnRNP H/F (heterogeneous nuclear ribonucleoprotein H/F). This mechanism keeps the RG4 unstructured and controls the translational efficiency of mRNAs that are involved in aggressive forms of brain tumors. This study revealed this sequential mechanism. For CNBP, a similar "bind-unfold-lock" mechanism was also proposed, leading to an increase in protein synthesis. RNA helicases have been shown to be significant participants in the RG4 dynamics associated with mRNA translation, and RBPs may have a role in their recruitment on particular mRNAs that contain RG4 [9,10].

Results

The discovery that RG4 folding regulates the expression of transcripts essential to human pathologies, including those encoded by the tumor suppressor TP53, the oncogene NRAS, and the Epstein-Barr virus (EBV) protein EBNA1, first raised suspicions about the significance of RG4s in disease. Numerous models have been put forth to explain how RG4s influences various diseases. This includes trans-mechanisms that either use RG4s to sequester gene expression regulatory protein factors or result from the mutation or altered expression of RG4-binding proteins. Cis-mechanisms involve RG4s resulting from repeat expansion mutations in the untranslated regions, which modify mRNA translation (by blocking it or inducing alternative translation initiation). The cell cycle, apoptosis, differentiation, proliferation and survival, and other processes are among those that are hijacked by abnormal RG4 regulation. Apart from neurodegeneration, microbial pathogenesis, and cancer, current research suggests that RG4 dysregulation may also have an impact on obesity and congenital heart disease.

Discussion

According to recent research, RG4s might be involved in the immune evasion tactics used by cancer cells or pathogenic organisms to elude the host immune system. When it comes to viruses, RG4s suppress the expression of viral proteins, some of which limit the presentation of antigen to cytotoxic T cells and thus modulate immune responses. This permits the virus to survive in infected cells and evade detection by the host immune system. The viral proteins EBNA1 and LANA, which are functional homologs of EBV and Kaposi's sarcoma-associated herpesvirus, respectively, have been linked to two distinct mechanisms. The first takes advantage of RG4s' capacity to prevent these proteins from being translated in the mRNA coding sequences for EBNA1 and LANA. By adjusting RG4's folding, the structure-immune function relationship.

Host cell protein factors (hnRNP A1 and nucleolin for LANA and EBNA1 mRNAs, respectively) participate in this regulation by interacting with RG4 structures, though the molecular mechanism is still unclear. This is in line with the finding that terms linked to viral infection have an overrepresentation in datasets on cellular RG4-protein interactions. Further research bolsters the idea that nucleolin functions as a host factor for antiviral immunity and implies that viral infection controls the expression of nucleolin. According to the suggested model, hepatitis C virus infection induces nucleolin, which binds to viral core RG4s and suppresses the virus's ability to replicate.

Conclusion

The second mechanism suggests that viral proteins bind to RG4s directly. This was expected for EBNA1, but it has only been thoroughly shown for LANA recently. LANA binds its mRNA through this RG4-binding activity. Thus, by competing with hnRNP A1 for association with RG4s at the LANA mRNA and mRNA sequestration in the nucleus, LANA self-regulates its expression .The mechanism pertaining to the nsp3 of SARS coronavirus has also been documented for SARS-CoV (severe acute respiratory syndrome coronavirus) [90] and SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) . The co-optation of host proteins and LLPS-dependent viral RNA packaging may also be facilitated by the interaction between RG4s and viral proteins. Examining whether, when, and how SARS-RG4 interactions impair the immune response of host cells is crucial, given that the SARS-CoV-2 coronavirus is the primary cause of the coronavirus disease 2019 (COVID-19) pandemic and that the expression of host genes in SARS-CoV-2-infected cells is severely inhibited.

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