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Molecular Determinants of RNA G-Quadruplex Formation and Its Role in Translational Regulation of Oncogenes

Ana Costa, Mikhail Petrov, Maria Santos, Tariq Mahmoud

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ABSTRACT
RNA G-quadruplexes (rG4s) are non-canonical secondary structures formed by guanine-rich sequences in RNA molecules. These structures play a crucial role in post-transcriptional regulation, particularly in the translation of oncogenes. Emerging studies indicate that rG4s influence mRNA stability, localization, and translational efficiency, thereby contributing to oncogenesis and cancer progression. This review explores the molecular determinants governing rG4 formation, their mechanistic impact on oncogene translation, and potential therapeutic interventions targeting rG4 structures for cancer treatment.

INTRODUCTION:

The role of RNA secondary structures in gene regulation has gained substantial attention in recent years. Among these structures, RNA G-quadruplexes (rG4s) are of particular interest due to their ability to modulate translation by interacting with RNA-binding proteins and ribosomes. Several oncogenes, including MYC, KRAS, and BCL-2, harbor rG4-forming sequences within their untranslated regions (UTRs), which influence their expression. This paper aims to delineate the molecular basis of rG4 formation and elucidate its functional role in oncogene translation.

2. Structural Basis of RNA G-Quadruplex Formation

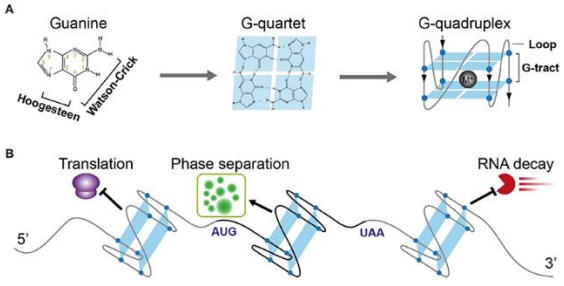

Fig. Structural Basis of RNA G-Quadruplex Formation

2.1 Sequence and Structural Determinants

rG4s are formed by guanine-rich RNA sequences that stack into tetrad arrangements stabilized by Hoogsteen hydrogen bonds. The stability of these structures depends on factors such as loop length, sequence composition, and cationic interactions,

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particularly with potassium (K+) ions.

2.2 Biophysical and Computational Approaches for rG4 Prediction

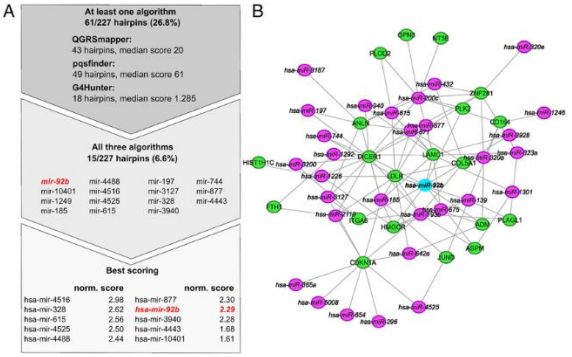

Fig. rG4 Prediction

Experimental techniques such as circular dichroism (CD) spectroscopy, nuclear magnetic resonance (NMR), and single-molecule fluorescence have been instrumental in studying rG4 dynamics. Additionally, computational tools like QGRS Mapper and G4Hunter aid in the genome-wide identification of potential rG4-forming sequences.

3. Role of RNA G-Quadruplexes in Oncogene Translational Regulation

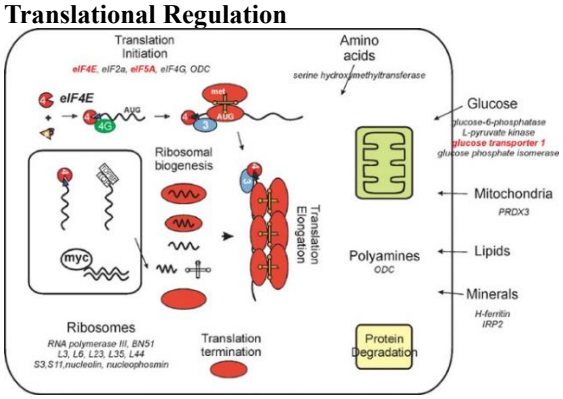

Fig.Oncogene Translational Regulation

3.1 Impact on Ribosome Stalling and Translation Inhibition

rG4s located in the 5' UTRs of oncogenes are known to impede ribosome scanning, leading to reduced translation initiation. This phenomenon has been observed in the MYC oncogene, where rG4-mediated repression directly correlates with decreased protein synthesis.

3.2 Interaction with RNA-Binding Proteins and Helicases

Specific RNA-binding proteins, such as DHX36 and FMRP, regulate rG4 unwinding and influence translation. Helicases like eIF4A and DHX36 are crucial for resolving these structures to ensure proper gene expression.

4. Therapeutic Targeting of RNA G-Quadruplexes in Cancer

4.1 Small Molecule Stabilizers and Their Effect on Oncogene Translation

Several small molecules, including BRACO-19 and pyridostatin, have been identified as rG4 stabilizers. These compounds selectively bind rG4 structures, inhibiting oncogene translation and inducing apoptosis in cancer cells.

4.2 RNA G-Quadruplexes as Biomarkers for Cancer Diagnosis

rG4 structures serve as potential biomarkers for cancer detection and prognosis. Advances in high-throughput sequencing and imaging technologies have facilitated the identification of rG4-enriched transcripts in tumor samples.

5. CONCLUSION AND FUTURE DIRECTIONS:

RNA G-quadruplexes (rG4s) are non-canonical secondary structures that play a crucial role in gene regulation, particularly in oncogenes. Understanding the molecular determinants of rG4 formation is essential for deciphering their role in cancer progression and therapeutic intervention. These structures influence key cellular processes such as transcription, translation, and mRNA stability, making them attractive targets for cancer treatment.Recent studies have shown that rG4s are prevalent in untranslated regions (UTRs) of oncogene transcripts, where they regulate gene expression by affecting ribosome binding and translation efficiency. The identification of specific nucleotide sequences, structural stability factors, and interactions with cellular proteins is critical for targeting rG4s with high specificity. Small molecules that stabilize or destabilize rG4 structures have demonstrated potential in modulating oncogene expression, opening new avenues for drug discovery.

Future research should focus on designing rG4-targeted therapeutics that selectively modulate their function without disrupting normal cellular processes. Additionally, integrating rG4-based biomarkers into clinical oncology could enhance cancer diagnosis, prognosis, and personalized treatment strategies. Advanced computational and experimental approaches will further aid in uncovering novel rG4 targets, ultimately contributing to more effective and precise cancer therapies.

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