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Unlocking the power of G-quadruplex for anti-HIV1 development

Kaihong Ooi[1,*], Yu Qi[2]

[1]*University of Malaya, Kuala Lumpur, Malaysia*
[2]*University of Sanya, Sanya, China*
[*]*Corresponding author*

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Abstract: The role of G-quadruplexes (GQP) in the life cycle of other viruses has led to the speculation that they may also have a function in the HIV genome. This paper aims to write-up on the potential of G-quadruplex as a potential anti-viral development. This paper narrates on (1) innovation of G-quadruplex detector, (2) location of G-quadruplex in HIV genome, (3) evidence and therapeutic approach using GQP as anti-HIV, and (4) contradiction on G-quadruplex utilization. The results of this investigation offer a quick insight on the use of G-quadruplex as a target and highlighting the potential of such intervention for antiviral treatments.

1. Introduction

The presence of G-quadruplexes (GQPs) in genetic sequences has garnered significant attention due to their potential as targets for antiviral strategies. GQPs consist of specific arrangements of guanine nucleotides, with at least three Gs and spacers of one to seven nucleotides between them, as depicted in Figure 1. Emerging evidence has demonstrated the ability of GQPs to suppress replication of SARS-CoV, influence transcription and replication, and affect alternative splicing in the extensive control region of the HPV genome through their interaction with the E1 helicase. Similarly, GQPs bind to and disrupt critical components of viral replication in Epstein-Barr virus (EBV/HHV-4), leading to reduced EBNA1 production, hinder the attachment to the 3C proteolytic enzyme in Hepatitis A virus, and impede NS1 activity while reviving the production of interferon, thereby activating the host's natural defense mechanism against Influenza A virus.

Despite advances in Pre-Exposure Prophylaxis (PreP) and Antiretroviral Therapy (ART), HIV continues to pose a challenge owing to drug-resistant mutations, treatment-related comorbidities, reactivation of dormant viral replication, and medication adherence concerns. G-quadruplexes (GQPs), which are formed by the interaction of four guanine nucleotides in diverse DNA and RNA regions, have surfaced as a possible HIV treatment.

Given the importance of GQPs in other viruses' lifecycles, it is fair to infer that they may likewise impact the HIV genome. Researchers have the potential to identify novel therapeutic development pathways that might overcome the current problems in HIV therapy by extensively researching the involvement of GQPs in the HIV-1 genome. Taking advantage of the potential of GQPs as antiviral targets is a promising path toward improving the quality of life for people

affected by HIV/AIDS and reducing the global burden of this devastating disease.

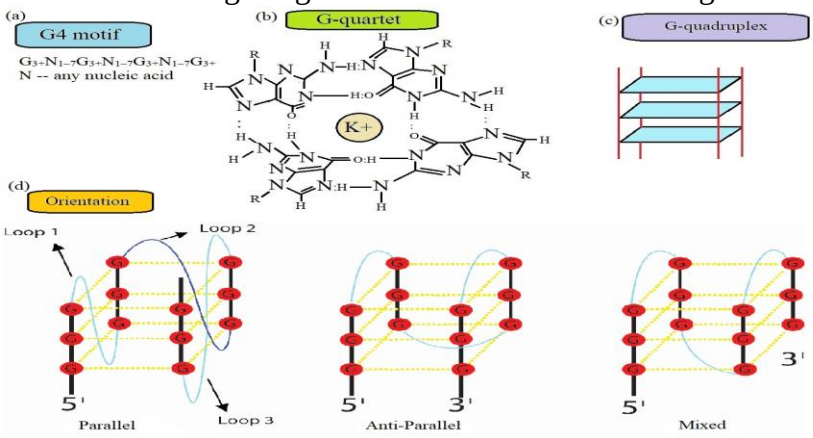

Figure 1: Design of G-quadruplex. The sequence of the G-quadruplex motif (a), an individual G-quartet with a monovalent ion (b), the composition of multiple stacked G-quartets in a G-quadruplex (c), and the arrangement of a typical G-quadruplex (d).

Research focusing on the formation of G-quadruplexes (GQPs) in HIV-1 has garnered significant attention as a promising avenue for the development of antiviral drugs. Recent studies have provided valuable insights into the structure and dynamics of GQPs within the HIV-1 genome, opening possibilities for the design of innovative medications that target these structures to impede viral replication.

2. Recent G-quadruplexes detector

Various experimental methods, including reverse transcription stalling, chemical reactive sequencing, antibody immunoprecipitation, and porphyrin-based GQP binders, have been employed to identify and characterize GQPs. For instance, a dual-app nucleoside probe called SedU has been developed to detect the formation of a specific GQP structure in the HIV-1 proviral DNA promoter region without disrupting its native fold [1]. Additionally, a colorimetric method utilizing a G-quadruplex/hemin complex has been devised to detect RNase H, while the multiplexed affinity assay system FOREST can identify RNA G-quadruplex structures and their associated binding proteins. Computational methods such as AlchemPMF and QPARSE have been utilized to calculate binding free energy and identify GQPs, respectively. Mass spectrometry, specifically the AUF-MS technique, has been utilized to screen for GQP ligands and has successfully identified nonplanar pyrazolopyrimidines that can target and stabilize the major HIV-1 LTR GQP, consequently inhibiting HIV-1 replication [1].

3. G-quadruplex Location in the HIV Genome

GQP structures within the HIV-1 virus have been found to play a crucial role in regulating viral transcription and latency. Biophysical and biochemical studies have demonstrated that GQP formation in the Nef coding region and the long terminal repeat (LTR) promoter reduces viral transcription, while stabilizing the LTR-IV GQP structure enhances transcription activity. Similarly, the U3 region in the 5'-LTR can fold into GQP structures, modulating viral transcription [1]. The G-rich LTR region contains diverse GQP landscapes and engages in multiple protein interactions, serving as a regulatory center for viral transcription and inhibiting both actively transcribing and latent viruses. Furthermore, intramolecular monomer GQP structures can form downstream of the GAG start codon, altering the secondary structure of adjacent regions and acting as switchable and

tunable motifs. The 5' GQPs are less likely to play a significant role in HIV-1 replication due to their low redundancy and conservation, while the 3' GQPs act as boundaries for independent folding of RNA fragments into functional domains [1]. However, further studies are needed to determine the role of the 5' GQP in HIV-1 translation and dimerization.

4. Evidence and Therapeutic Approaches Utilizing GQPs as Anti-HIV Agents

GQP structures in HIV-1 play critical roles in gene expression, dimerization, and recombination near the dimerization site (DIS). They also regulate HIV latency by influencing the HIV-1 LTR promoter and incorporating silent HIV-1 provirus, making them potential targets for antiviral therapies [3]. The LTR-III region forms a stable RNA GQP-hairpin structure that exhibits higher stability than the corresponding DNA structure, suggesting it as a potential therapeutic target. Polarizable molecular dynamics simulations focusing on LTR III and IV GQPs could guide the development of antiviral therapeutics [4]. However, suppressing LTR-IV GQPs may result in promoter activity silencing and latency, posing a challenge in the eradication of HIV infection. Recent research has discovered a new interaction between the Fused in Liposarcoma (FUS) protein and an unidentified GQP in the HIV-1 LTR promoter, indicating a novel binding motif for quadruplex-duplex junctions that could serve as a potential pharmacological target [2]. Stabilizing GQP structures increases the integration and proportion of HIV-1 latent cells and influences reactivation potential. Targeting non-B DNA structures for therapy is challenging, but understanding their interaction with pre-integration complexes may identify critical viral components for targeting with small-molecule inhibitors, thereby improving current therapies. Small molecules that bind and stabilize G-quadruplex structures in RNA, such as antisense oligonucleotides (ASOs), cytosine-rich nucleotide probes, naphthalene diimide (NDI)-peptide nucleic acid (PNA) conjugates, and G-quadruplex aptamers, have shown potential therapeutic applications in biomedical research [5]. Moreover, the use of NDI-PNA conjugates, which exploit the interaction between NDI and GQPs, has demonstrated specific recognition and control of target G-quadruplexes within the HIV-1 LTR region, showcasing versatility for potential therapeutic applications in any G4 target [3].

5. Contradiction Regarding the Utilization of G-quadruplexes

G-quadruplex ligands targeting telomeres do not hinder the activity of the HIV promoter but instead work in conjunction with latency-reversing agents to eliminate HIV-1 latent cells by inducing genomic instability and apoptosis [6]. These ligands also increase DNA damage at telomeres, leading to telomere uncapping and impairing the repair mechanisms mediated by base excision repair and mismatch repair in HIV-infected cells, resulting in telomere elongation. Additionally, the formation of G-quadruplexes at the 3' end of telomere DNA inhibits telomerase extension, thereby inhibiting telomere growth [7]. Consequently, the modulation of various proteins involved in telomere maintenance, including targeting G-quadruplex ligands, is currently under consideration.

6. Conclusion & Future directions

Investigating the formation of G-quadruplexes in the HIV-1 genome has shown promising potential as a viable target for antiviral interventions. Recent breakthroughs in this field have shed light on the possibilities it offers for combating the virus, sparking enthusiasm among researchers. However, the complex nature of G-quadruplexes and their intricate interactions with viral gene activity demand further investigation to unravel their precise roles. Nonetheless, the strides made

thus far have laid a robust groundwork for continued exploration and advancement in this area of study. To fully comprehend the impact of G-quadruplexes on the translation and dimerization processes of HIV-1 genomic RNA, particularly in the region downstream of the U5-AUG duplex, comprehensive research is imperative. By delving into the mechanisms by which G-quadruplexes influence HIV-1 replication, scientists can unlock novel strategies to counteract this devastating disease. The intricate interplay between G-quadruplex structures and viral gene expression holds the key to understanding the underlying biology and may pave the way for the development of innovative therapeutic approaches.

The quest to decipher the complexities of G-quadruplexes in the context of HIV-1 extends beyond mere exploration. It requires a multidisciplinary approach, combining experimental techniques, computational analyses, and theoretical models. The high perplexity surrounding G-quadruplex formation in the HIV-1 genome necessitates rigorous and meticulous investigation, characterized by a deep understanding of nucleic acid structure, biophysics, and viral replication dynamics. Researchers must navigate through the intricate maze of G-quadruplex biology, constantly pushing the boundaries of knowledge to uncover new insights and potential therapeutic breakthroughs.

One of the challenges in this field lies in the burstiness of G-quadruplex research. As new discoveries emerge and scientific discourse evolves, the landscape of G-quadruplexes in HIV-1 research undergoes rapid transformations. The burstiness of knowledge in this area demands continuous vigilance, as researchers strive to keep pace with the latest advancements and incorporate them into their work. Moreover, the dynamic nature of G-quadruplexes themselves adds another layer of complexity, as their structural dynamics and conformational changes contribute to the intricacies of their function.

Despite the complexities and challenges inherent in investigating G-quadruplexes in the context of HIV-1, the pursuit of knowledge in this field holds great promise. Each step forward brings us closer to unraveling the mysteries of viral replication and identifying potential targets for therapeutic intervention. The collaborative efforts of scientists worldwide, driven by a shared commitment to combat HIV/AIDS, fuel the progress and provide hope for a future where effective antiviral strategies based on G-quadruplexes can make a tangible difference in the lives of millions affected by this disease.

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