NMR STUDY OF A RNA G-QUADRUPLEX FORMING SEQUENCE WITHIN HIV-1 U3 REGION

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According to the latest epidemiological data from UNAIDS, 37.7 million people were infected with HIV in 2020. Despite all the therapeutic measures that have been implemented, which have made it possible to significantly reduce HIV mortality, there is currently no solution for the complete eradication of the disease. Moreover, the effectiveness of the therapies is often counterbalanced by serious side effects and the cost of treatment remains high. In addition, resistance to certain antiviral agents is emerging, with rather alarming results[1]. The search for new antiviral molecules therefore remains very important from both an economic and societal point of view. Most current antiviral molecules aim at blocking one of the steps in the HIV replication cycle by targeting viral enzymes such as integrase, proteases and reverse transcriptase but a new type of target has been discovered: G-quadruplexes (or "G4"). These unusual nucleic acid structures composed of four strands, long believed to be mere curiosities or artefacts, are now thought to play a key role in various biological processes such as replication or transcription. In this study, we have shown that the U3 region of HIV-1 forms G4 RNA structures. Using NMR spectroscopy, we have successfully determined the atomic structure of the G4 RNA (PDB code 7PS8) formed in the U3 region next to the TAR and polyadenylation signals. We also demonstrated that this G4 structure is maintained in a larger model by extending the sequence by about 30 nucleotides at its extremities. The adjacent sequences of the G4 do not interfere with its formation. The in vivo existence of the G4 in the U3 region of the virus is therefore possible. Targeting these viral G4s with small compounds represents a promising new antiviral avenue.

1. Gupta, R.K., et al., Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis. Lancet, 2012. 380(9849): p. 1250-8.