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Computational and Experimental Characterization of Ribosomal DNA and RNA G-Quadruplexes SAMUEL CHO, Wake Forest University — DNA G-quadruplexes in human telomeres and gene promoters are being extensively studied for their role in controlling the growth of cancer cells. Recent studies strongly suggest that guanine (G)-rich genes encoding pre-ribosomal RNA (pre-rRNA) are a potential anticancer target through the inhibition of RNA polymerase I (Pol I) in ribosome biogenesis. However, the structures of ribosomal G-quadruplexes at atomic resolution are unknown, and very little biophysical characterization has been performed on them to date. Here, we have modeled two putative rDNA G-quadruplex structures, NUC 19P and NUC 23P, which we observe via circular dichroism (CD) spectroscopy to adopt a predominantly parallel topology, and their counterpart rRNA. To validate and refine the putative ribosomal G-quadruplex structures, we performed all-atom molecular dynamics (MD) simulations using the CHARMM36 force field in the presence and absence of stabilizing K+ or Na+ ions. We optimized the CHARMM36 force field K+ parameters to be more consistent with quantum mechanical calculations (and the polarizable Drude model force field) so that the K+ ion is predominantly in the G-quadruplex channel. Our MD simulations show that the rDNA G-quadruplex have more well-defined, predominantly parallel-topology structures than rRNA and NUC 19P is more structured than NUC 23P, which features extended loops. Our study demonstrates that they are both potential targets for the design of novel chemotherapeutics.

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