Nucleic Acids Chemistry beyond the Watson-Crick Double Helix (85): Investigation of accumulation mechanism for RNA G-quadruplexes with G_4C_2 repeats and poly-dipeptides

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The expansion of G_4C_2 repeats on *C9orf72* is focused on as a cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). It was reported that the accumulation of RNAs transcribed from *C9orf72* and dipeptide repeats translated from the RNA cause cytotoxicity and leads to neurodegenerative disease. Previous studies suggested that liquid-liquid phase separation occurs when only dipeptide repeats or only RNAs accumulate. On the other hand, RNA of G_4C_2 repeats forms parallel-type G-quadruplex, and we hypothesized that the RNA G-quadruplex promote the accumulation.[1-3] In this study, we investigated that interactions of RNA G-quadruplex consisting of $r(G_4C_2)_4$ with dipeptide repeats of Gly-Arg ($(GR)_8$), Gly-Ala ($(GA)_8$), Gly-Pro ($(GP)_8$) using molecular dynamics (MD) simulations and electronic state calculations by fragment molecular orbital method (Figure 1).

Our MD simulations showed that $(GR)_8$ bound to the G-quadruplex remained in the same position on the backbone until the end of MD simulations. Electronic state calculations for these structures indicated that interactions between RNA G-quadruplex and $(GR)_8$ were dominated by electrostatic energy, which is due to electrostatic interactions and hydrogen bonds. On the other hand, $(GA)_8$ and $(GP)_8$ formed not only their clusters but also with RNA G-quadruplex. The MD calculations were also performed for the two RNA G-quadruplexes of $r(G_4C_2)_4$ and the dipeptide repeats. The results showed that RNA G-quadruplexes formed their cluster not only by stacking interactions between G-quartets but also interactions between loop bases. We will discuss the detailed interactions and dynamics for these dipeptide repeats and RNA G-quadruplexes.

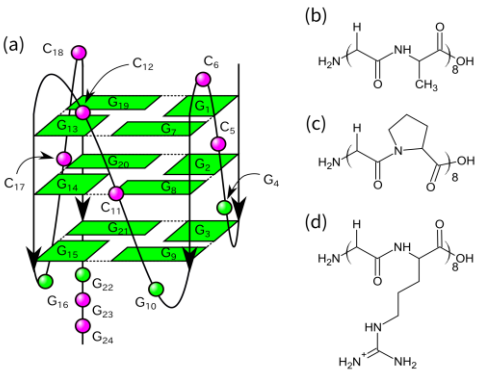

Figure 1. Structures of (a) RNA G-quadruplex of $(G_4C_2)_4$, (b) $(GR)_8$, (c) $(GA)_8$ and (d) $(GP)_8$.

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