RNA Guanine Quadruplex and SARS-CoV Unique Domain: Understanding their Interaction

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It has been reported that a possible interaction between the SARS Unique Domain (SUD) and RNA in guanine quadruplexes (G4) conformation can take place. This interaction has been proposed as a process involved in eluding the defensive response of the host, thus favoring viral infection of human cells. To confirm this finding and to get further insight into the structure and dynamics of this interaction, we have performed an extended all-atom molecular dynamics (MD) study of this system. Furthermore, the free-energy surface of the system has been explored to better sample the multidimensional conformational space and to quantify the strength of the interactions coming into play.

The results have evidenced the existence of two different interaction modes, one at the subdomains interface (dimeric binding mode, Figure) and another involving only one of the SUD monomers (monomeric binding mode). We found that the first one is mostly governed by electrostatic interactions (between the charged RNA backbone and the highly positive interaction pockets of the SUD complex), while the second one is driven by non-covalent interactions. Moreover, the first one is more stable and is essential in rigidifying the protein dimer, stabilizing the SUD-G4 interface. However, we conclude that the monomeric binding mode may also act in the process of recruitment of RNA, anchoring the oligomer that can subsequently be displaced through the interface area. Regarding the free-energy profiles, two relevant variables have been selected: the distance between G4 and SUD, and the separation between the two SUD subdomains. Analyzing the profile, it is observed a principal minimum (blue region in figure) corresponding to the G4 interacting through the dimer mode, characterized by a free-energy stabilization of 6 kcal/mol.

Hence, this work presents a general mechanism and rationalization of the SUD/RNA G4 interaction which may represent one of the reasons of the high pathogenicity of SARS agents. Moreover, thanks to the detailed characterization of the binding region, this study can guide the proposal of G4 ligands destabilizing the SUD/RNA G4 interaction, appealing potential therapeutic strategies.

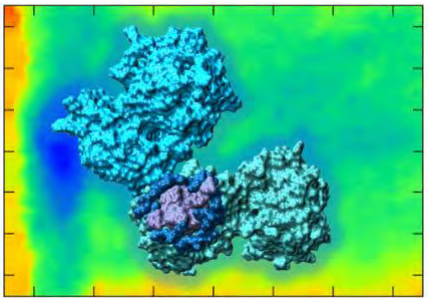

Figure: Representation of the dimeric binding mode and the free-energy profile.

References

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