Programmed cell death and SARS-CoV-2; two RNA G-quadruplexes in the focus of metal ions, their complexes, and small molecules

R. K. O. Sigel
Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland
roland.sigel@chem.uzh.ch

RNA G-quadruplexes (RNA G4s) are non-canonical nucleic acid structure, that are known to occur abundantly in cells playing crucial roles in gene regulation. They exert their function presumably by interacting with proteins, enzymes or certain metabolites, the intrinsic internal dynamics of RNA G4s, i.e. shifts in base pairing and extrusion of nucleobases into solution, thereby being a major and so-far very poorly understood characteristic and basis. The interaction with metal ions is crucial for the formation, stability, and dynamics of such RNA G4s. At the same time, numerous small molecules are known to interact with their DNA G4 equivalents, having been a major research area for decades. In contrast little is known for the interaction of small molecules, including metal ion complexes with RNA G4s. Such metal ion complexes are designed and developed to specifically interact with G4s and interfere with their biological function in order to alter gene expression.[1]

We will present our results on two important RNA G4 quadruplexes; (i) The BCL-2 (B-cell lymphoma 2) RNA G4 is located in the 5'-untranslated region of the respective gene and has been shown to be involved in the regulation of the respective protein, being an essential factor in programmed cell death,[2] and (ii) the Nsp10 RNA G4 (non-structural protein 10) within the SARS-CoV-2 genome.[3] The BCL-2 RNA G4 is a highly dynamic G4 encompassing an ensemble of different structures with alternating Gs incorporated, as we now could show by solving the respective NMR structures, being the first pure monomolecular RNA G4 structures available in general. At the same time this G4 interacts strongly with a set of Pt(II) complexes, as followed in detail by fluorescence time-correlated lifetime and dynamic anisotropy measurements, revealing the stoichiometry, affinity of binding, as well as structural changes. The SARS-CoV-2 Nsp 10 G4 is special as it only encompasses two quartets but is nevertheless stable at room temperature. We could show that the G4 stability is significantly enhanced upon interaction with specific antiviral compounds: along the same line, these compounds are also active in antiviral tests of cells infected with the coronavirus.

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