Topologically controlled unusual nucleic acid structures: assembly and applications from biology to biotechnology

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DNA and RNA G-quadruplexes (G4) are unusual nucleic acid structures consisting of stacked tetrads of hydrogen-bonded guanine bases that are stabilized by monovalent cations and which are connected by loop-forming sequences. There are now compelling evidences that suggest that the formation of G4 in key regulatory regions of the human genome and transcriptome affects cellular processes. As a consequence, the regulation of gene expression by inducing/stabilizing G4 *in vivo* has emerged as a promising therapeutic approach to treat human diseases. Several families of G4-ligands have been assembled leading to promising anti-cancer drug candidates. On the other hand, the intrinsic structural features of synthetic G4 motifs have been exploited to develop DNA based sensing platforms, logic gates and catalytic species. Nonetheless, both in the development of potent and selective therapeutic drugs and in the assembly of reliable nano-biotechnological tools, G4 inherent structural polymorphism have to be carefully examined. Indeed, G4 exhibit a wide diversity in structural topologies seeing that the length, polarity and number of guanine DNA and RNA tracts and loops may vary. Furthermore, G4 folding has been found to be strongly affected by environmental conditions and short synthetic G-rich sequences usually exist as a dynamic mixture of G4 topologies in solution. To gain control over G4 folding topologies, we are connecting G4-forming DNA and RNA sequences onto regioselectivly addressable cyclopeptide platforms, via up to three orthogonal chemical ligations, and we demonstrate that such conjugates are able to fold into thermally stable and monomorphic G4 structures. I will report on the construction and application of those biologically relevant G4 mimics for the development of structure-selective G4 ligands of biological interest and for the identification of G4 cellular binding partners. I will also report on the potentials of those well-defined conjugates as molecular decoys, to affect cellular processes, and as enzyme mimicking catalysts.