

G4 self-assembly as an intrinsic nucleic acid function

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Abstract

It is now commonly acknowledged that G-rich polynucleotide sites can fold into G-quadruplex (G4) structures *in vivo*. In terms of molecular programming, the G4-folding propensity can be regarded as a build-in nucleic acid function with multiple implications for genomic regulation. Here we review several important advances in the studies of G4 self-assemblies in genomic context. We discuss prerequisites and consequences of G4 formation upon transcription or replication and analyze recent data on G4-dependent genomic rearrangements, including translocation and recombination. Hypothetical mechanisms of those G4-dependent rearrangements suggest self-association of G-rich sites. We outline the general molecular basis for possible self-association pathways, i.e., formation of intermolecular G4 assemblies or interquadruplex stacking. Intermolecular G4s and multimeric G4 stacks attract widespread interest as scaffolds for the development of complex junctions in DNA nanotechnology and have prospects in aptamer design, but in this review we focus on fundamental aspects of such higher-order G4 assemblies. Copyright © 2018 VBRI Press.

Keywords: G-quadruplex, self-assembly, DNA damage, chromosomal rearrangements.

Introduction

Compelling evidence for *in vivo* existence of noncanonical nucleic acid (ncNA) structures, such as triplexes, i-motifs, and G-quadruplexes (G4s), has recently been obtained [1-3]. Particular attention is given to G4s because of their significance for telomere maintenance and regulation of transcription, translation and replication [4-6]. Putative quadruplex sites (PQS) in the human genome are associated with DNA instability and related pathologies [7-8], while bacterial and viral PQS may participate in virulence control [9-11]. In this regard, genomic G4s appear to be attractive targets for therapeutic intervention [12]. Much effort, for instance, is currently put into anticancer strategies that address promoter and/or telomeric G4s [13]. In parallel to G4-targeting ligands, G4-based therapeutics (aptamers) and sensors are being developed [14] [15].

The knowledge of ncNA structures is constantly evolving, and the definition of G4s has been broadened to include so-called imperfect quadruplexes (imGQs) with defects (mismatches, bulges or vacancies) in G4 cores. imGQs are comparable to classical (perfect) quadruplex structures in terms of protein recognition and interactions with small molecule ligands, therefore, genomic imGQs are likely to be affected G4-targeted drugs (this should be taken into account in respective therapeutic strategies) [16-17].

Despite rapid progress in the studies of ncNA folding and conformational dynamics [15, 18-19], many key aspects await future research. One such aspect is the possibility of polynucleotide interactions *via* ncNA. In this mini-review we analyze several advances in the G4 field that have implications for genomic rearrangements and highlight the functional potential of G-rich DNA sites.

G4 folding *in vitro* and *in vivo*

Conformational polymorphism, an intrinsic property of polynucleotides, is accounted for by the many-sided H-bonding potential of the nitrogenous bases (e.g., the potential for Watson-Crick and Hoogsteen base pairing). In G4s, each guanine tetrad is stabilized by Hoogsteen bonds, and additional stabilization arises from *p-p* stacking of the tetrads. Although G4s are commonly referred to as four-stranded helical structures, this general definition applies primarily to the quadruplex core, and the strands (G-tracks) may actually be connected by loops, suggesting inter- *vs* intramolecular structures. Comprehensive analysis of G4 topological diversity can be found in the literature [17, 20]. Available software for PQS search in genomic sequences [17, 21-22] was developed mainly for intramolecular G4s, while realization of intermolecular structures and

interquadruplex contacts *in vivo* is relatively hard to predict and verify.

Molecular microenvironment and NA sequences both inside PQS and in the flanking regions should be considered when assessing G4 folding propensity. Physical factors, such as temperature, pressure [23], torsional stress [24] and molecular crowding [25] affect the ss/dsNA \leftrightarrow ncNA equilibrium. Chemical stimuli for G4 folding include metal cations, endogenous small molecule ligands [26-29] and exogenous (synthetic) ligands [30-32]. The impacts of xenobiotics and metabolites on ncNA are currently the subjects of extensive studies. The ongoing search for new G4-targeting drugs and investigation of G4-dependent pathology development will hopefully stimulate further fundamental studies of the G4 interactome.

Biopolymers, proteins in the first place, play diverse roles in the dynamics of quadruplex DNA: from G4 unwinding (specific helicases [33]) to inducing G4 folding (chaperons [4]) or stabilization of the prefolded structures. A number of G4 RNA binding partners has been identified [34-35], but in general the G4 RNA interactome is relatively poorly characterized (in part because the sheer existence of G4 RNA in eukaryotes is a matter of debate [35-36]).

Conformational dynamics of DNA PQS (ss/dsNA \leftrightarrow ncNA transitions) may lead to “opening” of the “masked” transcription factor binding sites (e.g., G4 recognition by the Sp1 transcription factor [37]) or change patterns of the nucleoprotein complex formation (one relevant example is cooperative binding of the epidermal growth factor with telomeric G4s as opposed to its non-cooperative interactions with dsDNA [38]).

The ss/dsDNA \leftrightarrow ncDNA equilibrium is typically analyzed *in vitro* using simplified models - short oligonucleotides; advanced models account for the duplex flanks [39-40]. Similarly, most G4 predicting algorithms and tools fail to evaluate the influence of the duplex media or G4 competition with other ncNA structures and hairpins (one notable exception is the second-generation PQS search tool G4Hunter [21]). The dsDNA \rightarrow ncNA transition *in vitro* and *in vivo* can be initiated by invasion of the third strand. For instance, a short peptide nucleic acid (PNA) complement to the PQS-opposing fragment can be used to induce G4 folding in the duplex media. Alternatively, PNA probes can target, invade and trap PQS by forming hybrid PNA:DNA G4s [41-44]. The reverse (ncDNA \rightarrow dsDNA) transition is helpful for manipulating G4 therapeutics. A complementary (“antidote”) strand can induce G4 unfolding, that would result in the loss of a G4 function, and/or facilitate G4 recovery from nucleoprotein complexes (e.g., the complexes with blood proteins). This has been demonstrated for the G4 anticoagulant agent TBA (thrombin binding aptamer) [45]. One more well-characterized G4 aptamer – AS1411 (aptamer to nucleolin), primarily known for its antiproliferative activity, is now also attracting much

attention with respect to ncDNA transitions due to its conformational polymorphism and the unusual left-handed (Z-G4) topology [46]. It is also a remarkable example of a pseudo-dimeric (i.e., pseudo-intermolecular) intrastrand G4.

Recently, new types of intermolecular G4 assemblies - interlocked G4s [47] and G4 stacks (associates of intramolecular structures stabilized by interquadruplex stacking of external tetrads) [14-15] have been described. The latter type of G4 assemblies could be biologically significant and explain packaging of PQS clusters - especially in microsatellites, such as telomeric repeats [16-19]. To date, the topologies adopted by human telomeric quadruplex motifs under various conditions have been analyzed in detail. The reported structures include antiparallel [48], parallel and hybrid intramolecular G4s [49-51], as well as higher-order assemblies [50].

Intracellular assembly of tetramolecular G4 structures (antiviral aptamers) has been confirmed in living oocytes of *Xenopus laevis* using in-cell NMR spectroscopy [52]. (Analogous NMR monitoring of G4s in human cells has also been performed [53]). Importantly, the dominating conformation of the tetramolecular G4 structure assembled *in vivo* was very similar to that obtained *in vitro* in the presence of potassium ions. Higher-order ncNA associates with lengthy G4 cores are known as G-wires [49]. *In vivo* relevance of G-wires is unlikely, but they are potentially interesting for DNA nanotechnology.

To summarize this section, G-rich polynucleotide fragments can adopt multiple topologies; and the transitions between G4s and canonical nucleic acid conformations can be monitored and controlled *in vitro* and *in vivo*. Deleterious consequences of *in vivo* G4 formation, such as chromosomal fragility, are discussed in subsequent sections.

G4s in R-loops as possible drivers of transcription-associated DNA damage

Upon exiting RNA polymerase, the nascent RNA molecule can hybridize with the template DNA strand to generate R-loops – structures that comprise DNA:RNA hybrids and ssDNA (the displaced non-template strand). General physiological relevance of R-loops has been outlined previously in several reviews [54-55]. We focus here on presumed roles of G4s in R-loop formation and surveillance, as well as R-loop-driven recombination and other chromosomal alterations.

First, there is an apparent correlation between R-loop accumulation, G4 folding and active transcription [56-57], but whether supercoiling and ssDNA exposure in R-loops are primary prerequisites and G4 formation is a consequence or *vice versa* is an unresolved question. Transcription generates positive supercoils in DNA ahead of the advancing RNA polymerase complex (RNAP) and negative supercoils behind it (Fig. 1a) [54]. Negative supercoiling may induce G4 folding [58]; and the folded structure supposedly prevents further propagation of the

torsional stress (**Fig. 1b**) [59]. Importantly, the torsional stress *per se* (in the absence of R-loops) may be insufficient for G4 folding, as has been demonstrated in experiments with supercoiled plasmids and FRET-based systems: suppression of R-loop formation or their enzymatic removal inhibited G4 folding and accelerated unfolding, respectively. At the same time, a G4 structure in a template strand would prevent reannealing of the DNA duplex, and thus favor lengthy DNA:RNA hybrids (**Fig. 1c**) [60]. In the case of a G-rich non-template strand, the hybrid may contain intermolecular DNA:RNA G4s (**Fig. 1d**). For example, hybrid G4s are supposedly formed upon transcription of CG-rich CBSII elements in mitochondria and could explain remarkable stabilities of the respective R-loops [61]. To make the long story short, R-loops aid G4 formation and may in turn be induced/stabilized by G4s, so the processes appear to be synergistic.

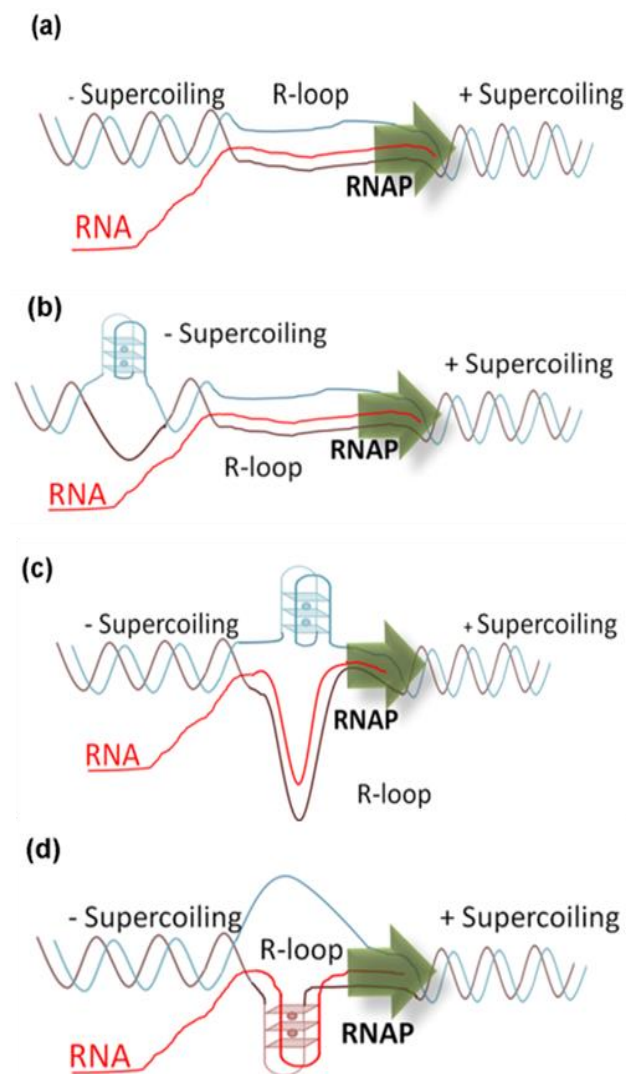


Fig. 1. (a) General schematic representation of an R-loop, (b) RNA displaces the non-template strand from the DNA duplex and thus facilitates G4 formation, (c) G4 in the non-template strand prevents reannealing of the DNA duplex and thus favors R-loop propagation, (d) Intermolecular G4 stabilizes the RNA:DNA hybrid and the overall R-loop structure.

Next, the connection between G4s and transcription-associated DNA damage seems even more complex. ssDNA breaks (SSBs) may arise from G4 processing by structure-specific nucleases [62]. For instance, transcription-associated lesions of G-tracks in human cell may be attributed to the attacks of FEN1, EXO1 and DNA2 nucleases. Alternatively, the dominating role of G4s in DNA damage could be indirect, i.e., via the abovementioned stabilization of an overall R-loop structure with a “vulnerable” (susceptible to nicking) ssDNA fragment. One vivid example of the later pathway is class-switch recombination at G4-prone S regions of Ig heavy chains in B lymphocytes [63-64]. Transcription of the S regions is accompanied by R-loop formation, and the ssDNA fragments in the R-loops are exposed to the activation-induced cytidine deaminase, that converts cytosines into uracils. The resulting mismatching dU residues can be processed to SSBs by base excision repair enzymes. SSBs can be converted to DSBs, but the underlying mechanisms are not well understood. One notable hypothesis suggests replication stress, i.e., the collisions between replication forks and the transcription elongation machinery due to R-loop-induced RNAP stalling. The hypothesis has been outlined elegantly in the previous reviews on R-loops [54-55]; G4s colocalization with replication origins is analyzed in [65-66], and G4 roles in replication stalling are summarized in [67].

Finally, R-loop-associated DSBs may eventually lead to recombination, and the intriguing question in that broader context is juxtaposition of the recombining non-homologous fragments, their possible interactions (synapsis) and the underlying molecular basis. In the last section of this mini-review we analyze possible pathways of G4-dependent DNA synapsis.

G4-junctions and chromosomal rearrangements

Recombination and translocation typically require transient synapsis of the exchanging DNA fragments. A growing body of evidence suggests involvement of G4s and other ncNA structures in DNA interactions upon homologous, as well as nonhomologous recombination [68-70]. Possible role of intermolecular G4s in alignment of sister chromatids during meiosis has been revealed in the studies of *Saccharomyces cerevisiae* telomeric repeats [68]. Later, formation of G4s and i-motifs in the opposing strands was confirmed for G/C-rich sites of the *Saccharomyces cerevisiae* genome that are associated with meiosis-specific DSBs [71]. Hop1, the component of the synaptonemal complex, was shown to recognize such G/C-rich ncNA sites and promote their pairing, which argues strongly for ncNA-driven synapsis and recombination.

Major types of quadruplex-based intractions that may facilitate duplex alignment and strand exchange can be classified as follows: intermolecular G4-junctions and pseudo-intermolecular G4:G4-junctions (**Fig. 2**). The formation of G4-junctions between non-complementary DNA strands with G₆ sites embedded in duplex media has been clearly demonstrated *in vitro* using DNA origami

and AFM techniques [72]. The design of the model origami system allowed for both parallel and antiparallel G4-junctions. As concerns genomic G-rich sites, an all-parallel dimeric G4-junction has been proposed for the human c-kit2 PQS [70]. The authors postulated that recombination could be realized *via* nicking of parallel strands in the dimeric G4 (e.g., by endonucleases), rotation of the G4 fragments (presumably with assistance of topoisomerases) and subsequent strand rejoining.

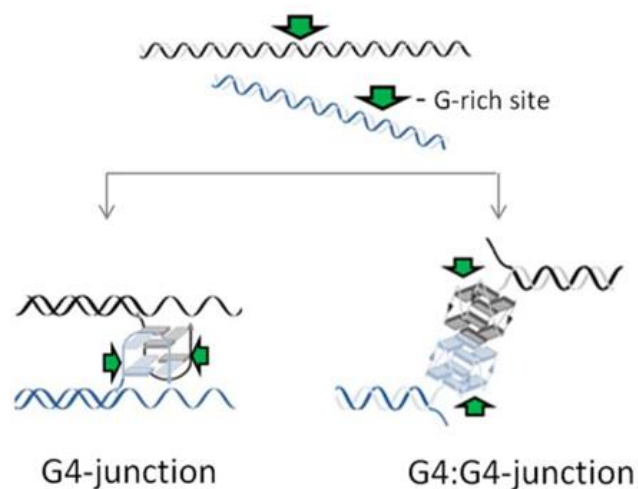


Fig. 2. Presumed structures of G4 DNA synaptic complexes (schematic representations).

Recently, G4 and G4:G4 junctions have also been considered for human G-rich repetitive elements. Recombination hotspots of human genome and DSB loci associated with copy number variations and related diseases are mostly colocalized with PQS sites and Alu elements [73]. Alu retrotransposons are primate-specific short interspersed repeats that make up more than 10% of the human genome and are implicated in chromosomal rearrangements. Conformational polymorphism of Alu DNA G-rich sites has been investigated for consensus Alu Sx [74] and a representative Alu repeat from the intron of the bcl prooncogen [75-76]. Two of the three Alu PQS fragments that have been proven to fold into G4s *in vitro*, are evolutionary conservative and coincide with DSB motifs. When incorporated into mutually remote fragments of a model lengthy DNA strand, those two PQS sites assembled into a dimeric G4, and the resulting DNA junctions were somewhat similar to the abovementioned c-kit2 G4-junctions. The third Alu PQS site was less conservative, but noteworthy for its extra-stable intramolecular parallel quadruplex structure with interquadruplex stacking potential, suggesting the possibility of G4:G4 Alu junctions.

Conclusion

The reviewed data illustrate the diversity of G4 assemblies obtained *in vitro* and visualized *in vivo*; highlight significance of genomic G4s for key bioprocesses, such as transcription regulation and

chromosomal rearrangements, and point to their participation in the rearrangement-preceding DNA synapsis. Accumulation of intrastrand DNA G4s or bimolecular hybrid DNA:RNA G4s (e.g., in R-loops) is now regarded as an important DSB-stimulating factor, while interstrand DNA G4 assemblies or interquadruplex DNA junctions are presumed to directly promote strand exchange. This is in line with the observed association between recombination hotspots and G4-prone regions, such as Alu repeats, in the human genome. It can be concluded that G4 formation is an integral function of the DNA machinery, essential for genome dynamics.

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