Plant Science 269 (2018) 143–147

Contents lists available at ScienceDirect

Plant Science

journal homepage: www.elsevier.com/locate/plantsci

Review article

Review: Plant G-quadruplex (G4) motifs in DNA and RNA; abundant, intriguing sequences of unknown function

Brianna D. Griffin, Hank W. Bass*

Department of Biological Science, 319 Stadium Drive, Florida State University, Tallahassee, FL, 32306-4295, USA

ARTICLE INFO

Keywords:
G-quadruplex
G4
Gene regulation
cis-regulatory element

ABSTRACT

DNA sequences capable of forming G-quadruplex (G4) structures can be predicted and mapped in plant genomes using computerized pattern search programs. Non-telomeric G4 motifs have recently been found to number in the thousands across many plant species and enriched around gene promoters, prompting speculation that they may represent a newly uncovered and ubiquitous family of *cis*-acting elements. Comparative analysis shows that monocots exhibit five to ten times higher G4 motif density than eudicots, but the significance of this difference has not been determined. The vast scale and complexity of G4 functions, actual or theoretical, are reviewed in relation to the multiple modes of action and myriad genetic functions for which G4s have been implicated in DNA and RNA. Future experimental strategies and opportunities include identifying plant G4-interactomes, resolving the structures of G4s with and without their binding partners, and defining molecular mechanisms through reporter gene, genetic, or genome editing approaches. Given the global importance of plants for food, clothing, medicine, and energy, together with the potential role of G4 motifs as a widely conserved set of DNA sequences that could coordinate gene regulation, future plant G4 research holds great potential for use in plant improvement strategies.

1. Introduction

Genetic *cis*-regulatory elements control gene expression. These elements exist in DNA and RNA in a variety of structural forms. Among these, the non-B-form DNA structures have fascinated biologists for decades (reviewed in [1]), classified into categories such as Z-DNA, hairpin and cruciform DNA, slip-stranded DNA, triplex DNA, and G-quadruplex (G4) DNA. Here we review the relatively young field of plant G4 research. The G-quadruplex is a 4-stranded nucleic acid structure formed by G-G Hoogsteen base pair stacking in the presence of monovalent cations (such as potassium or sodium) as diagrammed in Fig. 1. The common and defining feature of a G4 structure is the planar stacking of guanine quartets (reviewed in [2,3]). The intrinsic properties of guanines to self-assemble and gel into non-random arrangements was first reported by Bang in 1910 [4]. The helical arrangement of stacked planes of guanine quartets was later described by Gellert et al. [5], providing a structural framework for our modern concept of G-quadruplex structures that form not only in solutions of guanylic acid but also in G-rich polymers of DNA and RNA. There also exists a remarkable amount of structural heterogeneity in both the number of structures a single sequence can form [6], and the variations in the G4s themselves resulting from strand polarities, and the size and composition of loops and bulges, as shown in part in Fig. 2 (reviewed in [7]).

G4s were initially recognized as a hallmark of telomere repeat sequences for most eukaryotic species [8,9]. More recent studies implicate G4s in multiple genetic functions that include gene expression, DNA replication, recombination, and DNA repair [10,11]. It is now widely accepted that G4s can impact many genetic processes as summarized in Fig. 3. The genomic distribution of G4 motifs in and around genes has led to research investigating their roles as *cis*-acting regulatory elements [7,10,12–14]. One of the most active areas of G4 research focuses on the role of mammalian G4s in cell-cycle control and cancer [7,15–21].

In contrast, relatively little is known about G4s in plants, despite the widespread occurrence of these motifs in the genomes of eudicots and monocots [22–25]. This review summarizes recent studies on plant G4s, including species comparisons of genome-wide surveys, computer programs used to identify motifs, their locations relative to genetic elements, and their potential roles in both DNA and RNA processes. Finally, we discuss future experimental approaches needed to further identify and characterize the functional roles for DNA and RNA G4s in plant species.

* Corresponding author.
E-mail addresses: bdg13@my.fsu.edu (B.D. Griffin), bass@bio.fsu.edu (H.W. Bass).

https://doi.org/10.1016/j.plantsci.2018.01.011
Received 22 November 2017; Received in revised form 12 January 2018; Accepted 20 January 2018
Available online 02 February 2018

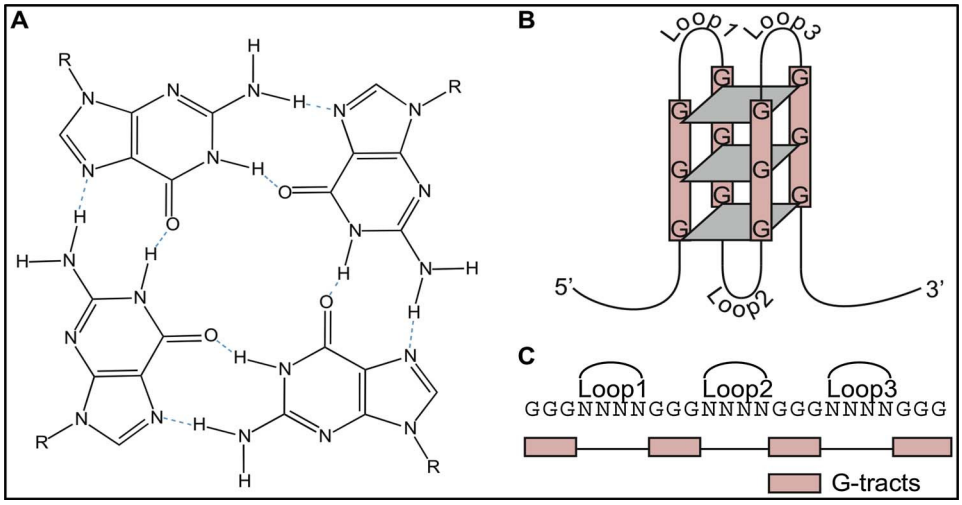

Fig. 1. Representations of G-quadruplex structures (A) G-quartet showing the four guanine bases that are hydrogen bonded to form one plane of a G-quadruplex. R represents the location of the sugar-phosphate backbone (not depicted). (B) Intramolecular G-quadruplex consisting of three G-quartets (grey planar squares). Typical intramolecular G4s have four stems (G-tracts) and three loops (Loop1-3). Not depicted here are the monovalent cations (typically K+ positioned in the center of the G4 and intercalated between each pair of adjacent, stacked planes). The structure depicted is but one of many possible topological variants of G4s. (C) Linear G-quadruplex motif sequence marking the locations of the G-tracts and the loop nucleotides. Figure reproduced from Fig. 1 in [56].

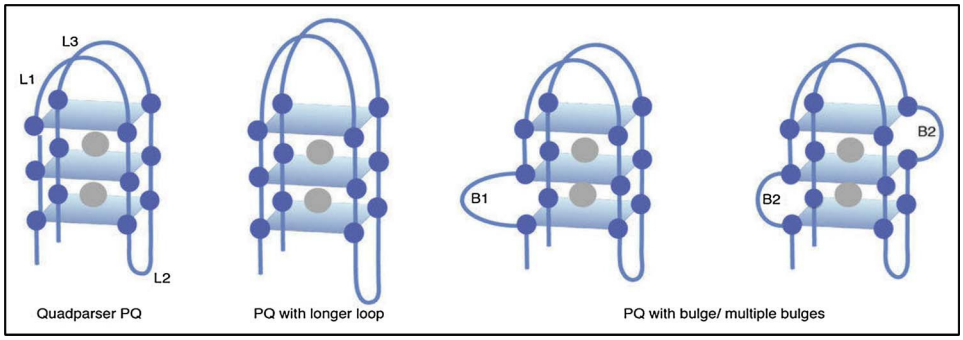

Fig. 2. Various types of G-quadruplex structures. Sample schematics of predicted quadruplexes (PQ) with normal (L1, L2, L3, 1st structure) loops or longer (2nd structure) loops. The last two structures depict G-quadruplexes with bulges in which stacked guanines are interrupted by extruded bases (bulges, B1, B2). Not depicted here are additional conformations that G4s can adopt depending on the direction of the strands in each stem of the quadruplex. Figure reproduced from Fig. S8 in [57].

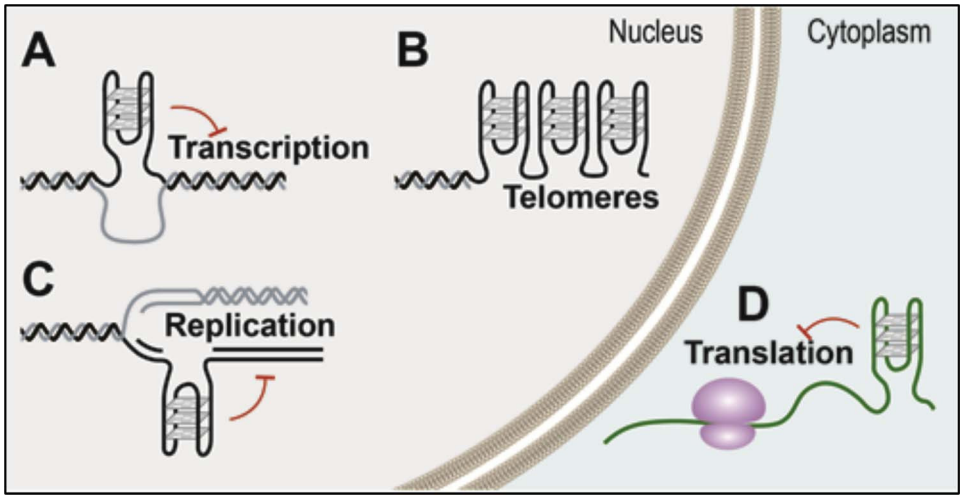

Fig. 3. Major processes involving G4s. Summary diagram of genetic processes (transcription, replication, translation) and structures (telomeres) associated with G4s. (A) In transcription, G4s can form upstream or downstream of the transcription start site and impede or increase (not depicted) transcription. (B) Telomeres can have G4s in the 3′ G-rich strand, depicted here in the single-stranded region. (C) During replication, G4s can impede fork progression. (D) In translation, G4s can impede protein synthesis or form structures recognized by various ligands (not depicted). Figure reproduced from Fig. 2 in [12].

2. Genome-wide plant G4 motifs and informatics

Most plant G4 studies begin with a bioinformatic screen of genomic sequence data to find sequence patterns, or motifs, using one or more algorithms [26–28]. Genome-wide surveys show that G4 DNA sequence motifs with the potential to form G-quadruplexes are pervasive in plant genomes [22–25,29,30] and are notably abundant in monocots, as summarized in Fig. 4. For direct comparison, using the so-called canonical G4 search pattern (G_3L_{1-7}), Arabidopsis has only 9 G4 motifs/Mbp whereas rice has 92 G4 motifs/Mbp, a 10-fold difference. Gene ontology analysis has yet to point to any universally common plant function in conserved G4-containing genes, but the reason for this remains unclear. The assignment of G4-containing genes to multiple different gene ontologies is not limited to plants but is also true for animals and bacteria [31–34]. In plants, it is possible that G4 elements evolve relatively quickly compared to other sequences, allowing them to be redeployed or acquire new functions in divergent taxa. Alternatively, it is possible that they have a shared function that is not easily recognized by examination of the genes that they reside in.

3. Numerous conceivable modes of action for all major genetic processes

Among the more intriguing and challenging aspects of G4 research are their vast array of possible roles and biochemical functions (reviewed in [13]). Indeed, they comprise a diverse collection of

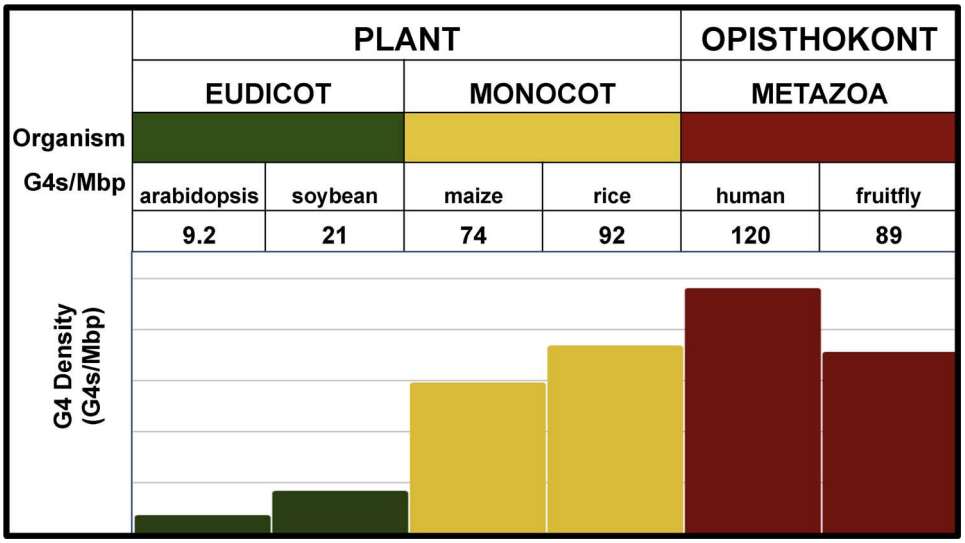

Fig. 4. G4 density in select plant and animal species. G4 density (number of G4s/Mbp) varies in plants and animals. Notably, eudicots have fewer G4s than monocots. Monocots, like many animal species, typically have > 50 G4s/Mbp. Eudicots typically have < 50 G4s/Mbp. Values are taken from [22] using the so-called canonical G_3L_{1-7} sequence motif pattern search.

Table 1
Functional Classification Grid for G4 Elements.

	Genetic Process[a]				
	Gene Regulation		*Genome Maintenance*		
	Transcription	Translation	Replication	Recombination	DNA Repair
Mode of Action[b]					
Duplex opening	Yes	Maybe[c]	Yes	Yes, V(D)J recombination	Yes
Binding site	Yes	Yes	Yes	Maybe	Yes
Polymerase impediment	Yes, RNA polymerase	Yes, Ribosome	Yes, DNA polymerase	Maybe	Maybe
Supercoiling	Yes	Does not apply	Maybe	Maybe	Maybe

[a] The list of genetic processes is not comprehensive and does not include, for example, splicing, RNA transport, genome maintenance, or telomere metabolism.
[b] Mode of action refers to the potential molecular mechanism by which a G4 might act, noting that these are not necessarily mutually exclusive or a comprehensive list.
[c] "Maybe" entries refer to actions that could occur in principle, but are not documented or well characterized.

functional elements deployed across most if not all species. The "functional roles" for G4s can be described as either (1) **genetic processes** or (2) **modes of action**, as partially depicted in the matrix in Table 1. Notably, for each genetic process, G4s can function in multiple different ways. This may account in part for the complex and expansive body of contemporary literature on G4 biology. Most reviews on G4s focus on the core genetic processes, which in turn can be further subdivided into one of two broad categories: (a) *genome maintenance*, which includes DNA replication, DNA repair, and recombination and (b) *gene regulation*, which includes chromatin structure, transcription, splicing, and translation. From a reductionist point of view, however, a focus on the mode of action is appealing in that it may offer a more effective way to disprove alternative hypotheses, leading to a more direct path forward. In either case, it will be important to consider both types of roles when designing experiments and summarizing the literature.

With regard to *gene regulation* in plants, several studies have focused on the bioinformatic analysis of G4 distribution relative to genetic elements and gene ontology enrichment [22–24,29,30,35]. Evidence for plant G4s in regulating gene transcription comes from studies on the frequency and location of G4s in and around promoters, start codon regions, and introns. Some genes have multiple G4 motifs, as depicted in Fig. 5. The most conspicuous and abundant G4 motif hotspot is found in the region overlapping or in close proximity to the transcription start site as seen for arabidopsis, rice, poplar, and grape [23]. In maize (*Z. mays*), around 3800 genes have G4 motifs located in the antisense 5′ UTR (A5U) and proximal promoter region [25]. In rice (*O. japonica*), the 5′ UTR was also found to be a G4 hotspot, more so than other regions of the gene [30]. Similarly, G4 motifs are enriched around the promoter from which LTR retrotransposons are transcribed [24].

G4 elements can also function in gene expression as RNA elements where they may operate by one or more of the modes of actions summarized (Table 1). Reviews [36,37] highlight the difficulties and controversies associated with obtaining evidence for *in vivo* RNA G4 formation. A recent and elegant study showed that dimethyl sulfate probing assays reveal which G4 motifs are folded *in vivo*, as inferred from subsequent RT-stop profiling experiments [38]. This approach showed that mammals and yeast have robust RNA G4-unfolding machinery, but that bacteria do not. This may explain why bacterial genomes are depleted for RNA G4 motifs, which appear in genome-wide bioinformatic surveys as sense strand motifs. In plants, G4 motifs in transcripts have been observed and characterized bioinformatically [25,39], but whether plants have robust animal-like G4 unfolding machinery remains unknown. In Arabidopsis, G4 motifs in RNA have been found to be enriched in enzyme-coding genes, and under-represented in non-coding RNAs [22], with folding properties consistent with a regulatory, ion-sensitive switch [40,41]. Detailed analysis using in-line structural probing together with a reporter gene and other assays showed that a 5′ UTR G4 could act as a translational repressor [35]. Given the importance of RNA in all of biology (Reviewed in [42]), one can anticipate a future growth in RNA G4 research.

With regard to *genome maintenance*, there are few studies that specifically address this aspect of plant G4 function, but such roles are

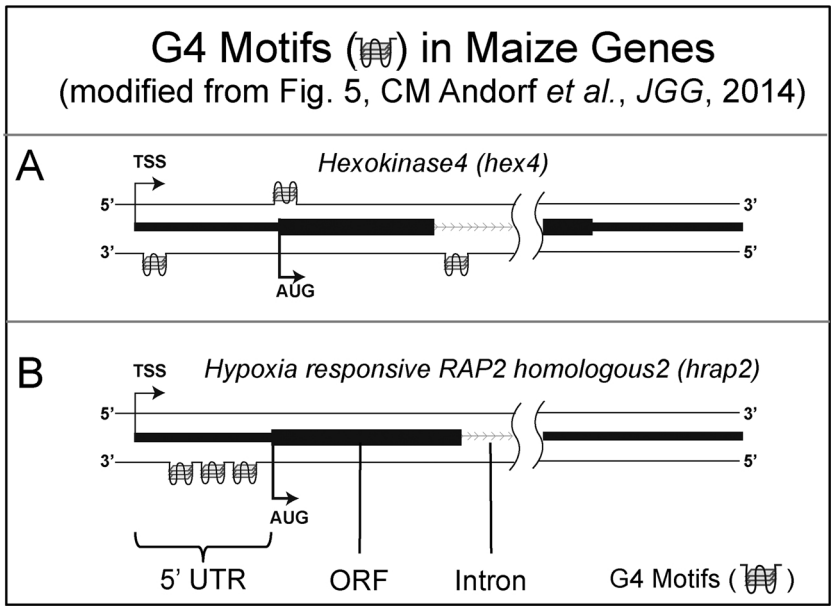

Fig. 5. Examples of multiple G4 motifs in two maize genes, *hex4* and *hrap2*. Examples of G4 motifs in maize genes (A) *hex4* and (B) *hrap2* illustrate various motif locations: antisense 5′ UTR (DNA only); sense overlapping start codon region (DNA and mRNA); and the antisense 5′ end of the intron (DNA only). Labeled gene structures are transcription start site (TSS), translation start site (AUG), untranslated region (UTR), open reading frame (ORF), and G-quadruplex motifs (G4). Figure reproduced from Fig. 2 in [58].

likely considering their prevalence in other organisms such as yeast, [43,44], worms [45], and mammals (reviewed in [11]). Similarly, G4s have been coupled to origins of DNA replication and repair, where they may act as fork stalling factors, structural roadblocks to DNA synthesis, or hotspots for DNA repair and mutation [10,46]. Indeed, G4s have been shown or speculated to contribute to nearly every genetic process involving DNA metabolism or function.

With regard to modes of action, we list a small but important subset of modalities (Table 1), recognizing that other conceivable modes of action could exist. These include enzymatic and electron transport activities [47–49]. For the modes listed, the “duplex opening” could also be considered as an “alternate structure” because the nucleic acid can be either a G4 or non-G4, acting as a reversible or conditional structure, with properties of a switch. As an alternative structure or polymerase impediment, the substructure may not matter, whereas, for binding site, the substructure could afford a wide array of different and specific binding sites.

4. Plant G4 binding proteins: one down, many to go

So far, only one such G4-binding protein has been identified and biochemically characterized [50]. Using a G4-ligand binding screen of maize cDNA expression library, cDNAs encoding nucleoside diphosphate kinase (NDPK) were identified and shown to bind to a biotinylated G4 folded oligonucleotide from the antisense strand of the 5′ UTR of the maize *hexokinase4* gene (Hex4-A5U/G4v2-53046) with an apparent K_d of 6.8 nM [50]. The enzyme was shown to be active even in the G4-bound state. Interestingly, a human homolog of NDPK, NM32-H2, has also been shown to bind G4 DNA and is implicated as a possible transcription factor for the cMYC and other genes [51,52]. Not yet described but likely to be encoded in plant genomes are a large number of proteins that interact with G4s [53] to regulate telomere metabolism, transcription, or translation. Specifically, homologs of G4 resolving helicases can be found in plants, but have yet to be directly tested for G4-binding activity.

5. Charting a path forward in plant G4 research, in search of functional evidence

Despite the impressive amount of information now available on G4 motifs in many species, including plants, there remains a major challenge to consolidating evidence-based working models of G4 functions. Only recently has a detailed molecular mechanism for G4-dependent gene activation been proposed using mammalian cell reporter gene assays to examine a complex series of steps involving 8-oxo-Guanine and DNA repair enzymes in mammalian cells [54]. Such specificity in the models of G4 action are currently the exception, not the rule. The challenges for understanding G4s are great, owing at least in part to the vast array of different possible modes of actions associated with G4s, which could affect any or all major genetic processes (Table 1). Going forward, two complementary approaches can be stated in general terms as either *descriptive* or *functional* analyses.

G4 *descriptive analyses* in plants have uncovered tens or hundreds of thousands of G4 motifs with tendencies to be located around promoters, suggestive of regulatory functions. Gene ontology analysis of G4 motif-containing genes gives some clues about function, but the pathways and categories identified by this approach are broad and highly varied [23]. As more plant genomes are surveyed and analyzed, the comparative power and ability to identify common pathways will increase. Another descriptive approach has focused on the locations of plant G4 motifs relative to gene or transposable element structures [23–25,55]. These studies, like those from animals, point to transcriptional regulatory functions, but direct empirical evidence is needed in order to rule out some of the many hypothetical mechanisms [25].

G4 *functional analyses*, such as biochemical, molecular, or genetic approaches, are nearly lacking in plants but are needed to advance the field. One important biochemical goal is to define the G4 interactomes of plant species. This could be achieved via ligand-binding screens using select or common G4s to screen through *a priori* animal homolog candidates [53] or through unbiased biochemical ligand-binding screens using G4s together with plant cDNA expression libraries as done by Kopylov et al. [50]. Once G4-binding proteins have been identified, further analysis of their biochemical, structural, and biophysical properties will provide clues about the molecular workings of G4s. Ultimately, reporter gene approaches offer a reductionist approach that will be key to defining the rules that apply to G4s in relation to the regulation of gene expression. G4 reporter gene assays, along with different mutant controls, offer a promising albeit low throughput strategy to assign *in vivo* G4 functions. Finally, genetic and genome editing experiments that target the *cis*-acting G4s themselves or their cognate trans-acting factors can directly test emerging models and hypotheses on the biological roles of plant G4s.

Given the global importance of plant science, plant G4 research represents exciting new directions, with major implications for the

development of novel rules for plant gene regulation, while informing strategies for plant and crop improvement.

Authors contribution

All authors have contributed to the review, and have read and approved the version being submitted.

Acknowledgements

We thank ZM Turpin, M. Kopylov, JR Reza, GG Hoffman for helpful discussions and comments. We thank T.W. Okita for the kind invitation to submit a review on this topic. The authors are supported by a grant to HWB (NSF Plant Genome Research Program, IOS Award 1444532) and undergraduate research fellowships to BDG (V Vaughn-Jordan, FE Fisher, and the FSU Women In Math Science and Engineering program).

References

[1] R.D. Wells, Non-B DNA conformations, mutagenesis and disease, Trends Biochem. Sci. 32 (2007) 271–278.
[2] J.L. Huppert, Four-stranded nucleic acids: structure, function and targeting of G-quadruplexes, Chem. Soc. Rev. 37 (2008) 1375–1384.
[3] J.L. Huppert, Structure, location and interactions of G-quadruplexes, FEBS J. 277 (2010) 3452–3458.
[4] I. Bang – Biochemische Zeitschrift, Untersuchungen über die Guanylsäure, (1910), (1910).
[5] M. Gellert, M.N. Lipsett, D.R. Davies, Helix formation by guanylic acid, Proc. Natl. Acad. Sci. U. S. A. 48 (1962) 2013–2018.
[6] R.W. Harkness 5th, A.K. Mittermaier, G-register exchange dynamics in guanine quadruplexes, Nucleic Acids Res. 44 (2016) 3481–3494.
[7] Y. Qin, L.H. Hurley, Structures, folding patterns, and functions of intramolecular DNA G-quadruplexes found in eukaryotic promoter regions, Biochimie 90 (2008) 1149–1171.
[8] D. Sen, W. Gilbert, Formation of parallel four-stranded complexes by guanine-rich motifs in DNA and its implications for meiosis, Nature 334 (1988) 364–366.
[9] J.R. Williamson, M.K. Raghuraman, T.R. Cech, Monovalent cation-induced structure of telomeric DNA: the G-quartet model, Cell 59 (1989) 871–880.
[10] M.L. Bochman, K. Paeschke, V.A. Zakian, DNA secondary structures: stability and function of G-quadruplex structures, Nat. Rev. Genet. 13 (2012) 770–780.
[11] N. Maizels, L.T. Gray, The G4 genome, PLoS Genet. 9 (2013) e1003468.
[12] D. Rhodes, H.J. Lipps, G-quadruplexes and their regulatory roles in biology, Nucleic Acids Res. 43 (2015) 8627–8637.
[13] R. Hänsel-Hertsch, M. Di Antonio, S. Balasubramanian, DNA G-quadruplexes in the human genome: detection, functions and therapeutic potential, Nat. Rev. Mol. Cell Biol. 18 (2017) 279–284.
[14] A. Varizhuk, D. Ischenko, V. Tsvetkov, R. Novikov, N. Kulemin, D. Kaluzhny, M. Vlasenok, V. Naumov, I. Smirnov, G. Pozmogova, The expanding repertoire of G4 DNA structures, Biochimie 135 (2017) 54–62.
[15] J. Beckett, J. Burns, C. Broxson, S. Tornaletti, Spontaneous DNA lesions modulate DNA structural transitions occurring at nuclease hypersensitive element III(1) of the human c-myc proto-oncogene, Biochemistry 51 (2012) 5257–5268.
[16] T.A. Brooks, L.H. Hurley, The role of supercoiling in transcriptional control of MYC and its importance in molecular therapeutics, Nat. Rev. Cancer 9 (2009) 849–861.
[17] L.A. Cahoon, H.S. Seifert, Transcription of a cis-acting, noncoding, small RNA is required for pilin antigenic variation in Neisseria gonorrhoeae, PLoS Pathog. 9 (2013) e1003074.
[18] J.L. Huppert, S. Balasubramanian, G-quadruplexes in promoters throughout the human genome, Nucleic Acids Res. 35 (2007) 406–413.
[19] D. Yang, K. Okamoto, Structural insights into G-quadruplexes: towards new anticancer drugs, Future Med. Chem. 2 (2010) 619–646.
[20] L. Yuan, T. Tian, Y. Chen, S. Yan, X. Xing, Z. Zhang, Q. Zhai, L. Xu, S. Wang, X. Weng, B. Yuan, Y. Feng, X. Zhou, Existence of G-quadruplex structures in promoter region of oncogenes confirmed by G-quadruplex DNA cross-linking strategy, Sci. Rep. 3 (2013) 1811.
[21] H.-Y. Weng, H.-L. Huang, P.-P. Zhao, H. Zhou, L.-H. Qu, Translational repression of cyclin D3 by a stable G-quadruplex in its 5′ UTR: implications for cell cycle regulation, RNA Biol. 9 (2012) 1099–1109.
[22] M.A. Mullen, K.J. Olson, P. Dallaire, F. Major, S.M. Assmann, P.C. Bevilacqua, RNA G-Quadruplexes in the model plant species Arabidopsis thaliana: prevalence and possible functional roles, Nucleic Acids Res. 38 (2010) 8149–8163.
[23] H. Takahashi, A. Nakagawa, S. Kojima, A. Takahashi, B.-Y. Cha, J.-T. Woo, K. Nagai, Y. Machida, C. Machida, Discovery of novel rules for G-quadruplex-forming sequences in plants by using bioinformatics methods, J. Biosci. Bioeng. 114 (2012) 570–575.
[24] M. Lexa, E. Kejnovský, P. Steflová, H. Konvalinová, M. Vorlícková, B. Vyskot, Quadruplex-forming sequences occupy discrete regions inside plant LTR retrotransposons, Nucleic Acids Res. 42 (2014) 968–978.
[25] C.M. Andorf, M. Kopylov, D. Dobbs, K.E. Koch, M.E. Stroupe, C.J. Lawrence, H.W. Bass, G-quadruplex (G4) motifs in the maize (Zea mays L.) genome are enriched at specific locations in thousands of genes coupled to energy status hypoxia, low sugar, and nutrient deprivation, J. Genet. Genomics 41 (2014) 627–647.
[26] A. Bedrat, L. Lacroix, J.-L. Mergny, Re-evaluation of G-quadruplex propensity with G4Hunter, Nucleic Acids Res. 44 (2016) 1746–1759.
[27] J.L. Huppert, S. Balasubramanian, Prevalence of quadruplexes in the human genome, Nucleic Acids Res. 33 (2005) 2908–2916.
[28] A.S. Kudlicki, G-quadruplexes involving both strands of genomic DNA are highly abundant and colocalize with functional sites in the human genome, PLoS One 11 (2016) e0146174.
[29] R. Garg, J. Aggarwal, B. Thakkar, Genome-wide discovery of G-quadruplex forming sequences and their functional relevance in plants, Sci. Rep. 6 (2016) 28211.
[30] Y. Wang, M. Zhao, Q. Zhang, G.-F. Zhu, F.-F. Li, L.-F. Du, Genomic distribution and possible functional roles of putative G-quadruplex motifs in two subspecies of Oryza sativa, Comput. Biol. Chem. 56 (2015) 122–130.
[31] P. Armas, A. David, N.B. Calcaterra, Transcriptional control by G-quadruplexes: in vivo roles and perspectives for specific intervention, Transcription 8 (2017) 21–25.
[32] Z. Du, Y. Zhao, N. Li, Genome-wide colonization of gene regulatory elements by G4 DNA motifs, Nucleic Acids Res. 37 (2009) 6784–6798.
[33] S.G. Hershman, Q. Chen, J.Y. Lee, M.L. Kozak, P. Yue, L.-S. Wang, F.B. Johnson, Genomic distribution and functional analyses of potential G-quadruplex-forming sequences in Saccharomyces cerevisiae, Nucleic Acids Res. 36 (2008) 144–156.
[34] P. Rawal, V.B.R. Kummarasetti, J. Ravindran, N. Kumar, K. Halder, R. Sharma, M. Mukerji, S.K. Das, S. Chowdhury, Genome-wide prediction of G4 DNA as regulatory motifs: role in Escherichia coli global regulation, Genome Res. 16 (2006) 644–655.
[35] C.K. Kwok, Y. Ding, S. Shahid, S.M. Assmann, P.C. Bevilacqua, A stable RNA G-quadruplex within the 5'-UTR of Arabidopsis thaliana ATR mRNA inhibits translation, Biochem. J. 467 (2015) 91–102.
[36] M.M. Fay, S.M. Lyons, P. Ivanov, RNA G-quadruplexes in biology: principles and molecular mechanisms, J. Mol. Biol. 429 (2017) 2127–2147.
[37] S. Rouleau, R. Jodoin, J.-M. Garant, J.-P. Perreault, RNA G-quadruplexes as key motifs of the transcriptome, Adv. Biochem. Eng. Biotechnol. (2017), http://dx.doi.org/10.1007/10_2017_8.
[38] J.U. Guo, D.P. Bartel, RNA G-quadruplexes are globally unfolded in eukaryotic cells and depleted in bacteria, Science 353 (2016), http://dx.doi.org/10.1126/science.aaf5371.
[39] M. Yang, Y. Wu, S. Jin, J. Hou, Y. Mao, W. Liu, Y. Shen, L. Wu, Flower bud transcriptome analysis of Sapium sebiferum (Linn.) Roxb. and primary investigation of drought induced flowering: pathway construction and G-quadruplex prediction based on transcriptome, PLoS One 10 (2015) e0118479.
[40] M.A. Mullen, S.M. Assmann, P.C. Bevilacqua, Toward a digital gene response: RNA G-quadruplexes with fewer quartets fold with higher cooperativity, J. Am. Chem. Soc. 134 (2012) 812–815.
[41] X. Ji, H. Sun, H. Zhou, J. Xiang, Y. Tang, C. Zhao, Research progress of RNA quadruplex, Nucleic Acid Ther. 21 (2011) 185–200.
[42] T.R. Cech, The RNA worlds in context, Cold Spring Harbor Perspect. Biol. 4 (2012) a006742.
[43] K. Paeschke, J.A. Capra, V.A. Zakian, DNA replication through G-quadruplex motifs is promoted by the Saccharomyces cerevisiae Pif1 DNA helicase, Cell 145 (2011) 678–691.
[44] K. Paeschke, M.L. Bochman, P.D. Garcia, P. Cejka, K.L. Friedman, S.C. Kowalczykowski, V.A. Zakian, Pif1 family helicases suppress genome instability at G-quadruplex motifs, Nature 497 (2013) 458–462.
[45] I. Cheung, M. Schertzer, A. Rose, P.M. Lansdorp, Disruption of dog-1 in Caenorhabditis elegans triggers deletions upstream of guanine-rich DNA, Nat. Genet. 31 (2002) 405–409.
[46] Y. Wu, K. Shin-ya, R.M. Brosh Jr., FANCJ helicase defective in Fanconia anemia and breast cancer unwinds G-quadruplex DNA to defend genomic stability, Mol. Cell. Biol. 28 (2008) 4116–4128.
[47] D.J.-F. Chinnapen, D. Sen, A deoxyribozyme that harnesses light to repair thymine dimers in DNA, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 65–69.
[48] I. Saito, M. Takayama, H. Sugiyama, K. Nakatani, A. Tsuchida, M. Yamamoto, Photoinduced DNA cleavage via electron transfer: demonstration that guanine residues located 5'to guanine are the most electron-donating sites, J. Am. Chem. Soc. 117 (1995) 6406–6407.
[49] G.I. Livshits, A. Stern, D. Rotem, N. Borovok, G. Eidelshtein, A. Migliore, E. Penzo, S.J. Wind, R. Di Felice, S.S. Skourtis, J.C. Cuevas, L. Gurevich, A.B. Kotlyar, D. Porath, Long-range charge transport in single G-quadruplex DNA molecules, Nat. Nanotechnol. 9 (2014) 1040–1046.
[50] M. Kopylov, H.W. Bass, M.E. Stroupe, The maize (Zea mays L.) nucleoside diphosphate kinase1 (ZmNDPK1) gene encodes a human NM23-H2 homologue that binds and stabilizes G-quadruplex DNA, Biochemistry 54 (2015) 1743–1757.
[51] E.H. Postel, S.J. Berberich, S.J. Flint, C.A. Ferrone, Human c-myc transcription factor PuF identified as nm23-H2 nucleoside diphosphate kinase, a candidate suppressor of tumor metastasis, Science 261 (1993) 478–480.
[52] S. Sharma, A. Sengupta, S. Chowdhury, NM23/NDPK proteins in transcription regulatory functions and chromatin modulation: emerging trends, Lab. Invest. (2017), http://dx.doi.org/10.1038/labinvest.2017.98.
[53] V. Brázda, L. Hároníková, J.C.C. Liao, M. Fojta, DNA and RNA quadruplex-binding proteins, Int. J. Mol. Sci. 15 (2014) 17493–17517.
[54] A.M. Fleming, Y. Ding, C.J. Burrows, Oxidative DNA damage is epigenetic by regulating gene transcription via base excision repair, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 2604–2609.
[55] V. Yadav, N. Hemansi, N. Kim, P. Tuteja, G. Yadav, Quadruplex in plants: a ubiquitous regulatory element and its biological relevance, Front. Plant Sci. 8 (2017) 1163.
[56] J.A. Capra, K. Paeschke, M. Singh, V.A. Zakian, G-quadruplex DNA sequences are evolutionarily conserved and associated with distinct genomic features in Saccharomyces cerevisiae, PLoS Comput. Biol. 6 (2010) e1000861.
[57] V.S. Chambers, G. Marsico, J.M. Boutell, M. Di Antonio, G.P. Smith, S. Balasubramanian, High-throughput sequencing of DNA G-quadruplex structures in the human genome, Nat. Biotechnol. 33 (2015) 877–881.
[58] X. Xu, Editors' selection of papers from China's academic journals, Natl. Sci. Rev. 2 (2015) 253–254.