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A bouquet of DNA structures: Emerging diversity

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ABSTRACT

Structural polymorphism of DNA has constantly been evolving from the time of illustration of the double helical model of DNA by Watson and Crick. A variety of non-canonical DNA structures have constantly been documented across the globe. DNA attracted worldwide attention as a carrier of genetic information. In addition to the classical Watson–Crick duplex, DNA can actually adopt diverse structures during its active participation in cellular processes like replication, transcription, recombination and repair. Structures like hairpin, cruciform, triplex, G-triplex, quadruplex, i-motif and other alternative non-canonical DNA structures have been studied at length and have also shown their *in vivo* occurrence. This review mainly focuses on non-canonical structures adopted by DNA oligonucleotides which have certain prerequisites for their formation in terms of sequence, its length, number and orientation of strands along with varied solution conditions. This conformational polymorphism of DNA might be the basis of different functional properties of a specific set of DNA sequences, further giving some insights for various extremely complicated biological phenomena. Many of these structures have already shown their linkages with diseases like cancer and genetic disorders, hence making them an extremely striking target for structure-specific drug designing and therapeutic applications.

Contents

1. Introduction

In eukaryotic cells, deoxyribose nucleic acid (DNA) is present in its supercoiled form which is stabilized by ancillary proteins. However, during the biological processes such as replication and

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transcription, DNA gets unwind and may form structures that differ from the Watson–Crick B-form of DNA. This biological phenomenon of adopting various conformations by this marvelous biomolecule is known as structural polymorphism and it depends upon a number of factors like oligonucleotide sequence, solution condition, hydration, ions, proteins, ligands and superhelical stress. B-form of DNA double helix, proposed by Watson and Crick, generally accounts for most of the DNA behavior in the cell [1]. Widely studied DNA conformations are A, B and Z forms, while DNA structures like bulge, hairpin, cruciform, parallel-stranded DNA, triplex, quadruplex, and i-motif are also well documented. These alternative DNA structures might not only be important for interactions with proteins involved in replication, gene expression and recombination but these would also have an impact on DNA damage, repair and genetic stability [2]. They also play different roles in the formation of nucleosomes and other supramolecular structures involving DNA [3].

With the exception of the A-form, which is usually adopted by RNA duplexes and is capable of accommodating any sequence, all known DNA structures are sequence-dependent. The sequence requirement for Z-DNA is an alternating purine–pyrimidine/GC-rich sequence and such Z-DNA forming sequences have shown their occurrence near chromosomal breakpoints involving the *c-MYC* and *BCL-2* genes [4]. DNA sequences containing $(CGG)_n$ repeats have been shown to form Z-DNA at high salt and millimolar concentrations of Ni^{2+} ions [5]. Further, their stability can be enhanced with methylation of CGG repeats. The conformational properties of DNA sequences containing $(CCA)_n$ and $(TGG)_n$ repeats were reported by Zemánek et al. using CD spectroscopy, polyacrylamide gel electrophoresis, and UV absorption spectroscopy. This study revealed that $(CCA)_n$ repeats associate to form i-motif structure at acidic pH, while it existed as single strand at alkaline or neutral pH. DNA sequences containing $(TGG)_n$ stretches form antiparallel homoduplex or hairpin structure at low salt concentrations, whereas these sequences adopt G-quadruplex structure in the presence of potassium ions at physiological pH [6]. The inverted repeat DNA sequences are capable of forming cruciform structures, while the G-quadruplex and i-motif formation require a contiguous stretch of guanines and cytosines respectively [7,8]. Some of the sequence requirements for the formation of various non-canonical DNA structures are summarized in Table 1. Most of these non-canonical DNA structures have already shown their *in vivo* existence, making them biologically very significant. Some of these fascinating DNA structures (Fig. 1) are discussed in the following sections.

2. Cruciform DNA

DNA supercoiling and base sequences are the two prime factors which are responsible for the structural complexity of DNA molecule. A cruciform structure is formed when interstrand base pairing in duplex DNA with inverted repeats, convert to intrastrand base pairing. It is well documented that an essential requirement for cruciform DNA formation is an inverted repeat DNA sequence which should be embedded in an A+T-rich region [9]. It is of great importance in many biological processes, including the nucleosome positioning, replication and regulation of gene expression. Two mechanisms are proposed for the formation of cruciform structure which differ in salt concentration, activation energy and temperature [10]. The thermodynamic stability of cruciform is very less in comparison to normal B-DNA and showed highly retarded mobility in polyacrylamide gel. Two classes of cruciform have been found till now, one with four-fold symmetry with all arms perpendicular to each other, and another with arms at an acute angle. Cruciform structures are generally a preferential target for many proteins such as HMG proteins, H1, H5 histones, and help to target many diseases [9].

Table1
Summarizing the sequence requirements for various DNA structures.

S.No.	Structures	Sequence	Reference
1.	Parallel-Stranded DNA	5′-CCTATTAAATCC	[51]
		5′-AAAAAAAAAATAATTTTAAATATTT	[52]
2.	Hairpin	$(CAG)_n/(CTG)_n$	[35]
		5′-TGGGGA/GCCCCA (Hairpin and duplex)	[11,12]
3.	Cruciform	5′-ATGGTCTTACCTA	[92]
4.	Triplex	5′-$(AAG)_5$ (Intermolecular triplex)	[93]
		5′-$C_2TC_5TC_2T_5G_2AG_5AG_2T_5G_2AG_5AG_2$	[58]
5.	i-motif	5′-CCCTAACCCTAA (Bimolecular)	[65,66]
		5′-$(CCCTAACCCTAA)_2$ (Unimolecular)	[66]
6.	Quadruplex	5′-$AG_6AG_3AG_3TG_2$ (Dimeric parallel-stranded)	[73]
		5′-GGTTGGTGTGGTTGG (Antiparallel unimolecular)	[94]
		5′-TTAGGGTTAGGG (Antiparallel tetramer)	[70]
7.	Z-DNA	5′-$(CGCGCGCGCGCG)_2$	[95]
8.	A-DNA	5′-$(GCGGGCCCGC)_2$	[96]

3. Hairpin DNA

DNA sequences with inverted repeats (IRs) or palindromes lead to the formation of hairpin structure, which might also be in equilibrium with duplex DNA, depending upon salt or oligomer concentrations. A single nucleotide polymorphism (SNP) in an 11-mer DNA oligonucleotide (d-TGGGG(A/G)CCCCA) had been shown to exhibit equilibrium between duplex and hairpin [11,12], while its RNA counterpart (UGGGG(G/A)CCCCA) adopted only hairpin structure [13]. This polymorphism of DNA sequences of Locus Control region (LCR) of beta-globin gene had been discussed from our laboratory in a review [14]. Hairpins have a base-paired stem and a small loop of unpaired bases, which are usually formed *via* two main mechanisms. In the first mechanism, hairpin is formed in the same way as cruciform structure is formed from double stranded DNA. In the second mechanism, single stranded DNA (ssDNA), produced during various cellular processes like replication on the template for lagging-strand synthesis, DNA repair, rolling-circle replication (RCR), and infection by some viruses leads to hairpin formation [15]. Single strand DNA binding protein (SSB) facilitate the binding of RecA to ssDNA without sequence specificity and leads to hairpin formation [16]. Basically, the possibility of hairpin or cruciform formation at the protein binding site can affect the coiling state of DNA which may either facilitate or prevent the DNA–protein interactions, and alter the gene expression. Although hairpins forming long palindromes are genetically unstable, yet the hairpin structure is known to play a key role in a number of cellular processes such as gene expression, recombination, and transcription.

Poly(dG)●Poly(dC) sequences exhibit A- as well B-forms depending on the solution conditions. These sequences adopt A-form of DNA at higher (molar) salt conditions, while at low (millimolar) salt concentration, they exist in B-form [17]. The transition from B- to A-form can be induced in the presence of methanol or hexamine cobalt or spermine or with the use of high oligomer concentration [18–21]. On the basis of CD spectroscopy, NMR spectroscopy and unrestricted molecular dynamics, d(CCCCGGGG) was shown to exhibit A- as well as B-like DNA characteristics. This study suggested that stacking between bases is accountable for A-form, while backbone framework is responsible for B-DNA signatures [22].

On the contrary, the sequence with inverted guanine and cytosine tracts *i.e.* d(GGGGCCCC) showed both B- as well as A-form

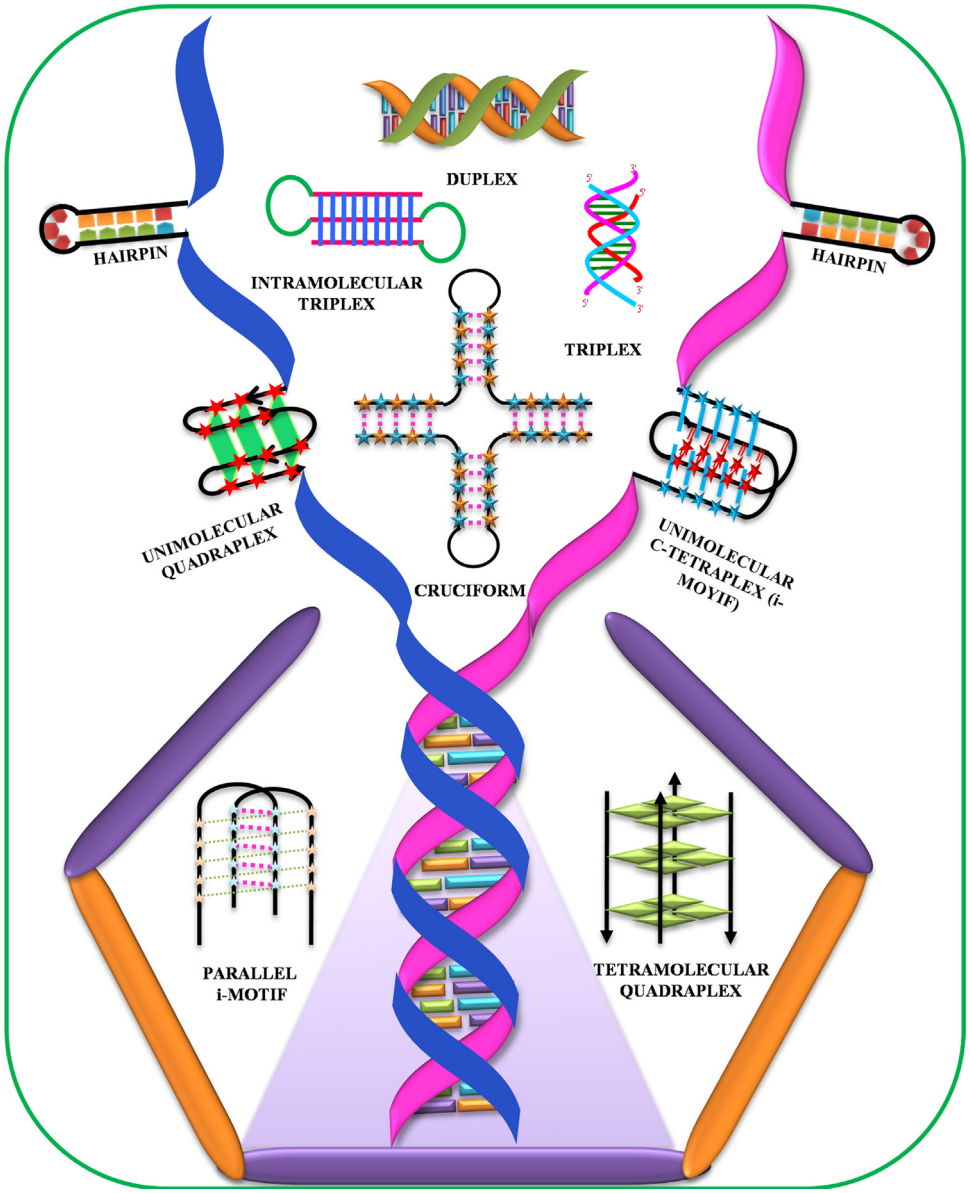

Fig. 1. Bouquet of non-canonical DNA structures.

characteristics which were the attributes of base stacking of cytosine and guanine bases respectively [23]. It had been reported that A-like base stacking geometry of guanine bases in B-DNA is recognized by transcription factors [24] and, therefore, such sequences may play an important role in cellular processes such as transcription and replication [25].

4. DNA bubble or bulge duplex

These DNA structures are formed in double-stranded DNA due to the presence of unpaired nucleotides on one strand and their structure determination along with the dynamics have been reviewed by Turner [26]. Bulges can have one or more nucleotides and are classified in different types depending on their location: on one strand, on both strands (internal loop) or at a junction. These bulges may resemble the replication or transcription bubble thereby affecting the DNA–protein interaction during such events [27]. In addition, DNA bulges are capable of releasing the bending energy of highly bent duplex DNA, thereby enhancing the process of wrapping of DNA around histones and thus acting as a pivotal element for DNA condensation [28].

5. Slipped DNA (S-DNA)

S-DNA is formed by sequences containing stretches of direct repeats and is involved in frame shift mutagenesis during replication. Slippage of several repeat units produces a three way junction in the form of a bulge or a hairpin which is thermodynamically unfavorable, relative to the duplex DNA [29]. Adding or deleting a single base shifts the reading frame, thereby encoding the amino acids different from those present in wild-type protein. Moreover, S-DNA involved in GC-rich triplet repeat mutagenesis $(CTG)_n \bullet (CAG)_n$, and $(CGG)_n \bullet (CCG)_n$ have been associated with genetic neurodegenerative diseases or fragile sites [30,31]. Originally, expansions were limited to trinucleotide repeats only. Later, it was found that tetrameric $(CCTG)_n \bullet (CAGG)_n$ [32], pentameric $(TGGAA)_n \bullet (TTCCA)_n$ [33] and dodecameric $(C_4GC_4GCG)_n \bullet (CGCG_4CG_4)_n$ [34] repeats are also associated with a number of human genetic diseases [35].

6. Bent/Curved DNA

The phenomenon of sequence-directed DNA bending was discovered more than 30 years ago; when restriction fragments from the kinetoplast body of Leishmania tarentolae appeared to migrate anomalously slow on polyacrylamide gels [36]. A subsequent study comparing the electrophoretic migration of circularly permuted DNA molecules of the same length, with the bend positioned differently in each, localized the phenomenon to short stretches of 4–6 adenines, which were repeated in phase with the helical repeat [37].

Bending is important in DNA packaging and in regulating diverse cellular processes. A nucleosome core particle consists of 147 base pairs of DNA wrapped around a histone octamer. The phenomenon of preferential binding of histone octamer at particular positions on a long piece of DNA is called nucleosome positioning. It plays an important role in gene regulation since nucleosome binding to specific DNA regions impede transcription factor binding at these sites, thereby influencing transcription both negatively as well as positively [38]. DNA bending is also believed to facilitate the initial recognition of the mismatched base for repair mechanisms in the cell [39].

7. Parallel-stranded DNA

Apart from the usual antiparallel duplex, DNA also has the ability to form parallel-stranded duplex (ps-duplex), which is stabilized by reverse Watson–Crick or Hoogsteen hydrogen bonding. They may play an important role in regulation of transcription, mutational processes and chromosomal folding.

Purine-rich sequences $(dG{\bullet}dA)_n$ are over-represented in the eukaryotic genome [40] including centromeres and are involved in various biological processes. Such sequences are capable of forming peculiar structures like antiparallel homoduplex, parallel stranded homoduplex (ps-homoduplex), hairpin, and DNA triplex depending on the solution conditions [41,42]. The sequences with GA repeats, $(GA)_n$ associate together to adapt ps-homoduplex at physiological conditions [43], while a single-stranded helical structure [44–46] was formed at low pH, where adenine is protonated. Such single stranded helical structure is also formed in the presence of ethanol, where adenine is not protonated [47]. A similar sequence $(AG)_{20,30}$ had been shown to exist into ps-homoduplex having $A^+{\bullet}A^+$ and G•G pairs [46].

DNA, RNA triplex and quadruplex could also be formed using parallel-stranded stretches as a template [48,49]. Ps-duplexes were shown to be less stable than the antiparallel duplexes [50]. Parvathy et al. demonstrated that C^*C^+ bonding on both sides of a sequence containing complementary A-T base pairs is responsible for the formation of ps-duplex at acidic pH, which is further confirmed by NMR [51]. Recently, modified nucleosides (dG.isoCd) and (dC.isoGd) have been introduced in order to stabilize ps-duplexes containing G:C pairs [52].

8. Triplex DNA

Triplexes are formed by recognition of oligopurine•oligopyrimidine duplex by single-stranded triplex-forming oligonucleotides (TFOs) in a sequence-specific manner *via* Hoogsteen or reverse Hoogsteen hydrogen bonds. The existence of triplexes was first shown in 1957, by Felsenfeld et al. [53] which initiated the idea that double helices containing only purines in one chain could bind a third strand polynucleotide containing either pyrimidines [54] or purines [55]. A potential biological function of triplex was discovered in 1968, when Morgan and Wells reported that triplex formation was able to inhibit transcription [54]. The biological relevance of triplexes were not paid any attention for almost 20 years, until two research groups led by Peter Dervan [56] and Claude Hélène [57] in 1987 simultaneously published that short oligonucleotides could be used to induce a DNA cleavage at a specific site on DNA through triplex formation.

Triplexes can be formed either from RNA or DNA chains or their combinations, giving rise to intramolecular or intermolecular triplex, which can occur in both the purine and pyrimidine motifs. Formation of triplex DNA depends on several factors like oligonucleotide length, base composition, pH, divalent cation, and temperature. In a report from our own laboratory, the formation of an intramolecular purine–motif triplex containing human *c-jun* proto-oncogene target was reported [58]. Specificity and selectivity of the third strand in duplex recognition has led to a variety of potential applications of triplexes in molecular biology, diagnostics, and therapeutics [59–61]. It was also shown that the triple helix-forming oligonucleotides may inhibit transcription of a specific gene [62]. The research on triplex has become very significant after the detection of triplex within human cells using psoralens [63].

9. i-motif DNA

The complementary strand of G-rich sequences, creates a very interesting structure by making C^*C^+ base pair, in which two parallel cytosine-rich strands forming duplex are intercalated in antiparallel orientation, resulting into the formation of “intercalated-motif or i-motif DNA” [64–66]. These structures are known to be formed by one, two or four strands leading to the formation of uni-, bi- and tetramolecular structures, which differ in the strand orientation, sequence length, number of C^*C^+ base pairs etc. [65,66]. These structures are stabilized by acidic pH and hence are quite extensively being used as pH switches for a large number of nanotechnology applications [67]. It is assumed that these pH switches or molecular motors will have the ability to function as the natural proteins motors, which are present inside the cells. Also, various ligands have now been designed to stabilize i-motif structures so that they can be explored for more biological applications [64].

10. Guanine quadruplex

Based on the cyclic arrangement of four guanines forming G-tetrads through Hoogsteen hydrogen bonding, a new family of nucleic acid structures was discovered in 1962 by Gellert et al., which was called as G-quadruplex [68]. Guanine-rich DNA sequences have shown their occurrence in most extensively characterized telomeric region of eukaryotic chromosomes [69]. Bioinformatics had been extensively used for investigating the prevalence of G-rich sequences forming quadruplexes in the genomes of various organisms, especially in regions like promoter, 5′-UTR, and oncogenes.

G-quadruplexes are highly polymorphic in nature and may form intramolecular/intermolecular, and parallel/antiparallel structures. Our parent laboratory had also reported an antiparallel tetrameric quadruplex formed by the double repeat (d-TTAGGGTTAGGG) of human telomeric sequence [70]. The observed high stability of quadruplex is due to hydrogen bonding occurring within each quartet, stacking of hydrophobic quartets upon one another and coordination of monovalent counterions (Na^+, K^+). G-quadruplexes can be classified in terms of strand stoichiometry (uni-, bi- and tetramolecular), orientation (parallel, anti-parallel and mixed), shapes (chair or basket) and loops (lateral, propeller, diagonal, V-shaped) [71]. Some advanced structures like (3+1)

G-quadruplex, G-triplex and G-quadruplex with bulges have also now been well documented [8].

Till recently, reports had been limited to uni-, bi- or tetramolecular G-quadruplexes [72], but an interesting dimeric quadruplex formed by human CEB1 Minisatellite had now been reported, which had two stacked subunits involving a parallel snapback arrangement. This scaffold comprises of three double-chain reversal loops, a V-shaped loop and three G-quartet layers. These two subunits are stacked by facing their 5′-end away from each other giving rise to multiple stacking rotamers [73]. So far, only right-handed quadruplexes have been studied, but recently, a left-handed G-quadruplex has also been reported [74]. NMR and X-ray studies of a G-rich sequence from AGRO100 exhibited anti-proliferative activity against cancer cells and had been shown to adopt a parallel-stranded quadruplex motif. The CD spectra showed an inverted profile from that of right-handed topology, confirming its left-handed conformation [74]. Several intriguing structures expand the repertoire of G-quadruplex for the better understanding of this highly polymorphic structure [75,76].

11. Biological applications of alternative DNA structures

In the last few decades, DNA has been granted the status of 'Book of life' with the complete set of instructions to decipher it. As researchers uncover the veil over the existence of wealth of unusual DNA structures, they were baffled over their biological relevance and considered them as transient structures. Scientists have characterized almost more than a dozen of non-canonical DNA structures, among which quadruplex, triplex, cruciform and slipped structures are most common [77]. However, many researchers advocate that these structures represent hotspots for mutations, such as deletions or expansions and also participate in various biological processes governed by the interaction of proteins such as recombination, repair, replication and translocation etc. [78,79]. Biological applications of various alternative DNA structures are systematically summarized and illustrated in Fig. 2.

Structured forms of DNA, with intrastrand pairing with inverted repeat sequences form hairpin or cruciform and their thermodynamic stability comes from the relaxation of negative supercoiling and thus affects the degree of DNA supercoiling as well as the positioning of nucleosomes *in vivo*. There are three ways in which such stem-loop systems can interact with proteins and impact cell physiology: (i) cruciform formation modifies the coiling state of DNA, which is known to affect the binding of regulatory proteins; (ii) the DNA–protein interaction can be inhibited, if a hairpin overlaps a protein recognition site; [80] and (iii) proteins can directly recognize and bind DNA hairpins (Fig. 3a) [9,15,30].

Likewise, triplex forming sequences are located predominantly in non-coding regions and may play a significant role in regulation, recombination and evolution [81]. The intramolecular DNA triplexes may exist *in vivo* and may act as molecular switches to modulate gene expression and other DNA metabolism events in a structure-dependent manner, in addition to the well-established sequence-specific regulation [82]. Moser and Dervan demonstrated specific cleavage of plasmid DNA with a short oligonucleotide conjugated to EDTA-Fe and suggested its potential use in chromosome mapping [56]. Effect of pharmaceutical compounds on triplexes [83,84] and transcription directed therapeutics might extend their applications in future.

It is well known that G-quartet structures play crucial roles in various cellular processes like in maintaining chromosomal ends, transcription, translation etc. [72], along with their wide application in nanotechnology because of their self-assembly formation and stability [85–87]. The role of G-quadruplex structure in neurodegenerative diseases and non-coding transcriptome has also recently been reported [88].

An illustration showing G-quadruplex formation at chromosomal telomeres suggests its clear biological relevance during the spindle formation in cell division of eukaryotes (Fig. 3b). Recently, G-quadruplex formation has been visualized in the mammalian living system [89] and in the promoter region of oncogene using cross-linking strategy [90]. A quadruplex-forming aptamer with an ability to bind to certain cellular proteins have been found to inhibit proliferation in various cancer cells. It has also been reported that G-quadruplex formation may provide a mean for long-range sensing and communication between distal genomic locations to coordinate regulatory transactions in genomic DNA [91].

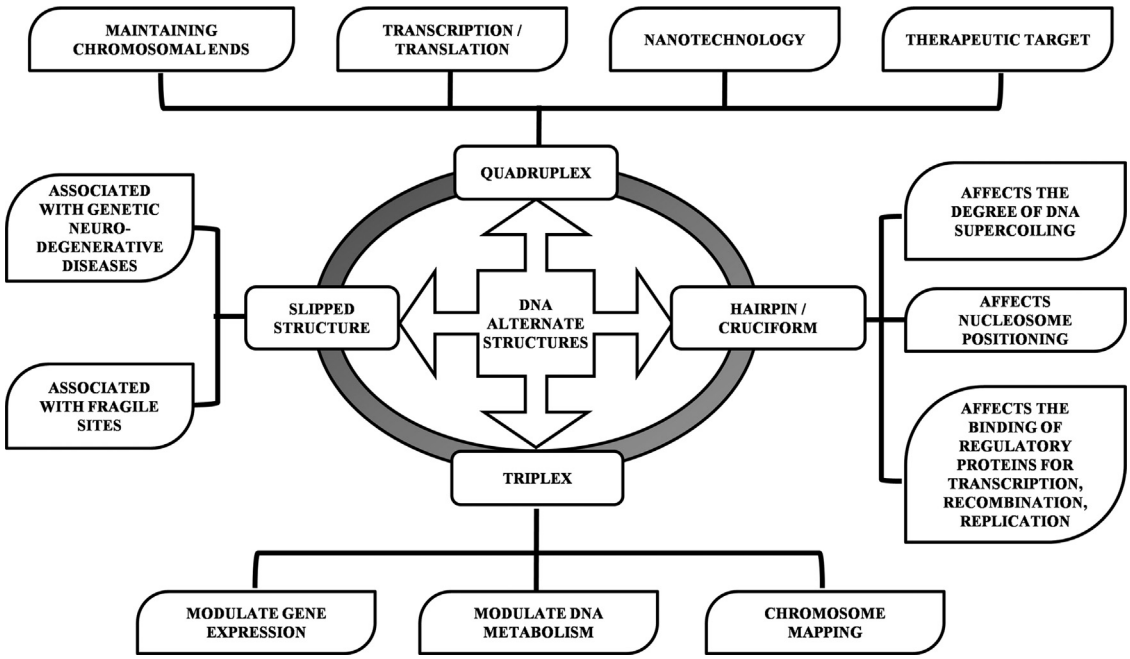

Fig. 2. Pictorial representation of biological applications of non-canonical DNA structures.

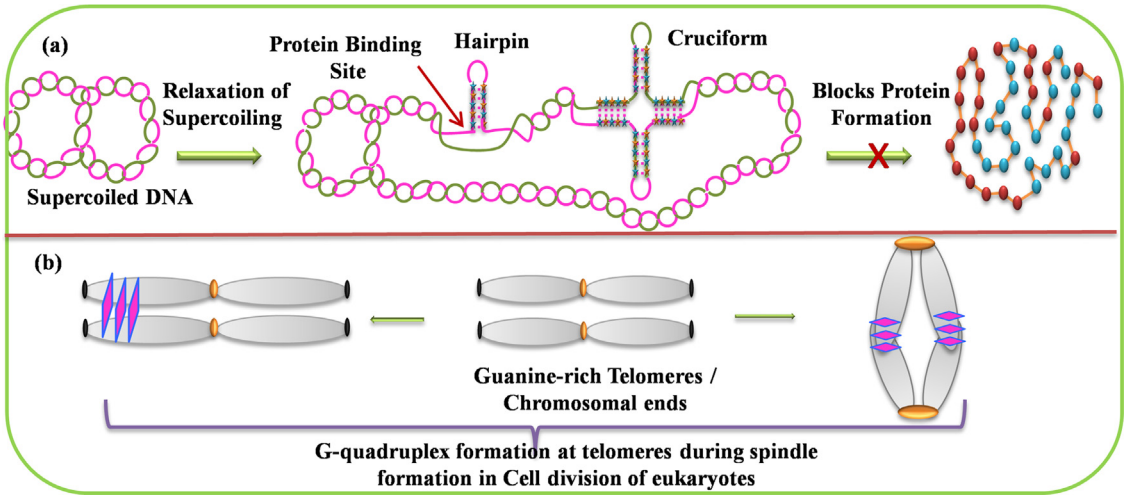

Fig. 3. Biologically relevant structures. (a) Hairpin and Cruciform at protein binding site. (b)Formation of Guanine-quadruplex at chromosomal ends/telomeres.

12. Outlook and future directions

Understanding about non-canonical DNA structures further opens up a new arena of exploring their biological applications which might be relevant for understanding the mechanism of regulations of the cellular processes. As most of these DNA structures have already shown their *in vivo* existence in recent past, the mechanistic models of their functioning should now be the focus of the scientific community. Many of these structures like guanine quadruplex have now been linked with the diseases such as cancer and genetic disorders, providing the clues for the future correlation of the same with customized designing of various therapeutic targets. This review reinforces the role of alternative DNA structures in gene regulation along with emphasizing upon the need of understanding their formation and control mechanisms at various genomic locations. Profound insights into these mechanisms of non-canonical DNA structures could also help us devise efficient strategies to combat diseases by altering gene expression.

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Appendix A. Transparency Document

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bbrep.2016.01.013.

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