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Understanding B-DNA to A-DNA transition in the right-handed DNA helix: Perspective from a local to global transition

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ABSTRACT

The right-handed DNA helix exhibits two major conformations, A-DNA and B-DNA, depending on the environmental conditions. The B-DNA to A-DNA (B→A) transition is sequence specific, cooperative, and reversible. The reduced water activity due to the addition of solvents like ethanol or the presence of protein or drug molecules causes B→A transition. In several biological cases, B→A transition occurs at a local level where small fragments of a long DNA sequence undergoes B→A transition. In this review, we have discussed various aspects of B→A transition such as the role of water, sequence specificity, mechanism of B→A transition, etc. The review primarily focuses on the B→A mechanism involved at a local level, and finally its connection to the global transition in theoretical and experimental studies.

Contents

1. Introduction

The polymorphism exhibited by DNA is a prerequisite for various biological processes. The right-handed DNA helix prominently displays B-DNA and A-DNA conformations in many protein-DNA complexes (Lu et al., 2000). Franklin and Gosling (1953a; 1953b; 1953c) coined the terms “Structure A” and “Structure B” while studying the “dry” and “wet” forms of DNA fibers, respectively. Fig. 1 shows the X-ray fiber diffraction patterns of A-DNA (dry form) and B-DNA (wet form) studied by Franklin and Gosling. Later, Kopka et al. observed (Kopka et al., 1983) the presence of “biological” water molecules clinging to the outer sugar-phosphate backbone in the B-DNA. This observation supports the role of water in

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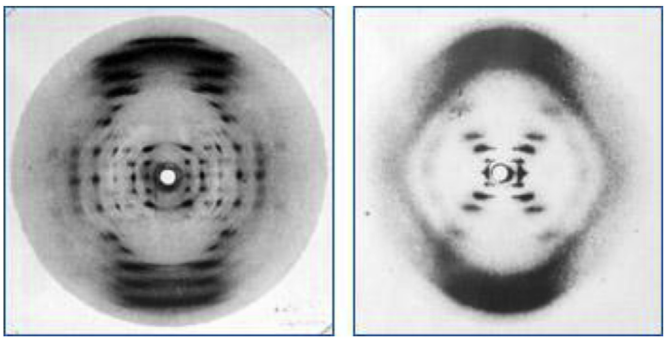

Fig. 1. Figure showing the X-ray diffraction patterns for A-DNA (Left) and B-DNA (Right) studied by Franklin and co-workers (*source:* http://undsci.berkeley.edu/article/0_0_0/dna_06).

the structural integrity of DNA conformation, as confirmed by various studies till date.

B-DNA to A-DNA (B→A) transition depends on various factors such as base composition of a sequence, ion concentration, water activity, etc. At the low relative humidity (RH) of less than 75%, the dielectric constant of the solvent medium decreases, resulting in increased inter-strand phosphate repulsion. The positively charged counterions such as Na^+, K^+ screen the phosphate-phosphate repulsion in the A-form. Hence, their presence at high concentration affects the stability of the DNA forms. The higher concentration of Na^+, K^+, Cs^+ ions stabilizes the A-form in solution. The stabilization of A-form by counterions depends on strong or weak hydration shell of these ions. For example, the strongly hydrated ions (Bokma et al., 1987) such as Mg^{2+} and Li^+ inhibit B→A DNA transition, whereas less hydrated ions such as Na^+, K^+, Cs^+ assist B→A DNA transition at certain concentrations (Cheatham et al., 1997; Piskur and Rupprecht, 1995). The interaction of ions with negatively charged phosphate backbone as well as their interaction with groove atoms decides the fate of B→A DNA transition (Cheatham et al., 1997).

The phosphate backbone protrudes out during B→A transition due to phosphate-phosphate repulsion, exposing the buried hydrophilic groups of sugar-phosphate backbone in A-DNA conformation. This results in its strong binding with the closest water molecules making them a coherent part of the A-DNA structure. The analysis of protein-DNA complexes by Colasanti et al. (Andrew V. Colasanti et al., 2013) revealed the presence of hydrogen bond donating atoms of amino acid residues around the local A-form stabilizing the A-DNA structure (See Fig. 2(a) and (b)). Also, it has been proposed earlier that the "economy of hydration" (Saenger et al., 1986) is achieved in A-DNA by bridging water molecules in the phosphate backbone of DNA through hydrogen bonding.

DNA is a chemical instrument to store and process genetic information of an organism. The inherent conformational flexibility of DNA and its capability to survive in stringent conditions make DNA an ideal candidate to store genetic information. A-DNA conformation has an important biological role in the context of cellular defense mechanisms under harsh conditions (Lee et al., 2008). The A-form of DNA protects Bacillus *Subtillis* spores from UV damage (Mohr et al., 1991). Recently, Whelan and co-workers have shown fully reversible B→A DNA transition in living bacterial cells on desiccation and rehydration using FTIR spectroscopy (Whelan et al., 2014). Extremophiles like SIRV2 virus (*Sulfolobus islandicus rod-shaped virus 2*) survive at extreme temperatures of 80 °C and acidity of pH 3 by adopting the complete DNA in the A-form and thereby aids protein to encapsidate DNA (DiMaio et al., 2015).

Apart from its involvement in defense mechanisms of cells, the remarkable presence of the A-form of DNA is noted in many biological processes. Certain protein-DNA interactions involve direct recognition processes that require the sugar phosphate backbone of DNA to be exposed. Proteins such as polymerases, endonucleases, etc. perform cutting and sealing operations and cause B-DNA to A-DNA transition at the local level. The B→A transition involves a change in the major and minor groove widths, hence making buried parts of DNA available for interactions. During Transcription processes (Whitley et al., 2014), certain transcription factors employ indirect readout mechanism and look for local A-form in the genome to bind. Apart from A-form conformations of DNA, the other biologically important molecules such as RNA or RNA-DNA hybrid structures (Xiong and Sundaralingam, 1998) with polypurine RNA strand adopt A-form conformation. The RNA-DNA hybrid structures play an important role in replication and transcription processes of nucleic acids. These structures exhibit conformations similar to A-DNA or B-form/A-form intermediate structures (Hantz et al., 2001; Zimmerman and Pheiffer, 1981). The therapeutically important modified nucleotides such as 2′-O-methyl or 2′-O-methoxyethyl, 2′-Fluorine RNA or locked nucleic acids possess A-form and binds strongly to a specific nucleotide sequence. This strong binding opposes DNA/RNA cleavage by enzymes like endonuclease and prevents termination of further biological processes (Kawasaki et al., 1993; Moreno and Pego, 2014). This example points to the relevance of A-DNA conformation in the present nucleotide chemistry. However, the understanding the global and local level effects in case of RNA-DNA hybrid structure or

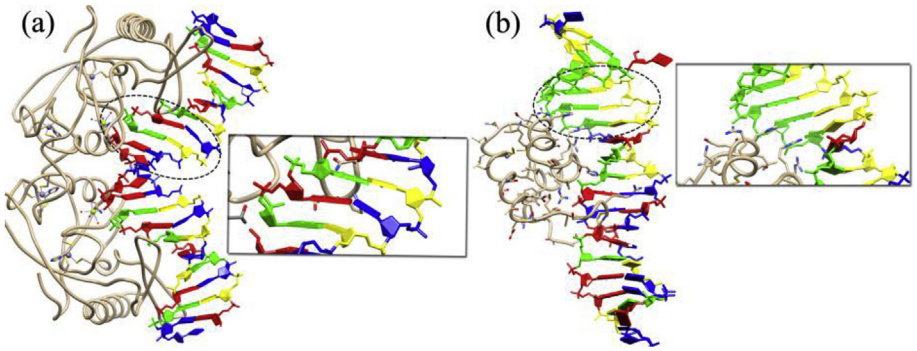

Fig. 2. Figure showing protein-DNA interactions in case of (a) DNA-endonuclease complex (Flick et al., 1998) with a local A-form (PDB ID: 1A73), (b) the close interactions of hydrogen bond donating groups (e.g., -NH_2, etc.) of the protein with DNA steps in the A-form taken from the crystal structure of Tc3 transposase (van Pouderoyen et al., 1997) of *C. elegans* (PDB ID: 1TC3).