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A review on type of interaction of DNA with DNA binding agents

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Abstract
The study of selective interactions of drugs, proteins and small molecules with DNA is very exciting and significant not only in understanding the mechanism of interaction, but also for the design of new drugs. Understanding how drug molecules interact with DNA has become an active research area at the interface between chemistry, molecular biology and medicine. The interaction of protein with DNA plays a crucial role in the function of regulatory proteins. In this review article, we attempt to bring together topics that cover the breadth of this large area of research *via* explaining the covalent and non-covalent binding.

Keywords: Interaction, DNA, drugs. Binding, proteins

Introduction

DNA structure

In 1896, the German biochemist named Frederich Miescher first observed DNA. It consists of molecule called nucleotides. 'Each nucleotide contains a phosphate group, a sugar group and a nitrogen base [3]. The four types of nitrogen bases are adenine (A), thymine (T), guanine (G) and cytosine (C) [3]. The order of these bases is what determines DNA's instructions, or genetic code. Human DNA has around 3 billion bases, and more than 99 percent of those bases are the same in all people [3]. In 1953, Watson and Crick discovered the three-dimensional double helical structure of DNA molecule. DNA nucleotides assemble in chains, the deoxy-ribose sugar of one nucleotide and the phosphate groups of next having two formal negative charges are linked together by phosphodiester bonds (Fig. 1) in the DNA polymer, this structure known as the sugar-phosphate backbone [4]. The two polynucleotide strands are organized in an anti-parallel arrangement and round each other to form a double helix. The purine (adenine 'A' and guanine 'G') and pyrimidine (cytosine 'C' and thymine 'T') bases are the interior of helix.[3] The double helical structure of DNA is stabilized by the inter-strand complementary base pairing through hydrogen bonding and π-π stacking interactions among the adjacent base pairs along the helical column, where 'A' bind to 'T' and 'C' binds to 'G' (fig. 2) [5-7]. The amount of 'A' is always equal to the amount of 'T', and the amount of 'C' is always equal to the amount of 'G' [5-7]. There are three types of DNA- A DNA, B DNA and Z DNA, however the very common structure of DNA is B-from which is a right-handed double helix mainly characterized by major grooves and minor grooves [8].

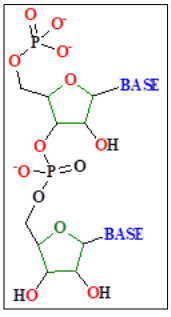

Fig 1: Phosphodiester bond in DNA

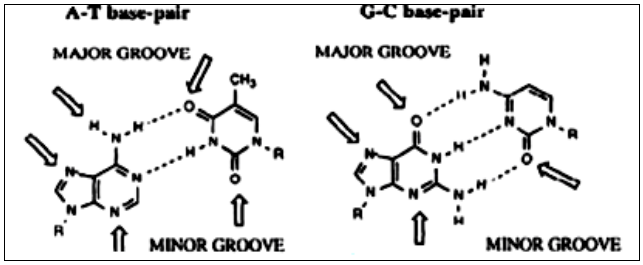

Fig 2: Base pairing between A-T, G-C

DNA interaction with drugs or small molecules

The selective interaction of drugs or small molecules with DNA may result in various therapeutic activity including anticancer, antitumor activities. Drugs interacting with DNA are currently in resurgence of interest to utilize them in the treatment of many diseases ranging from cancer, to chronic inflammation, as well as in fighting against resistant bacteria or viral infections [1]. Small molecules interaction studies with different nucleic acid base sequence have been focused on the potential applications of such ligands, which can bind with the nucleic acid as gene regulators and/or as a therapeutic agents [9]. The main objective is to determine the mode of binding of these molecules to DNA. It has been reported that these binding agents can interact either through oxygen atoms of phosphate, sugar or atoms of the nucleobases (N, C, O) [1]. These interactions could be either strong covalent or non-covalent. It has been reported that these ligands are also able to interact with their nucleic acid hosts by different modes, including intercalation and groove binding [9]. Mode(s) of ligand binding, the binding affinity, and the nature of the ligand-nucleic acid interactions that results to the observed affinities and specificities can be elucidated by the biophysical studies. This binding mode information would be important in proposing the mechanism(s) of ligand bioactivity and for more rationally designing modified ligands with altered binding properties and biological activities [10]. Nucleic acid binding ligands are generally classified by the mode by which they interact with their nucleic acid hosts. For example, ethidium is known as a classic intercalator [11] while netropsin is judged to be a classic groove binder [12].

DNA interaction with proteins

Protein- DNA interactions play important role in many vital processes such as regulation of Gene expression, DNA replication and repair, transcription and packaging [13]. Proteins can interact with DNA either specifically or non-specifically. Studying the specificity with which protein recognise the target site on DNA is of considerable theoretical and experimental importance and its basis has been demonstrated through experimental and theoretical analysis of Protein- DNA complexes [13]. The interaction of protein with DNA could be the direct interactions of amino acids with the bases of DNA. Understanding these interactions would help in understanding the various biological mechanisms like transcription [1].

Covalent binding

This type of binding is generally shown by the soft metals, which binds to the nucleophilic centres of heterocyclic bases of DNA. N7 (Fig. 3a) on guanine, N3 on cytosine (Fig. 3b), N1 and or/N7 on adenine (Fig. 3c), O4 on thymine and deprotonated N3 position on thymine and uracil [14]. The covalent binding mode is irreversible [15]. Inorganic complexes, such as *cis*-platin and bimetallic rhodium acetate shows antitumor activity by covalent bonding to DNA [15]. The *cis*-platin and simple dirhodium carboxylate lantern complexes (e.g. $Rh_2(\mu\text{-}O_2CR)_4L_2$, R = Me, Et, Pr, CF_3; L=solvent) interacts with polynucleotide strand through coordination of platinum centre to the N7 positions of adjacent guanine bases of one strand, as a consequences there is intra-strand cross-linking between neighbouring guanine residues.[16] The transition metal with lesser degree of softness may show some sort of Covalent bonding with oxygen atoms of phosphate group transition metal. These types of covalent interactions are rather less common with sugar moiety but may exist with some heavy metal compounds like osmate esters. The covalent bonding, completes the inhibition of DNA processes ultimately leading to cell death [15]. The covalent bulky binders can cause the distortion in the backbone of DNA, which would then affect both the transcription and replication processes [17].

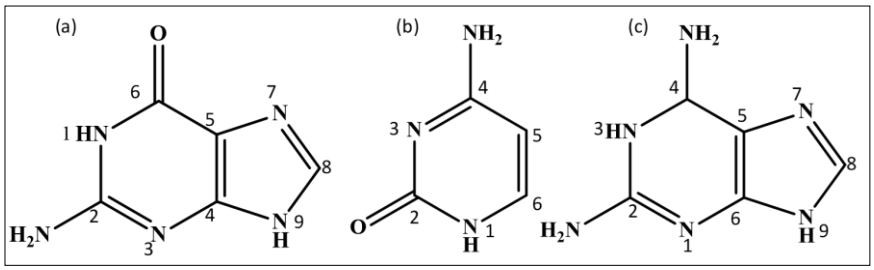

Fig 3: (a) Guanine (b) Cytosin (c) Adenine

Non-covalent

Molecules interact with DNA through hydrogen bonding, electrostatic forces, Vander Waal's force, hydrophobic interactions or intercalation [18]. Non-covalent binders have less cytotoxic agents than a covalent binder. This effect has been not well characterised but the important impacts on DNA includes the conformational changes, perturbation in structure, changes in DNA torsional tension, interruption with the protein–DNA interaction, which would ultimately lead to the breaking of DNA strand [19]. This mode is typically preferred over covalent mode of binding.

There are three fundamental modes of non-covalent DNA binding.

1. External or electrostatic interaction,
2. Groove or surface interaction and
3. Intercalation

i) External binding or electrostatic binding

External binding is the electrostatic interaction between positively charged metal ion and negatively charged phosphate backbone of DNA or electron donor groups of nucleobases.[17] Charge of the molecule, the ligand

hydrophobicity and the total size of the ion predominantly governed the binding strength [1]. This type of DNA interaction gives rise to association of DNA duplexes to form aggregates or condensed structures [17]. Some metal complexes also interact with DNA through external binding e.g., binding of Ru^{2+} complexes and cations like Mg^{2+} also usually interacts by this mode [20].

ii) Groove binding or surface binding

Groove binding involves lodging of drug molecules into the grooves of the double, triple or G-quadruplex helices of DNA [1]. This binding result in only slight changes in structure, and the DNA remains essentially in an unperturbed 'B' form and it also enhances the stability of DNA. Generally, the groove binders should not distort the DNA backbone to a larger extent. They should have flexible structures, unlike intercalators which exhibit planarity and rigidity [16]. It is stabilized by electrostatic, H-bonding and Van der Waal's interactions which makes the drug-DNA complexes more stable than those resulted by intercalation only [21]. Hoechst 33258 is a known as groove binding agent [22-24]. Groove binding of molecules with DNA may occur in two distinct ways: (i) *via*. major groove (Fig. 4a) which has been observed in DNA binding proteins or gene-targeted oligonucleotides and (ii) *via*. minor groove (Fig. 4b) which has been observed in case of small molecule. Major groove binders possess multiple interaction sites and exhibit comparatively stronger binding ability with guest molecules. Minor grooves may serve as better receptors for small, flat and cationic DNA binding molecules, but they are not rich in chemical information. The minor grooves are somewhat A-T specific. As a general rule, molecules binding through minor groove cause little or no perturbation in the structure of DNA which is reflected by little or no change in the DNA circular dichroism. Distamycin, metallobleomycins and Sigman's bis (1, 10-phenanthroline) copper(I) complex are some major groove binders [13].

iii) Intercalation

Intercalation (Fig. 4c) was first reported by Lerman in 1961. He tried to explain the strong affinity of certain heterocyclic aromatic dyes such as acridines for DNA [17]. In this binding a planar ligand moiety is inserted between adjacent base pairs, stabilized by π-π stacking interactions, dipole-dipole interactions and hydrogen bonding interactions with planar aromatic bases [25]. This binding results in a considerable change in DNA structure, and causes augmentation of DNA equal to the height of one base pair, stiffening, and slight unwinding of the helix at the intercalation site and enhanced DNA stability [1]. For intercalation, the planar molecule is in close proximity with the DNA base pairs, and is oriented roughly perpendicular to the DNA [26]. However, the overall structure of DNA remains unperturbed after intercalation. Intercalating ligands and metal complexes should possess extended planar aromatic ring system of suitable size and chemical nature to slot between base pairs axis [27]. DNA intercalators have been used for the chemotherapeutic treatment in order to stop the replication of DNA in a growing cancerous cell [28]. The intercaltors are independent of sequence of DNA. Intercalation is also possible in between the intra-base pairs of DNA and RNA. Examples are planar organic moieties such as ethidium daunomycin [29-31] and metal complexes bearing planar aromatic ligands like phen (1, 10-phenanthroline), phe (9, 10-phenanthrenequinone diimine) [11].

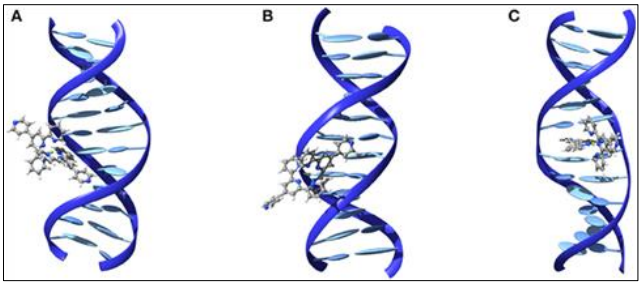

Fig 4: (a) Major groove binding, (b) Minor groove binding and (c) Intercalation binding

There are two modes of interacalation:

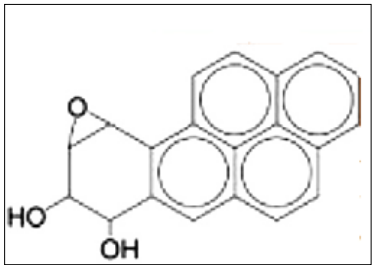

Fig 5: Structure of benzo[a]pyrene (BP)

a) Classic intercalation: Classical intercalators, bind to DNA duplexes with their aromatic system inserted between the GpG base pairs and example for this type is such as benzo[a]pyrene (BP) (Fig. 5) [32].

b) Threading intercalation: Threading intercalators have the two side chains on the opposite side of a planar ring. In these type of intercalation binding mode, one of the side chain slides through the intercalation cavity to form the complex with the DNA. The stability to these intercalators is provided by the binding with both the major and minor grooves as it can bind to both the grooves simultaneously [33]. Example: The threading intercalation of acridine-4-carboxamides into the duplex 50-d(CG(5-BrU)ACG)2-30 (Fig. 6) [34].

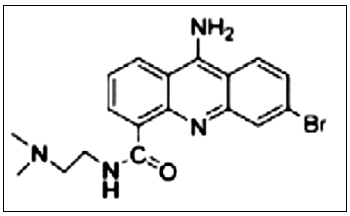

Fig 6: structure of acridine-4-carboxamides into the duplex 50-d(CG(5-BrU)ACG)2-30

In addition to these three fundamental modes, there are few alternative modes for DNA interaction. Insertion is one of these alternative pathways in which there is binding with DNA helix through separation and displacement of base pairs [13]. Metalloinsertors containing a planar aromatic ligand which can act as a π- π stacking replacement in the DNA base stack and eject the bases of a single base pair [20].

Conclusions

We discussed all the possible mode of DNA interactions with the drugs, small molecules and proteins. Understanding the mode of interaction would help in pharmacology for the designing of new drugs and their pharmacological activities

like anticancer drugs behaviour *i.e*. how do they function in our body as an anticancer drug. These modes would also makes the better understanding of biological mechanisms like DNA replication, transcription etc.

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