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Research Article

DNA Interaction of Drug Molecules for Cancer Treatment

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Abstract

The deoxyribonucleic acid (DNA) is the molecule of life that controls all the chemical changes that take place in cells. It is the molecular target for many of the drugs that are used in cancer therapeutics, and is viewed as a non-specific target of cytotoxic agents. The interaction of drugs with DNA is among the most important aspects of biological studies in drug discovery and pharmaceutical development processes. Moreover, the knowledge of specific targets in rational design of chemotherapeutics is a fundamental factor, principally, for the design of molecules that can be used in the treatment of oncologic diseases. Observing the pre- and postsigns of drug-DNA interaction provides good evidence for the interaction mechanism to be elucidated. Also, this interaction could be used for the quantification of drugs and for the determination of new drugs targeting DNA. Approaches can provide new insight into rational drug design and would lead to further understanding of the interaction mechanism between anti-cancer drugs and DNA. The intention of this review is to study of anticancer drugs, DNA interaction, and the mechanisms of interaction in order to understand the influence of several interaction factors in the capacity and selectivity of the anticancer drugs to interact with DNA. In addition, different experimental approaches to detect and to evaluate the anticancer drugs' interactions with DNA were also mentioned.

Keywords: DNA; Anticancer; Drug; Intercalation; Minor Grooving; Cisplatin.

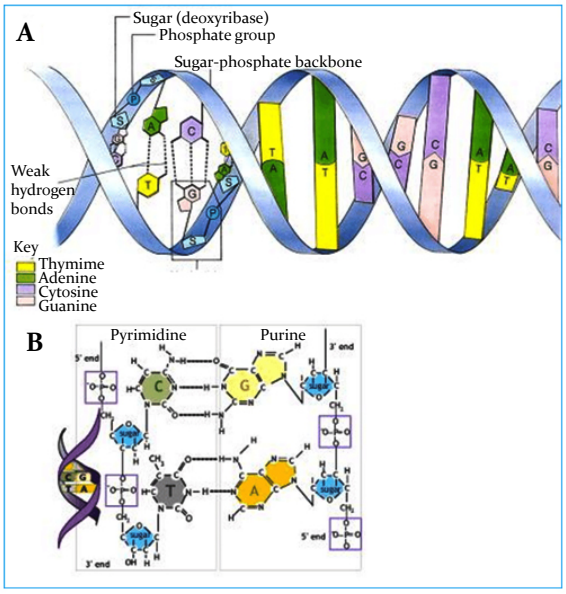
Introduction

DNA information is stored in the form of a code that constitutes four chemical bases namely: cytosine (C), adenine (A), thymine (T), and, lastly, guanine (G). The human DNA has approximately 3 billion bases, and not <99% of these bases are similar in all individuals. The sequence of these bases governs the available information for maintaining and building an organism, similar to the manner in which alphabetical letters are arranged to form sentences and words [1]. The chemical bases in a DNA pair up (C with G and A with T), in order toproduce units known as base pairs. In addition, each base is attached to a phosphate molecule and a sugar molecule. Together, a phosphate, sugar, and base are referred to as a nucleotide. The nucleotides are organized in two long strands thereby forming a spiral known as a double helix. A double helix's structure resembles a ladder, with the phosphate and sugar molecules forming the ladder's vertical side pieces. On the other hand, the base pairs form the rungs of the ladder. Many anti-cancer drugs in clinical use interact with DNA through intercalation, which can be defined as the process by which compounds containing planara romatic or heteroaromatic ring systems are inserted between adjacent base pairs perpendicularly to the axis of the helix and without disturbing the overall stacking pattern due to Watson-Crick hydrogen bonding [2-15].

DNA Structural Features

DNA consists of two complementary anti-parallel sugar phosphate poly-deoxyribonucleotide strands that are associated with specific hydrogen bonding between nucleotide bases. The two strands are held together primarily through Watson-Crick hydrogen bonds where A forms two hydrogen bonds with T and C forms three hydrogen bonds with G (Figure 1). The structure of these paired strands defines the helical grooves, within which the edges of the heterocyclic bases are exposed. The biologically relevant B-form of the DNA double helix is characterized by a shallowwide major groove and a deep-narrow minor groove. The chemical structure (feature) of the molecular surfaces in a given DNA sequence is well known in either groove. This forms the basis

Figure 1. (A) DNA molecule and (B) Watson-Crick pairing between purine and pyrimidine bases in complementary DNA strand [17].



for molecular recognition of duplex DNA by small molecules and proteins [16, 17].

Anti-Cancer Drug-DNA Interaction

Anti-cancer agents that target DNA are some of the most effective agents in clinical use and have produced significant increases in the survival of cancer patients when used in combination with drugs that have different mechanisms of action. But, unfortunately, they are extremely toxic [18]. DNA as carrier of genetic information is a major target for anti-cancer drug interaction because of the ability to interfere with transcription and DNA replication, a major step in cell growth and division. There are three principally different ways of anti-cancer drug binding.

First is through control of transcription factors and polymerases. Here, the anticancer drugs interact with the proteins that bind directly to DNA. Second is through RNA binding to DNA double helices to form nucleic acid triplehelical structures or RNA hybridization to exposed DNA single strand regions that will be forming DNA-RNA hybrids and it may interfere with transcriptional activity. Third is through small aromatic ligand molecules that bind to DNA double helical structures through non-covalent interaction either by intercalating binder or by minor groove binders (Figure 2). [19-34].

Therefore, intercalation can be defined as the processby which compounds containing planar aromatic or heteroaromatic ring systems are inserted between adjacent base pairs perpendicularly to the axis of the helix and without disturbing the overall stacking pattern due to Watson-Crick hydrogen bonding [37]. In addition, intercalation binding involves the insertion of a planar molecule between DNA base pairs, which results in a decrease in the DNA helical twist and lengthening of the DNA. While groove binding, unlike intercalation, does not induce large conformational changes in DNA and may be considered similar to standard lock-and-key models for ligand-macromolecular binding. In addition, Groove binders are usually crescent-shaped molecules that bind to the minor groove of DNA [38].

In order to accommodate the binder (like intercalation binder), DNA must undergo a conformational change to create a cavity for the incoming chromophore. The double helix is therefore partially unwound, which leads to distortions of the sugar-phosphate backbone and changes in the twist angle between successive base-pairs (Figure 3) [37]. Once the drug has been sandwiched between the DNA base. pairs, several non-covalent interactions such as Van der Waals interaction and hydrogen bonding optimizes the stability of the complex.

DNA- Cisplatin interactions

Cisplatin (cis-[$PtCl_2(NH_3)_2$]) is the most widely used anti-cancer drug today.

Since the development of cisplatin became one of the main biological targets forthe antitumor compounds. It is used against ovarian, cervical, head and neck, esophageal and non-small cell lung cancer. However, chemotherapy treatment by cisplatin comes with a price of severe side effects including nausea, vomiting and ear damage, as cisplatin not only attacks cancer cells, but also healthy cells. It is there fore important to elucidate the details of the cisplatin mode of action to design new cisplatin analogs that specifically target cancer cells. Furthermore, most cancer cells are insensitive towards cisplatin or develop resistance. There is therefore, alsoa need for cisplatin analogues with a broader range of cytotoxicity. The search fornew analogues and the elucidation of the complete mode of action have been goingon for more than 40 years and there is an enormous amount of data available forresearchers. Still, the picture of how cisplatin works is incomplete [39, 40].

Techniques for studying Drug-DNA Interactions

Various analytical techniques have been used for studying drug-DNA interactions (interaction between DNA and small ligand molecules that are potentially of pharmaceutical importance). Several instrumental techniques (emission and absorption spectroscopic) such as infrared (IR), UV-visible, nuclear magneticresonance (NMR) spectroscopies, circular dichroism, atomic force microscopy (AFM), electrophoresis, mass spectrometry, viscosity measurements (viscometry), UV thermal denaturation studies, and cyclic, square wave and differential pulse voltammetry, etc.,

Figure 2. (A) Groove binding to the minor groove of DNA and (B) the intercalation into DNA [35, 36].

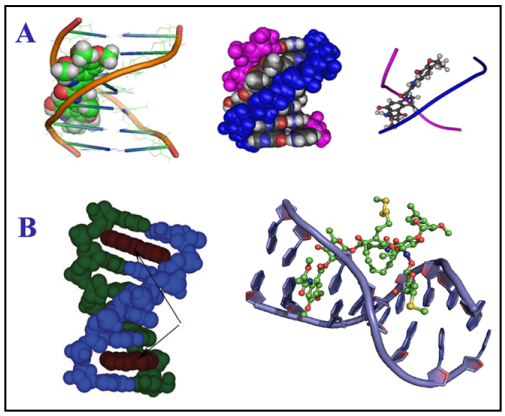
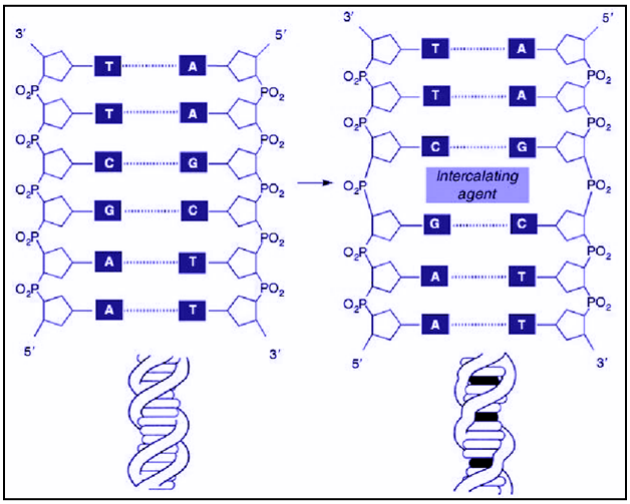


Figure 3. DNA Deformation by an intercalating agent [37].



were used to study such interactions. These techniques have been used as a major tool to characterize the nature of drug-DNA complexation and the effects of such interaction on the structure of DNA. In addition, these techniques are regularly applied to monitor interactions of drugs with DNA because these optical properties are easily measured and tend to be quite sensitive to the environment. Moreover, these techniques provide various types of information (qualitative or quantitative) and at the same time complement each other to provide full picture of drug-DNA interaction and aid in the development of new drugs. In addition, the information gained from this part might be useful for the development of potential survey for DNA structure and new therapeutic reagents for tumors and other diseases. In this part of the chapter, we will focus on FT-IR, UV-Visible, NMR, AFM and viscosity measurements [41].

Future Directions

Almost all the DNA-targeting agents that are used incancer chemotherapy are derived from compounds inwhich the mechanism of action was only determined after their antitumour activity had been established. This is the reverse of strategies that are being used to identify cancer therapeutics. In the usual course of events, aunique cancer target is identified and validated, and screening or structure-based strategies are implemented to discover a drug lead. This approach, if successful, will reduce the failure rate for new agents that are introduced into the clinic and provide an entirely new repertoire of cancer-selective therapeutics. Although there is a continued, but reduced, effort to find new DNA-reactive drugs that are similar to those previously used (for example, screening of natural products libraries and synthesis of analogues of existing compounds), increased effort is now focusing on rational approaches. These relyon insight into the design of DNA code-reading molecules, on the targeting of cytotoxic drugs using cancer specific antibodies, and on the selective activation of cytotoxic drugs in target cells that are normally too toxic for therapeutic use. The remaining challenges are not so much related to pharmacodynamics properties as to issues that relate to obtaining sufficient concentrations of the drug in target cells and, more specifically, in the cell nucleus, to achieve modulation of the molecular target without undue side effects.

Conclusion

DNA is the molecular target for many of the drugs that are used in cancer therapeutics, and isviewed as a non-specific target of cytotoxic agents. Fundamentally, drugs interact with DNA through two different ways, covalent and/or non-covalent modes. Covalent binders act as alkylating agents as they alkylate the nucleotides of DNA, while, thenon-covalent binders interact by three different ways: (i) intercalation, (ii) groove binding, and (iii) external binding (on the outside of the helix). Different spectroscopic techniques are generally, powerful tools to study interactions of DNA with drugs and the effects of such interactions in the structure of DNA, providing some insights about the mechanism of drug action. The binding stoichiometry, the relative binding affinities and the binding constants for DNA double helices of various sequences. There is good reason to expect DNA to be a clinically important target for many years to come. More selective and less toxic compounds are in preparation and strategies to use the newer agents that target molecular receptors, in combination with DNA reactive drugs,will maintain interest in DNA as a molecular target.

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