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Review Article

HERBAL DRUGS TARGETING DNA AND RNA

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ABSTRACT

DNA is a fundamentally attractive drug target. The essence of the "antigene" strategy is that it is advantageous to attack drug targets at their source – the level of gene expression. A protein drug target is the product of a particular gene. At each stage of progression through the central dogma (DNA makes RNA makes protein), the absolute number of target molecules to be hit by a drug inhibitor increases. A single gene makes multiple copies of mRNA, which in turn are translated to make multiple copies of the target protein. The number of target molecules is amplified at each stage in the process. By targeting the single gene, rather than the numerous resultant protein molecules, drug action should become both more selective and efficient. Antigene agents can be either small molecules or triplex forming oligonucleotides, alkaloids, flavonoids. There is a great demand for targeting herbal medicines in the developed and developing countries because of their wide biological activity, higher safety margin than synthetic drugs as a result of this Herbal drugs have a great potential in the global market. Extensive research on DNA-targeting herbal drugs is in progress in many research institutes all over the world.DNA targeting herbal drugs have a great utility in the treatment of genetic disorder and widely used for the treatment of cancer, microbial infection, natural cell death (cell suicide), growth disorder, etc.

KEY WORDS: DNA, Protein marker, Herbal drugs, Gene Expression

INTRODUCTION

In recent years, small organic molecules have attracted a great deal of interests of scientists in new drug design targeting biological macro-molecules, such as proteins, enzymes, receptors and nucleic acids (DNA and RNA). The interactions of drug with DNA comprise noncovalent binding and covalent bonding. The former

one is reversible but the later one is irreversible. Most of the interactions between drugs and DNA belong to reversible binding, except for aristolochic acids in some toxic herbs from Aristolochiaceae which damage DNA irreversibly.

Deoxyribonucleic acid, DNA, is a molecule of great biological significance. The total DNA content of a cell is termed the *'Genome'*. The *'Genome'* is unique to an organism, and is the information bank governing all life processes of the organism, DNA being the form in which this information is stored. Stretches of DNA called *'genes'* have the extremely important function of coding for proteins. The function of the rest of the genome, loosely termed as *'non-gene'* regions, is not very clearly known.

DNA has two main functions,

1. *Transcription:* Information is retrieved from the DNA by ribonucleic acid, RNA, and utilized to synthesize proteins in the body. Proteins are involved in all body processes and play many roles. e.g. as hormones, enzymes, carriers, structural proteins, receptors, regulators etc.

2. *Replication:* DNA is responsible for its own regeneration, i.e., DNA self replicates.

DNA is present in the body in the form of a double helix, where each strand is composed of a combination of four nucleotides, adenine (A), thymine (T), guanine (G) and cytosine (C). Within a strand these nucleotides are connected via phosphodiester linkages. The two strands are held together primarily via Watson Crick hydrogen bonds where A forms two hydrogen bonds with T and C forms three hydrogen bonds with G Specific recognition of DNA sequences by proteins/ small molecules is achieved via the combination of hydrogen bond acceptor/donor sites available on the major groove or minor groove. e.g. the A-T base pair offers a hydrogen bond acceptor, N7, a donor N6, and an acceptor, O4 on the major groove side.

Drugs derived from natural resources represent a significant segment of the pharmaceutical market as compared to randomly synthesized compounds. It is a goal of drug development programs to design selective ligands that act on single disease targets (DNA or RNA) to obtain highly effective and safe drugs with low side effects. Although this strategy was successful for many new therapies, there is a marked decline in the number of new drugs introduced into clinical practice over the past decades. Phytotherapy, whose therapeutic efficacy is based on the combined action of a mixture of constituents, offers new treatment opportunities. Because of their biological defence function, plant secondary metabolites act by targeting and disrupting the cell membrane, by binding and inhibiting specific proteins or they adhere to or intercalate into RNA or DNA[1].

DNA-Drug Interaction[1]

Transcription and replication are vital to cell survival and proliferation as well as for smooth functioning of all body processes. DNA starts transcribing or replicating only when it receives a signal, which is often in the form of a regulatory protein binding to a particular region of the DNA. Thus, if the binding specificity and

strength of this regulatory protein can be mimicked by a small molecule, then DNA function can be artificially modulated, inhibited or activated by binding this molecule instead of the protein. Thus, this synthetic/natural small molecule can act as a drug when activation or inhibition of DNA function is required to cure or control a disease

DNA activation would produce more quantities of the required protein, or could induce DNA replication; depending on which site the drug is targeted. DNA inhibition would restrict protein synthesis, or replication, and could induce cell death. Though both these actions are possible, mostly DNA is targeted in an inhibitory mode, to destroy cells for antitumor and antibiotic action.

Drugs bind to DNA both covalently as well as non-covalently.

Covalent binding in DNA is irreversible and invariably leads to complete inhibition of DNA processes and subsequent cell death. Cis-platin (cis-diamminedichloroplatinum) is a famous covalent binder used as an anticancer drug, and makes an intra/interstrand cross-link via the chloro groups with the nitrogens on the DNA bases.

Non-covalently bound drugs mostly fall under the following two classes:

1. **Minor groove binders-** Minor groove binding drugs are usually crescent shaped, which complements the shape of the groove and facilitates binding by promoting van der Waals interactions. Additionally, these drugs can form hydrogen bonds to bases, typically to N3 of adenine and O2 of thymine. Most minor groove binding drugs bind to A/T rich sequences. This preference in addition to the designed propensity for the electronegative pockets of AT sequences is probably due to better van der Waals contacts between the ligand and groove walls in this region, since A/T regions are narrower than G/C groove regions and also because of the steric hindrance in the latter, presented by the C2 amino group of the guanine base. However, a few synthetic polyamides like lexitropsins and imidazole-pyrrole polyamides have been designed which have specificity for G-C and C-G regions in the grooves.

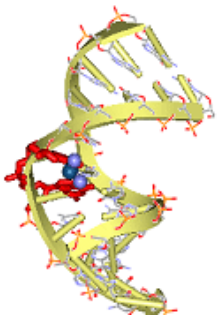

Fig.1 DNA covalently bound to cisplatin [1]

2. Intercalators- These contain planar heterocyclic groups which stack between adjacent DNA base pairs. The complex, among other factors, is thought to be stabilized by π-π stacking interactions between the drug and DNA bases. Intercalators introduce strong structural perturbations in DNA.

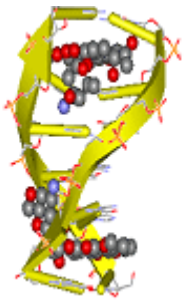

Fig.1 DNA complexed with Actinomycin-D as intercalator[1].

Non-covalent binding is reversible and is typically preferred over covalent adduct formation keeping the drug metabolism and toxic side effects in mind. However, the high binding strength of covalent binders is a major advantage.

Proteins are large molecules and bind quite strongly to the DNA, with binding constants in the nanomolar range. It has been difficult to achieve similar specificity and affinity using small non-covalent binders, and remains a major challenge to the design of drugs for DNA.

Forces involved in DNA-drug recognition[1]:

Understanding the forces involved in the binding of proteins or small molecules to DNA is of prime importance due to two major reasons. Firstly, the design of sequence specific drugs having requisite affinity for DNA requires a knowledge how the structure of the drug is related to the specificity/affinity of binding and what structural modifications could result in a drug with desired qualities. Secondly, identifying the forces/energetics involved in such processes is fundamental to unraveling the mystery of molecular recognition in general and DNA binding in particular.

Some of the forces that are known to contribute to biomolecular recognition and also to DNA-drug binding are direct electrostatic interactions, direct van der Waals/packing interactions, complex hydration/dehydration contributions composed of hydrophobic component, solvation electrostatics, solvation van der Waals, ion effects and entropy terms.

Consider DNA-drug binding in an aqueous environment. DNA is polyanionic in nature and the drug molecule is also often charged. The associated counterions lie near the charged groups and are also partially solvated. When binding occurs, it results in a displacement of solvent from the binding site on both the DNA and drug. Also, since there would be partial

compensation of charges as the DNA and drug are oppositely charged, some counterions would be released into the bulk solvent and are solvated fully. Also, the binding process would be associated with some structural deformation/adaptation of the DNA as well as the drug molecule in order to accommodate each other[1].

All these events are associated with some energetic gains/losses, the comprehensive estimation of which is a major challenge. DNA-drug binding may be described in the following manner.

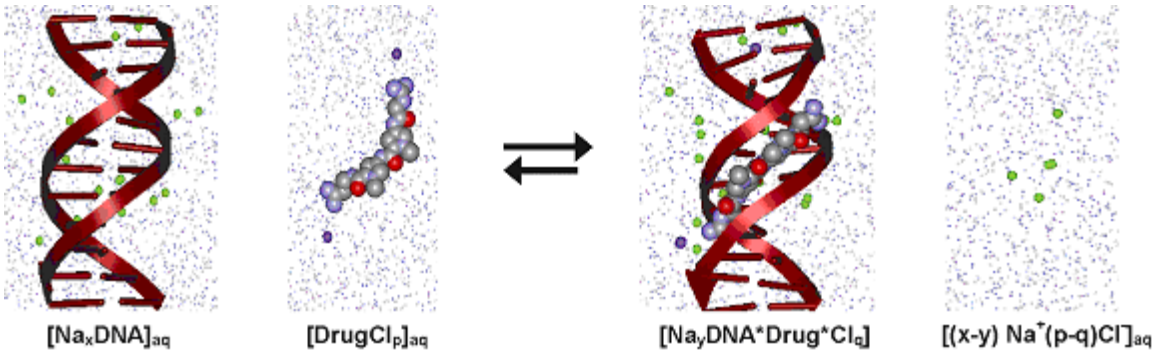

Fig3. DNA-drug binding

G-Quadraplex as drug target (Telomerase Inhibitors)

Most recently four-stranded quadruplex DNA (G4 DNA) has emerged as a unique and active target. This structure is of special interest because of its high stability under physiological conditions. Quadruplexes are stabilized by guanine quartets and may be formed in guanine-rich DNA or RNA regions; they may be important inhuman cells for genome stability, transcription, replication, RNA translation, splicing, as well as telomere maintenance. The current issue explores the recognition of DNA G-quadruplexes by proteins or small ligands, using a variety of in silico, biochemical and biophysical methods. Since the original discovery of a quadruplex ligand[2], a number of compounds interacting with G4 DNA have been described in the litterature (for a review[3]). New protocols are presented here to identify new ligands and analyze their binding affinities and selectivities.

While direct and indirect evidence supports the presence and biological relevance of G-quadruplex structures located in the 3' single-stranded overhangs of ciliate telomeres in vivo (presented in Section 4), much less information is available regarding the potential relevance of the equilibrium, where certain G–C rich DNA sequences can exist as a mixture of G-quadruplex/i-motif and canonical duplex DNA in vitro.[4,5]. Cell-permeable ligands that selectively bind to one or more of these structures might provide a means for probing the existence and/or controlling the function(s) associated with these structures. These same interactions might also provide a new source of therapeutic agents and targets.

RNA AS DRUG TARGET

RNA as a Drug Target

On the basis of its chemical structure, RNA does not appear to bea very promising drug target : It is made of only four different, planar bases and every nucleotide is negatively charged.On the other hand, one can argue that the intricate architectures. that RNA moleculescan adopt lead to the formation of pockets and cavities where shape-specific rather than sequence-specific binding could be achieved.

Several observations then come to mind:

1) The formation of RNA cavities necessitates a close proximity ofphosphate groups, which leads to a heightened importance of electrostatic forces and the roles of tightly bound water

molecules and ions, especially the divalent magnesium ions,which can be partly dehydrated.

2) The formation of pockets or enlarged grooves requires the presence of non-Watson ± Crick pairs and bulged residues. The optimist will stress the fact that function arises through the assembly of existing RNA motifs, which are clearly diverse in architecture[8].

Functions of RNA

- Slower development of drug resistance against small molecules
- RNA functional domains are more highly conserved and perhaps
- more accessible than the shapes of enzyme active sites.
- Small RNA-molecule RNA-binding motifs are capable of
- discriminating between closely related molecules.

EFFECTS OF BINDING OF SMALL LIGAND

Binding of small ligands can influence the biological activity of the RNA by:

- preventing the binding of the relevant macromolecule (protein orRNA)
- Distorting the RNA active conformation and forcing an alternativeconformation on the RNA
- inhibiting RNA catalysis
- Competitive binding for a cofactor binding site

Targeting RNA

- different RNAs:
- ribosomal RNA
- catalytic RNA
- Targeting RNA components of HIV replication

Where to bind on the RNA:

- deep groove of RNA: negatively charged phosphate groups
- shallow groove of RNA: large and slightly concave surface of
- hydrophobic character

Targeting catalytic RNAs

- targeted by aminoglycosides
- Inhibition is a process governed by electrostatic competition of the cationic aminoglycosides with magnesium ions required for catalysis.

Targeting RNA has some advantages as compared with targeting

proteins:

- More sites are accessible at the RNA level, whereas the active site of a protein is often the only target.
- Proteins that share a common substrate like ATP or ligands are difficult to inhibit specifically.
- It is possible to develop multivalent drugs to target RNA or drugs that target a RNA sequence that is essential for encoding an important sequence of a protein[6].

LIST OF HERBAL DRUGS INTERACTING WITH DNA /RNA.

Sr.No.	Herbal drugs	Drug DNA/RNA Interaction	References
1.	Berberin 9-ω-Amino Alkyl Ether Analogs from the Plant Alkaloid (Berberine)	G-qaudraplex DNA	14
2.	Curcumin	curcumin binds to the major and minor grooves of DNA duplex and to RNA bases.	12
3.	Morin, Apigenin, Naringin (flavonoids)	intercalation and external binding of to DNA duplex with overall binding	13
4.	Quercetin , kaempferol Delphinidin	intercalate t-RNA duplex with minor external binding to the major or minor groove and the backbone phosphate group.	15
5.	Sanguinarine	G-quadruplex DNA interaction	11
6.	Vincristine	intercalative and external binding	16
7.	Protoberberine	$tRNA^{phe}$ weaker interactionsingle, double and triple stranded RNAs.	17
8.	Palmitine	t- RNA^{phe} weaker interaction-single, double and triple stranded RNAs.	17
9.	Aristololactam-β-D-glucoside	$tRNA^{phe}$ weaker interaction-single, double and triple stranded RNAs.	17
10.	Vinblastine	anchored in the minor groove through carboxylic acid terminus.	18

CONCLUSION

The drug discovery community is running out of protein targets. A critical assessment of potential drug targets concluded that only 10–15% of the human proteome was "druggable", in which the term is defined as the intersection of sets of proteins that are both capable of binding "drug-like" molecules and are the product of disease modifying genes . The number of potential viable protein drug targets may therefore be surprisingly small, so it is essential to consider options for drug discovery that target other biomolecules (i.e DNA /RNA).

The recent completion of the human genome project (HGP) revealed that there are 20,000-25,000 protein-coding genes. However, the experimental and computational annotation of human genome have shown that among the family of 3000 or more disease related genes, only 600-1000 genes can be targeted with small molecule drugs. This small number of genes and their corresponding protein products constitute the real "drug targets" in the human genome. However to find a small molecule drug against those disease related genes/proteins, which is the basis of traditional drug discovery approach, is increasingly difficult and that is clearly evident in the very slow progress being made in this area in recent times. It has been estimated that it takes 15 years of research and billions of US dollars to develop a protein targeting small molecule drug. Therefore, instead of targeting the protein itself if we can target gene (DNA) or the intermediate messenger RNA (mRNA) by a short oligonucleotide complementary to the target sequence, it is possible to stop the protein production. This provides ample opportunity to specifically target any disease causing gene, even if it's undruggable by conventional medicine. The hypothesis was first validated by using antisense oligonucleotides targeting viral RNAs in 1978. Although enormous amount of research has been devoted to the development of antisense-based drugs, there are still problems remaining in terms of potency, specificity and delivery of these molecules inside cells and tissues. As a result there is an urgent need for employing alternate mechanisms and tools for efficient gene down-regulation. There is a great demand of target herbal medicines in the developed and developing countries because of their wide biological activity, higher safety margin than synthetic drugs as a result of this Herbal drugs have a great potential in the global market.

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