DNA quadruplex : a potential target for anticancer therapy

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Abstract

Cancer is one of the most important health problems and very common in different populations in the world. The main objective of newly synthesized molecules has selectivity against tumor cells with low-toxic effect. The use of different methods and molecules depends on the stage and type of cancer. This process defines the compounds containing planar aromatic or hetero aromatic ring systems embedded between adjacent base pairs perpendicularly to the axis of the helix and without disturbing the overall arranging pattern due to Watson–Crick hydrogen bonding. Last few years, fluorescence intercalating agents, fluorescence probe and sensor in biophysical chemistry and molecular biology, photosensitized molecule in fluorescence-decay reactions as DNA strainers became very important. G-quadruplex structures and epigenetic enzymes have raised much interest as potential anticancer targets. Several agents acting on DNA are clinically used, but the severe driving side effects limit their therapeutic application. G-quadruplex are DNA secondary structures that are located in key zones of human genome, such as oncogene promoters and telomeres. Targeting quadruplex structures could allow obtaining an anticancer therapy more free from side effects. On the other end, in the last years it has been proved that epigenetic modulation can control the expression of human genes, thus allowing the presence of different variants determining the disease. The epigenetic regulation of gene expressions plays a crucial role in carcinogenesis and, in particular, an abnormal expression of histone deacetylase enzymes (HDACs) are related to tumor onset and progression, making them attractive targets for new anticancer drugs and therapies.

Keywords: Cancer therapy, G-quadraplex, DNA-quadraplex

INTRODUCTION

Cancer is a term used for diseases characterized by out of control cell-growth: the principal feature of cancer is rapid creation of abnormal cells which able to grow beyond their usual boundaries, invading adjoining parts of the body and spreading to other organs. Cancer, by definition, is a disease of genes. Throughout people's lives, cells are growing, dividing and replacing themselves. Many genes produce proteins that are involved in controlling the processes of cell growth and division. An alteration (called mutation) of DNA can disrupt these genes and produce faulty proteins; in this case the cell becomes abnormal and loses its restraints on growth. The abnormal cell begins to divide uncontrollably and eventually forms a new growth known as a "tumor" or neoplasm (medical term for cancer meaning "new growth").

DNA G-quadruplexes, besides being a potential drug target proven by Eckhardt et al. The nucleic acid are large biomolecule indispensable which include deoxyribonucleic acid [DNA] and ribonucleic acid [RNA]. The nucleic acid can adopt distinct noncanonical, highly compact secondary structure. Lee and Hong et al. suggested G-quadruplex in dynamic reason of chromosomal DNA and RNA transcripts in telomeric sequence

and promoter reason of numerous gene including oncogene such as Bcl-2 [1,2], VEGE [3,4], Cmyc [5].There are 376,000 putative quadruplex sequence [PQR] in human genome that have been identified based on a quadruplex folding rule [6]. Recently, the existence of DNA G-quadruplex has been visualized on chromosome in human cell [7]. These quadruplex are active target of drug discovery. The G-quadruplex from promoter oncogene have been shown to produce potential target of anticancer activity [8, 9]. The activity of enzymes telomerase has been shown to regulate which maintain the length of telomerase and involved in 85% of all cancers. eg.Telomestatin [10,11], [S2T1-60TD] telomestain synthetic derivatives [12]. SyuIQ-5[13] interact with G-qudrauplex formed telomere and myc squences and show the inhibitory activity in cancer cell growth.

G-quadruplex are very condensed structure and formed by ganosine[G] rich DNA and RNA sequence of several strucked G-tetrades. G-tetrads as for guanine arrange in a square planar arrangement and held together by hoogstern bonding. G-quadruplex structure is stabilize by the presences of monovalent cation mainly potassiumStructure of G-quartet, the basic unit of the G-quadruplex structures..The G-quadruplex could affect gene activity either by upregulation or downregulation [14].

DNA and RNA G-quadruplex can be from a modified RNA nucleotide called locked nucleic acid[TNA]using INA based oligonucleotide for therapeutic purpose [13]. They are now developing a new LNA based hepatitis C drug called microversen targeting mir-122 which phase 2 clinical testing [15] There are another artificially synthesized polymer similar to DNA or RNA called peptide nucleic acid [PNA] which form G-qudrauplex.They do not naturally but [PNA] oligomers used in recent years in moleculer biology procedure antisense therapies [16].

DNA structure are highly dynamic and associated function are potential diverse duplex structures single stranded DNA fold into wide variety of hairpin triplex, G-quadruplex I motif structure containing noncanonical base pair [17] It is important to remember that the metabolically active forms [s] complex are more biologically relevant RNA, DNA potential forming large complex of DNA [eg. during replication, transcription, repair and recombination] one might even take the extreme point of the douple helix is actually the inactive from of DNA and single standard DNA and their protein x structure is limited by energetic driving forces of duplex formation. Single stranded DNA viral genomes and telomeric DNA circle are nonexception small molecules binding and negative supercoiling [18,19]. The selectivity stabilized by potassium ions at concentration [10-50 mm] well below the 120 mm of kcl found in most cell types [20]. G-quadraplex can exhibit thermodynamic stabilities comparable to the corresponding duplex structure [21] intermolecular G-quadraplex structures have been proposed by as intermediate or precursors recombination or viral integration [22] molecular crowding synthetic and endogenous chaperones and dehydrating condition inside the nucleus might also accelerate the rate of G-quadruplex formation in vivo [23]. This same interaction might also provide a new sources of therapeutic and targets. Qudrauplex [G4S] are higher order of nuclic acid arrangement involving a core of pia-pia spacked guanine quarts rather than Watson crick base pair of douple helical nuclic acid. The promoter are 5'UTR sequence of gene involved in cellular proliferation the recent demonstration of precences of G4s in human cells [24] appropriate small molecules an serve to stabilized G4s and resulting complexes can act as impediments to telomere maintainance transcription or translation depending on the nature of quadruplex target site these effect shown in several target genes of relevancs to human cancer such as C-MYC7and C KIT8. Large number of small molecules chemotype have been repoted as G4 binding ligands. The majority of heteroaromatic with large flat surfaces design to complement surface of terminal G quartet in a typical quadruplex structure. Second class of ligand represented by cyclic polyoxazole natural product telomestatin [25]. G4 stabilization was initially evaluated using dual labeled F2lT (human telomeric

21mer) and C-KIT2 (a tyrosine kinase oncogene) it has duplex DNA sequence. The most active compound subsequently against and expanded panel of plurorecently labeled promoter G4 forming sequence with HSP90A, HSP90B [promoter the K-RAS oncogene] K-RAS21 [26]. G4 recently identified in promoter of androgen receptor. DNA targeting anticancer drug continue to be develop as evidence by the recent approval of belotecan [27]. The chemotherapatic agent bind to DNA specifically (Eg. Cisplatin, mitomycin C, daunomycin, etc.) development of small molecule that specifically bind to particular DNA secondary structure improve to cancer specific targeting and decrease side effect with chemotherapeutic treatment [28]. G-quaduplex DNA structure are highly attractive target the abundance of detail information available thermodynamic stabilities and potassium biological activity some of the cancer specific.

G –quadruplex structures

DNA is the molecular target for many of the drugs that are used in cancer therapy, and is viewed as a non-specific target for cytotoxic agents. Anticancer agents targeting this macromolecule are some of the most effective agents in clinical use and have produced significant increases in the survival rate of patients, especially when used in combination with drugs acting through different mechanisms. A large percentage of chemotherapeutic anticancer drugs are compounds that interact with DNA directly or prevent the proper relaxation of DNA (through the inhibition of topoisomerases). In addition, DNA-targeting anticancer drugs continue to be developed, as evidenced by the recent approval of belotecan [29].

Kola et al. proposed the crystal structure of a G-quadruplex shows that the G-quartet can be considered as an aromatic square whose dimensions are much larger than those of the base pair of the Watson-Crick double DNA model and this difference constitutes the basis for the design of specific ligands. G-quartets are stacked one above the other to form four propellers G-quadruplex. These structures have a wider diversity and structural polymorphism respect to the double helix DNA; this polymorphism deriving mostly from the nature of the cycle, such as variations in the stoichiometry of the chain, the polarity, the angle of twist of glycosides, and the position of the rings connecting the filament of guanine. Furthermore, in physiological conditions, the presence of metal ions, molecules that interact with the DNA or molecular crowding conditions, can affect the topology of the G-quadruplex. The G-quadruplex can be made up by a single sequence of guanine that forms intramolecular interactions or by intermolecular association of two (dimeric) or four (tetrameric) separated strands. Even the arrangement of the filament, depending on the different variations of polarity, can give rise to structural polymorphism. For example, the polarities of the four strands in a G-quadruplex can be parallel, three parallel and one antiparallel, adjacent parallel, alternating or antiparallel, resulting in different conformations denominated as parallel and antiparallel G-quadruplex. Adjacent linked parallel strands require a connecting loop to link the bottom G-tetrad with the top G-tetrad, leading to propeller type loops; in parallel quadruplexes all the guanines have glycosidic angles in an *anti*-conformation. Quadruplexes are designated as anti-parallel when at least one of the four strands is anti-parallel to the others and in these structure it is possible to have lateral or edge-wise loops join adjacent G-strands or diagonal loop joins opposite G strands. Anti-parallel quadruplexes have both *syn* and *anti*-guanines, arranged in a way that is particular for a given topology and for each different set of strand orientations, since different topologies have the four strands in differing positions relative to each other. Even the same sequence can assume different conformations depending on the environment as proposed by Kola et al. (Fig. 1).

G4 in RNA biology

Although G4s have been well characterized in DNA, studies showing convincing evidence of their existence and biological importance in RNA are still limited RNA G4s can be observed in the cytoplasm of human cells and the single-stranded nature of RNA molecules makes them more prone

to forming G4s. There is evidence that G4s do exist in telomeric RNA and G4s have also been invoked in studies on translation initiation 30-end processing and alternative splicing [33].

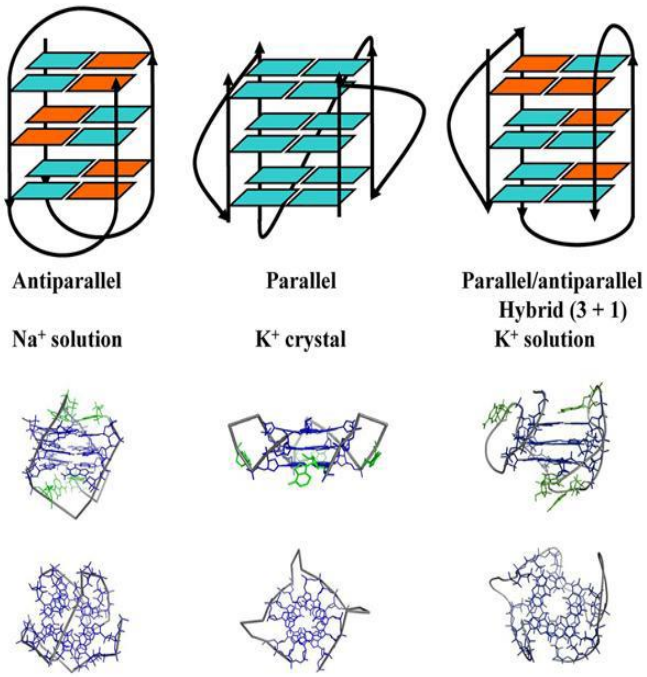

Fig. 1. The structures observed for the intramolecular quadruplex formed by the human telomeric repeat sequence in different conditions: solution structure in Na+, crystal structure in the presence of K+ and solutionstructure in K+.
G4 in RNA biology

Current common strategies for determining the presence of G4s include:
(1) identifying G4-forming sequences by using bioinformatics predictive tools;
(2) making synthetic DNA or RNA oligonucleotides containing the putative G4-forming sequence and performing various biophysical studies;
(3) determining the importance of the nucleotides involved by site-directed mutagenesis;
(4) using G4-stabilizing ligands to observe changes in functional assays.

RNA G4s exist and play significant biological roles in RNA processing, or other processes in the cell. These examples might explain why RNA G4s are less well characterized than their DNA counterpart and strongly suggest that new bioinformatics tools must be developed for the identification of RNA G4s [34].

DNA intercalation

DNA intercalation consists in the insertion of a small ligand or fragment between two adjacent base pairs in the DNA strand, forming stable sandwich-like structures. As a result, intercalation leads to significant perturbations to the DNA double helix, causing the opening of a space between base pairs and the unwinding of the helical twist (Fig. 2)

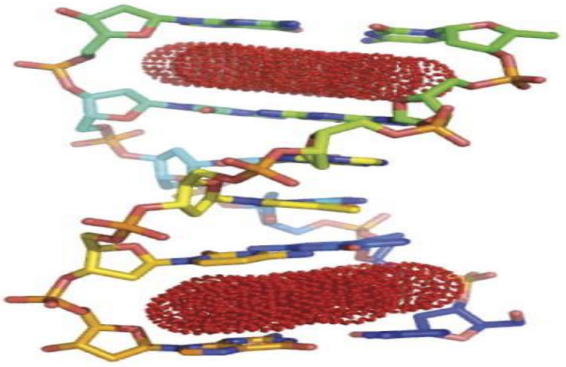

Fig. 2. Mechanism of action of an intercalator

Intercalators can be divided into three main groups (Fig.2):
a) typical intercalators consisting of fused rings, e.g. 9-aminoacridine;
b) atypical intercalators, containing non fused ring systems, e.g. Chlorpheniramine
c) bis-intercalators, molecules consisting of two intercalating heterocyclic moieties usually linked together with an alkyl chain. Linker can be based on different structural motifs like a polyamine, which is capable to create multiple hydrogen bonds with the DNA structure, as in elinafide.
In the recent years, with the advent of new molecular targets such as kinases and cell surface receptors that can achieve selectivity for cancer cells, the interest in DNA-targeted drugs has decreased, even though they are still the mainstay of most treatment regimens [34]. The first glimpse of a new era for DNA-targeted therapeutics came through the realization that telomeres can form four-stranded DNA structures that are termed

G quadruplex [35]. Intramolecular G-quadruplex are very interesting due to their potential formation in telomeres and oncogene promoter regions, so they have recently emerged as a new class of novel.

G-quadruplex location and functions:

The efforts spent for the structural characterization of G-quadruplexes are closely related to the fact that they are located in key regions of the human genome. These regions include the telomeres, regulatory elements as oncogene promoters, ribosomal DNA, mini satellites, the switch region for the immunoglobulin heavy chain and mutational hot spots [36]. The main role of G-quadruplex may be the ability to "turn on" or "off" some physiological events through the regulation of gene transcription or telomere length.

DNA strands separated and prevent the formation of the basal transcriptional complex. When this promoter region is in duplex form the transcription can be initiated. Specific G-A mutations that decrease the number of guanines in this region destabilizing the quadruplex structure, are known to enhance the transcription of c-Myc [37]. Ligands able to stabilize the quadruplex form of the silencer element can decrease the oncogene overexpression and reduce its activity in the progress of the tumor, so a lot of efforts are spent in the research of c-Myc silencer element ligands.

G-quadruplex and telomerase

Linear DNA fragments are toxic to mammalian cells so many mechanisms such as degradation or reparation of the fragments, cell cycle arrest or death are used to deal with them. The natural ends of linear chromosomes resemble DNA breaks and their repair would lead to deleterious chromosome fusions and therefore has to be avoided. This is prevented thanks to the presence of telomeres, specialized ribonuclein proteins able to cap both ends of the chromosome. Telomeres are made up of long, repetitive TTAGGG sequences which extend for 9-15 kb in humans, associated with a variety of telomere-binding proteins known as shelterins. The repetitive and G-rich nature of telomeric DNA allows the ends of the chromosomes to form higher order DNA secondary structures, such as G-quadruplexes that can help to regulate the replication of cells [38]. The telomeres are fragile structure of DNA, in order to protect them the shelterin six proteins complex has evolved (Fig. 2). Three of its components bind in a sequence-specific manner to the TTAGGG repeats, specifically TRF1 and TRF2 bind the duplex repeat regions and POT1 binds the single-stranded overhangs [27]. The other proteins bind the first three component of the shelterin through protein-protein interactions: RAP1 binds TRF2, TPP1 binds POT1, and TIN2 binds TRF1, TRF2, and TPP1 simultaneously, thus playing an essential role in stabilizing the shelterin complex and linking the single- and double-stranded binding components of shelterin. Each shelterin has a particular role in telomere maintenance [40].

G ligands quadruplex

According to what previously stated, stabilization of quadruplex structure that are able to interfere with oncogene expression and to block telomerase activity by small molecules is emerging as a potential anticancer approach [41].The ligands can interact with G-quadruplex trough different binding mode: external stacking, intercalation, or groove binding (Fig. 1). However, the intercalation between G-tetrads inside the quadruplex is very difficult to achieve, since the G-quadruplex is an extremely stableand rigid structure, so the distortion of quadruplex integrity requires a very high energy cost .

G-quadruplex location and functions

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G-quadruplex in gene promoters

G-quadruplexes are present in oncogene promoter regions and, due to this localization, are viewed as

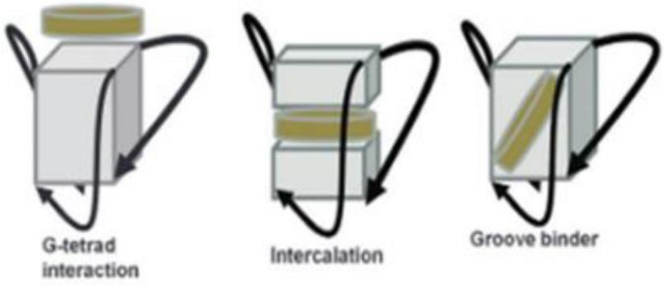

Fig. 3. Representations of ligand-G-quadruplex possible binding modes.

emerging therapeutic targets in oncology, both as through the stabilization or the repression of oncogenes. Many G-quadruplex gene promoters have physicochemical properties and structural characteristics that make them druggable and their complexity may allow achieving selectivity, as a consequence G-quadruplexes can be important therapeutic targets. The structure of gene promoter sequences was studied and it was discovered that it contains a continuous stretch of a G-quadruplex sequence with four or more G-tracts folded into an intramolecular G-quadruplex, but other conformations are possible, such as bimolecular G-quadruplexes [43, 44]. G-quadruplex structures in gene promoters can be studied through NMR and crystallographic techniques, circular dichroism and chemical foot printing bioinformatics show that the promoters of human oncogenes and regulatory genes (for example, transcription factors) are more likely than the average gene to contain quadruplex motifs, whereas these structures are less represented in the promoters of housekeeping and tumor suppressor genes[45]. It is well known that supercoiling can influence the transcription either positively or negatively and quadruplex structures are considered a result of supercoiling induced stress during transcription, indeed their creation can compensate for the negative supercoiling [46] These secondary structures of DNA can enhance or inhibit the transcription. The transcriptional event can be blocked if the quadruplex is on the template strand, blocking the access to polymerase; while it can be enhanced if the quadruplex is on the non-template strand, helping in this way the transcribed strand in a single strand conformation and facilitating the access to polymerase. Furthermore G-qudruplexes can bind proteins such as transcriptional enhancers or receptors, indirectly influencing the transcription. Quadruplex structures in promoters are constrained by the duplex nature of DNA so they have to compete with this most common structure; while the telomeric quadruplexes are easily formed because of the presence of the single-stranded DNA template at the 3′ end of human telomeres.

Epigenetic and cancer

In the cells, DNA can exist in various forms and these different conformations are closely related with the different phases of the cell cycle. The macromolecule is usually packaged as chromatin, that is a highly organized and dynamic protein-DNA complex whose roles are to reduce DNA volume, allow mitosis, control replication and transcription processes, and prevent DNA damage. The nucleosome, the basic unit of chromatin, is made up of a segment of DNA wound in sequence around eight histone proteins. The nucleosome core particle consists of an H3 and H4 tetramer and two H2A and H2B dimers, surroundedby 146 bp of DNA.

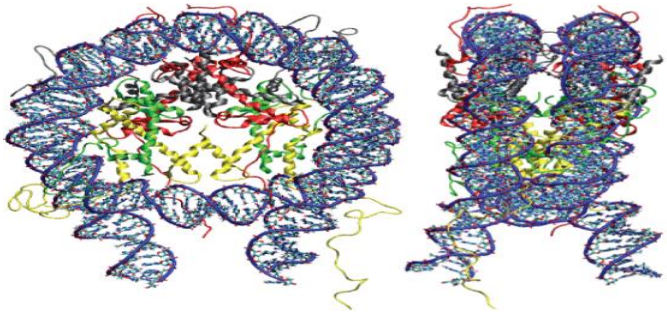

Fig. 4. Structure of the nucleosome core particle consisting of histones H2A in red, H2B in grey, H3 in yellow and H4 in green, and DNA.
(http://malone.bioquant.uni-heidelberg.de/methods/modeling tml).

The organization of the DNA that is achieved by the nucleosome cannot fully explain the packaging of the nucleic acid observed in the cell nucleus. Further compaction of chromatin into the cell nucleus is necessary, but that is not well understood yet; it is known that a chain of nucleosomes can be

arranged in a 30 nm fiber, depending on the presence of the H1 histone. These fibers can create loops along a central protein in order to give chromatin, the transcriptionally active form of DNA, while further compaction generates the transcriptionally inactive form heterochromatin. Local chromatin architecture is now generally recognized as an important factor in the regulation of gene expression. The term "epigenetic" literally means "in addition to changes in genetic sequence". Epigenetic studies any process that alters gene expression without changing the DNA sequence, and leads to heritable modifications (although experiments show that some epigenetic changes can be reversed). Many types of epigenetic processes have been identified and some of them are natural in cells and lead to the expression only of the genes that are necessary for their own activity, while other genes are silenciated. However when epigenetic changes occur improperly, they can give origin to diseases. For example, epigenetic changes in histone acetylation cause lupus-like symptoms in mice, and that was confirmed by the fact that the treatment with the well-known histone deacetylase inhibitor Trichostatin A can reverse these modifications. Among all the research in the epigenetic field conducted so far, the most extensively studied disease is cancer and the evidence linking epigenetic processes with cancer is becoming "extremely compelling". For a long time, cancer has been considered to be the result of a wide variety of genetic and genomic alterations, such as amplifications, translocations, deletions, and point mutations of proto-oncogene tumors.

Author suggested in the picture presents, however, significant limitations: it remains unclear what is the engine at the base of the progressive stage, the role of the environment in the development of the pathology and the age and the long latency period that characterizes the majority of tumors. Cancer can also be considered an epigenetic disease, since a tumor originates from an alteration of the genetic material, which leads to an increase of the cell turnover, to an alteration of the cellular functions and cell invasiveness[46].

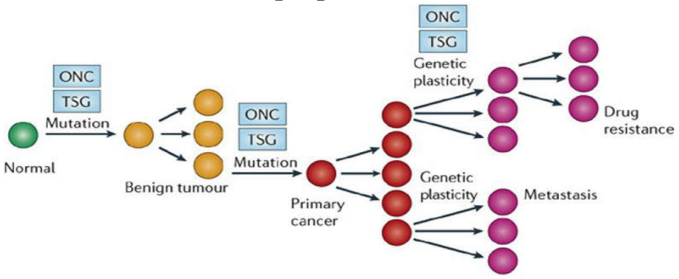

Fig. 5. *The genetic model of cancer*

An alteration of the DNA structures that reduces or increases the accessibility to the transcription and translation of genes is configured as an epigenetic event that alters the cellular balance and leads to the disease. Epigenetic alterations are able to influence the penetrance of the variants of a particular gene, and can help to understand these issues. A gene, in fact, can have one or multiple variants determining the disease, but their expression is epigenetically controlled. It is becoming clear that gene expression regulated by epigenetic changes plays a crucial role in carcinogenesis[47].

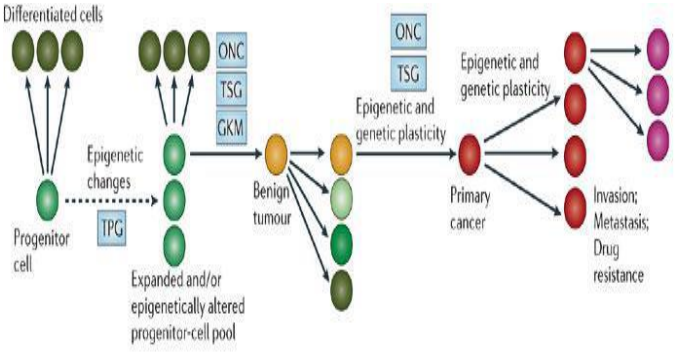

Fig. 6. *Epigentic model of cancer*.

A wide range of post-translational enzyme-catalyzed modifications have been reported, most of them affecting the N-terminal tail of histone, such as acetylation, methylation, ubiquination and sumoylation. Furthermore, ADP-ribosylation can occur to the residues of lysine and glutamate in the histone tail and also methylation of dinucleotides

CpG in 5' position that leads to gene silencing[48]. The two major post-translational histone modifications consist in the addition or removal of acetyl and methyl groups. Acetylation/deacetylation and methylation/demethylation are the two most studied epigenetic alterations regulated by a wide range of proteins. The presence of acetylated lysine in the histone tails gives the transcriptionally active chromatin structure, while deacetylation of lysine residues is associated with heterochromatin and transcriptional gene silencing. Methylated histones can positively or negatively affect transcription, according to the site affected and the degree of methylation. Until now DNA methylation, and in particular silencing of tumor-suppressor genes by promoter hyper methylation, has been the most widely studied epigenetic modification in human tumors.

• Alteration of gene expression and cellular determinants of the variants of the disease;

• Cooperation with other cellular proteins and with tissue-specific transcription factors sensitive to environmental stimuli. Since cancer is a disease with epigenetics bases, epigenetic enzymes are very important targets for the treatment of these diseases; among them HDAC and LSD1 are very promising tion of lysine residues of histones. Researchers has been targeting the DNA since long time, still it needs studies to target the DNA[49].

CONCLUSION:

In this article we have discussed the different types of small organic molecules which target DNA and DNA associated processes. But many of these when used as chemotherapeutic agents manifest one or more side effects. Therefore, there is always a challenge remaining with these designer DNA-binding molecules, to achieve maximum specific DNA-binding affinity, and cellular and nuclear transport activity without affecting the functions of the normal cells. For many of the newer targeted therapeutics that are under development for the treatment of cancer, it is however, expected that these new putative drugs will be used in combination with the more traditional drugs molecules such as *cis*-platin or doxorubicin. In combination with DNA-interactive drug, the chemotherapeutic agent might exert considerably enhanced clinical efficacy as anticancer agents. The future challenge will be to 'conjugate' these agents appropriately on the basis of firm scientific principles. Combination of the other tools genomics and proteomics might provide a new opportunity towards this end.

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