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A NEW POSSIBLE WAY FOR CANCER CURE - DNA FOUR STRAND

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Abstract: *DNA is the active ingredient of all the biological operations of the cell because it stores genetic information in the configuration of genes. It is a very well recognized fact that DNA has a double helical structure; recently, it was reported to have another unusual four-stranded form at the genome of living cells. Generally, G-quadruplexes are located in human telomeres and oncogene-promoter regions where guanine is abundantly present. Recently, DNA G-quadruplexes have been used for the novel molecular target for cancer treatment. They have been regulated and targeted in different ways with many proteins and drugs. G-quadruplex ligands can disable the enzymatic activity of telomerase, which is overactive in cancer cells. G-quadruplex has a fused ring arrangement, which is capable of heaping on the interface of the terminally present G. It is an extraordinarily stable and rigid structure abundantly found when cells are ready to divide normally. Cancer cells divide rapidly, cause defects in their telomeres. The G-quadruplex is an important form in cancer cells where G-quadruplex ligands can bind and inactivate the activity of the telomerase enzyme. This has strategized by targeting G-quadruplex to prevent the replication of DNA that will ultimately block cell division in cancer cells.*

KEYWORDS: *G-quadruplex, Guanine, anticancer, Telomere, Drug design, Ligand.*

INTRODUCTION

Deoxyribonucleic acid is the inherited fabric of most of the living beings. It carries genetic information, which is inherited from parent cells to daughter cells. James Watson, Francis Crick, Maurice Wilkins, and Rosalind Franklin discovered the double-stranded structure of DNA in 1953[1]. Recently, Prof. Balsubramanian and cancer biologist Prof. Steve Jackson has discovered a new G-quadruplex form of DNA[2]. G-quadruplexes are tertiary structures formed in areas rich in guanine. Four guanine bases are connected through hydrogen bonding called Hoogesteen to form a quadrangle shaped guanine tetrad[3]. The G-quadruplex structure is stabilized by the potassium cation that is in the middle of each pair of tetrads[4] (Figure 1).

Scientists have thought that 'G-quadruplex structures' formed in the DNA of existing cells, as firstly reported in prokaryotes in 2009. The investigators now recognize that G-quadruplex can also be found in the DNA of human cells[2]. The specific antibodies against telomeric DNA G-quadruplexes identified G-quadruplexes *in vivo*[5]. Its presence has first reported by the immunological stain in the micronuclei of *Stylonychia lemnae*[6].

ROLES OF G-QUADRUPLEX

The properties of guanine to associate among themselves and form four-stranded helix are known since 1960[7]. G-quadruplexes are extremely polymorphic and because of the folding of intra- or intermolecular G-rich strands it grows[3]. The formation of G-quadruplex plays an important role in the immunoglobulin heavy chain alteration. G-quadruplexes are the tertiary structures of DNA that serve in the protection of telomeric ends and regulate the length of telomere[7]. G-quadruplexes are important, as these regions can be used as ligands in DNA

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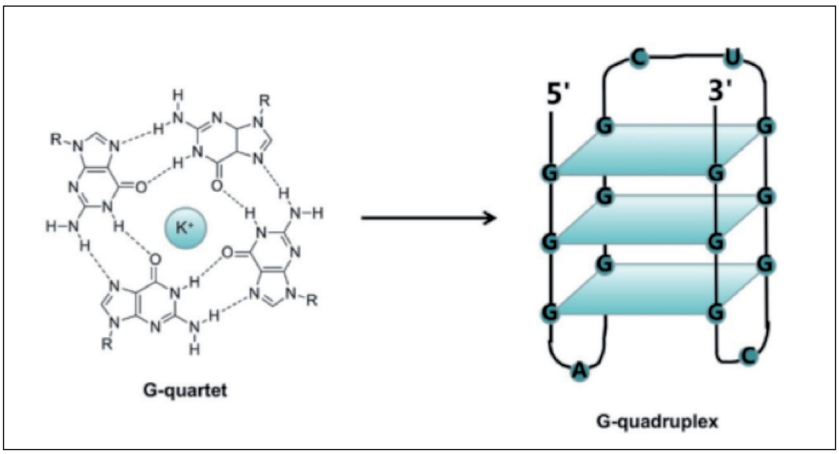

Fig. 1. G-quadruplex structure. By Hoogsteen hydrogen bonds, four guanines construct a G-quartet. Two or three stacks of G-quartets form a G-quadruplex structure. The structure is stabilized by univalent metal cations (Na^+ or K^+) locate in the central channel of the G-quartet.

replication and transcription, and for the interaction of anti-cancer drugs to oncogenes promoter regions at telomeres. DNA contains over 300,000 sequences, which are potential candidates to form G-quadruplexes[8]. Localization of G-quadruplex is not random, is ground in highly dynamic and working constituents of the DNA, and highly conserved among the species. These sequences are also present in bacteria, human RNA, and DNA viruses[9]. G-quadruplex was profusely present at telomeres, which is approximately 5 to 10,000 bp in humans in a sequence TTAGGG repeat[10]. G-quadruplexes are likewise present in gene promoters, at the sequence between introns and exons. They are also helpful in both the initiation and termination of transcription[11].

CANCER AND G-QUADRUPLEX

Cancer

The cell divides for the normal growth and development of an organism. In normal cells, there is always a balance between the rate of cell growth and the rate of cell death. In cancer cell, this equilibrium is upset by the deprivation of growth control or the passing capacity of cell to go for apoptosis[12]. Cells become cancer when the cell does not replicate by following the rules of the cell cycle, thus increasing its possibility to undergo genetic mutations. The uncontrolled multiplication of these cells damages nearby tissues[12]. To avert the damage or mutation in necessary gene sequences, the remainder of each chromosome is equipped with a special sequence telomere. Telomere plays a critical part in maintaining cell integrity. Telomeres have evolved to prevent the unlimited increase of cells by blocking cell division[13]. In normal cells, there is no demand for maintaining telomere length. During cell division, telomeres decrease in length by 200 base pairs from the terminal region[14]. As the cell divides, telomere getting shorter and ultimately the cells undergo apoptosis. All normal cells undergo division, but stem cells, germline cells, and cancer cells do not shorten with repetitive cell division. This non-carving up state is senescence[15]. An important characteristic of tumor cells is to maintain telomeres at a constant length. The human telomeres sequence of DNA consists of simple-short sequence of nucleotides (TTAGGG) repeated many times[16] and the most significant feature of telomere region is that it is Guanine (G) rich[17]. Telomerase is an enzyme that aids in the care of the telomeres. With the help of telomerase in a cell, the overall lengths of telomeres are always maintained for every subsequent cell division[5]. For cancer detection, the activity of telomerase can be use as a marker. The telomerase may be used to ascertain the presence and severity of cancer. Afterwards, it will be possible to find out whatever possible and appropriate treatment[13].

Worldwide cancer is a leading case of decease. G-quadruplex was present in the genome involved

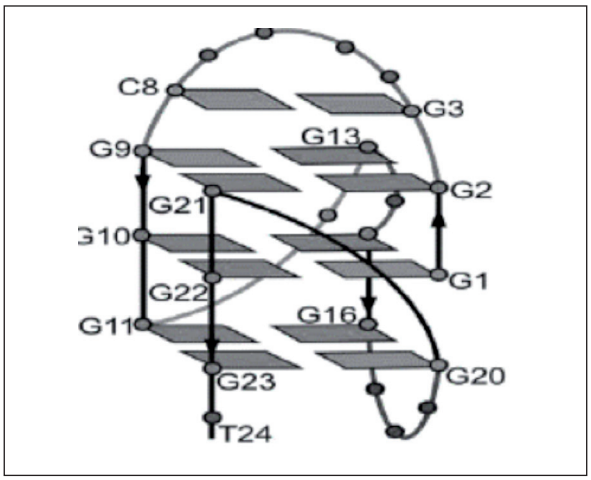

Fig. 2. Structure of VEGFR-17T G-quadruplex. VEGFR-17T G-quadruplex is a potential drug target to inhibit tumour angiogenesis (vascular endothelial growth factor).

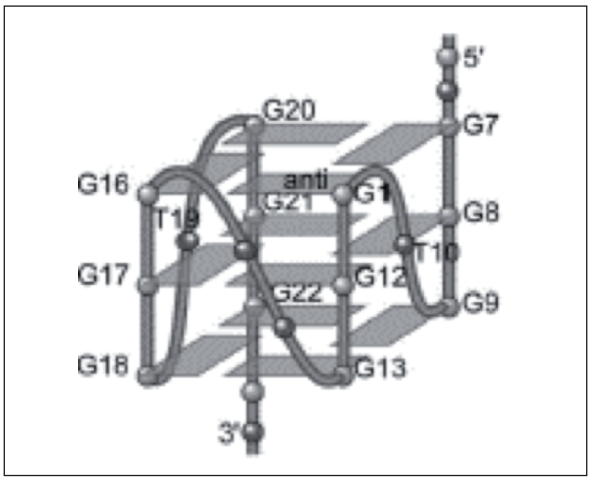

Fig. 3. The major G-quadruplexes formed in the human c-MYC gene promoter.

in regulating genes, especially in some cancer-making factors. The G-quadruplexes have the potential to associate among themselves. G-quadruplexes are targeted with the supporter of artificial molecules that trap and clutch these structures of the DNA. DNA G-quadruplex acts as a ligand for blocking cell division by preventing the cells from replicating their DNA[18]. G-quadruplexes are present in that portion of the DNA that controls genes that are over-expressed like cancer cells. They can switch genes expression on or off[19]. Studies showed that G-quadruplexes would be a new-targeted approach for cancer therapy as these structures form in cancer cells by using a pyridostatin, as synthetic drug[20]. G-quadruplex ligand only harms cancer cells and not healthy ones[21]. G-quadruplex inhibitor does not require long-time, since only in one-month the anti-tumour activity can be observed. In the tumor inhibition process, extensive telomere shortening is not required. It is, thus, a selective technique than other cell growth inhibitors and is very speedy. The toxicity of this method is depressed as compared to others. The latest ligands are acridines, which allow another interaction with a G-quadruplex third groove. Acridines increase the activity of G-quadruplex as a ligand and decrease its risk of toxicity[22]. The first confirmation of G-quadruplex as anti-cancer therapeutic was showed in c-myc oncogene, one of the commonest cancer genes in human and a prominent target for anti-gene therapy[20].

Advantages of using G-quadruplex

Anti-telomerase therapies affect only tumor cells and do not affect normal somatic cells[23]. Telomerase activity inhibition leads to a modulation in the growth rate of cancer cells without affecting the function of the surrounding cells[14]. By inhibiting telomerase activity in the cell, there is a certain potential that undesirable side effects might occur[23]. Nevertheless, experiments suggest it is minor as compared to cancer cells, because of the presence of higher numbers of telomeres found in these cells[14]. Telomerase inhibitors do not possess toxic effects as other drugs, especially if they are administered in the long-term.

CONCLUSIONS

The division and multiplication in cancer cells are endless; researchers are working to evolve ways to heal cancer. The latest progress in cancer cure is G-quadruplex structure of DNA and its constancy in the human genome. G-quadruplex can inhibit the action of telomerase. It presents a great perspective in killing the cancer cells without adding toxicity in normal cells. This scheme is efficacious in inhibiting growth and cancer cells from going for senescence as the blueprints improve, the signification of their anti-tumor activity increases. The 'quadruple helix' introduction on DNA structure by trapping 'quadruple helix' with the synthetic molecule may be a stately way to suppress cancer cell propagation and proliferation only.

Conflict of Interest:

The authors declare that they have no conflict of interest.

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