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Editorial OMICS International

Regulation of Oncogene Expression via Targeting i-Motif in Nucleic Acids

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Editorial

The basic molecules required for sustaining life on earth include carbohydrates, lipids, proteins, and nucleic acids (DNA and RNA). DNA is considered to be the building block of life and can adopt various types of secondary structures. Gehring et al. revealed for the first time that DNA sequences having long cytosine stretch can form unconventional secondary structures called i-Motifs [1]. These i-Motifs are very dynamic intercalated, quadruple-helical structures and known to exist under acidic conditions. These cytosine stretches are not erratically located throughout the genome but enriched in the promoter regions of several oncogenes within the genome and in telomeres, the terminal regions of chromosomes. The formation and stabilization of i-motif may play a crucial role in gene expression [2-4], such as, the stabilization of the human telomeric i-motif by carboxylated single-walled carbon nanotubes inhibit telomerase that leads to telomere uncapping, DNA damage response and apoptosis [5].

These i-Motif structures are formed by hemi protonated cytosine-cytosine base pairs, which require protonation of one of the cytosines in the base pair (that is done by lowering the physiological pH *in vitro*). However, recent study using molecular crowding conditions, mirrored by carboxyl modified single-walled carbon nanotubes, have been shown to selectively induce human telomeric i-Motifs formation even at pH 8.0 [6]. The i-Motif structures can be formed from four strands, two strands or single strand of DNA. This single strand i-motif is referred to as intramolecular i-Motif which is considered to be potentially biologically relevant and is divided into two classes: class I having shorter loops regions (e.g., telomeric i-Motif) [7,8] and class II that has longer loops regions (bcl2 promoter i-Motif) [3]. The class II i-Motifs are more stable than class I i-Motifs due to extra stabilizing interactions induced within the longer loop regions.

The significance of i-motif structures has not been explored much *in vivo*. Its potential role in gene regulation has been proposed only recently [2-4,9-11]. Some examples include, B-cell lymphoma gene 2 (a pro-survival oncoprotein) which is over expressed in some cancers like breast cancer, pancreatic cancer and under expressed in some neurodegenerative diseases such as Alzheimer's and Parkinson's disease, thus leaving the cells more susceptible to apoptosis. The i-Motif formation on the cytosine rich bcl2 promoter region provides a mechanism for modulation of gene expression on being targeted by the compounds, IMC 48 (cholestane derivative) which up regulates transcription whereas IMC 76 (pregnanol derivative) down regulates gene expression [9]. Thus targeting the bcl2 i-motif by these compounds can help in regulating the gene expression. Another example is c-myc promoter i-Motif. This c-myc gene codes for transcription factor that has various function such as regulation of cell cycle, progression and cell growth [12]. The gene expression of c-myc is controlled by several proteins which bind to single strand cytosine rich repeats (e.g., heterogeneous ribonucleoprotein K). With the formation i-Motif on the cytosine rich strand followed by its stabilization through small molecule compound may lead to suppression of gene expression [13].

Besides these above-mentioned i-Motifs, there are other promoter i-Motifs that have been under study, like vascular endothelial growth factor promoter region can form an i-Motif *in vitro* at acidic pH [14]. The cytosine rich promoter region of c-kit, kras, PDGF, c-myb, HIF-1α and hTERT are also known to form i-Motif structures [15-17]. The cytosine rich repeats in RNA can also form i-Motif [18] but they are highly unstable due to the steric interactions in the sugar and repulsive interactions between 2' hydroxyl groups of the ribose sugars in the minor groove. Besides this, other less stable i-Motifs are: DNA-RNA hybrid i-Motif [19] and peptide nucleic acids i-Motif [20].

Targeting i-motif structure with small molecules may lead to prospective cure for cancer and other genetic disease and hence can be a potential target for drug design and modulation of gene expression. At present only few compounds have been tested that bind to i-Motif structures but they also show non-specific binding to other targets as well. The first binding study on telomeric i-Motif was done in 2000 [21]. They showed binding of TMPyP4 to telomeric i-motif. Besides this, there are other telomeric i-motif targeting compounds, such as, BisA [22], phenanthrolines [23], perylene-neomycin conjugate [24], and crystal violet [25], amino acid complexes of Terbium [26], ruthenium complexes [27] and mitoxantrone [28]. The bcl2 i-Motif targeting compounds are IMC 48 and IMC 76 [9]. In addition, i-Motif structure has vast application in the field of nanotechnology, for example, as sensors to map pH changes in living cells [29,30], switches for logic operations [31-33], designing Nano machines [34,35] and assembly of gold nanoparticles.

At present, i-Motif target based drug design is an emerging field. Since targeting i-Motif with small molecules is currently a challenging problem as there are not any compounds/drugs in the market that can specifically bind to a particular i-Motif. Researchers still have to go long way in order to find a potential drug candidate that can target, induce and stabilize i-Motif formation in the promoter region of oncogene thereby regulating its gene expression, which can be a breakthrough development in the field of cancer therapy.

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