

Non-Coding Ribonucleic Acid: A New Anticancer Drug Target

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Editorial

Ribonucleic acid (RNA) plays a central role in the pathway from DNA to proteins and acts as central dogma of molecular biology. It is a polymeric molecule, found usually in a single-stranded form and comprised of one or more nucleotides. Each nucleotide consists of a ribose sugar, a phosphate and a base (adenine/cytosine/guanine/uracil). RNA plays a vital role in gene expression as well as protein synthesis. The genetic information of an organism is encoded as a linear series of bases in the Deoxyribonucleic acid (DNA) of the cell. During the process of gene expression, DNA is copied into messenger Ribonucleic acid (mRNA), which is further translated by ribosomes to form proteins. However, in the cell, there are some other kinds of RNAs as well, which are referred to as non-coding RNAs (ncRNAs). These ncRNAs are not translated into protein but perform other significant roles which lead to attain substantial focus as a remarkable target for therapeutic intervention.

These ncRNAs can function as genetic material (in some viruses), as a structural element and the catalytic subunit of many ribonucleoprotein (RNP) particles [1]. They are also known to be coupled with RNA-binding proteins (RBPs) that facilitate RNA interactions with other biomolecules or can act catalytically on RNA [2,3]. These explicit interactions of proteins with RNAs make it possible to target distinct RNA motifs with small molecule. In the recent past, studies on the interaction of small molecules with RNA have achieved major consideration by various pharmaceutical companies and academia. Some of the RNA-binding antibiotics (a class of naturally occurring compounds) that interact with RNA include: (a) amino acid derivative chloramphenicol, (b) macrolide erythromycin, (c) aminoglycoside neomycin, (d) tetracycline, and (e) thiopeptide thiostrepton [4,5]. The ncRNAs can be divided into two groups: (1) Small regulatory RNAs (e.g., siRNA, miRNA, piRNA) less than 30 nucleotides [6,7]. (2) Long non-coding RNAs (e.g., lncRNA) more than 200 nucleotides in size.

Recently, microRNA (miRNA) therapeutics is in the limelight due to the discovery of first cancer-targeted microRNA drug, MRX34 by Mirna Therapeutics Inc. MRX34, a liposome-based miR-34 mimic that inhibits cell cycle progression and induces cancer cell death. It has entered phase I clinical trial in April 2013. It can be used to cure patients with advanced hepatocellular carcinoma. Besides this, there are other drugs [8-10] that are under Phase I clinical trial for treatment of solid tumors, such as CALAA-01 (by Calando Pharmaceuticals) targets Ribonucleotide Reductase M2, ALN-VSP02 (by Alnylam Pharmaceuticals) targets VEGF, SiG12D LODER (by Silenseed Ltd.) targets KRAS, and Bcr-Abl siRNA (by Duisburg University) targets Bcr-Abl.

Lately, a new technology has been introduced called 'RNA interference' (RNAi). It is one of the most important technological

breakthroughs in modern biology. RNA interference (RNAi) method utilizes small regulatory RNA [11] and can be used as an encouraging method to cure cancers by silencing genes that are either upregulated in tumor cells or involved in cell division [12,13]. RNAi is a biological process in which short RNA molecules reduce gene expression, usually by degrading specific mRNA molecules and thus hindering protein synthesis. Since it is challenging to introduce long dsRNA strands into mammalian cells due to the interferon response, usage of small regulatory RNA for RNA interference (RNAi) process has been more efficacious for cancer therapy [14].

Cancer therapy is one of the chief objectives for RNAi-based treatment. This therapy can be used for the treatment of the single-gene disorders and also the conditions associated with overexpression of proteins [15]. There are various types of small synthetic RNA that can be used in cancer therapy, such as, siRNA, miRNA, shRNA and bishRNA. This kind of cancer therapy compensates for other therapies due to the silencing mechanism, specificity and absence of side effects [16]. In addition, RNAi process can also do the crucial function of shielding cells against parasitic nucleotide sequences (viruses and transposons).

Although till date, the widely studied non-coding RNAs are small regulatory RNA, the importance of long non-coding RNAs (lncRNAs) is also being recognized gradually. Their roles in cancer, novel mechanisms of action, and the strategies in designing lncRNA-targeting therapeutics, along with the associated challenges are under investigation. Soon lncRNA will also be used as a regular diagnostic test for miscellaneous diseases, followed up by RNA based therapy for curing the incurable diseases like cancer. lncRNAs have been classified according to their genomic location, and they are as follows: (i) sense lncRNA, (ii) antisense lncRNA, (iii) bidirectional lncRNA (iv) intronic lncRNA and (v) intergenic lncRNA. A variety of approaches can be used to target lncRNAs for therapeutic purpose, such as, targeting through small molecule inhibitors, RNAi mediated gene silencing, antisense oligonucleotides, plasmid based targeting and by gene therapy [17-20].

In summary, the incurable disease like cancer requires novel as well as efficient biomarkers and curative strategies. The identification of new functional ncRNAs, present in the human genome, will help to make advancement in the field of cancer therapy [21] as this will help us to better understand the cellular circuitries governing eukaryotic cells, thus controlling tumor growth. Various pharmaceutical companies like RaNa Therapeutics, CuRNA, Sarepta, Smart Therapeutics, Allen Institution for Brain Science, Regulus, Miragen Therapeutics, Santaris Pharma etc. have been stepping forward in developing the ncRNA based medicines. Thus the advent of ncRNA based therapeutic medicines will provide unique and perhaps

improved treatment options to patients and eventually will help in the development of drugs targeting nucleic acids.

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