RNA as a Drug Target and its Tools and Databases

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Abstract

Earlier, during the 19th century, there was a concept that RNA is a passive carrier of genetic information. However, with advancement, now it is well established that RNA performs a number of vital roles in the cell, and its malfunction may lead to a disease. The recent advancement in the knowledge about diversity, structural and functional information related to RNAs has put them in the limelight as a drug target. Here, in this mini-review, discussion has been done that coding as well as non-coding RNA regions have potential as a drug target. Besides, a few databases and tools used for the RNA target prediction have also been discussed.

Keywords: mRNA; Non coding RNA; Therapeutic target; MicroRNA; Genome; RNA interference

1. Introduction

Generally, when drug targets are considered, the focus has been on the proteins. However, in recent years, researchers also diverted their minds towards nucleic acids as drug targets. The new discoveries of RNA expand the cellular roles for this macromolecule. Rather than an intermediary between genomic information and the primary sequence of proteins, RNA is now being recognized as an essential component in various processes just like protein. Now it has been shown that RNA has an important role in the transcription regulation, regulation of the translation, catalysis, protein function, protein transport, peptide bond formation and RNA splicing [1]. New findings have identified RNA as a potential target in a multitude of diseases, including bacterial/viral infections and cancer. Just like proteins, RNAs can form well-defined tertiary structures, such as double helices, hairpins, bulges, and pseudo-knots.

The tertiary structure is considered to be the structural base for designing therapeutic agents. However, due to non-availability of RNA-specific modeling techniques/tools, it is being realized that there is an urgent need to develop new tools for RNA-targeted rational drug design [2].
Compared to DNA, RNA is being considered to be a better therapeutic since RNA displays a greater structural diversity and lacks repair mechanisms. Like proteins, RNA has three-dimensional folding that gives rise to complex structures, allowing the highly specific binding of effector molecules. The capability of RNA as drug target was first revealed in bacteria and viruses. However, with discovery of new RNA classes and their sequencing, disease related roles of RNA in mammals also are being explored [3]. Targeting these RNAs offers opportunities to therapeutically modulate numerous cellular processes, including those linked to ‘undruggable’ protein targets. Currently, only linezolid antibiotics that target RNA are being used clinically [4]. Therefore, much work is required in this field to identify the RNA that can act as drug target and to design smaller molecules that can act on them.

It is known that only less than two percent of total mammalian genome codes for proteins, and rest of the genome earlier considered as junk DNA is now known for non-coding RNAs (ncRNAs). Many ncRNAs have now been characterized including miRNA, snRNA, shRNA, repetitive RNAs, intronic RNAs, long ncRNAs (lncRNAs) and many others. RNA that can be used as a drug target, may belong to coding as well as non-coding RNA category [5]. Here, we have focussed on different RNAs that have been used as drug targets and also on available tools and databases used to identify the RNA target.

1.1 Targeting bacterial RNA elements
The first RNA which was identified as a drug target was prokaryotic 16S rRNA [3]. Since then, rRNA has been the most exploited RNA target. Bacterial ribosome comprises of 30S and 50S ribonucleo-protein subunits that contain a number of binding sites for known antibiotics. The differences between prokaryotic and eukaryotic rRNAs enable rRNA-targeting that reduces protein translation and thereby inhibits bacterial growth. The rRNA has been targeted against a broad spectrum of pathogenic bacteria. Aminoglycosides are well-known antibiotics that target rRNA aminoacyl-tRNA site (rRNA A-site). The antibiotic binds to the 16S rRNA near the A-site of the 30S subunit resulting decrease in the translational accuracy and inhibition of the translocation of the ribosome [6]. The other antibiotics like lincosamide, tetracycline and chloramphenicol have also been reported to inhibit protein synthesis [7-9].

1.2 Targeting viral RNA elements
The viral genome also contains structured RNA elements. For a variety of viral systems, genetic studies have clearly demonstrated the absolute requirement for defined RNA elements in many important processes like RNA synthesis, transcriptional regulation and protein translation. Most RNA elements involved are highly conserved and predominantly reside in the 5’ and 3’ non-coding regions of the viral genome. One of the examples includes Rev response element (RRE) RNA in HIV (Human immunodeficiency Virus). Export of viral RNAs from the host nucleus into the cytoplasm involves the Rev protein. The Rev accomplishes this task by binding to a highly structured RNA segment called as Rev response element (RRE) RNA. It is composed of a series of stem-loop structures. Many researchers have demonstrated the inhibition of Rev-RRE interaction by various aminoglycosides [10]. The inhibition of Rev-RRE interaction by various aminoglycosides prevents viral replication and maturation.
Another complex RNA element is internal ribosomal entry site (IRES) in HCV (Hepatitis C Virus). The IRES in HIV is a highly structured 345 nucleotides region which helps in using host translational machinery for synthesis of proteins coded by the RNA of HIV. It is highly conserved in many serotypes and is considered to be a practical target for antiviral intervention [11]. Targeting viral RNA is extensively studied for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) which provide valuable insight for the future exploration of RNA targets in other viral pathogens including severe respiratory syndrome coronavirus (SARS CoV), influenza A, and insect-borne flaviviruses (Dengue, Zika, and West Nile) as well as filoviruses (Ebola and Marburg) [12].

1.3 Targeting microRNAs (miRNAs)
MicroRNAs (miRNAs) are evolutionarily conserved small non-coding RNAs that negatively regulate gene expression by degrading messenger RNA (mRNA) or by suppressing mRNA translation. These are involved in various processes such as cellular development, differentiation, proliferation, stem-cell self-renewal and apoptosis [13]. Miravirsen, the first miRNA-targeting drug, has been successfully tested for the treatment of hepatitis C in clinical Phase II trials [14]. The miRNAs are high-potential drug targets but the development of miRNA-targeting drugs is challenging due to their chemical structure comprising short ribonucleic acids. Several approaches have been developed to modulate the function of miRNA in the hope of potential therapeutic use. Some of them include the use of anti-sense agents that modulate miRNA either by mimicing leading to gene silencing or by binding to a target miRNA resulting in translational arrest [15]. Another approach to modulate miRNA is by targeting the AGO2 (Argonaute 2) protein. AGO2 is a primary executer of miRNA function. It has been targeted using miRISC loading inhibitors [16].

1.4 Targeting RNAi (RNA interference)
RNA interference (RNAi) is a cellular mechanism in which double-stranded RNA (dsRNA) causes degradation of the complementary mRNA. It is used for target-specific gene silencing by inhibiting translation and/or mRNA degradation. This approach has been used as a powerful tool for the exploration of pathogenesis of disease. The use of RNAi as a tool for gene therapy has been extensively studied, especially in viral infections, cancer, inherited genetic disorders, cardiovascular and rheumatic diseases [17]. In 2008, DeVincentz [18] reported the RNA interference strategies as therapy for respiratory viral infections. In 2010, Santel et al. [19] reported the use of Atu027 (a novel RNA interference therapeutic) to treat the prostate cancer. Over the past decade, more than 21 RNAi based therapeutics have been developed for more than a dozen of diseases including various cancers, viruses, and genetic disorders [20].

2. Bioinformatics Tools and Databases
2.1 miRDB
miRDB is an online database available at http://mirdb.org. This source is used for miRNA target prediction and functional annotations. The first version of miRDB was established in 2008. Till then, it has been updated regularly, and the latest updated version is comprised of 2.1 million predicted gene targets regulated by 6709 miRNAs. All the
targets in miRDB are predicted using MirTarget (a bioinformatics tool). MirTarget was developed by analyzing thousands of miRNA-target interactions from high-throughput sequencing experiments. It predicts targets in five species namely human, rat, mouse, dog and chicken. Recently, a new feature of web server interface has been added in miRDB which allows submission of user-provided sequences for miRNA target prediction [21].

2.2 LncTar
It is an efficient tool for predicting RNA targets of lncRNAs (long non-coding RNA). It predicts lncRNA-RNA interactions by means of free energy minimization. Its standalone software was released in 2014 and web server was released in 2015 which is available at http://www.cuilab.cn/lnctar. It is not specific for lncRNAs only. It can be used for predicting putative interactions among various types of RNA molecules such as mRNA and noncoding RNAs including lncRNAs, pre-miRNAs. LncTar runs fast and therefore, can be used for large-scale identification of RNA targets for long non-coding RNAs. It does not have limit to RNA size, indicating that LncTar can be used to all RNAs. It has a high prediction accuracy [22].

2.3 TarBase
TarBase contains manually curated collection of experimentally tested miRNA targets in human/mouse, fruit fly, worm, and zebrafish. It describes each supported target site by the miRNA that binds it, the gene in which it occurs, the location within the 3′ UTR, the nature of the experiments that were conducted to validate it, and the sufficiency of the site to induce translational repression and/or cleavage. The total number of target sites recorded in TarBase exceeds 550. It can be accessed at http://www.diana.pcbi.upenn.edu/tarbase [23].

2.4 psRNATarget
psRNATarget is a plant small RNA target analysis server available at http://plantgrn.noble.org/psRNATarget. A number of miRNA target prediction algorithms and programs have been developed for animal miRNAs. The plant miRNAs are significantly different in the target recognition process. This difference demanded the development of this server which is especially designed for plant RNA target. It incorporates recent discoveries in plant miRNA target recognition and reports the number of small RNA/target site pairs that may affect small RNA binding activity to target transcript [24].

2.5 MiRanda
MiRanda is intended to identify potential microRNA target sites in genomic sequences. It is available at http://www.microrna.org. It is one of the earlier miRNA target predictor tool and is continuously updated. It was originally used to find targets in Drosophila. Afterwards, its algorithm was modified so that it can be used to predict targets in human also. MiRanda is available online as part of the miRanda-mirSVR tool. It provides information about set of genes potentially regulated by a particular miRNA, co-occurrence of predicted target sites for multiple miRNAs in an mRNA and miRNA expression profiles in various mammalian tissues. Users are allowed to customize the algorithm, numerical parameters, and position-specific rules [25-26].
3. Conclusion

Considerable progress has been made towards the goal of targeting RNA. RNAs are reported to be drug targets for various diseases and infection including bacterial and viral infections, cancer, inherited genetic disorders, cardiovascular and rheumatic diseases. In spite of so many efforts, drugs fail in the clinical studies due to various hurdles. Therefore, significant hurdles must be overcome in order to turn the therapeutic potential of RNA as a drug target.

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Conflict of Interest

The authors confirm that they have no conflict of interest.

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