J Biotechnol Biomed 2019; 2 (1): 009-014 *DOI: 10.26502/jbb.2642-9128005*

Review Article

RNA as a Drug Target and its Tools and Databases

Nikita Chordia, Anil Kumar*

Bioinformatics Sub-Centre, School of Biotechnology, Devi Ahilya University, Khandwa Road, Indore, India

***Corresponding Author:** Anil Kumar, Bioinformatics Sub-Centre, School of Biotechnology, Devi Ahilya University, Khandwa Road, Indore-452001, India, E-mail: ak_sbt@yahoo.com

Received: 21 December 2018; **Accepted:** 02 January 2019; **Published:** 14 January 2019

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, DeVincenzo [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.

Acknowledgements

Authors acknowledge the facilities of the Department of Biotechnology, Ministry of Science and Technology, Government of India, New Delhi (DBT) under the Bioinformatics Sub Centre as well as M.Sc. Biotechnology program used in the present work.

Conflict of Interest

The authors confirm that they have no conflict of interest.

References

1. Pyle A. Metal ions in the structure and function of RNA. JBIC Journal of Biological Inorganic Chemistry 7 (2002): 679-690.
2. Chen L, Calin GA, Zhang S. Novel insights of structure-based modeling for RNA-targeted drug discovery. Journal of chemical information and modeling 52 (2012): 2741-2753.
3. Moazed D, Noller HF. Interaction of antibiotics with functional sites in 16S ribosomal RNA. Nature 327 (1987): 389.
4. Warner KD, Hajdin CE, Weeks KM. Principles for targeting RNA with drug-like small molecules. Nature Reviews Drug Discovery 17 (2018): 547.
5. Munshi A, Mohan V, Ahuja YR. Non-coding RNAs: A dynamic and complex network of gene regulation. Journal of Pharmacogenomics Pharmacoproteomics 7 (2016): 3-11.
6. Rando RR. Aminoglycoside binding to human and bacterial A-site rRNA decoding region constructs. Bioorganic and medicinal chemistry 9 (2001): 2601-2608.
7. Douthwaite S. Functional interactions within 23S rRNA involving the peptidyltransferase center. Journal of bacteriology 174 (1992): 1333-1338.
8. Gottesman ME. Reaction of ribosome-bound peptidyl transfer ribonucleic acid with aminoacyl transfer ribonucleic acid or puromycin. Journal of Biological Chemistry 242 (1967): 5564-5571.
9. Douthwaite S. Interaction of the antibiotics clindamycin and lincomycin with Escherichia coli 23S ribosomal RNA. Nucleic acids research 20 (1992): 4717-4720.
10. Zapp ML, Stern S, Green MR. Small molecules that selectively block RNA binding of HIV-1 Rev protein inhibit Rev function and viral production. Cell 74 (1993): 969-978.
11. Rijnbrand RCA, Lemon SM. Internal ribosome entry site-mediated translation in hepatitis C virus

replication. In The Hepatitis C Viruses Springer, Berlin, Heidelberg (2000): 85-116.

12. McKnight KL, Heinz BA. RNA as a target for developing antivirals. Antiviral Chemistry and Chemotherapy 14 (2003): 61-73.
13. Ambros V. MicroRNA pathways in flies and worms: growth, death, fat, stress, and timing. Cell 113 (2003): 673-676.
14. Lindow M, Kauppinen S. Discovering the first microRNA-targeted drug. Journal of Cell Biology 199 (2012): 407-412.
15. Schmidt MF. Drug target miRNAs: chances and challenges. Trends in biotechnology 32 (2014): 578-585.
16. Masciarelli S, Quaranta R, Iosue I, et al. A small-molecule targeting the microRNA binding domain of argonaute 2 improves the retinoic acid differentiation response of the acute promyelocytic leukemia cell line NB4. ACS chemical biology 9 (2014): 1674-1679.
17. Hokaiwado N, Takeshita F, Banas A, et al. RNAi-based drug discovery and its application to therapeutics. IDrugs: the investigational drugs journal 11 (2008): 274-278.
18. DeVincenzo JP. RNA interference strategies as therapy for respiratory viral infections. The Pediatric infectious disease journal 27 (2008): 118-122.
19. Santel A, Aleku M, Roder N, et al. Atu027 prevents pulmonary metastasis in experimental and spontaneous mouse metastasis models. Clinical Cancer Research (2010): 1078-0432.
20. Burnett JC, Rossi JJ, Tiemann K. Current progress of siRNA/shRNA therapeutics in clinical trials. Biotechnology journal 6 (2011): 1130-1146.
21. Wong N, Wang X. miRDB: An online resource for microRNA target prediction and functional annotations. Nucleic acids research 43 (2014): 146-152.
22. Li J, Ma W, Zeng P, et al. LncTar: A tool for predicting the RNA targets of long noncoding RNAs. Briefings in bioinformatics 16 (2014): 806-812.
23. Sethupathy P, Corda B, Hatzigeorgiou AG. TarBase: A comprehensive database of experimentally supported animal microRNA targets. Rna 12 (2006): 192-197.
24. Dai X, Zhao PX. psRNATarget: A plant small RNA target analysis server. Nucleic acids research 39 (2011): 155-159.
25. Enright AJ, John B, Gaul U, et al. MicroRNA targets in Drosophila. Genome biology 5 (2003): R1.
26. John B, Enright AJ, Aravin A, et al. Human microRNA targets. PLoS biology 2 (2004): 363.

Citation: Nikita Chordia, Anil Kumar. RNA as a Drug Target and its Tools and Databases. Journal of Biotechnology and Biomedicine 2 (2019): 009-014.