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Web–Based Tools and Databases for Micro-RNA Analysis: A Review

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***Abstract*—**MicroRNAs (miRNAs), a class of approximately 22 nucleotide long non coding RNAs which play critical role in different biological processes. The mature microRNA is usually 19–27 nucleotides long and is derived from a bigger precursor that folds into a flawed stem-loop structure. Mature micro RNAs are involved in many cellular processes that encompass development, proliferation, stress response, apoptosis, and fat metabolism by gene regulation. Resent finding reveals that certain viruses encode their own miRNA that processed by cellular RNAi machinery. In recent research indicate that cellular microRNA can target the genetic material of invading viruses. Cellular microRNA can be used in the virus life cycle; either to up regulate or down regulate viral gene expression Computational tools use in miRNA target prediction has been changing drastically in recent years. Many of the methods have been made available on the web and can be used by experimental researcher and scientist without expert knowledge of bioinformatics. With the development and ease of use of genomic technologies and computational tools in the field of microRNA biology has superior tremendously over the previous decade. This review attempts to give an overview over the genome wide approaches that have allow for the discovery of new miRNAs and development of new miRNA target prediction tools and databases.

***Keywords*—**MicroRNAs, computational tools, gene regulation, databases, RNAi.

I. Introduction

MICRORNA is small non coding RNAs with ~21-23 nucleotide, have important roles in diverse biological process that encompass the development, apoptosis, tumerogenesis, proliferation, stress response and fat metabolism [1]-[3]. Field of microRNA biology emerged with the discovery of that C. elagans lin4 gene product, a ~22 nt noncoding RNA (ncRNA), regulates the expression of lin14 by partial sequence complementarity [3]-[5]. The microRNAs are transcribed originally in the nucleus as hundred to thousand nucleotides with hairpin structure, called pri-miRNA. This pre-miRNAare generated by RNA polymerase II in all eukaryotes or by RNA polymerase III in some viruses [6], [7]. Primary miRNA are cropped and trimmed to 60 to 100 nucleotides with a stem loop structure called precursor miRNA [pre-miRNA] that are processed in the nucleus by the RNase type III Drosa [8].

These pre miRNAs are exported to the cytoplasm by Exportine 5 to be secondarily processed into miRNA duplexes by the RNase type III Dicer. The dicer removes the loop region of the hairpin and release the ~22 nucleotide mature miRNA duplex [9], [10]. Mature MiRNA are involved in many cellular processes including post transcriptional gene silencing and inhibition of infected viral replication. It discovered those viruses that are capable to produce high level of miRNA. The resulting miRNA duplex assembles with RNA-induced silencing complex (RISC) [11], [50]. The one of the miRNA strand called “passenger” is removed by a helicase activity, while the “guide” miRNA is guided to the target mRNA to either degrade or block translation (Fig. 1). Therefore miRNA play important role in the gene regulation and expression in terms of gene silencing [12].

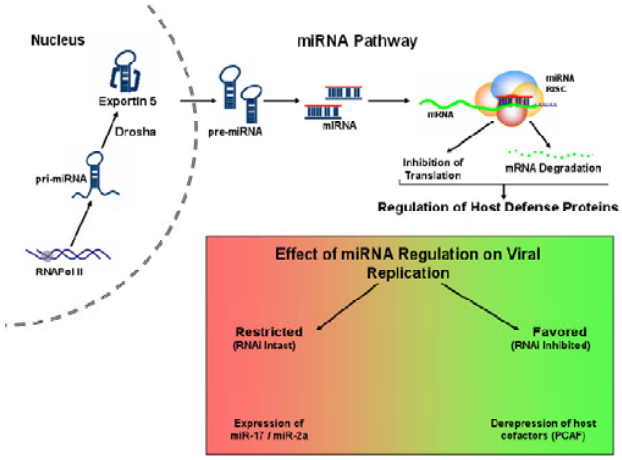

Fig. 1 Systamatic diagram of the restriction on virus replication imposed by host cell microRNA response

Human miRNA implicated in many cellular processes such as cell proliferation, apoptosis, angiogenesis and homeostasis [13]. Many research described that miRNA play a critical role of great magnitude in regulation of virus infection and interplay between virus and host cell response [14]. Some finding showed viral encoded miRNAs from DNA and RNA viruses including Epistein-Barr-Virus [15], Herpies viruses [16], Simian virus 40 [17] and Human Immunodeficiency virus-1 [18]. Host miRNA can also target viral gene and involve with the replication of many incoming viruses such as vesicular stomatitis viruses [19], primate foamy virus type 1 [20], and Hepatitis C virus [21]. Here we review the web based methods that have allowed for the discovery of the new miRNA, the prediction of their targets and a system-level view

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of their impact (Tables I and II).

II. MiRNA Databases

A. General Purpose Databases

MiRBase: MiRBase is a primary central online database for microRNA nomenclature, annotation, sequence data and target prediction. The current release [10.0] contains over 5000 sequences from 58 species, expressing 5922 distinct mature microRNA. The MiRBase database resource provides a range of data for the study of miRNA genomics. MiRBase provides a programmed pipeline for the prediction of targets for all available animal microRNA. MiRBase targets are a comprehensive new and efficient database for the prediction of MiRNA target genes [22].

MiRNAmap: MiRNAmap 2.0 is an online database; collect experimentally verified miRNA and miRNA target genes in human, rat, mouse, and other metazoan genomes. MiRanda RNA hybrid and target scan are the three computational tool user employed to identify miRNA target in the 3'UTR of genes and the known miRNA targets. Quantitative PCR user performed to monitor the expression profile of 224 human miRNA in 18 major normal tissues. The interface is also enhanced and redesigned [23].

B. Specialized Databases

MiR2Disease: MiR2disease is a normally curated database to provide a comprehensive resource of miRNA deregulation in various human diseases miR2Disease having 1939 curated relationship between 299 human miRNA and 94 human diseases.MiR2Dsease entry contains detailed information on a miRNA disease relationship, disease name miRNA ID, the expression pattern of microRNA and detection method of miRNA expression. MiR2Disease is freely available user friendly interface for an easy retroviral of each entry by miRNA ID, disease name and target gene. Researchers also subunit established microRNA disease relationship that is not documented. After the approval submitted records will be in included in the database [24].

MiRSel: MiRSel is web microRNA–gene association database. MiRsel combines text-mining result with existing database and computational prediction. Text mining is very useful for reliable extraction of microRNA, genes protein occurrence as well as their relationship from texts. We can increases the number of human rat and mouse miRNA-gene association resource miRsel having the largest collection of miRNA gene association which are important for the development of miRNA target prediction tools and the analysis of regulatory network. MiRsel is a freely available online database [25].

MiRTarbase: miRTarbase is an online database curate experimentally verified microRNA-target interaction with experimental support is necessary to elucidating microRNA function in different condition by manually serving significant literature after data mining more than 3500. MiRNA-target interactions are accumulated on MiRTarbase database. MiRTarbase contain 3576 MTIs between 657 miRNA and 2297 target gene among 17 species. MiRTarBase provide a large quantity of positive samples to build up computational method for identifying miRNA and target interaction [26], [27].

MiRortho: MiRortho is an online database of the result of a wide-ranging computerized survey of microRNA gene candidate with the majority of metazoan genomes. In this database a three-tier analysis pipeline is applied and design SvH-based *ab initio* screening for potent hairpin and homologous of knowing microRNA. The second is on ontology delineation procedure and the third is a SvH based classifier of the ortholog multiple sequence alignment. The MiRortho web interphase provides direct access to putative miRNA annotation, RNA secondary structure conservation orthology multiple sequence alignment and sequence data. The information of miRortho one corresponding to the miRBase catalog of experimentally confirmed sequences [28].

MiRwalk: MiRwalk is a comprehensive database on MiRNA, which hosted predicted as well as validated information of miRNA binding site on all known genes of human rat and mouse. MiRwalk and another eight already established programs for putative miRNA were used to analyze all miRNA, mitochondrial genes and 10 kb upstream franking regions of all known genes of human rat and mouse. MiRwalk can be used to predict and validate information on miRNA target interaction. MiRwalk enable researchers to validate new targets of miRNA on 3'UTR and on the other region of all known genes [29].

Tarbase: Tarbase database is a manually curated collection of experimentally tested miRNA a target in human, mouse, zebra fish, worm and butterfly distinguish between those that tested positive and those tested negative. Each positive target site is described by the miRNA, the involved gene, the nature of experiments, the induction of translational repression and cleavage and related papers. Tarbase database a large inter linked with the several other databases such as UCSC genomes browser and gene ontology. Tarbase 6.0 hosts more than 65000 targets which are manually curated experimentally validated miRNA gene interaction [30].

MiRDB: MiRDB is a new online database system can be used for the miRNA target prediction and functional annotation. MiRNA functional annotations in miRDB are presented with a primary focus on mature miRNA. These are the functional carrier of microRNA mediated gene expression regulation. In MiRDB a flexible web search interface was developed for the Retrieval of target prediction result. The Wiki editing interface allows anyone with internet access to make contributions on microRNA functional annotation. All data stored in miRDB are freely accessible. MicroRDB contain 1437 microRNA, 389726 gene target and 47, unique gene target [31].

MiRgene: MiRgene is an integrated database of positional two programs. First is the positional relationship between animal microRNAs and genomic annotation set second is animal miRNA targets according to combination of generally used target prediction program. MiRgen is mainly used for study of the association between miRNA genomic

organization and miRNA. The genomic interface of miRGene allows the user to investigate where full a genome collection of miRNA is positioned with respect to UCSC genome browser annotation set such as known genes, genscan predicted genes, refseq genes, pseudogenes and CpG islands. Target interface helps microRNA for their experimentally support target gene as well as computationally predicted target genes. The features of miRgen are designed to investigate the genomic organization co-translation and targeting of miRNA. [32]

FAME: FAME [functional Assignment of miRNA via enrichment] is a latest permutation-based statistical method that tests for over or under representation of miRNA target gene FAME utilizes confidence values for the miRNA target pair, account for the number of miRNAs regulate each target and can use for analysis of any group of microRNA. The direct inference of miRNA function uses a set of gene sharing a common annotation. Tortuous inference of miRNA functions by using matched miRNA expression data and prediction of function for a genomic cluster of miRNA. A full list of the mRNA function is freely available [33].

TABLE I
MIRNA DATABASES AND THEIR URL

Name	URL
General purpose Databases	
miRBase	http://microrna.sanger.ac.uk/
miRNAMap 2.0	http://miRNAMap.mbc.nctu.edu.tw/
Specialized Databases	
miR2Disease	http://www.miR2Disease.org
miRSel	http://services.bio.ifi.lmu.de/mirsel
miRTarBase	http://miRTarBase.mbc.nctu.edu.tw/
miROrtho	http://cegg.unige.ch/mirortho
miRWalk	http://mirwalk.uni-hd.de/
TarBase	http://www.diana.pcbi.upenn.edu/tarbase
miRDB	http://mirdb.org
MiRGen	http://www.diana.pcbi.upenn.edu/miRGen
FAME	http://acgt.cs.tau.ac.il/fame/

III. MIRNA TOOLS

SSc profiler: SSc profile is a web based computational tool for the identification of putative miRNA genes in the having genome. This tool utilizes a probabilistic method based on profile hidden markov models to predict new microRNA precursor. SSc profile has high accuracy, sensitivity, and specificity on a large set of human miRNA gene. SSc profiler is a freely available and highly accurate tool which can be used for the prediction of novel MiRNA gene candidate in the human genome [34].

MiR finder: MiR finder is a tool for the higher throughput and excellent performance computational pre-mRNA predication. This tool can be used for genome wise, pairwise sequence from the related species. MiRNA finder has better sensitivity and speed compared to other miRNA prediction root. MiRNA finder improved its performance by utilizing set of new features: (a) correlation between mutation and secondary structure and (b) Local secondary structure. It is a universally useful software for prediction of novel pre mRNA of different species [35].

CID MiRNA: CID miRNAis a web based server which can be used for the prediction of novel miRNA precursor in the human genome. This CID miRNA utilizing secondary structure based filtering system and an algorithm based on stochastic background free grammar trained on human miRNA. It can be used for the scanning of large genomic sequence for the presence of potential miRNA precursor of potential miRNA precursor. CID miRNA scan putative miRNA precursor and form miRNA like structure of the entire potential region [36].

Mireval: Mireval is an online tool which can search sequence of up to 10 to 10000 bp for microRNA predication in multiple organisms. This is a useful addition to exiting miRNA resource such as miRNA base that enables similarity searches with known microRNA. Mireval is mainly used for the analysis of DNA sequence of up to 10,000 bp based on four criteria; secondary structure analysis, cluster analysis, conservation analysis and miRNA base BLAST [37].

SplamiRNA: Many biological processes resulted by miRNA in plant and animal. SplamiRNA is a web based method used for the prediction of spliced miRNA in the plant. Genomic sequence and the sequence of potential target miRNA used as input in SplamiRNA. SplamiRNA operation finished in two phases, in first phase a database of complementary sequence pair is created for the target genomic sequence. These are encoded for RNA folding in to stem loop structure in the second phase of splamiRNA this database is searched for the sequence with complementarily to the given miRNA [38].

IV. MIRNA DEEP SEQUENCING TOOLS

MiRTool: Deep sequencing technology has been applied to investigate various the small RNA transcriptomes and their computational method. MiRtool is used to comprehensively characterization of small RNA transcriptome. This comprehensive web server allows user to filter low-quality reads and 3/5 adaptors form raw sequence, align the large scale short reads and classify small RNA candidates in different known categories. MiRtool also provide detailed annotation and identify novel expressed miRNA [39].

Deepbase: Deepbase is a novel database, which can be used to facilitate the widespread annotation and discovery of small RNA form transcriptomic data. The deepbase contains deep sequencing data from 185 small RNA libraries from different cell line tissue of human, mouse, testinalis chicken, *D. melanogaster*, *C. elegans*, and *A. thaliana*. After analysis of 14.6 million unique reads, 38000 unique ncRNA-associated small RNA (nasRNA), ~4.0 million unique exon associated small RNAs (easRNA) 1.5 million unique promoters-associated small RNAs (pasRNAs) and ~6 million distinctive repeats- associated small RNA (easRNAs).2038 miRNA and 1889 snoRNA candidate were predicted by miRDeep and snoseeker. For comparative analysis deepbase provides an interactive integrative and versatile interface [40].

TABLE II
VARIOUS MIRNA TOOLS AND THEIR URL

Name	URL
miRNA Prediction tools	
SSCprofiler	http://www.imbb.forth.gr/SSCprofiler.html
MiRfinder	http://www.bioinformatics.org/mirfinder/
Splamir	http://www.uni-jena.de/SplamiR.html
CID-miRNA	http://mirna.jnu.ac.in/cidmirna/
Mireval	http://tagc.univ-mrs.fr/mireval
miRNA Deep Sequencing tools	
MiRTool	http://59.79.168.90/mirtools
deepBase	http://deepbase.sysu.edu.cn/
miRExpress	http://miRExpress.mbc.nctu.edu.tw
miRanalyzer	http://web.bioinformatics.cicbiogune.es/microRNA/
miRNA Target Prediction Software	
DIANA-microT	www.microrna.gr/microT
DIANA-mirPath	http://microrna.gr/mirpath
MicroInspector	http://www.imbb.forth.gr/microinspector
miRecords	http://miRecords.umn.edu/miRecords
miRGator	http://genome.ewha.ac.kr/miRGator/
Plant miRNA targets	
SoMART	http://somart.ist.berkeley.edu
TAPIR	http://bioinformatics.psb.ugent.be/webtools/tapir

MiRExpress: MiRexpress is a database efficient and flexible tool for prediction of miRNA expression profile. The software is used for generating microRNA expression profiles from high throughput sequencing of RNA without the required for sequenced genome. MiRexpress extracting miRNA expression profile from sequenced reads obtained from second generation sequencing technology to find novel microRNA. MiRexpress contain microRNA information from miRbase and efficiently detect expression profiles by aligned sequenced reads against the sequenced of known miRNA. MiRexpress can be used to find new microRNA candidate by aligning reads with known microRNA of different species [41].

MiRAnalyser: The next generation sequence method allows the sequencing of small mRNA molecule and also estimates their expression levels. MiRAnalyser is a web based tool for the analysis of deepsequencing experiments for small mRNA. A list of inimitable reads and its copy number are required as input file for the MiRAnalyser. Web server MiRAnalyser detect all known microRNA sequences annotated in MiRbase find all perfect matches against other library and predict new microRNA. MiRAnalyser provide easy user interface and summarized the entire described step in a single output page. This output provides a widespread overview of the analysis at high speed and sensitivity and low cost [42].

V. MIRNA TARGET PREDICTION SOFTWARE

DNAmicroT: DNAmicroT is a web based server as the user interface for microRNA target prediction. This online web server can be used for miRNA prediction by target gene interaction with a user friendly interface, provided that extensive connectivity to online biological resource miRNA function and target can be elucidated through Kyoto Encyclopedia of gene and genes [KEGG] pathway. The DNAmicroT web server has many links to sequence and protein database, nomenclature and user are facilitated genes using different functional and feature Nomenclature in biological pathways. The target prediction algorithm calculates support parameter of each miRNA [43].

DIANAmiRpath: DIANAmiRpath is a web-based tool developed to identify molecular pathway pot initially altered by the expression of microRNAs. This computational tool used to be from an enrichment analysis of multiple microRNA targets comparing with all known KEGG pathways. The Result of analysis of providing an overview of the parts of the pathway modulated by microRNA. DIANAmiRpath is also used in the functional analysis of miRNAs associated with human metastatic cancer cell and identifies both mitogensis and motility pathway to be extended down regulated by the combine action of these three miRNAs. DIANAMiRpath is able to give a systemic explanation of two observed phenotype [44].

MiRNA inspector: MiRNAcontrol mRNA degradation or translation inhibition through microRNA binding to complementary site. Microinspector is a web based tool used to detect the occurrence of binding site on mRNA for known and register microRNA. The web based program allows variation in temperature, selection of different miRNA database and settling of energy values. Microinspector can be based to scanning the correct site for miRNA interaction in target mRNA. The microinspector program is easy to use and available online freely [45].

Mirecords: Predicted miRNA target produce by 11 miRNA prediction program more than 700 mature miRNA have been identified in the human genome. MiRecords is a new resource for the prediction of miRNA target interaction miRecord divided into two components. The validated target component is a large-high quality database of experimentally validated miRNA targets. It emphasizes systematic and structured documentation of experimental RNA-target interactions. This data base also provides a large-high quality dataset that will facilate the development of the tool. The predicted targets are an integration of predicted miRNA target produced by 11 established miRNA target prediction program. MiRecords database includes 1135 records of validated miRNA-target and predicted target component stores [46].

Migator: MiRgator is a novel database, which integrates the target prediction gene expression data, functional analysis and genome annotation. MiRNA function is predicted by Miranda, Pictar and target can program for statically enrichment test, each term is performed for gene ontology, pathway and disease annotation miRgator integrates public expression data for expiration analysis of miRNA with those of mRNA protein miRgator supports divers query type including miRNA name gene ontology gene symbol pathway and disease term miRgator can compare expression correlation between miRNA and target mRNA/protein. It is freely available and supports the human and more genome. Computational tool use in miRNA target prediction has been changing drastically in recent year. Many of the methods have

been made available on the web and can be used by experimental researchers without expert knowledge of bioinformatics. This review over the miRNA target prediction tools and databases [47].

VI. Plant MiRNA Target

Somart: Computational prediction and small RNA [sRNA] cloning are the most essential approaches for discovery of miRNA, tasiRNA and their targets. The smart is a web based server for the prediction of miRNA and tasiRNA. It is designed for researchers who are interested in identifying miRNAs and tasiRNA that potentially regulated genes of interest somart web server includes four set of tools for different predication process slicer detector for detecting siRNA input genes dRNA mapper for prediction of degrading RNA product derive from input genes. A pre MIR detector for identifying miRNA or tasiRNA precursor of input SRNAs, on to input genes. These tools are freely available at SOMART web server [48].

TAPIR: TAPIR is a web server for the identification of plant miRNA targets, including target mimic. This server allows for researchers to search for plant miRNA targets using a fast and precise algorithm. It is useful to find less perfectly paired miRNA target duplex and allows the prediction of target mimics which are characterized by a miRNA target duplex making large loop. TAPIR is a fast and precise method for prediction of plant miRNA targets. The TAPIR web server is freely available user friendly interface [49].

VII. Conclusion

Many of the tools and databases available on the internet and can be used by experimental researchers without expert knowledge of bioinformatics. Here we discussed detail information about the available web- based tools and databases for the prediction of microRNA and their targets. These tools are based on different algorithms and methodologies and having strength and weakness. This review is very helpful for the prediction of microRNA by using various methodologies.

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