

miRTarBase 2020: updates to the experimentally validated microRNA–target interaction database

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ABSTRACT

MicroRNAs (miRNAs) are small non-coding RNAs (typically consisting of 18–25 nucleotides) that negatively control expression of target genes at the post-transcriptional level. Owing to the biological significance of miRNAs, miRTarBase was developed to provide comprehensive information on experimentally validated miRNA–target interactions (MTIs). To date, the database has accumulated >13,404 validated MTIs from 11,021 articles from manual curations. In this update, a text-mining system was incorporated to enhance the recognition of MTI-related articles by adopting a scoring system. In addition, a variety of biological databases were integrated to provide information on the regulatory network of miRNAs and its expression in blood. Not only targets of miRNAs but also regulators of miRNAs are provided to users for investigating the up- and downstream regulations of miRNAs. Moreover, the number of MTIs with high-

throughput experimental evidence increased remarkably (validated by CLIP-seq technology). In conclusion, these improvements promote the miRTarBase as one of the most comprehensively annotated and experimentally validated miRNA–target interaction databases. The updated version of miRTarBase is now available at <http://miRTarBase.cuhk.edu.cn/>.

INTRODUCTION

MicroRNAs (miRNAs) are a family of small non-coding RNAs with 18–25 nucleotides; they are transcribed from DNA sequences into primary miRNAs and then processed into precursor and mature miRNAs in animals and plants. Perfect or near-perfect complementary binding of miRNAs to their target mRNAs negatively regulates gene expression in terms of accelerating mRNA degradation or suppressing mRNA translation (1). Many investigations have reported that miRNAs play crucial roles in numerous biological processes, such cell cycle, cell proliferation, cell differentiation, apoptosis, metabolism, and cellular signaling

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(2,3), and various diseases. The study of miRNA–target interactions (MTIs) has been gaining a surge of interest from researchers due to the causal relationship between miRNAs and disease development. An increasing number of studies (4–6) have reported extracellular/circulating miRNAs in biological fluids, such as plasma, serum, cerebrospinal fluid, saliva, breast milk, urine, tears, colostrum and peritoneal fluid. Most importantly, dysregulated expression patterns of miRNAs may serve as potential biomarkers for disease diagnosis and prognosis.

Owing to the biological significance of miRNAs, a number of online resources have been developed for the data warehousing and functional analysis of MTIs. miRBase is the primary miRNA sequence repository that facilitates the inquiry for comprehensive miRNA nomenclature, sequence and annotation data (7). DIANA-TarBase accumulates manually curated interactions between miRNA and gene with the annotations of detailed meta-data, experimental methodologies and conditions (8). HMDD can provide functional enrichment information on miRNAs and the regulatory network of MTIs (9,10). miR2Disease can provide users disease-associated MTIs based on the information on miRNA–disease relationships obtained from research articles (11). In recent years, a variety of computational methods have been published for the identification of target binding sites of miRNAs, mainly according to the base pairing of miRNA and target sequences (12). However, these approaches developed on the basis of perfect seed pairing may result in false-positive predictions of MTIs (13). Therefore, these predicted results based on wet-lab experiments, such as real-time quantitative reverse transcription–polymerase chain reaction, enzyme-linked immunosorbent assay, immunohistochemistry and western blot, must be verified. Additionally, reporter assay is widely used in examining the physical interaction between miRNA and its target through the evidence of decreased expression level of a reporter protein (14). Given the surge of high-throughput sequencing technologies (15), the sequencing data obtained from CLIP (16), PAR-CLIP (17) and CLASH (18) can be used to explore miRNAs and their targets with expression evidence.

In post-transcriptional regulations, understanding how miRNAs downregulate target genes and transcription factors (TFs) regulate miRNAs is critical. More evidence has indicated that aberrant regulation of miRNAs by TFs can induce phenotypic variations and diseases. TransmiR is a knowledge base of comprehensive transcriptional networks between TFs and miRNAs that serve as gene dysregulators in different diseases (19). DIANA-miRGen (20) and mirTrans (21) were designed to provide annotations of cell-specific miRNA TSSs and discovery of TF–miRNA regulation networks, respectively. SomamiR is a database of somatic mutations affecting mRNAs and noncoding RNAs between miRNAs and their targets; miR2GO is a computational tool in miRNA seed regions for knowledge-based analysis of genetic variants and somatic mutations (22,23). miRNA sponges are competing endogenous RNAs (ceRNAs); miRSponge was established as an experimentally supported database that contains 599 miRNA-sponge interactions and 463 ceRNA relationships from 11 species (24).

Owing to an increasing number of miRNA–target interaction studies being published over the past 10 years, miR-TarBase (25–28) was developed to integrate MTIs and their functional roles in various biological processes. In this update, miRTarBase aims to accumulate experimentally validated MTIs, which are subsequently manually curated, based on a high-accuracy text-mining system. Furthermore, the upstream (TFs to miRNAs) and downstream (miRNAs to targets) regulations of miRNAs in different diseases have been integrated into this updated resource to enhance the functional analyses of miRNAs.

SYSTEM OVERVIEW AND DATABASE CONTENT

Since the first version of miRTarBase was released in 2011, the number of experimentally validated MTIs has increased drastically over the last 10 years. Meanwhile, the web interface of miRTarBase has been enhanced constantly to provide users more effective and efficient accessing experience. In recent upgrades, miRTarBase was further dedicated to provide a comprehensive MTI repository with a finer user interface. Figure 1 presents the highlighted improvements of this update. With an attempt to provide users the most comprehensive information on MTIs, a text-mining system was enhanced to search for more MTI-related articles against PubMed literature database. Our curators then manually curated these MTI-related articles to extract validated miRNA–target interactions with promising experimental evidence. In addition, many biological databases and standalone tools were integrated to increase the academic value of miRTarBase: miRNA information from miRBase (7); target gene information from National Center for Biotechnology Information (NCBI) Entrez (29) and RefSeq (30); miRNA regulators information from TransMir (19), miRSponge (24), and SomamiR (22,31); disease information from HMDD (9,10); gene and miRNA expression profiling from Gene Expression Omnibus (GEO) (32); The Cancer Genome Atlas (TCGA) (33,34); Circulating MicroRNA Expression Profiling (CMEP) (35). Table 1 displays a list of the databases that have been integrated into miRTarBase. Furthermore, in this update, users can access all relevant information on MTIs of interest through a user-friendly and interactive visualization interface.

UPDATED DATABASE CONTENT AND STATISTICS

Table 2 presents the improvements and updated content of miRTarBase 2020. As indicated in the table, the number of curated articles, MTIs and species increased substantially. Up to September 2019, this update (version 8) has significantly increased the number of MTIs compared with miRTarBase 7.0. A total of 479,340 curated MTIs between 4,312 miRNAs and 23,426 target genes were collected from 11,021 research articles. In addition, this updated version has integrated additional 100 CLIP-seq data from nine independent studies that can be used to support many MTIs (Supplementary Table S1).

A scoring system has been incorporated into the automatic text-mining system for further manual curations to enhance the recognition of MTIs and a high score means that the article is more related to MTIs. We have also up-

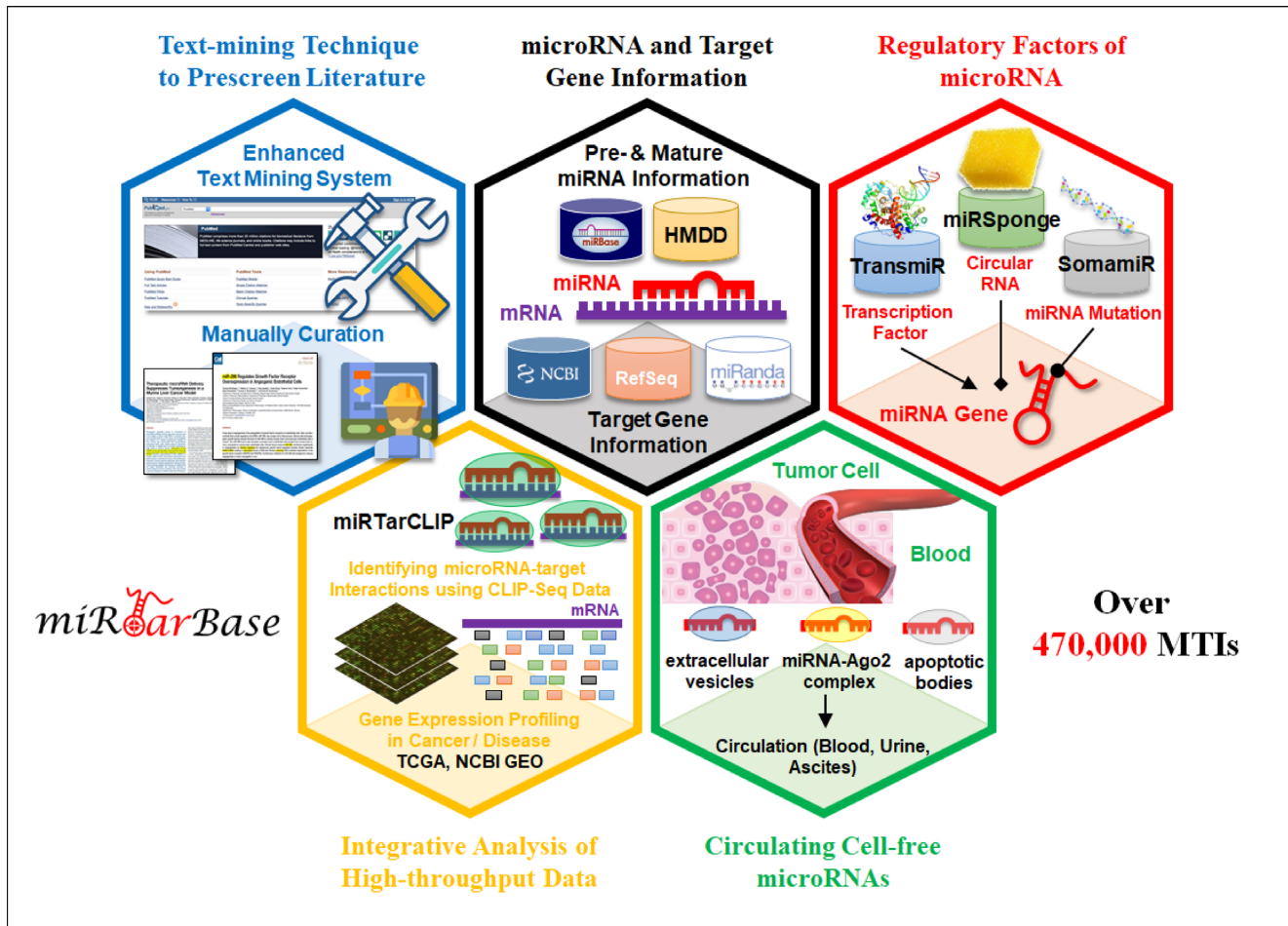


Figure 1. Highlighted improvements of miRTarBase 2020. As the most comprehensive resource on miRNA–target interactions, this update accumulates >470,000 manually confirmed MTIs supported with experimental evidence.

Table 1. List of the databases that are integrated by miRTarBase

Type	Database name
Gene and miRNA-specific databases	miRBase (7), NCBI Entrez gene (29), NCBI RefSeq (30)
SNP or mutation related databases	SomamiR (22,31)
miRNA–disease association Database	HMDD (9,10)
The regulation of miRNAs	TransMir (19), miRSponge (24)
miRNAs expression	CMEP (35), Gene Expression Omnibus (GEO) (32), The Cancer Genome Atlas (TCGA) (33,34)

dated the version of previously integrated databases to include miRNA information, miRNA–disease associations, gene information, and mRNA sequences. Data contents provided by TransMir (19), miRSponge (24), SomamiR (22,31) and CMEP (35) were recently integrated to improve the information related to the regulation of miRNAs and the presence of cell-free miRNAs. Additionally, an enhanced viewer for displaying the TF–miRNA target relationships is embedded into the miRTarBase web interface.

Circulating miRNA expression

Circulating cell-free miRNAs as potential biomarkers of diseases have been stably presented in blood (36). Researchers have focused on the discovery, development,

and evaluation of diagnostic, prognostic, and predictive biomarkers and technologies. In this update, we have integrated the data from CMEP (35) to represent the miRNA expression profiling in blood, including 10,419 samples obtained from 66 datasets. We believe that the information on circulating miRNA expression can enable biological and clinical researchers to gain biological insights into these interesting miRNAs and develop novel non-invasive biomarkers for clinical diagnosis.

Regulatory networks among miRNAs, regulators and targets

Post-transcriptional regulation mediated by miRNAs is an important control mechanism of gene expression. miRNAs have been reported to be widely detected in diverse types

Table 2. Improvements and the number of miRNA–target interactions with different validation methods provided by miRTarBase 8.0

Features	miRTarBase 7.0	miRTarBase 8.0
Release date	2017/09/15	2019/09/15
Known miRNA entry	miRBase v21	miRBase v22
Known Gene entry	Entrez 2017	Entrez 2019
Species	23	32
Curated articles	8,510	11,021
miRNAs	4,076	4,312
Target genes	23,054	23,426
CLIP-seq datasets	231	331
Curated miRNA–target interactions	422,517	479,340
Text-mining technique to prescreen literature	Enhanced NLP	Enhanced NLP+Scoring system
Download by validated miRNA–target sites	Yes	Yes
Browse by miRNA, gene, and disease	Yes	Yes
Regulation of miRNAs	No	Yes
Cell-free miRNA expression	No	Yes
MTIs Supported by strong experimental evidences		
Number of MTIs validated by ‘Reporter assay’	9,489	13,922
Number of MTIs validated by ‘Western blot’	7,258	12,179
Number of MTIs validated by ‘qRT-PCR’	8,210	13,263
Number of MTIs validated by ‘Reporter assay and Western blot’	6,032	10,257
Number of MTIs validated by ‘Reporter assay or Western blot’	10,581	15,710

of cancers and other diseases (37–42). Hence, miRNAs can play an important role for diagnostics and treatment of diseases (43,44). Recent studies have been conducted to understand the mechanisms of miRNA-mediated post-transcriptional regulation (downstream regulation) by constructing miRNA–mRNA regulatory networks (45–49). Although several studies over the past decade have shown considerable changes in miRNA expression profiles in various diseases (50–55), less attention has been paid to the regulatory mechanisms of miRNA expression (upstream regulation). Constructing a comprehensive miRNA regulatory network for understanding how miRNAs are regulated is necessary to study changes in the expression level of miRNAs.

Owing to the upregulation of miRNAs expression by TFs, this update has effectively integrated the relationships between miRNAs and TFs to connect TF to the miRNA regulatory network. TransmiR is a database for TF–miRNA regulations, and it provides experimentally validated regulatory relations between TFs and miRNAs (56). The information regarding the pairs of TF–miRNA, the position of 5′ transcription start site, TF binding site, action type, tissue, species, and the evidence reference is obtained from TransmiR. Moreover, circular RNA (circRNA), another type of regulatory noncoding RNAs, has also been considered in this update. Recent studies have indicated that circRNAs can regulate gene expression by influencing mRNA translation through sponging miRNAs (57–59). The annotations of circRNAs were acquired from miR-Sponge, which provides experimental relationships between circRNA and miRNA (24). In particular, cancer somatic mutation in miRNAs, which can alter the interactions between miRNAs and their targets, such as mRNA, circRNA, ceRNA, and long noncoding RNAs (lncRNAs) (60), was also integrated into our repository based on the annotations of SomamiR (22,31).

Given a miRNA, both targets and their regulators are difficult to analyze based on a variety of online databases or tools. Thus, this update also aims to provide an ex-

tended platform for investigating the regulation mechanism of miRNAs by comprehensively constructing the regulatory networks among miRNAs, regulators, and targets.

ENHANCED WEB INTERFACE

As presented in Figure 2, the web interface has been redesigned to be more user-friendly, snappier, and aesthetically pleasing in this version. Users can search for the MTIs of their interest through different queries or directly browse the lists of miRNAs based on different categories: ‘by miRNA name’, ‘by target genes’, ‘by pathway’, ‘by validated method’, ‘by disease’, ‘by literature’, ‘by miRNA name’, ‘by target genes’, ‘by disease’ or ‘by species’. Users can also explore regulators, such as circRNA and TF, for the miRNAs of interest. The layout of MTI information and the regulators of miRNA expression have been rearranged to improve online readability according to user feedback. Meanwhile, the relationship between miRNAs and their regulators is illustrated with an interactive visualization of miRNA regulatory network. These improvements in web interface can promote miRTarBase as a popular online resource in miRNA research.

USERS OF MIRTARBASE

miRTarBase has been developed for 10 years; the first version, which came out in 2011, was followed by the fourth, sixth, and seventh versions in 2014, 2016 and 2017, respectively. Interestingly, the articles that have cited miRTarBase are distributed in different research areas, and they vary slightly between different versions, which may reflect the developing trend of miRNA studies (Supplementary Figure S1). Among the papers referenced to all releases of miRTarBase, ‘Biochemistry Molecular Biology’ is the most popular research field. For the miRTarBase version 1 (2011), in addition to ‘Biochemistry Molecular Biology’, the rest of the top 10 research areas include ‘Oncology’, ‘Science Technology Other Topics’, ‘Mathematical Computational Biol-

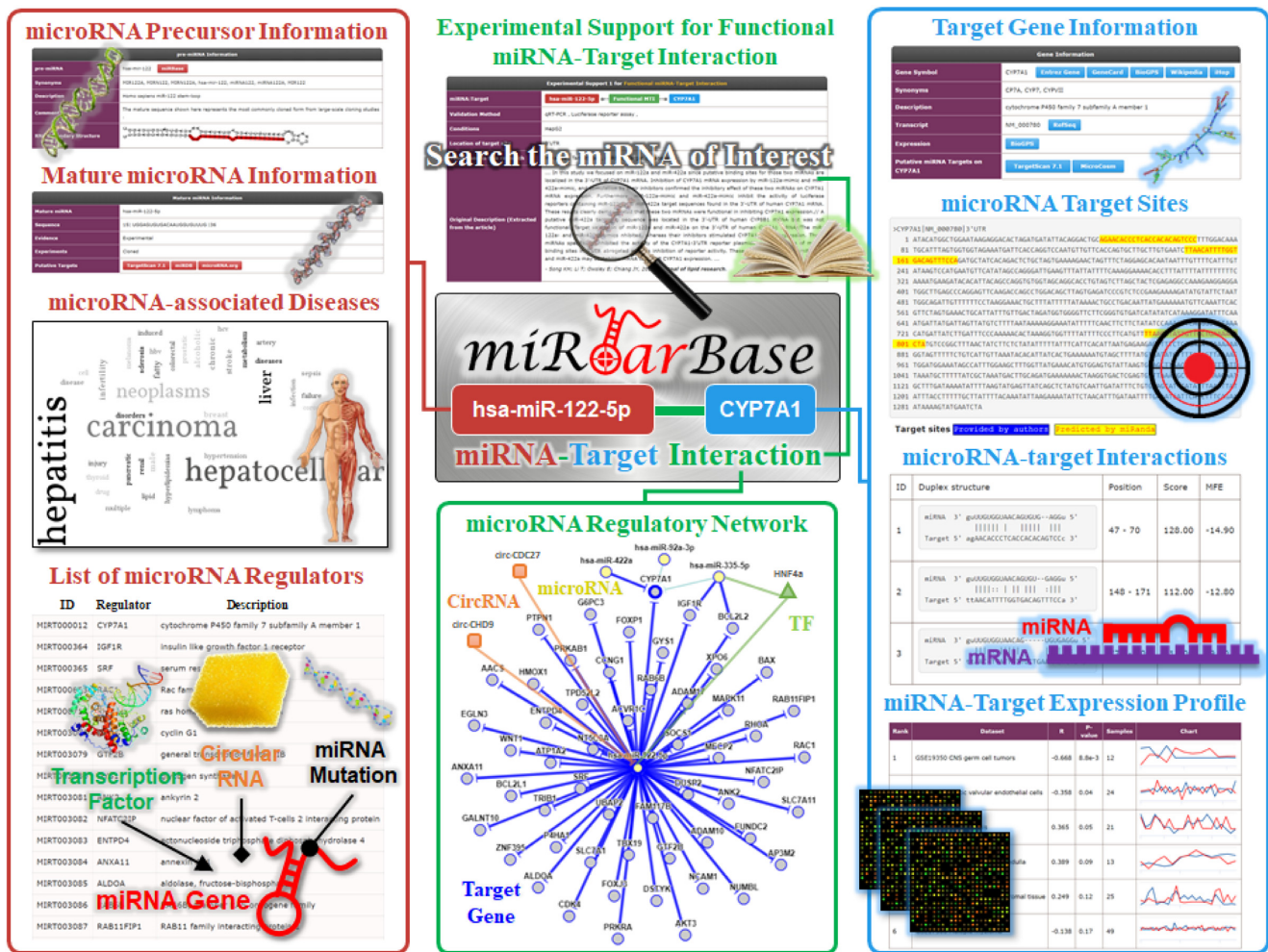


Figure 2. Enhanced web interface of miRtarBase. More comprehensive information related to miRNAs, such as miRNA precursor, mature miRNA information, miRNA-associated diseases, miRNA regulators, supporting evidence, display of miRNA regulatory network, target gene information, miRNA target sites, and the expression profiles of miRNAs and their targets, are provided on the web interface of miRtarBase.

ogy’, ‘Genetics Heredity’, ‘Biotechnology Applied Microbiology’, ‘Cell Biology’, ‘Research Experimental Medicine’, ‘Computer Science’ and ‘Neurosciences Neurology’. For the miRtarBase version 4 (2014) and later versions, articles in the field of ‘Oncology’ increased remarkably (ranked second continuously) compared with that in the miRtarBase version 1. For the miRtarBase version 7 (2018), articles related to ‘Pharmacology Pharmacy’ and ‘Physiology’ appeared in the top 10 research areas for the first time. However, the articles associated with ‘Computer Science’ and ‘Neurosciences Neurology’ dropped out of the top 10 fields temporarily. In addition, the number of papers cited in all versions on ‘Research Experimental Medicine’ indicated a gradual upward trend and has arisen into the top 4 areas, whereas the number of papers cited on ‘Mathematical Computational Biology’ declined regularly over time.

In summary, understanding how miRNAs downregulate target genes and TFs regulate miRNAs is critical to enhancing the functional analyses of miRNAs because aberrant regulation of miRNAs by TFs can induce phenotypic variations and diseases. Consequently, the latest update of miR-

tarBase addresses this issue and provides not only the targets but also the regulators of miRNAs, such as lncRNA and circRNA, to users for investigation of the up and downstream regulations of miRNAs.

SUMMARY AND PERSPECTIVES

Since the first release of miRtarBase in 2011, experimentally validated MTIs have been continuously accumulated for nearly 10 years. Thus far, we have collected > 11,000 articles with experimental evidence on MTIs. The latest release of miRtarBase 8.0 (15 September 2019) contains 479,340 curated MTIs between 4,312 miRNAs and 23,426 target genes. Previously, miRtarBase has reported disease associations of miRNAs and their targets, which can provide potential targets for disease diagnosis. To ensure the correctness of the MTI data collected from heterogeneous resources, we have repeatedly confirmed the content of the articles in miRtarBase with an improved data management system. The manual data-management interface has been optimized to enable data managers to proofread easily and accurately. In addition, we added treatment-related infor-

mation on miRNAs and described the treatment association of miRNAs in particular diseases to increase the researchers' awareness of the relevance of miRNAs to treatment in the future. In conclusion, as an important biological database, miRTarBase will continually aim at updating and increasing important information related to miRNA and provide a reliable database platform for a wide range of scientific researchers.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

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