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Databases and ontologies

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SM2miR: a database of the experimentally validated small molecules' effects on microRNA expression

Xinyi Liu†, Shuyuan Wang†, Fanlin Meng, Jizhe Wang, Yan Zhang, Enyu Dai, Xuexin Yu, Xia Li* and Wei Jiang*

College of Bioinformatics Science and Technology, Harbin Medical University, Harbin, China

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ABSTRACT

Summary: The inappropriate expression of microRNAs (miRNAs) is closely related with disease diagnosis, prognosis and therapy response. Recently, many studies have demonstrated that bioactive small molecules (or drugs) can regulate miRNA expression, which indicates that targeting miRNAs with small molecules is a new therapy for human diseases. In this study, we established the SM2miR database, which recorded 2925 relationships between 151 small molecules and 747 miRNAs in 17 species after manual curation from nearly 2000 articles. Each entry contains the detailed information about small molecules, miRNAs and evidences of their relationships, such as species, miRBase Accession number, DrugBank Accession number, PubChem Compound Identifier (CID), expression pattern of miRNA, experimental method, tissues or conditions for detection. SM2miR database has a user-friendly interface to retrieve by miRNA or small molecule. In addition, we offered a submission page. Thus, SM2miR provides a fairly comprehensive repository about the influences of small molecules on miRNA expression, which will promote the development of miRNA therapeutics.

Availability: SM2miR is freely available at http://bioinfo.hrbmu.edu.cn/SM2miR/.

Contact: jiangwei@hrbmu.edu.cn or lixia@hrbmu.edu.cn

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1 INTRODUCTION

MicroRNAs (miRNAs) are endogenous, single-stranded and non-coding RNAs, which regulate their target genes at the post-transcriptional level through inhibiting protein translation or degrading mRNA (Bartel, 2009). A miRNA can regulate hundreds of genes and plays key roles in many physiological and pathological processes, such as proliferation, differentiation and apoptosis (He and Hannon, 2004). The inappropriate expression of miRNAs is related to many kinds of critical illness, including cancer, cardiovascular disease, metabolic disease, inflammatory disease and so on (Sevignani *et al.*, 2006; van Rooij *et al.*, 2012). Various evidences are overwhelming that the abnormal expression of miRNAs is the hallmark of diseases. For example, Greither *et al.* (2010) confirmed that miR-155, miR-210, miR-222 and miR-203 were highly expressed by qRT-PCR in pancreatic tumor. The expression of let-7 was significantly reduced in colon cancer patients compared with that in adjacent non-cancerous tissue from the same patient (Akao *et al.*, 2006). In addition, miRNAs have several attractive features to be druggable, such as the specific secondary structures and the conserved sequences. Recently, many studies demonstrated that small molecules can regulate miRNA expression, which indicates that targeting miRNAs with small molecules is a new type of therapy for human diseases (Zhang *et al.*, 2010). For example, the expression levels of 22 miRNAs were changed after 5-fluorouracil treatment in human colon cell line through qRT-PCR (Rossi *et al.*, 2007). Rhodes *et al.* (2012) detected 22 up-regulated miRNAs and 10 down-regulated miRNAs after the treatment of trichostatin A in human breast cancer cell lines by microarray. To sum up, specific miRNA will be treatment target for majority of diseases. Therefore, the study of how small molecule drugs influence the expression levels of miRNAs is very significant.

Hitherto, diverse miRNA-related databases have been constructed. For example, miRBase (Griffiths-Jones *et al.*, 2008) is the central online repository of miRNA sequences and annotations. MicroCosm Targets (Griffiths-Jones *et al.*, 2008), TargetScan (Lewis *et al.*, 2005) and TarBase (Sethupathy *et al.*, 2006) provide the computationally predicted or the experimentally validated target genes for miRNAs. With the progression of research on the important roles of miRNAs in human diseases, several manually curated databases about the associations of miRNAs and diseases were developed, such as phenomiR (Ruepp *et al.*, 2012), HMDD (Lu *et al.*, 2008) and miR2Disease (Jiang *et al.*, 2009). However, the databases about how bioactive small molecules influence the expression levels of miRNAs are quite rare. The relevant information is scattered among the massive literatures, which is inconvenient for researchers to explore the relationships between small molecules and miRNAs. Yang *et al.* (2011) presented the miREnvironment database to describe the complex interactions between genetic factors and environmental factors, where a few small molecules appeared as environment factors. Thus, this manuscript described a curated database SM2miR, which offered more comprehensive information about the small molecules' effects on miRNA expression and filled the vacancy in this field.

*To whom correspondence should be addressed.
†The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First authors.

2 DATABASE CONTENT

We extracted the associations of small molecules and miRNAs from PubMed database using the keywords 'drug and miRNA', 'small molecule and miRNA', 'drug and miR' and 'small molecule and miR'. Approximately 2000 articles that were published before March 2012 were obtained. After manual screening, we got 2925 relationships of small molecules and miRNAs from nearly 200 articles, which included 151 small molecules and 747 miRNAs in 17 species. To provide more effective information about small molecules and miRNAs, a variety of biological databases were integrated, such as miRBase, U.S. Food and Drug Administration (FDA), PubChem and DrugBank. Each entry contained the detailed information about small molecules, miRNAs and their relationships, including species, small molecule name, DrugBank Accession number, PubChem CID, approved by FDA or not, miRNA name, miRBase Accession number, expression pattern of miRNA, experimental detection method, tissues or conditions for detection, evidences in the reference, PubMed ID and the published year of the reference. In total, 108 small molecules have CID, and 62 small molecule drugs are approved by FDA.

For verifying the small molecules' effects on miRNA expression, the researchers applied various experimental methods, including high throughput methods such as microarray and next-generation sequencing, low throughput methods such as PCR, northern blot and Reporter Gene Assays. High throughput experiments usually get more differentially expressed miRNAs, which may lead to a higher false-positive rate, whereas low throughput experiments are more credible. In our database, 2034 entries and 891 entries were got through high throughput method and low throughput method, respectively. Finally, SM2miR is developed using Struts, JSP, tomcat 6.0.33 and MySQL5.0 and runs under Cent OS 5.5 system.

3 WEB INTERFACE

SM2miR provides a user-friendly interface. The users can search a desired miRNA or small molecule through search pages, which offer four options: by miRNA name, by small molecule name, by CID and by DrugBank Accession number. Before searching, you should choose to view low-throughput or high-throughput experiment data or both. Searching by miRNA name supports fuzzy searching. The results list all potential miRNAs that are related to your inputted miRNA. Then, you can select several or all miRNAs and click 'Search' button for retrieving or click your desired miRNA directly. The basic information about the small molecules and your inputted miRNA will be returned. Through clicking 'more', you can obtain the detailed information. SM2miR database also provides a submission page for users to submit new data for updating the database and making it more comprehensive. If the records are approved by our review committee, they will be available in SM2miR. In addition, all data can be downloaded freely on the download page.

4 CONCLUSION

More and more evidences have proved that miRNA as a treatment target is meaningful and promising, and many small-molecule drugs can achieve this purpose. The restoration of the miRNA expression may cure many kinds of critical illness. The miRNA-based therapy may work through different ways. The small molecules can not only structurally bind to the grooves and pockets of miRNAs (Zhang *et al*., 2010) but also target the key enzymes and other cofactors of the process of miRNA synthesis (Melo *et al*., 2011; Watashi *et al*., 2010) or the transcription factors of miRNAs. Thus, drug-targeted protein may influence miRNA expression. However, miRNAs are important post-transcriptional regulatory factors and can regulate downstream protein expression. Even if the changed miRNA expression is the result of protein-targeted treatment, the miRNA may be a welcome addition to the current drug targets.

To provide a valuable and comprehensive resource about the influences of small molecules on miRNA expression, we manually retrieved the relationships of small molecules and miRNAs from literatures and developed the SM2miR database. SM2miR provides detailed information about small molecules, miRNAs and evidences of their relationships. The development and expansion of the SM2miR will continues to progress. In the future, the next version will incorporate more comprehensive information and become more powerful.

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