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Database issue

EVmiRNA2.0: an updated database for miRNA expression in comprehensive human extracellular vesicles

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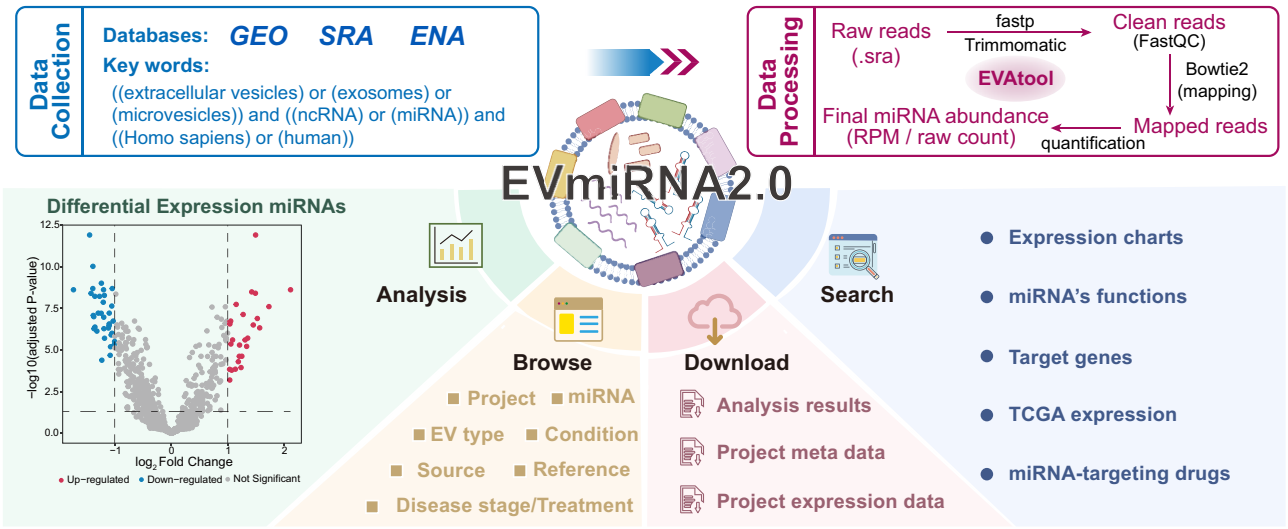
Abstract

Extracellular vesicle (EV)-derived microRNAs (miRNAs) are critical mediators of intercellular communication and play important roles in diverse physiological and pathological processes. However, existing EV miRNA databases are limited by outdated datasets, narrow sample diversity, and the absence of integrated analytical functions. Here, we present EVmiRNA2.0, a substantially updated database for miRNA expression in human EVs. EVmiRNA2.0 integrates 7254 human EV small RNA sequencing (smRNA-seq) samples from 45 distinct sources and 143 disease types. Compared with the previous version, EVmiRNA2.0 has the following key improvements: (i) a substantial increase in EVs datasets, expanding from 462 to 7254, a 15-fold augmentation in data volume; (ii) a flexible online differential expression analysis module, allowing users to filter and compare samples based on a project, EV subtype, sample source, and disease stage/treatment; (iii) an enhanced miRNA search system featuring cross-tissue, cross-fluid, and cross-cell-type expression profiles, along with curated functional annotation, predicted target genes, and drug interaction data; (iv) useful download options for both raw expression data and analysis results. With comprehensive datasets and improved functions, EVmiRNA2.0 will serve as a useful and indispensable resource for exploring the expression and function of EV-derived miRNAs. It is freely accessible at https://guolab.wchscu.cn/EVmiRNA2.0/.

Graphical abstract



Introduction

Extracellular vesicles (EVs) are membrane-bound nanoparticles secreted by virtually all cell types and are widely present in body fluids and tissues [1–4]. They mediate intercellular communication by transferring diverse molecular cargo, including RNAs, proteins, and lipids [5, 6]. According to the MISEV2018 guidelines [7], EVs are operationally classified by size into small EVs (sEVs, <200 nm) and large EV

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(lEVs, >200 nm). Among all kinds of EV cargos, microRNAs (miRNAs) have been widely studied due to their important biological functions. Increasing evidence shows that EV-derived miRNAs contribute to cancer progression, immune modulation, and drug resistance [8–10]. For example, miR-146b-5p promotes leukemic transformation of hematopoietic cells [11], while exosomal miR-1290 and miR-375 were prognostic markers in castration-resistant prostate cancer [12]. These findings highlight EV miRNAs as promising biomarkers and therapeutic targets.

Several databases have been developed to catalog the molecular contents of EVs, such as Vesiclepedia [13], ExoCarta [14], EVpedia [15], and exoRBase [16]. These platforms provide valuable resources for EV research. However, they primarily focus on broad cargo types [proteins, messenger RNAs (mRNAs), lipids, etc.] and place limited emphasis on miRNA-specific expression profiles or functional analyses. While ExomiRHub [17] focuses specifically on EV-associated miRNAs, it is restricted to sEVs and offers limited dataset coverage. These databases lack comprehensive profiling of miRNA expression across both sEVs and lEVs, particularly considering disease context and standardized analysis pipelines.

In 2019, we developed EVmiRNA, a curated database of EV miRNA expression profiles [18], and subsequently constructed EVAtlas, which encompasses seven types of noncoding RNAs (ncRNAs) from over 2000 EV samples [19]. As the functional importance of EV miRNAs continues to emerge and sequencing data rapidly accumulates, there is a growing need for more comprehensive and powerful analytical platforms to support EV miRNA analysis. Here, we updated the EVmiRNA database to version 2.0 (EVmiRNA2.0) with >15-fold data volume. In addition, EVmiRNA2.0 introduces enhanced functionalities, including comprehensive expression profiling across diverse biological contexts, improved miRNA annotation, and broad support for data downloads. Together, EVmiRNA2.0 provides a valuable platform for systematically investigating EV miRNA expression patterns and their potential roles in diseases.

Data collection and processing

EV miRNA data collection and curation

We systematically retrieved publicly available human EV small RNA sequencing (smRNA-seq) datasets from the Gene Expression Omnibus, Sequence Read Archive, and European Nucleotide Archive databases. The search was conducted using the following query: ((extracellular vesicles) OR (exosomes) OR (microvesicles)) AND ((ncRNA) OR (miRNA)) AND ((Homo sapiens) OR (human)), yielding over 10 000 candidate samples. To ensure consistent annotation across different datasets, we manually curated the associated metadata and reviewed relevant publications in accordance with the MISEV2018 guidelines [7]. Each sample was classified as either sEV or lEV based on the reported isolation methods and descriptions of EV physical size. For each dataset, we curated detailed metadata, including EV subtype, biological source (tissue, body fluid, or cell line), disease context, and the specific EV isolation protocol. Additionally, the GRCh38 version of human reference genome and corresponding genome annotations were obtained from Ensembl [20] for downstream alignment and quantification.

Next, we performed quality control and quantification of the raw smRNA-seq data using the EVAtool [21] with default parameters except for the RNA mapping type, which was set to 'miRNA'. Briefly, sequencing reads were subjected to adapter trimming and quality filtering using fastp (v0.19.5) [22] and Trimmomatic (v0.39) [23]. Reads were removed if they contained multiple N bases (>5), exhibited abnormal lengths after adapter removal (>45 nt or < 15 nt), or had low average quality scores (mean ≤ 20). The quality of the processed reads, including the efficiency of adapter removal, was subsequently evaluated using FastQC (v0.11.9). High-quality clean reads were then aligned to GRCh38 reference genome using Bowtie2 (v2.4.2) [24]. Samples with a mapping ratio of clean reads <40% were excluded. Finally, 7254 samples from 371 projects were retained for further analysis. These covered 45 distinct sample sources (tissues, body fluids, cells) and 143 disease types across 10 biological systems.

Identification of differentially expressed miRNAs

Differential expression analysis was performed using an R script with the DESeq2 package [25], enabling the identification of miRNAs that are differentially expressed under user-defined grouping conditions. In addition, we provide several *P*-value adjustment methods for users to choose, including Benjamini–Hochberg (default), Benjamini–Yekutieli, Bonferroni, and Holm. Users can further select differentially expressed miRNAs of interest based on the adjusted *P*-value (<.10 by default) and |fold change| > 2 (default). Differential expression between each disease and its matched healthy samples was also assessed using DESeq2, with batch effects across projects corrected. miRNAs with FC ≥ 1.5 and P ≤.05 were considered differentially expressed.

Functional annotation and expression of miRNAs

A broad spectrum of annotation data related to human miRNAs from multiple sources was gathered to support comprehensive understanding of their characteristics, functions, and biological relevance. The details are as follows: (i) basic miRNA information was obtained from miRBase [26], including accession IDs, precursor names, chromosomal locations, and referenced literature; (ii) functional annotations were retrieved from NCBI GeneRIF, curated from supporting literature and linked to PubMed publications; (iii) experimentally validated miRNA–target interactions were obtained from TarBase v9.0 [27], including target genes, validation methods, regulation direction, confidence scores, and supporting references; (iv) drug–miRNA interactions were integrated from ncRNADrug [28]. In addition, miRNA expression data across pan-cancer datasets from the Cancer Genome Atlas (TCGA) project were obtained from the Gene Set Cancer Analysis (GSCA) platform [29]. For each EV source and cancer type, average miRNA expression levels were calculated to represent the expression profile across conditions.

Improved contents and new features

Overview of updated data for EV miRNAs

EVmiRNA2.0 integrates 7254 human EV smRNA-seq datasets, encompassing 371 projects, 45 sample sources, and 143 disease types (Fig. 1A and Table 1). To demonstrate the comprehensiveness of the data, we systematically com-

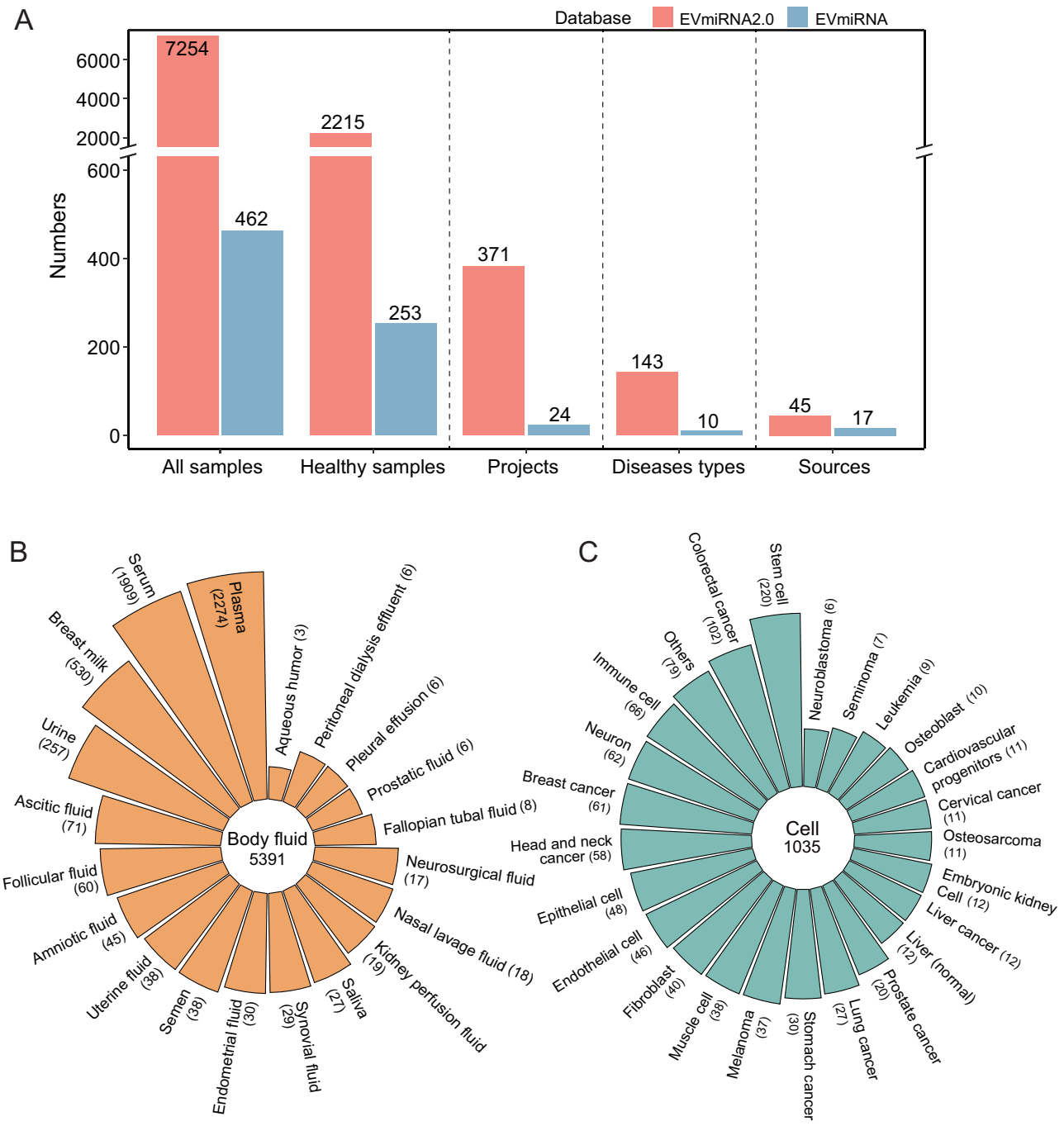

Figure 1. Overview of data in EVmiRNA2.0 and comparison with EVmiRNA. (**A**) Comparison of the numbers of all samples, healthy samples, projects, disease types, and sources in EVmiRNA2.0 and EVmiRNA. (**B**, **C**) The sample distributions of body fluid or cell-derived EV in EVmiRNA2.0. The number in the center of each circle represents the total number of samples, while each bar indicates the number of samples for the specific source. Categories containing fewer than five samples are represented as 'Others'.

pared EVmiRNA2.0 with existing EV miRNA databases (EVmiRNA, EVAtlas, ExomiRHub, and Vesiclepedia), all of which provide EV miRNA sample information (Table 1). The comparison considered multiple dimensions, including the number of projects, sample size, disease spectrum, functional annotations, and the availability of online differential expression analysis. EVmiRNA2.0 shows a 15-fold increase in sample size relative to the previous EVmiRNA database, along with a significant expansion of sample sources and disease coverage. These advancements establish EVmiRNA2.0 as the most comprehensive EV miRNA database currently available.

To better distinguish miRNA expression characteristics across different conditions, all EV samples are categorized into tissues, body fluids, and cells based on their sources. Among them, 5391 samples are derived from body fluids, and 1035 samples are derived from cells. Within the body fluid-derived sample category, sources with over 100 samples include plasma, serum, breast milk, and urine. Among them, plasma samples account for nearly 50% of all body fluid-

Table 1. Comparison of EVmiRNA2.0 with other EV databases including miRNA data

Databases	No. of Projects	No. of Samples	No. of disease types	EV types	Molecular types	Functional annotations	Differential expression analysis
EVmiRNA2.0	371	7254	143	sEV, lEV	miRNA	Basic Information, GeneRIF, Target Genes, Related Drugs	Yes
EVmiRNA	24	462	10	sEV, lEV	miRNA	Basic Information, GeneRIF, Target Genes, Related Drugs	No
EVAtlas	57	2030	~40	sEV, lEV	miRNA, tRNA, piRNA, rRNA, snRNA, snoRNA	Basic Information, GeneRIF, Target Genes, Related Drugs	No
ExomiRHub	154	4094	22	sEV	miRNA	Basic Information	Yes
Vesiclepedia	47	-	-	sEV, lEV	mRNA, miRNA, protein, lipid, metabolite, DNA	Basic Information	No

Table 2. Data summary of disease related EV samples in EVmiRNA2.0 database

Disease system	No. of projects	No. of samples	Tissue	Body fluid	Cell
Cardiovascular	12	249	161	166	0
Digestive	49	823	651	645	168
Endocrine	33	371	311	289	70
Genitourinary	42	719	468	558	57
Hematopoietic	10	186	176	167	16
Integumentary	9	78	71	36	30
Musculoskeletal	11	79	47	50	21
Nervous	24	683	657	657	11
Respiratory	19	136	116	100	27
Others	15	255	178	183	29

derived samples (Fig. 1B). Cell-derived samples include primary cells ($n = 528$) and cell lines ($n = 507$), with the former predominantly consisting of stem cells and the latter mainly comprising colorectal cancer cell lines (Fig. 1C). Furthermore, to support disease-focused analyses, EVmiRNA2.0 introduces a disease classification framework based on affected organ systems (Table 2). These include the cardiovascular, digestive, endocrine, genitourinary, hematopoietic, integumentary, musculoskeletal, nervous, and respiratory systems, as well as other conditions. This expanded classification improves user navigation and supports biologically meaningful comparisons across diverse clinical contexts.

New differential expression analysis function

To efficiently investigate different patterns of EV-derived miRNAs expression across diverse biological conditions, EVmiRNA2.0 incorporates a one-stop and user-friendly module for differential expression analysis. Users can initiate the differential analysis in two ways: either from the differential analysis page by clicking the "Analysis" button in front of each project on the "Analysis" page, or directly from the "Project Details" page by clicking the "Differential Expression Analysis" button when browsing a specific project/dataset.

The first step in differential expression analysis requires users to assign samples in a project into two groups. By default, these groups are labeled as "Control" and "Case". Next, users can also customize the analysis by selecting a *P*-value correction method, such as Benjamini–Hochberg (the default), and by adjusting significance thresholds. By default, the adjusted *P*-value threshold is set to <.10 and the |fold change| > 2, but users can adjust these parameters as needed. Upon task submission and completion of the analysis, it would generate a series of detailed visualizations and textual summaries, with all results available for download. These include an interactive volcano plot, a heatmap of differentially expressed miRNAs, and a comprehensive table of differential analysis results. This module empowers users to efficiently discover condition-associated EV miRNA signatures and supports further data-driven exploration.

Added interfaces for presenting EV miRNA expression profiles across diverse sources

The expression levels of miRNAs in EVs derived from different sources exhibit significant variability, which may be associated with their critical regulatory roles in disease processes [30]. As a newly introduced feature in EVmiRNA2.0, the database provides detailed average expression profiles for each miRNA across three biologically distinct EV source types: tissues, body fluids, and cells. This enhancement allows users not only to investigate the expression levels of individual miRNAs under specific conditions, but also to perform cross-source comparisons to uncover expression distribution patterns. Such comparative analysis is valuable for understanding the context-dependent roles of EV-associated miRNAs in physiological and pathological processes. Detailed expression distributions are available through the "miRNA" module of the database.

Expanded data access with enhanced flexibility

To support flexible data access and facilitate downstream analyses, EVmiRNA2.0 provides significantly enhanced download capabilities. In EVmiRNA2.0, the dedicated "Download" module grants access to curated metadata and expression data across all projects, enabling users to efficiently retrieve the datasets. It provides two types of miRNA expression data: Reads Per Milloin (RPM) values and raw count values. The metadata include sample IDs, sample sources, disease types and statuses, EV isolation methods, and detailed project descriptions. In addition, we provide a downloadable table of filtered differentially expressed miRNAs, including $\log_2$FC, *P*-value, P-adj, and the corresponding disease type in the "Download" module. Further, users can also download a wide range of searching and analysis-related results. These

include routinely retrieved results and graphical outputs, such as project-specific heatmaps of miRNA expression and expression data tables. Moreover, analysis results such as clustered heatmaps and detailed result tables of differentially expressed miRNAs are also provided. All these resources are available for download on their corresponding pages, enabling users to efficiently obtain data relevant to their analyses.

Database organization and web interface

The EVmiRNA2.0 database employs a modern frontend-backend decoupled architecture to enable efficient access, retrieval, analysis, and visualization of EV-derived miRNA sequencing data. The technology stack includes MongoDB, Flask, Vue.js, ECharts, Plotly, and Element Plus. The backend is primarily built with Flask and MongoDB, while the frontend leverages Vue.js along with ECharts and Plotly for interactive data visualization. In addition, the database architecture was optimized by employing MongoDB's GridFS to store large-scale data tables such as miRNA expression profiles and miRNA–target predictions. This strategy significantly improves query efficiency, reduces memory consumption, and enhances overall system performance.

EVmiRNA2.0 is freely accessible at https://guolab.wchscu.cn/EVmiRNA2.0/. The homepage features a centralized search bar that allows users to perform global searches by miRNA names. Additionally, three core functional modules are placed at the bottom of the homepage for quick access and efficient data retrieval. On the "Browse" page, users can explore EV sample sources across datasets, organized into the four major categories of tissue, body fluid, cell, and disease (Fig. 2A). The disease category is further divided into diseases of different organ systems. Thus it provides more comprehensive annotations of disease-derived EVs, enabling users to filter and access datasets by specific disease types. Furthermore, users may investigate specific information. For example, selecting the "Blood" icon allows users to browse all datasets derived from blood-related sources, such as serum and plasma. Upon selecting a specific project, users are presented with detailed project-level information, including the EV isolation method, a heatmap of the top 40 miRNAs, and individual miRNA expression levels (Fig. 2B).

In EVmiRNA2.0, a differential expression analysis function is embedded within the newly added "Analysis" module, providing an interactive platform for exploring miRNA expression differences under various conditions. Users can perform customized analyses either by selecting samples of interest during browsing or by directly navigating to the "Analysis" module. To begin a differential expression analysis, users must first select a dataset and designate two sample groups with default names. Results include an interactive volcano plot, a heatmap of differentially expressed miRNAs, and a downloadable result table (Fig. 2C). For example, differential expression analysis in project PRJNA589528, comparing hepatocellular carcinoma (HCC) samples to healthy controls, identified 18 upregulated and 17 downregulated miRNAs. Notably, hsa-miR-526b-5p, which is upregulated in HCC samples, has been reported to play a role in HCC progression [31]. Previous studies have shown that LINC01343 promotes HCC development by targeting miR-526b-5p and enhancing the expression of *ROBO1* [32].

On the "miRNA" page, users can search for any miRNA of interest and access a dedicated profile page that provides basic information, expression patterns across different EV sources and disease conditions. More importantly, the page also integrates essential information, including functional annotations of miRNAs, expression profiles of miRNAs in TCGA pan-cancer data, experimentally validated target genes, and miRNA-related drug information (Fig. 2D). These resources provide insights into the biological roles of miRNAs in various physiological and pathological processes.

Summary and future perspectives

In this study, we present EVmiRNA2.0, a significantly expanded and functionally enhanced database for exploring miRNA expression profiles in human EVs. Compared to the previous version, EVmiRNA2.0 incorporates significantly expanded (15-fold) datasets, including 7254 EVs smRNA-seq samples from 371 projects, covering 45 sample sources and 143 disease types. Moreover, EVmiRNA2.0 provides improved annotation, incorporating functional information from GeneRIF, validated miRNA–target interactions from TarBase, and drug-related associations from ncRNADrug. The database also introduces new analysis functions, including an integrated differential expression analysis module and comparative expression profiling across various tissues, body fluids, and cells. The web interface has been optimized to support interactive data visualization and flexible download of both raw data and analytical results. Overall, EVmiRNA2.0 offers a valuable and user-friendly platform for studying EV-associated miRNAs in health and disease. We believe it will be a useful and popular resource, as well as the previous version.

While EVmiRNA2.0 has collected nearly all publicly available EV miRNA data, it is not yet comprehensive. Going forward, we aim to both expand the number of collected datasets and build upon the functionality of EVmiRNA2.0. Specifically, we plan to (i) incorporate EV miRNA expression data from additional species to broaden its applicability; (ii) expand analytical tools, including pathway enrichment analysis of miRNA target genes; and (iii) improve visualization and user interaction to facilitate data exploration. Overall, both EVmiRNA and EVmiRNA2.0 will be regularly updated and maintained to ensure they remain valuable resources for EV miRNA research.

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Author contributions: Gui-Yan Xie and Dandan Song collected the data and wrote the manuscript. Gui-Yan Xie, Dandan Song, Tao Luo, and Yu Liao constructed the database. An-Yuan Guo and Qian Lei supervised the study and revised the manuscript.

Conflict of interest

None declared.

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Figure 2. The EVmiRNA2.0 web interface and its main modules. (**A**) Browse: Allows categorical filtering (tissue, body fluid, cell type, or disease) via the left panel. Selecting a category displays project images; Clicking an image shows detailed clinical and sample information. (**B**) Project details: Enables flexible filtering by project, EV type, source, condition, or disease, and presents project metadata along with a heatmap of the top 40 expressed miRNAs. (**C**) Analysis: Supports sample selection and parameter configuration for generating visualized differential expression results. (**D**) miRNA annotation: Provides basic information and functional annotations of miRNAs.

Data availability

EVmiRNA2.0 is a database with online and open access, available at https://guolab.wchscu.cn/EVmiRNA2.0/. All metadata, expression profiles, and differential expression analysis data across different diseases are freely available at https://guolab.wchscu.cn/EVmiRNA2.0/#/download/.

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