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SHORT COMMUNICATION

EV-COMM: A database of interspecies and intercellular interactions mediated by extracellular vesicles

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Abstract

Intra- and inter-organismal interactions play a crucial role in the maintenance and function of individuals, as well as communities. Extracellular vesicles (EVs) have been identified as effective mediators for the communication both within and between species. They can carry and transport molecular cargoes to transmit biological messages. Several databases (ExoBCD, ExoCarta, EVpedia, EV-TRACK, Vesiclepedia) complied the cargoes information including DNA, RNA, protein, lipid and metabolite associated with EVs. Databases that refer to the complete records on both donor and recipient information are warranted to facilitate the understanding of the interaction across cells and species. In this study, we developed a database that compiled the records equipped with a structured process of EV-mediated interaction. The sources of donor and recipient were classified by cell type, tissues/organs and species, thus providing an extended knowledge of cell-cell, species-species interaction. The isolation and identification methods were presented for assessing the quality of EVs. Information on functional cargoes was included, where microRNA was linked to a prediction server to broaden its potential effects. Physiological and pathological context was marked to show the environment where EVs functioned. At present, a total of 1481 data records in our database, including 971 cell-cell interactions belonging to more than 40 different tissues/organs, and 510 cross-species records. The database provides a web interface to browse, search, visualize and download the interaction records. Users can search for interactions by selecting the context of interest or specific cells/species types, as well as functional cargoes. To the best of our knowledge, the database is the first comprehensive database focusing on interactions between donor and recipient cells or species mediated by EVs, serving as a convenient tool to explore and validate interactions. The Database, shorten as EV-COMM (EV mediated communication) is freely available at http://sdc.iue.ac.cn/evs/list/ and will be continuously updated.

KEYWORDS
cross-kingdom interaction, database, extracellular vesicles, intercellular communication, miRNA

Jingyu Chen and Jing-Jing Lin contributed equally to the paper.

1 | INTRODUCTION

Frequent communication occurs between intra and interspecies (He et al., 2023; Straight & Kolter, 2009; Waters & Bassler, 2005). The communication is key for the synchronisation of various cells in an organism, as well as the coordination of individuals within a community. For instance, interactions between different species of microbiota can modify the susceptibility of members within a community to antibiotics. (Bottery et al., 2022; Radlinski et al., 2017). There are various ways of interactions. At the organism level, competition, predation, mutualism, commensalism and parasitism were well-known types of inter-species interaction. At the molecular level, we have seen large numbers of signalling molecules transported between single-cell organisms, as well as within cells in multicellular organisms. The exchange of molecules, including DNA, proteins, lipids, synchronises the behaviour of cells, and thus largely influences the entire population. Intercellular communication can be mediated either through direct cell-cell contact or transfer of secreted molecules. In the last two decades, a new mechanism for intercellular communication has emerged that involves intercellular transfer by extracellular vesicles (EVs) (Raposo & Stoorvogel, 2013).

EVs are double-layered phospholipid membrane vesicles that can be produced by a variety of organisms from prokaryotes to higher eukaryotes and plants (Keshtkar et al., 2018; Liu et al., 2019; Raposo & Stoorvogel, 2013; Yáñez-Mó et al., 2015). According to the International Society for Extracellular Vesicles (ISEV) guidelines, there are various nomenclatures of EVs (Théry et al., 2018). EVs contain a diverse array of bioactive cargoes, including proteins, nucleic acids (mRNA, microRNA, rRNA and tRNA), lipids and other metabolites (Liu et al., 2019; Maacha et al., 2019). A growing body of research has revealed that EVs are important mediators for intercellular communication (van Niel et al., 2022). EVs show the capacity to deliver cargoes between cells and act as signalling vehicles in the physiological processes, as well as pathological developments (van Niel et al., 2018). EVs can play a mediating role between different species as well. For instance, EVs derived from human airway cells can transport Let-7b-5p to *Pseudomonas aeruginosa*, thereby suppressing the expression of crucial antibiotic-resistance and biofilm genes, ultimately enhancing its antibiotic resistance (Koeppen et al., 2021). This cross-kingdom phenomenon has also been observed in interactions between plantae and animalia (Cao et al., 2019).

Due to the wide diversity of EVs-harbouring molecules currently, several databases have been developed to uniformise and provide the lists of EVs cargoes, including protein, lipid, RNA and miRNA. EVpedia provides high-throughput datasets of vesicular components (proteins, mRNAs, miRNAs and lipids) present on prokaryotic, non-mammalian eukaryotic and mammalian EVs (Kim et al., 2013). EV-ADD compiles EV-DNA datasets derived from human biofluid samples and contains validated experimental details thorough manual curation (Tsering et al., 2022). Most of EVs databases only focus on the collection of the bioactive molecules in EVs, but lack the collection of the information about a complete chain on the mediating roles of EVs. To fill this gap, a database, which describes the dynamic process of intercellular and intraspecific communication mediated by EVs, has been developed. Information on donor-recipient pairs, functional cargoes and phenotype was recorded in the database. Detailed data module information is shown in Figure 1. The present database would provide a chain of knowledge on the donors, recipients, EVs, cargoes, effector molecules, as well as the effect. EV-COMM can serve as a convenient tool for exploring and validating interactions mediated by vesicles. With the increasing availability of more data from the EVs communities, the database will be expanded.

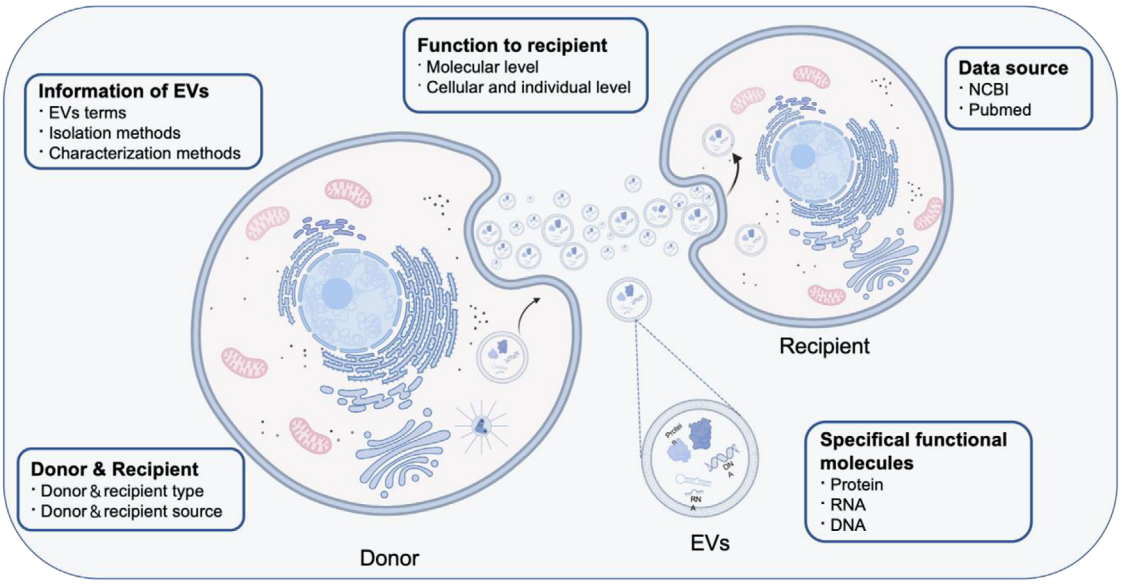


FIGURE 1 An overview of manually collated information in database.

2 | METHODS

2.1 | Data collection

We searched the NCBI PubMed by a series of keywords regarding the title and abstract, including: (1) EV-mediated intercellular interactions: "((extracellular vesicles) OR (exosomes) OR (microvesicles)) AND (intercellular)"; (2) EV-mediated interspecies interactions: "((extracellular vesicles) OR (exosomes) OR (microvesicles)) AND ((cross species) OR (interspecies) OR (interkingdom))." It is worth noting that various species terms such as "((plant) OR (fruit))," "(fungi)," "(bacteria)," "(parasite)," "((algae) OR (microalgae))," "(mycoplasma)," "((food) OR (milk))" are combined with the search term "((extracellular vesicles) OR (exosomes) OR (microvesicles))" for additional searches in search engines. The literature search was limited to the period from 1 January 2000, to 1 July 2023. We obtained a total of 7032 articles, with 4755 articles related to intercellular interactions and 2277 articles related to interspecies interactions. Out of the 7032 articles retrieved from the searching, a total of 2916 articles were excluded due to their classification as reviews. The remaining articles were manually screened based on their titles and abstracts, excluding those without access permission or unrelated to the topic. Information on donors and recipients of EVs, functional cargoes, as well as the impact on the recipients was clearly presented in articles. Noted that the isolation and characterisation of EVs should meet the basic criteria proposed by ISEV2018 (Théry et al., 2018). Eventually, we obtained 1492 articles relevant to the subject. The process is shown in Figure 2a. Due to the rapid development of EV-mediated information exchange research in the past five years, accounting for 75.24% of the total volume of screened articles, we have chosen to manually extract data from publications between 1 July 2018 and 1 July 2023 as our primary focus (Figure 2b). Currently, the database contains a total of 1481 records from 970 publications. In future, regular updates of the website will be carried out.

The critical information contains EVs isolation methods, EVs characterisation strategy, the context of interaction (in physiological or pathological condition), donors and recipients of EVs, specific functional molecules in EVs, downstream pathways related to the EVs containing functional molecules, as well as the phenotype in the recipient. Next, the information on donors/recipients was extended. The source tissue, organ, as well as species of cells were obtained from American type culture collection (ATCC). Refer to Table S1 for the unified nomenclature of cells. For individual species, the taxonomy information was obtained from the national centre for biotechnology information (NCBI).

2.2 | Website design

The EV-COMM website is hosted on a cloud-based server. It was built using SpringBoot which is written in the JAVA programming language and popular for constructing data websites and services. MySQL serves as the database to store EV-COMM information in the backend. The connection between the frontend and the backend is through Restful API (an architectural style that utilises HTTP requests to access or consume data through application program interfaces). The website provides a graph view for describing the relationship between donor and recipient with label of cargoes in EVs using EChart (a popular JavaScript library for drawing charts). It has a user-friendly graphical search menu, and search results are shown in a table while the graph view is changing simultaneously with each response.

3 | RESULTS

3.1 | Data statistics

3.1.1 | Intercellular interaction

Up to July 2023, we have collected a total of 1481 records on EV-mediated interactions, with 971 pairs on intercellular interactions and 510 records on interspecies interactions. These 971 records encompass 273 types of donor cells and 297 types of recipient cells, which are attributed to 46 different tissues/organs covering the major organ systems, including the digestive, nervous, circulatory, immune and reproductive systems. The highest number of EV donors are blood (160 records), followed by bone (115 records) and brain (82 records). The top 3 EV-acting recipient tissues/organs are brain (98 records), blood (92 records) and bone (87 records) (Figure 3a). More frequently, EV-mediated cell pairs of interactions are within the same tissues/organs, with 59 interactions between cells in the brain, 47 interactions within the liver and 38 interactions inside the bone. EVs also mediate cellular interactions across tissues/organs, including blood-umbilical cord, blood-lung, ascites-bone (Figure 3b). A multiple interaction network and the heatmap were developed for researchers to analyse and visualise these complex relationships (Figure 3c,d). The largest number of blood-umbilical cord and blood-lung interactions were recorded, respectively with 19 and 17 records. This suggests that EVs are remotely transported to other tissues/organs in the body via blood for intercellular communication

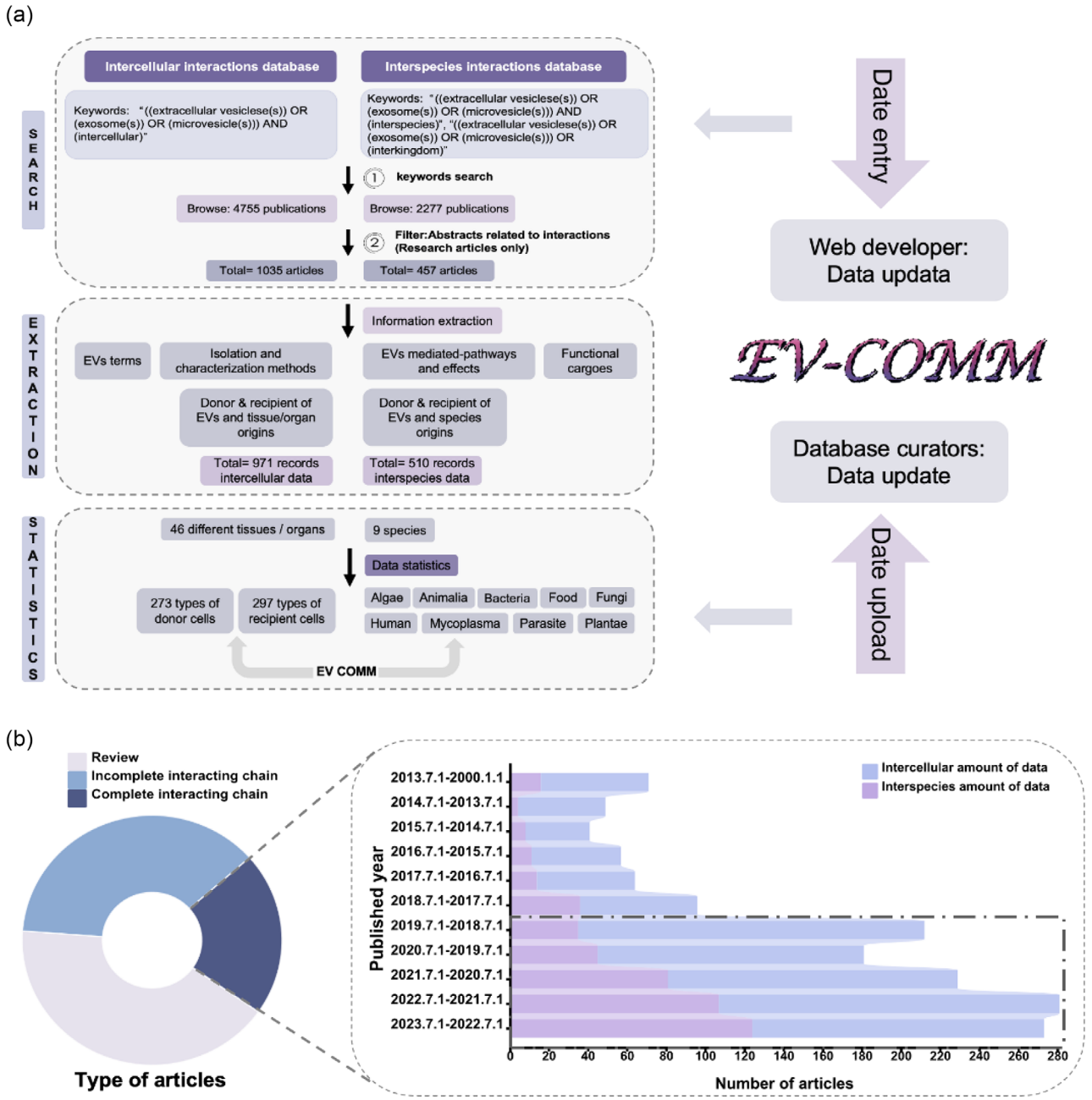


FIGURE 2 Summarised schematic workflow of EV-COMM database. (a) The workflow is divided into three steps: (1) Literature on vesicle interaction was searched and articles meeting the criteria were reviewed. (2) Extraction of key information, including donor and recipient information, functional cargoes, EVs mediated-pathways and effects, EVs terms, isolation and characterisation methods. (3) Data statistics and uploading EV-mediated interaction data to EV-COMM. (b) The article information has been recorded in EV-COMM database. Through keyword search, a total of 7032 articles were retrieved, which focus on intercellular and interspecies interactions mediated by EVs. By conducting manual review of abstracts, a total of 1492 articles with complete interaction chain were obtained. In a limited timeframe, we have recorded nearly 5 years' worth of articles with complete interacting chain. The coverage of articles in the EV-COMM database amounts to 75% of the total retrieved articles pertaining to EV-mediated interactions.

(Wang et al., 2021; Yang et al., 2022; Yuan et al., 2019). Regarding specific cell types, the communication occurred between various types of cells, including immune cells, epithelial cells, mesenchymal cells and fibre cells. Frequent interactions were also observed between normal cells and cancer cells. The diverse types of interacting cells may be related to the membrane structure of EVs, which have primitive cell surface receptors/ligands and have the potential to selectively interact with specific target cells (Zhang et al., 2012).

EV-mediated interactions between cells are associated with the development of diseases. A total of 64 disease-related datasets was collected in the database, including spinal cord injury (SCI), breast cancer (BC), sepsis, atherosclerosis (AS), colorectal cancer (CRC) and osteoarthritis (OA) and so on. And an increasing number of studies have reported that stromal cell-derived

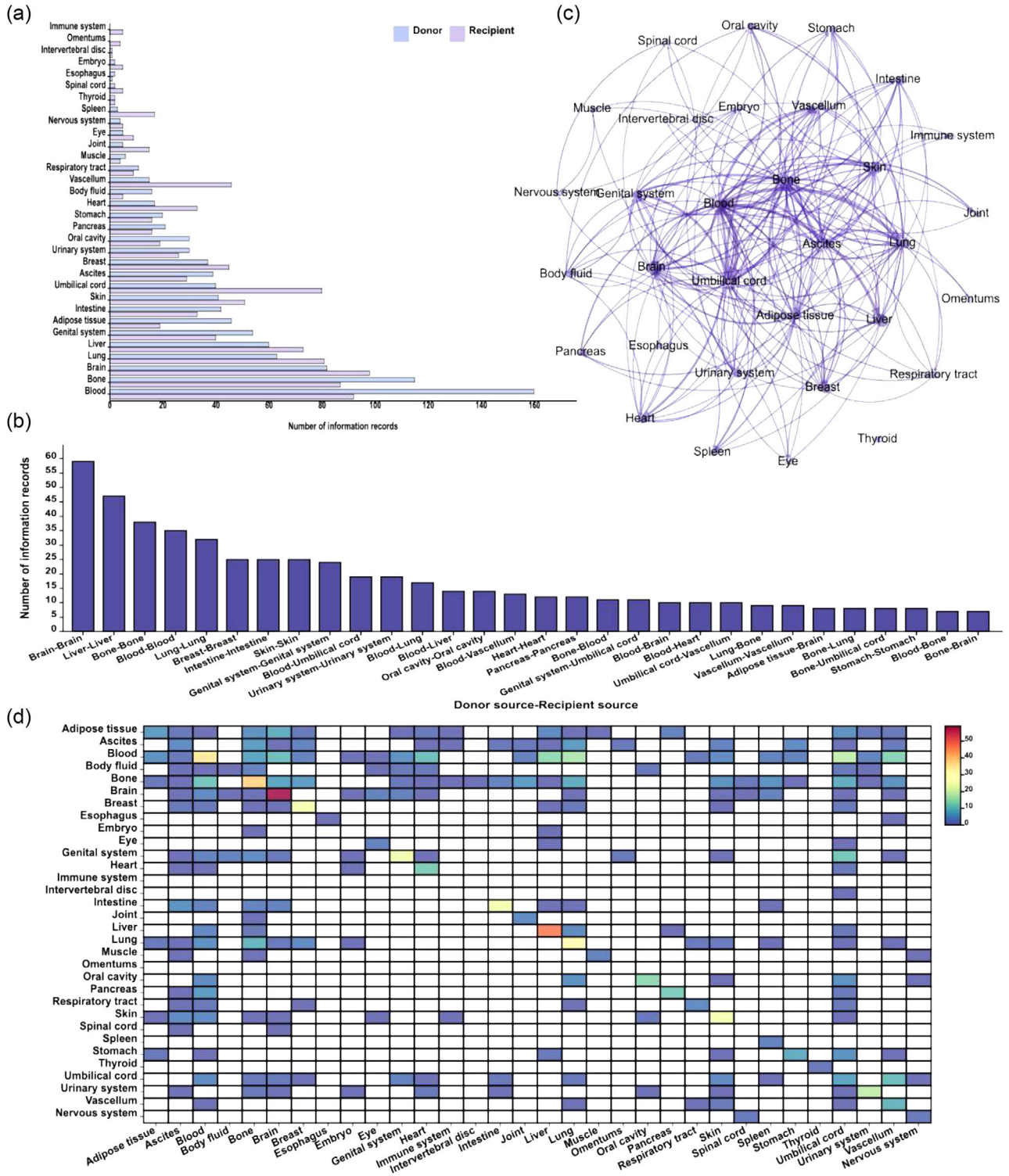


FIGURE 3 Intercellular interactions mediated by EVs. (a) Tissues/organs distribution of donor and recipient. (b) The first 30 interactions between donor and recipient source tissues/organs. (c) Network interaction diagrams among tissues/organs. The network data in Gephi software comprises of nodes representing various tissues/organs and edges denoting the interactions among these tissues/organs, and the thickness of edges indicates the number of information records supporting the interaction. (d) Heatmap of intercellular interactions with the x-axis representing tissues/organs to which the receptors belong, and the y-axis representing issues/organs to which the donors belong.

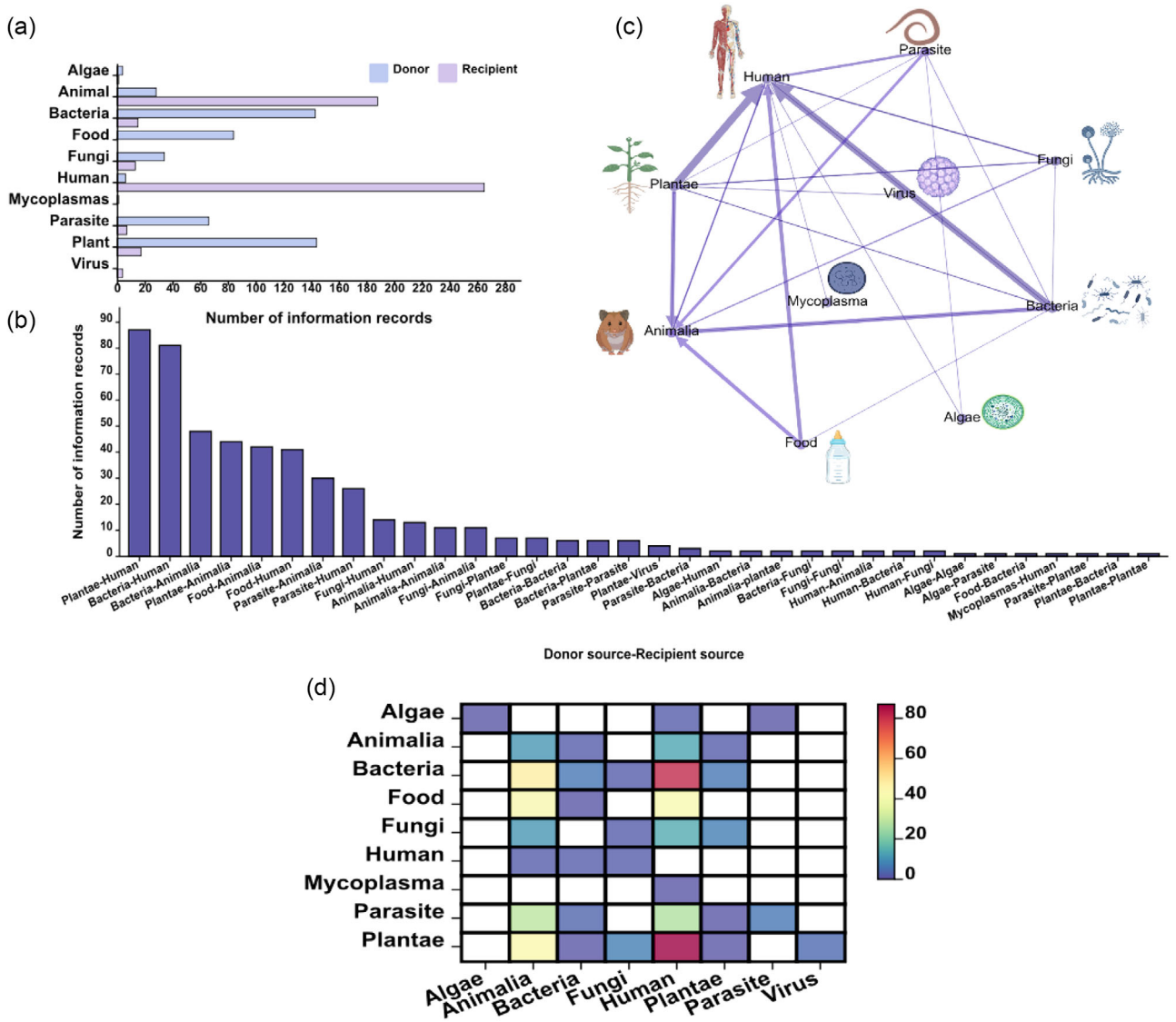


FIGURE 4 Interspecies interactions mediated by EVs. (a) Species distribution of donor and recipient. (b) Interspecies interactions mediated by EVs. (c) Network interaction diagrams among species. (d) Heap map of interspecies interactions.

EVs play a key role in regulating tumorigenesis and tumour microenvironment (TME) remodelling (Fu et al., 2022). This database facilitates the interactive exploration of intercellular communication mediated through EVs in a specific physiological context, such as diseases or certain stimulus.

3.1.2 | Interspecies interaction

A total of 510 entries have been collected in the cross-species data. The interaction can cross almost all the kingdoms, including bacteria, fungi, protista, plantae and animalia. Bacteria include pathogenic bacteria such as *Staphylococcus aureus, Aspergillus flavus* and probiotics such as lactic acid bacteria. In fungi, there are many microorganisms from the *Candida* genus, such as *Candida glabrata*, *Candida parapsilosis* and *Candida tropicalis*, as well as *Phellinus linteus*. The animal kingdom includes the phylum Arthropoda (such as mosquitoes), the phylum Mollusca, the phylum Chordata (such as mice, guinea pigs and duck). Among them, the largest number of donors is plantae (144 records), followed by 143 from bacteria and 84 from food. The largest number of recipients is human with 265 records (Figure 4a). The highest number of records is plantae-human interaction with 87 records, followed by bacteria-human interaction with 81 records and bacteria-animalia interaction with 48 records (Figure 4b). In order to clearly show the interaction between species, we also have drawn a network interaction diagram and a heatmap between species (Figure 4c,d). For example, plant-derived vesicle-like nanoparticles (PDVLNs) transport microRNAs to humans, and

regulate the expression of human genes involving in anti-tumour (Cao et al., 2019), protection of the vascular system (De Robertis et al., 2020), stimulation of nerve differentiation (Xu et al., 2021) and immune regulation (Cao et al., 2019). EVs derived from bacteria can promote skin inflammation similar to atopic dermatitis (Hong et al., 2011), lung injury (Kim et al., 2012) and promote tumour metastasis in lung cancer (Dinh et al., 2020). EVs can serve as a new mode of transportation, mediating cross-species interactions through the delivery of cargoes (Zhang et al., 2012).

3.1.3 | Functional cargoes

EVs exert their biological functions by transferring various types of bioactive cargoes including DNA, mRNA, miRNA, protein and lipid to their target cells through phagocytosis or endocytosis, which in turn mediate cell-cell communications (Huang & Xu, 2021). The functional contents recorded in the database mainly consist of RNA (607 records), Protein (314 records), lipid (17 records) and DNA (7 records). Most of the RNA are miRNA, with a total of 507 records. MiRNA is a small non-coding RNA molecule that regulates gene expression by binding to the 3′-untranslated region of the target mRNA, leading to mRNA degradation and translation inhibition (Huang & Xu, 2021), or modulating the expression of downstream molecules (Liu et al., 2019; Tang et al., 2023). EVs from different sources contain different miRNAs, and environmental changes can alter the composition of cell-derived EV miRNAs, which in turn participate in adaptive responses to metabolic stress (Huang & Xu, 2021). In addition to miRNAs, mRNA and long non-coding RNA (lncRNA) in EVs are also found to mediate intercellular and interspecies interactions. Protein cargoes can also be transported within cells or across tissues delivered by EVs (Han et al., 2021). EV-associated DNA has gradually become a new molecular biomarker and functional medium widely studied in various physiological and pathological states (Malkin & Bratman, 2020).

3.1.4 | EVs mediated-pathways and effects

Interestingly, after functional molecules enter the recipient, they can affect the mRNA, miRNA and protein levels, thereby affecting the role of the recipients. The affected molecules in recipients were recorded. Functional cargoes in EVs can affect a variety of pathways in recipients. This elicits diverse effects on recipient cells, either promoting or inhibiting cell proliferation, migration and invasion (Fu et al., 2022; Li et al., 2019), or promoting/inhibiting cellular inflammatory responses (Qin et al., 2021; Tang et al., 2023) and immune responses (Zhou et al., 2021); Among species, EVs mediate positive or negative effects of donor species on recipient species, such as pathogenic bacteria causing harm to the host (Hong et al., 2011) and probiotics benefiting the host (Shi et al., 2021).

3.1.5 | EVs terms, isolation and characterisation methods

In the latest recommendation from the ISEV, EV terms are distinguished based on their physical properties. They can be categorised into different subtypes based on their size or biogenesis mode, that is, exosomes (30–150 nm), microvesicles (100–1000 nm) and apoptotic bodies (1000 nm–5 μm). In the absence of specific markers and overlapping sizes, the term "small EVs" (sEVs) applies to both exosomes and microvesicles up to 200 nm in size and "medium and/or large EVs" (m/lEVs) refers to >200 nm in size (Rana et al., 2022; Théry et al., 2018). Different species use various names for extracellular vesicles (EVs), including EVs-like nanovesicles, exosome-like extracellular vesicles and exosome-like nanovesicles (ENVs). Due to the different definitions of EVs in different articles, we retained the naming of vesicles in the article. Accordingly, the database records a total of 44 terms related to EVs based on the references cited. Among these terms, "extracellular vesicles" has the highest frequency, accounting for approximately 41.26% of all terms, followed by "exosomes" with 38.71%.

Isolation of EVs refers to the separation of EVs from other non-EV components of the matrix (e.g., conditioned medium, biofluid, tissue). According to the ISEV guidelines (Théry et al., 2018), highly purified EVs are required to attribute functions or biomarkers to vesicles. At present, many methods have been developed for EVs isolation based on the characteristics of size, density, charge and affinity. Our database contains methods (Figure 5), with most studies utilising only one method. Some studies, however, have employed multiple isolation methods in combination to achieve better specificity of EVs or EVs subtype separation. It can be seen from the data statistics that ultracentrifugation is the most used and classic isolation and concentration technique for EVs, chosen by 61.28% of the users. The next most commonly used techniques are the commercial extraction kit and density gradient centrifugation, which is consistent with the results reported by ISEV (Théry et al., 2018). To be noted, we preserved the original brand names of the EV extraction kits in the database. But for statistical purposes, they are uniformly referred to as "Commercial kits" in Figure 5.

The morphology and purity of the isolated EVs were generally observed by transmission electron microscope (TEM). Particle characterisation can be measured using nanoparticle tracking analysis (NTA), dynamic light scattering (DLS) for small EVs and

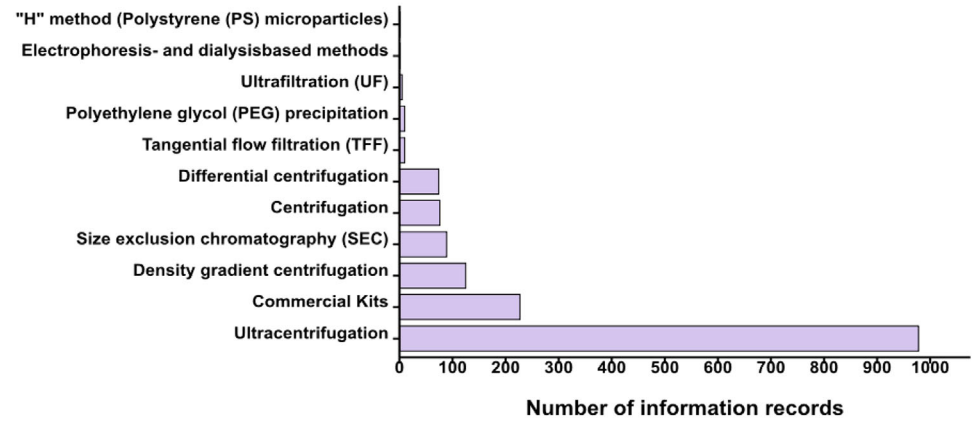


FIGURE 5 Statistics of EV-related information in the database. Data summary of various EVs purification techniques.

standard or high-resolution flow cytometry for large or small EVs, respectively. In addition, resistive pulse sensing (RPS) is used for size determination, depending on the pore size (Théry et al., 2018). Furthermore, EV markers are selected for EV characterisation, which generally involves transmembrane or GPI-anchored proteins located on the outer membrane of prokaryotic cells, as well as the plasma membrane and/or endosome of eukaryotic cells. Detecting their presence helps to evaluate the purity of EV preparations. The method for characterising surface proteins of EV markers is recorded as positive or negative, with 66.10% of articles using surface protein characterisation of EVs.

3.2 | Applications

The database provides information on the interactions between cells/species through EVs, answering the questions at three levels: which cells/species can interact with other cells/species through EVs? Which EVs cargoes are involved in the interactions? And what effects do the interactions have on the recipients? We can use an interactive search to understand the information on the interactions between cells/species through EVs. Specifically, we can learn what type of tissues, organs and species the vesicle donors and recipients come from respectively. For example, EVs derived from *Staphylococcus aureus* can promote skin inflammation similar to atopic dermatitis (Hong et al., 2011) and lung injury (Kim et al., 2012). Milk-derived EVs can also affect primary cancer in mice (Samuel et al., 2021).

EVs mainly exert functions through their contents, and we provide information on the contents that play a role in cells/species interactions, target molecules, downstream pathways and endpoint effects. Currently, a number of sophisticated bioinformatics approaches are available to perform effective prediction of miRNA target sites (Akhtar et al., 2019). Accordingly, there are many online websites as tools for miRNA prediction. TargetScan (McGeary et al., 2019) is a web-based tool primarily used for predicting the biological targets of miRNA. It scans for the presence of conserved 8mer, 7mer and 6mer sites that match the seed region of each miRNA. MiRDB (Wong & Wang, 2015) is also an online database frequently used for miRNA target prediction and functional annotation. Since miRNA is the main type of functional contents, we then provide additional links for predicting the target genes of the specific miRNA, further enriching the knowledge on the potential functions of EVs carrying miRNAs. For example, miR-210-5p derived from subchondral bone osteoblasts exosomes plays a role in the interaction between recipient and donor cells. Here, we can obtain the predicted target genes of miR-210-5p by an external link to a corresponding miRNA prediction website such as miRDB. Predicting miRNA target genes helps to determine the specific mechanism of miRNA action. It is also possible to speculate the potential impact on the development of another phenotype through a certain target gene pathway.

As heterogenous particles surrounding by a variety of co-existing particles, the quality of isolated EVs is key to the studies. Only by ensuring the quality of EVs isolation and identification can the credibility and reproducibility of the results be guaranteed (Lötvall et al., 2014). According to the guidelines recommended by ISEV, we extracted the information about the isolation and identification of EVs from the references. The isolation methods of EVs are clearly presented. The recruitment of identification methods including biophysical identification, quantitative detection, positive and negative biochemical markers authentication are depicted. This information contributes to a comprehensive evaluation of the quality of EVs. Users can check whether, and to what degree the specific references obtain the EVs. Data records in which all three EV Identification methods are implemented indicate higher quality of extracted vesicles, resulting in more robust and reliable results.

3.3 | Web interface and case study

3.3.1 | Web interface

Users can access the data through a free and open-source document-oriented database (http://sdc.iue.ac.cn/evs/list/). The database comprised three main functional modules: interspecies interactions, intercellular communication and miRNA prediction. In the search page, users can freely search for the donor source, recipient source and cargo type of EVs at both intercellular and interspecies levels (Figure 6a). When using the system, users have the option to not only search using a single filter box, but also search simultaneously using multiple filter boxes. This means that users can select multiple filter criteria on the same page in order to more accurately refine the content they are interested in. By utilising multiple filter boxes at the same time, users can interact with and compare data across different categories. To achieve consistency in the hierarchical structure of terminology, we stipulate that users need to initially specify their interest in either intracellular or interspecies interactions. After making this initial selection, they can proceed to filter the donors and recipients. The search yielded a graph wherein nodes represent tissues/organs/species origins and edges represent interactions, with the direction of edges indicating the direction of EVs transmission. Interactive features have been implemented on the website. Users can zoom in and out of the graph by using the mouse scroll wheel, as well as click and drag to adjust the position of the network graph within the display window. When browsing search results, users can obtain detailed information about the complete process of EV-mediated interactions by clicking on the edges. In addition to the graph, you also can obtain the data table by clicking on "data list" button. For detailed data, click the "Details" button. It is important to note that in the information list, "/" indicates that the information is not mentioned in the original text. All the data in the database can be downloaded into a spreadsheet for free. Users simply need to click the "Download" button located on the right-hand side of the page. This database can switch between English and Chinese.

When the EVs content type is miRNA, a hyper link present as "miRNA prediction" will be shown in the detailed table (Figure 6b). This can navigate to the predicted target genes of the miRNA, including the sequence, distribution and other relevant information. This feature enables the integration of EVs with the predictions of miRNA target genes, providing valuable insights into the regulatory mechanisms of EV-mediated gene expression control. Furthermore, we display data information regarding the distribution of tissues/organs and vesicle isolation of donors and recipients in the database on the statistics page, where users can click on "Statistics" to view relevant statistical charts. A "User Manual" is available in the navigation bar under "Help" for users to access detailed instructions on how to navigate and utilise the website (Figure 6a). Users have the option to access the "Upload Data" page, where they can conveniently download a standardised form. Subsequently, they are able to input the published data into the designated table and proceed to upload the fully completed form. We will review your submission and send you an email when it is approved and the data is uploaded.

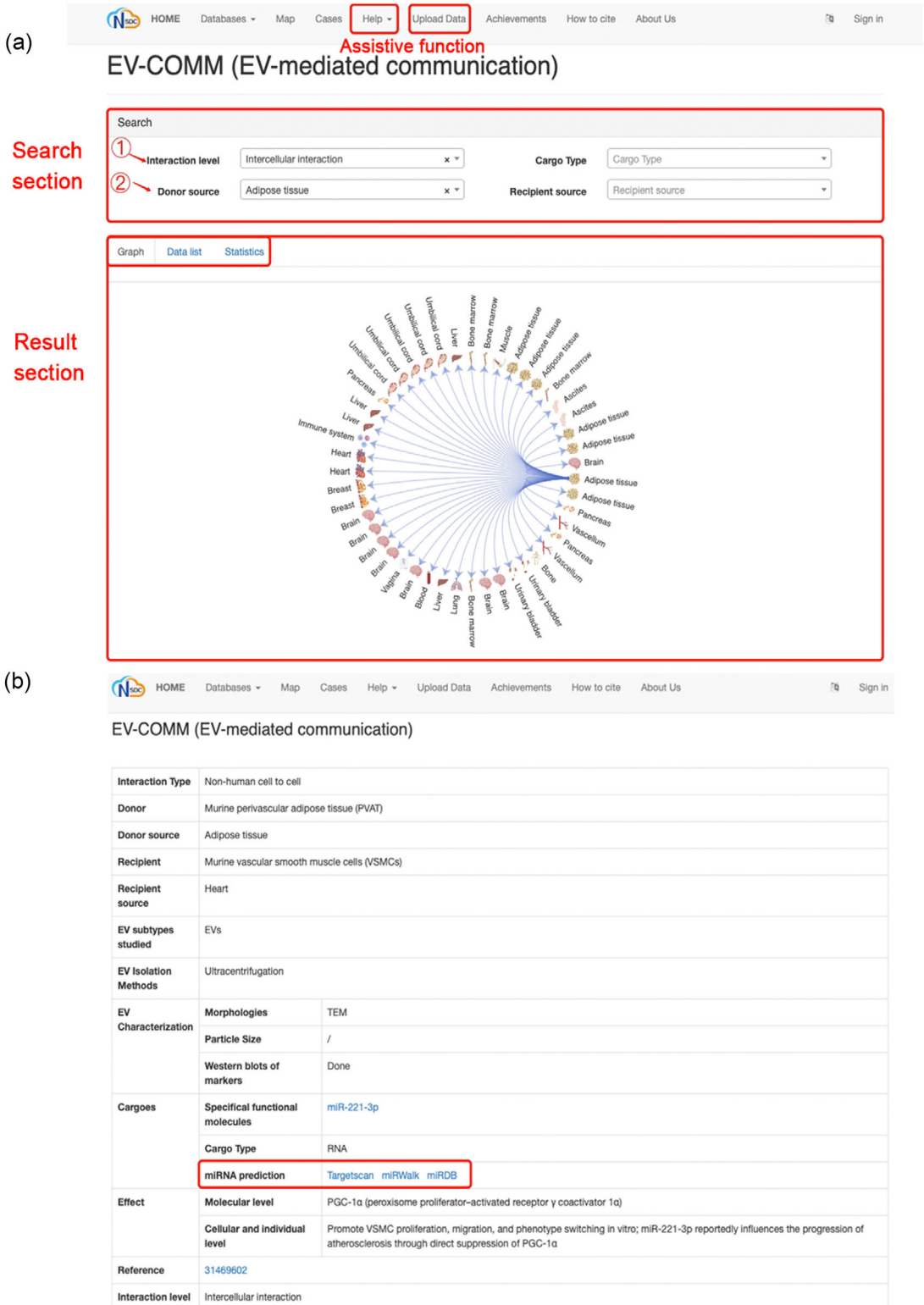
3.3.2 | Case study

Here, we utilise an example to show the function of website. Many types of cells in adipose tissue are known to secrete EVs, which in turn act in a paracrine or endocrine way to mediate intercellular and interorgan crosstalk that regulates adipose tissue and systemic homeostasis. To query which tissues/organs adipose tissue can interact through EVs, users can query our database. First, you need to select the level of interaction as "intercellular interaction," and then choose donor "Adipose tissue" in the search section. The results comprise 46 interactions involving in 18 tissues/organs origins, with a graphical displaying the interaction (Figure 6a). When we click on an edge representing the interaction between adipose tissue and the heart, the details page will show that EVs secreted by adipose tissue can promote vascular smooth muscle cells (VSMCs) proliferation, migration and phenotypic transformation (Figure 6b).

EV-COMM is also capable of directly predicting the target genes of miRNA molecules in EVs. To identify the downstream target genes of miR-221-3p molecules derived from adipose tissue-originated EVs, we can open the detailed page and proceed with further operations. We have introduced three miRNA target gene prediction websites and implemented the functionality of quick search by clicking on hyperlinks (Figure 6b). Taking the miRDB target gene prediction website as an example, clicking on the "miRDB" will open a new page showing the possible target gene list of hsa-miR-221-3p (Figure 6b). The GABRA1 gene is one of the target genes, clicking on it displays the Summary and Expression information for the gene. Data shows that it is expressed most in the brain, followed by the adrenal gland. We can wonder if the EVs secreted by adipose tissue contain miR-221-3p, and if the recipient is the brain, can they act on that target gene to exert the appropriate effect. This information may provide new ideas for researchers.

4 | DISCUSSION

EVs have been increasingly proved to be efficient mediators for the interaction. Through their ability to traverse various biological barriers, EVs serve as an intricate network that facilitates the exchange of important signals and molecular information across different tissues and organs throughout the entire body. In addition, the mediating roles of EVs can go across species, such as



Interaction Type	Non-human cell to cell	
Donor	Murine perivascular adipose tissue (PVAT)	
Donor source	Adipose tissue	
Recipient	Murine vascular smooth muscle cells (VSMCs)	
Recipient source	Heart	
EV subtypes studied	EVs	
EV Isolation Methods	Ultracentrifugation	
EV Characterization	Morphologies	TEM
	Particle Size	/
	Western blots of markers	Done
Cargoes	Specifical functional molecules	miR-221-3p
	Cargo Type	RNA
	miRNA prediction	Targetscan miRWalk miRDB
Effect	Molecular level	PGC-1α (peroxisome proliferator–activated receptor γ coactivator 1α)
	Cellular and individual level	Promote VSMC proliferation, migration, and phenotype switching in vitro; miR-221-3p reportedly influences the progression of atherosclerosis through direct suppression of PGC-1α
Reference	31469602	
Interaction level	Intercellular interaction	

FIGURE 6 Website function case display. (a) A cast study of a query for "Adipose tissue" as a search donor in EV-COMM. The graphical display of search results shows that Adipose tissue can interact with tissues/organs such as brain, heart and umbilical cord through EVs. (b) Details of interaction results, including donor/recipient information, EVs isolation and identification information, functional molecules and effects on recipients. The function of predicting miR-221-3p target genes has been achieved.

between plant, human and microbiota. It would be of great value to integrate the records of interaction together in a database, and thus provide a powerful tool for searching the interaction between cell to cell, species to species mediated by EVs.

Our database is the first comprehensive database providing integrated information on donors/recipients, as well as the functional cargoes in EVs and its effects. Several outperformed functions are provided in the database. First, it can serve as a convenient tool to explore and validate whether different cells or species is interactive through EVs. Previous studies provided the prediction of cell–cell communication via ligand-receptor interaction at the protein levels (Hou et al., 2020). Our repository can extend the interactive information at the level of EVs. Second, the database provides a new layer on complex and dynamic interactions at species levels, especially from the aspect on the molecular mechanisms. Previously, the pathogen-host interactions database (PHI-base) provided host-pathogen interaction (Urban et al., 2020). As an assemble of functional molecules, EV-mediated interaction will enrich the interactive ways. Third, existing data provide a full list of EVs cargoes (Kim et al., 2013; Pathan et al., 2019). In this study, the function cargoes were associated with their downstream pathways, the effects on recipients, as well as the functional conditions. This would give a more complete understanding on the roles of cargoes. In addition, we provide external link to predict the target genes, as well as potential function of the major cargo-miRNA. Users can go forward the study with our prediction.

EVs can be released under normal physiological conditions as well as during pathological processes. It has been increasingly recognised as contributors to many diseases, and their contents can be used for both pathology research and biomarker diagnosis. EVs can act both as positive or negative roles in the aetiology of diseases. EVs produced by cells in normal physiological states can mediate positive effects. Valdes et al. (2021) have demonstrated that dopamine in astrocytes can be oxidised into aminochrome. By inducing the expression of GSTM2 secreted by astrocytes using exosomes, they can protect dopamine neurons from the endogenous neurotoxin aminochrome (Valdes et al., 2021). MiR-873a-5p in EVs derived from activated astrocytes can alleviate neuroinflammation mediated by microglial cells and improve neurological dysfunction after TBI by inhibiting the NF-κB signalling pathway (Long et al., 2020).

The reciprocal exchange of EVs between the tumour microenvironment (TAM) and cancer cells also regulates cancer progression. TAM-derived EVs play an important role in promoting the speed of cancer occurrence and progression. TAM-derived exosomal miR-155-5p promotes the formation of intracranial aneurysms (IA) through GREM1 (Feng et al., 2019). Tumour-derived exosomal microRNA-106b-5p activates EMT-cancer cells and M2-subtype TAM interaction to facilitate CRC metastasis (Yang et al., 2021). In our database, the miRNA of these contents can be directly clicked to jump to the target gene prediction website, thus revealing the potential molecular mechanisms that may generate effects based on the downstream target genes.

In conclusion, our study provides compiled data on intercellular/interspecies interactions from the perspective of EVs. This database not only can provide readers with relevant information and methods regarding EVs, but also can access the donor-recipient information. It is convenient for users to access relevant information, as well as helping to analyse the biological function of vesicle information transmission from multiple perspectives. The database is beneficial for experimental, computational and clinical studies involving interspecies interactions and cell-cell interactions via EVs.

In the future, to maintain the lifespan of the database, we will organise professionals for regular maintenance and data updates. At the same time, we encourage researchers to join the data uploading campaign, aiming to integrate and harness limited data to unleash its greater potential. Meanwhile, with the continuous development of artificial intelligence (AI), we are committed to integrating advanced technologies, such as using advanced algorithms and automated methods, to extract key data fields from literature in batches. By combining the rapid development background of big data and AI technology, we strive to improve the integration, quality and efficiency of research data, providing a convenient information platform for the growing community of researchers in the field of vesicle research. We aim to provide more accurate, comprehensive and reliable data resource support for scientific research.

AUTHOR CONTRIBUTIONS

Jingyu Chen and Jing-Jing Lin manually collected and organised data, wrote the article and participated in website design. Congtian Lin designed and developed the website. Qiansheng Huang designed the project and participated in writing the article. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data underlying this article can be obtained at http://sdc.iue.ac.cn/evs/list.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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