

## User manual for EV-COMM database

### 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 (Fig.1a). 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 utilizing multiple filter boxes at the same time, users can interact with and compare data across different categories. In order 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 two versions: Chinese and English.

When the EVs content type is miRNA, a hyper link present as “miRNA prediction” will be shown in the detailed table (Fig.1b). 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. Users have the option to access the “Upload Data” page, where they can conveniently download a standardized 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.

## **Case study**

Here, we utilize 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 level 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 (Fig.1a). 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 (Fig.1b).

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 (Fig.1b). 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. 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



**Figure 1. Website function and case display**