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Xeno-miRNet: a comprehensive database and analytics platform to explore xeno-miRNAs and their potential targets

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Xeno-miRNAs are microRNAs originating from exogenous species detected in host biofluids. A growing number of studies have suggested that many of these xeno-miRNAs may be involved in cross-species interactions by targeting host mRNAs. To date, hundreds of xeno-miRNAs have been reported in different hosts at various abundance levels. Many more miRNAs could be potentially transferred to human circulation system based on computational predictions. There is a clear need for bioinformatics resources and tools dedicated to xeno-miRNA annotations and their potential functions. To address this need, we have systematically curated xeno-miRNAs from multiple sources, performed target predictions using well-established algorithms, and developed a user-friendly web-based tool - Xeno-miRNet to allow researchers to search and explore xeno-miRNAs and their potential targets within different host species. Xeno-miRNet currently contains 1,702 (including both detected and predicted) xeno-miRNAs from 54 species and 98,053 potential gene targets in six hosts. The web application is freely available at http://xeno.mirnet.ca .

Xeno-miRNet: a comprehensive database and analytics platform to explore xeno-miRNAs and their potential targets

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Abstract

Xeno-miRNAs are microRNAs originating from exogenous species detected in host biofluids. A growing number of studies have suggested that many of these xeno-miRNAs may be involved in cross-species interactions by targeting host mRNAs. To date, hundreds of xeno-miRNAs have been reported in different hosts at various abundance levels. Many more miRNAs could be potentially transferred to human circulation system based on computational predictions. There is a clear need for bioinformatics resources and tools dedicated to xeno-miRNA annotations and their potential functions. To address this need, we have systematically curated xeno-miRNAs from multiple sources, performed target predictions using well-established algorithms, and developed a user-friendly web-based tool - Xeno-miRNet to allow researchers to search and explore xeno-miRNAs and their potential targets within different host species. Xeno-miRNet currently contains 1,702 (including both detected and predicted) xeno-miRNAs from 54 species and 98,053 potential gene targets in six hosts. The web application is freely available at http://xeno.mirnet.ca.

Subjects: Bioinformatics, Computational Biology, Visual Analytics

Keywords: xeno-miRNA, network analysis

Introduction

MicroRNAs (miRNAs) are ~22nt non-coding small RNAs, which mediate post-transcriptional gene silencing by binding corresponding mRNA targets (Bartel 2004). Since its discovery, miRNA has been shown to be involved in many biological processes including cell proliferation, cell differentiation, cell migration, disease initiation, and disease progression (Ma et al. 2007; Png et al. 2012; Tay et al. 2008). More recently, there has been a growing interest in investigating the potential roles of xeno-miRNAs (miRNAs that have been detected in host biofluids, but originating from different species) in cross-species communications. For instance, studies on helminth infections have found that miRNAs carried by the parasite secreted exosomes were able to modulate host immune responses (Buck et al. 2014; Zamanian et al. 2015); It has been shown that miRNAs encoded by Epstein-Barr virus (EBV) could deliver immunomodulatory effect via targeted suppression of key host genes (Xia et al. 2008); Identified in human sera, a plant miRNA could target host genes to suppress the proliferation of breast cancer cells (Chin et al. 2016); Finally, miRNAs secreted by host gut epithelial cells can modulate the growth of gut microbiota (Liu et al. 2016). Despite the current controversies regarding xeno-miRNAs from dietary intake (Bagci & Allmer 2016; Chen et al. 2013; Dickinson et al. 2013; Witwer & Halushka 2016), there have been growing interests to understand the roles of these xeno-miRNAs due to their great potentials for translational applications.

Most of the current bioinformatics resources for miRNA studies were developed to help understand functions of miRNAs in the same organisms (Fan et al. 2016; Kozomara & Griffiths-Jones 2014; Lu et al. 2012; Ru et al. 2014; Vlachos et al. 2015). Tools for cross-species miRNA-target analysis have only started to appear since last year (Mal et al. 2018; Zhang et al. 2017; Zheng

et al. 2017). Here we introduce Xeno-miRNet, a web-based database and analytics platform that integrates multiple xeno-miRNA resources to support target search, visual exploration and functional analysis. The key features of xeno-miRNet include: 1) a comprehensive collection of experimentally detected and computationally predicted xeno-miRNAs; 2) systematic target predictions integrating two well-established algorithms; and 3) a fully-featured network visual analytics system that allows users to browse, search and visually explore the results in an intuitive manner.

Materials and Methods

Xeno-miRNA collection and curation

We performed a comprehensive literature review and manually collected xeno-miRNA entries from these papers and resources (Bernal et al. 2014; Buck et al. 2014; Chen et al. 2011; Cheng et al. 2013; Chin et al. 2016; Fromm et al. 2015; Gottwein 2012; Guo et al. 2017; Hao et al. 2010; Tritten et al. 2014; Zamanian et al. 2015; Zhang et al. 2012; Zheng et al. 2017; Zhu et al. 2016a; Zhu et al. 2016b). Xeno-miRNet currently contains 453 xeno-miRNAs from 54 species, detected in six host organisms (*H. sapiens, M. musculus, S. scrofa, G. gallus, D. melanogaster,* and *C. elegans*). Based on the pairing information on host and xeno-species, additional 1249 xeno-miRNAs were predicted to have high potential to be transferred to human circulation according to a recent computational analysis (Shu et al. 2015).

Xeno-miRNA target prediction

To identify the putative target genes of these miRNAs in the corresponding host organisms, we first downloaded the 3'UTR sequences of six host organisms from Ensembl database and the xeno-miRNA sequences from the miRBase (Kozomara & Griffiths-Jones 2014). We then applied two

well-established target prediction algorithms: miRanda (Betel et al. 2010) and TarPmiR (Ding et al. 2016). The following cutoff values are used: score >= 140 for miRanda and probability >= 0.5 for TarPmiR. Genes in their overlap were selected as potential targets for a given host. The miRNA-target interaction data was stored into an SQLite database (version 3.0) for fast retrieval. **Table 1** shows the summary of the xeno-miRNA database.

Xeno-miRNet implementation

The web framework was developed based on the JavaServer Faces (JSF) technology using the PrimeFaces (https://www.primefaces.org) component library (version 6.1). As one miRNA can target more than one mRNAs and one mRNA can be targeted by multiple miRNAs, we employed a network visualization approach to allow users to intuitively explore the "multiple-to-multiple" relationships between xeno-miRNAs and their potential gene targets. The JavaScript library *sigma.js* (http://www.sigmajs.org) was used for high-performance network visualization. The functional enrichment analysis was implemented using the R programming language. The entire system is deployed on a Google Cloud server with 30GB of RAM and eight virtual CPUs with 2.6 GHz each.

Results

Xeno-miRNet has been developed as a database and web-based analytical platform to allow users to query and explore xeno-miRNAs and their potential gene targets in multiple hosts. The website contains a comprehensive list of frequently asked questions (FAQs) and tutorials to help users to start using the tool. The overall design of Xeno-miRNet composed with three main steps - 1) data preparation, 2) target searching and network customization, and 3) network visualization and

functional analytics. **Figure 1** shows the overall flowchart of Xeno-miRNet. Based on users' queries, a variety of options and procedures will be provided to help users complete their tasks.

Data browsing and searching

From the home page, users can start with *Browse* or *Search* by clicking the button. To perform *Browse*, users should first specify the host organism. Next, users should select a source and a known xeno-species. For human host, there are 12 different tissue sources and more than 50 xeno-species. To perform *Search,* users should enter a list xeno-miRNAs (miRBase ID or accession number) or a list of host target genes (Ensembl ID, Entrez ID, or official gene symbol). In both modes, the next step is to choose whether to include the predicted xeno-miRNAs. It is important to note that including predicted data may return a large interaction result. To demonstrate the *Search* function, we will use an built-in example "miRNA list1" containing five highly expressed *S. japonicum* exosome miRNAs (*sja-miR-125b, sja-miR-2162-3p, sja-miR-2b-5p, sja-miR-61,* and *sja-miR-10-5p*) (Hao et al. 2010; Zhu et al. 2016a) and explore their potential functions in human host. This list is available as the first example when user click the "Try Examples" when users enter the *Search* page.

Interaction table refinement

In the returned interaction table, each row represents a pair of xeno-miRNA and predicted gene target with hyperlinks to their corresponding databases. The table also provides relevant evidence (RNAseq read counts, miRanda and TarPmiR prediction scores) to allow users to assess the quality of the interactions. The *Data Filter* function allows users to refine the results based on certain matching criteria. For example, users can keep the interactions which miRanda scores higher than

150 by choosing the *Target Column* as *miRanda*, typing in *150* in the frame, and selecting *Keep* (**Fig. 2A**). Users can save the original interaction result into a CSV file. The filtered result will be used for network construction in the next step.

Network creation and customization

The network builder page shows a summary table of the generated xeno-miRNA-target interaction network(s), with the number of nodes and edges displayed for each network. A large network (i.e. over 2000 nodes) often leads to a "hairball" effect in which edges are too densely connected to show any pattern. To overcome this issue, we have implemented the *Network Tools* to allow users to filter nodes according to their topological measures (degree, betweenness, and shortest path) to keep those major hubs while still maintain major connection patterns. The degree of a node is the total number of connections it has to other nodes, and nodes with high degrees are considered important "hubs" in a network. The betweenness value measures the number of the shortest path going through a node, and nodes with high betweenness values are important "connectors" in a network. The shortest path option is for reducing the number of edges within the network by keeping only one shortest path between the hub nodes (**Fig. 2B**). These functions can work with the previous *Data Filter* to allow users to have fine control over the resulting network to be visualized.

Network visual exploration

The overview of the network display is shown in **Fig. 2C**. The network visualization page is composed of four main components – 1) the top tool menu, 2) the *Node Explorer* panel on the left, 3) the central network display panel, and 4) the *Function Explorer* panel on the right. The top tool

menu allows users to specify which sub-network to display and to control the overall style of the network. The *Network* option provides a drop-down menu listing all networks that are available to display. Users can specify the currently displayed network and the default is the largest one ("xeno-mirnet1" in **Fig. 2C**). The *Background* option can be used to switch between black and white background. The *Layout* option allows users to arrange the node positions of the network. The *Scope* option allows users to control the nodes being affected when users manually drag or highlight a single or a group of nodes. The *View Options* allow users to modify the styles for nodes, edges, and highlighting. The *Node Explorer* on the left panel displays all the nodes in the current network. Nodes are identified by their IDs or names, together with degree and betweenness values. Users can sort the table by clicking a column header. Clicking a node will highlight it within the current network. In addition, user can select multiple miRNAs and then highlight the gene targets shared by them using the *Highlight* function. The central display area is for visual exploration of the network with a vertical toolbar on the left. The color palette located at the top of the toolbar allows users to define the current highlighting color for nodes selection. Users can perform zooming, highlighting, drag-and-drop, or extracting the highlighted nodes using a mouse movement in combination with functions in the toolbar. The button with a dotted rectangle icon allows users to manually select a group of nodes. After clicking this icon, users can use mouse to select a group of nodes of interest for further functional analysis. The *Function Explorer* on the right panel allow users to perform enrichment analysis to identify important functions defined by gene ontology (GO), KEGG or Reactome pathways. Two algorithms have been implemented – the *hypergeometric tests* and the *empirical sampling* as recently proposed by Bleazard *et al* (Bleazard et al. 2015) for more robust miRNA target enrichment analysis. The result is a list of functions ranked by their p-value. Users can highlight the nodes involving in the pathway by simply clicking

on the function name. **Fig. 2C** shows the result after performing the KEGG pathway analysis to the targets from the *S. japonicum* exosome miRNAs. The "Protein processing in endoplasmic reticulum" (highlighted in blue) and "Endocytosis" (highlighted with purple) were identified as significant pathways. When a network is too complex, users can extract a module or sub-network containing only the nodes of interest by using the *Extract* button on the central display toolbar (the bottom one). The extracted module will be listed as "module1" in the *Network option* on the top toolbar and the sub-network will be displayed in the center viewer. Users can perform further customization for the sub-network.

Discussion

To address the growing bioinformatics needs for xeno-miRNA research, several tools have been developed recently. For instance, Exo-miRExplorer is a database curating exogenous miRNAs detected from high-throughput small RNA sequencing experiments (Zheng et al. 2017); miRDis is a web service that supports discovery and annotation of exogenous miRNAs from small RNA sequencing data (Zhang et al. 2017); IIKmTA is a new tool that aims to support both inter- and intra- kingdom miRNA-target analysis (Mal et al. 2018). **Table 2** compares the key features between Xeno-miRNet and these recent tools. Based on the comparison, it is evident that Xeno-miRNet complements other tools by providing comprehensive support for functional analysis and network-based visualization. It is important to note that Xeno-miRNet currently focuses on supporting the six model organisms with extensive literature support. We intend to gradually expand the range of host organisms based on user feedback and available data.

197

198 **Conclusions**

199 Through comprehensive curation of xeno-miRNAs, systematic predictions of their targets in
200 multiple hosts, and integrating these resources into a high-performance web application, we have
201 developed Xeno-miRNet to help address the growing interest in understanding the roles of xeno-
202 miRNAs in cross-species interactions. Xeno-miRNet complements current tools and fills an
203 important bioinformatics gap by allowing researchers to obtain meaningful results and to develop
204 new hypotheses.

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Figure 1(on next page)

The workflow chart for Xeno-miRNet

The workflow consisting of three steps – data preparation, target search and customization, and the network visual analytics.

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Data preparation

Browse

Users choose a host, a tissue or cell line, and a known xeno-species

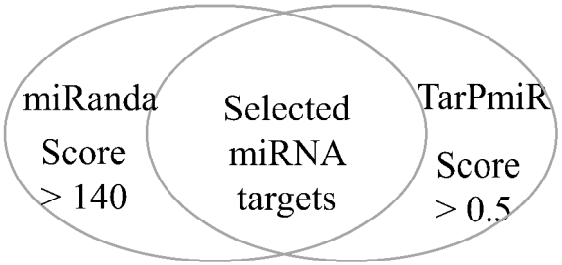
Search

To start, users can provide:

- A list of xeno-miRNAs
- A list of host genes

Target search & customization

miRNA-target database

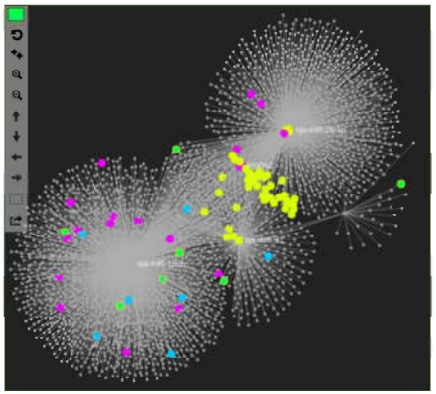


Target filtering

- Remove individual interaction;
- Batch filtering by prediction scores;
- Optimize network based on topology structure

Visualization & functional analysis

Network visualization



Enrichment analysis

Flexible analysis scope:

- All genes
- Highlighted genes

Enrichment algorithms:

- Hypergeometric tests
- Empirical sampling

Enrichment libraries:

- Gene Ontology (GO)
- KEGG/Reactome pathway

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Figure 2(on next page)

Network customization and visualization

(A) The data filter dialog. To keep the miRNA-target interactions which miRanda scores larger than 150. (B) Network tools for performing network refinement. Users can choose corresponding node types and input the cutoff to perform the filtering. (C) The network visualization system overview.

A

B

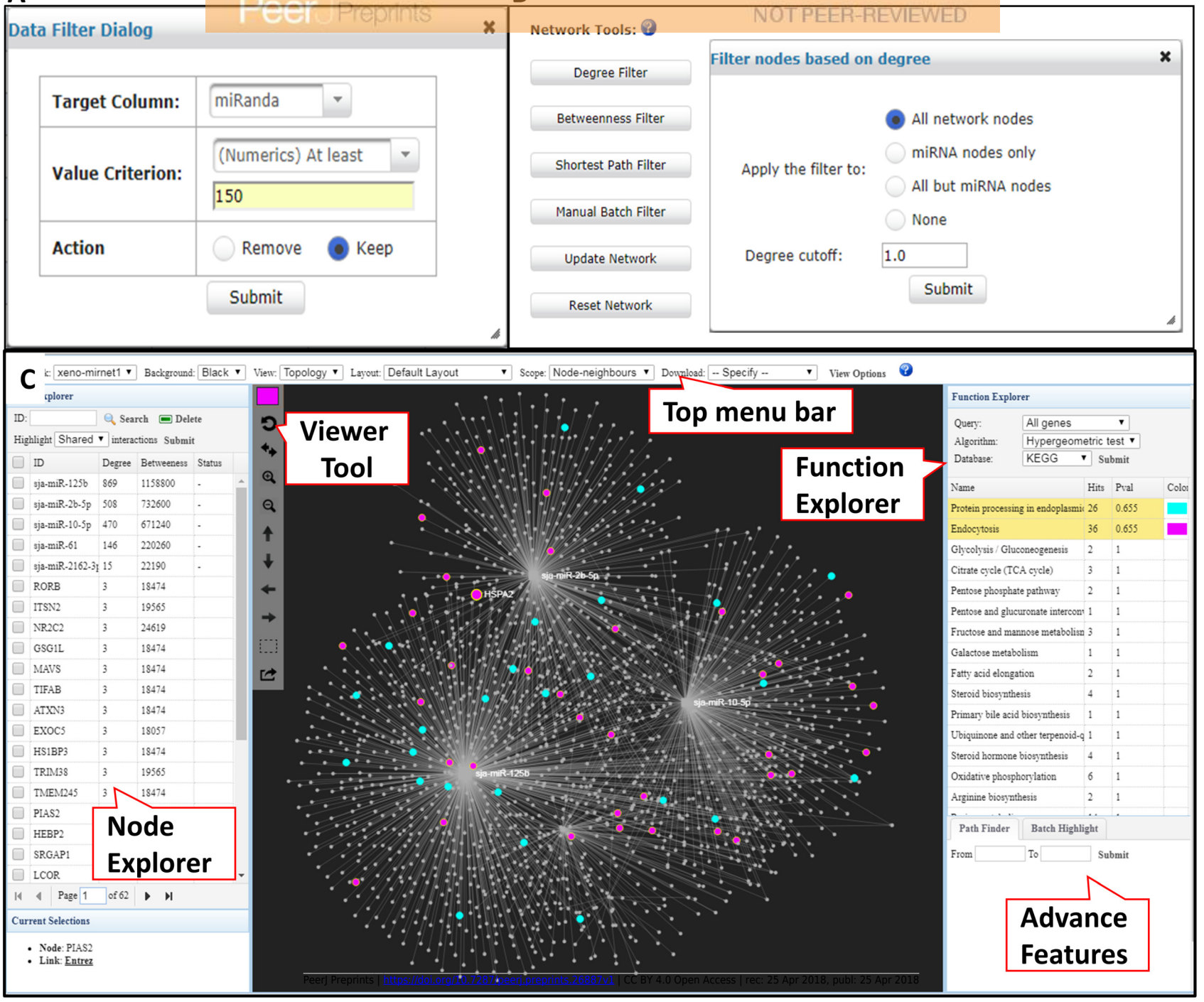

Table 1(on next page)

The summary statistics for the xeno-miRNet database

Table 1: The summary statistics for the xeno-miRNet database

Hosts	Tissue / sources	Xeno-species	Xeno-miRNAs (detected/ predicted)	Potential targets
Human	18	40	296 / 625	20,791
Mouse	18	27	83 / 418	19,430
Pig	4	14	20 / 116	12,537
Chicken	2	15	23 / 10	16,459
Fruit fly	6	6	16 / 44	12,445
C. elegans	8	6	15 / 36	16,391
Total	49	54 (unique)	1702	98,053

Table 2(on next page)

Comparison with other tools available for xeno-miRNA analysis

The “+” and “-” are used to indicated if features are present or not. More “+” indicate better support.

Table 2: Comparison with other tools available for xeno-miRNA analysis. The "+" and "-" are used to indicated if features are present or not. More "+" indicate better support.

Tools	Xeno-miRNet	Exo-miRExplorer	IIKmTA	miRDis
Hosts #	6	13	116	6
Xeno-species #	54	64	109	8
xeno-miRNA sources				
Experimental detected	+	+	-	+
Predicted	+	-	+	-
Input data				
miRNAs	+	+	+	+
Targets	+	-	-	-
Expression data	-	-	-	+
Result presentation				
Interactions table	+	-	+	-
Network visualization	+++	-	-	-
Enrichment analysis				
Hypergeometric tests	+	-	-	-
Empirical sampling	+	-	-	-

URL links:
Xeno-miRNet: http://xeno.mirnet.ca
Exo-miRExplorer: http://rna.sysu.edu.cn/exomiRDB/
IIKmTA: http://www.bioinformatics.org/iikmta/
miRDis: http://sbbi.unl.edu/miRDis/index.php