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Databases and ontologies

EVpedia: a community web portal for extracellular vesicles research

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Abstract

Motivation: Extracellular vesicles (EVs) are spherical bilayered proteolipids, harboring various bioactive molecules. Due to the complexity of the vesicular nomenclatures and components, online searches for EV-related publications and vesicular components are currently challenging.

Results: We present an improved version of EVpedia, a public database for EVs research. This community web portal contains a database of publications and vesicular components, identification of orthologous vesicular components, bioinformatic tools and a personalized function. EVpedia includes 6879 publications, 172 080 vesicular components from 263 high-throughput datasets, and has been accessed more than 65 000 times from more than 750 cities. In addition, about 350 members from 73 international research groups have participated in developing EVpedia. This free web-based database might serve as a useful resource to stimulate the emerging field of EV research.

Availability and implementation: The web site was implemented in PHP, Java, MySQL and Apache, and is freely available at http://evpedia.info.

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1 Introduction

Almost all living organisms on earth shed extracellular vesicles (EVs) into their microenvironment. EVs are spherical bilayered proteolipids with an average diameter of 20–1000 nm (Ellen *et al.*, 2009; Lee *et al.*, 2008; Théry *et al.*, 2009). Cells release EVs either constitutively or in a regulated manner and these vesicles harbor a specific subset of proteins, mRNAs, miRNAs, lipids and metabolites reflecting their originating cell types and conditions (Bellingham *et al.*, 2012; Choi *et al.*, 2014; de Jong *et al.*, 2012; Duperthuy *et al.*, 2013; Mayr *et al.*, 2009; Raimondo *et al.*, 2011; Simpson *et al.*, 2008; Subra *et al.*, 2007; Wai *et al.*, 2003). EVs are also found in various biological fluids, such as amniotic fluid, ascites, breast milk, plasma, saliva, semen, serum and urine (Asea *et al.*, 2008; Caby *et al.*, 2005; Cheng *et al.*, 2014a, b; Dai *et al.*, 2008; George *et al.*, 1982; Lässer *et al.*, 2011; Poliakov *et al.*, 2009; Raj *et al.*, 2012; Witwer *et al.*, 2013). Recent advances in this fast growing field (Fig. 1) have facilitated several insights: (1) EVs play multifaceted functions in intercellular communication (Cocucci *et al.*, 2009; Lee *et al.*, 2008; Simons and Raposo, 2009; Théry *et al.*, 2009); (2) EV-mediated intercellular communication is an evolutionarily conserved phenomenon (Deatherage and Cookson, 2012; Lee *et al.*, 2008, 2009); (3) EVs are rich sources of biomarkers for non-invasive diagnosis and prognosis of various human diseases (Chaput *et al.*, 2005; Choi *et al.*, 2013a; D'Souza-Schorey and Clancy, 2012; Mullier *et al.*, 2013; Sarlon-Bartoli *et al.*, 2013; Shedden *et al.*, 2003; Simpson *et al.*, 2009); and (4) Diverse therapeutic approaches have been pursued to utilize EVs and their mimetics for vaccine, chemotherapeutic drug and siRNA delivery (Alvarez-Erviti *et al.*, 2011; Chaput *et al.*, 2005; Jang *et al.*, 2013; Kordelas *et al.*, 2014; Lai *et al.*, 2010; Lee *et al.*, 2012; Simpson *et al.*, 2009; Sun *et al.*, 2010).

Publications on EVs have grown rapidly during the last several years, indicating that the field of EVs is expanding intensively (Fig. 1). The identification of vesicle-specific cargos could help us to unravel the molecular mechanisms underlying the cargo sorting and biogenesis of EVs. In addition, this will lead to better comprehension of the pathophysiological functions of EVs, and discovery of EV-based potential biomarkers of human diseases. Therefore, many

investigators have focused on categorizing these complex vesicular components by various high-throughput technologies, such as mass spectrometry-based proteomics and lipidomics as well as microarray- and next-generation sequencing-based transcriptomics (Barry *et al*., 1997; Choi *et al*., 2013b; Koh *et al*., 2010; Utleg *et al*., 2003; Valadi *et al*., 2007). Together with conventional biological approaches, these multiomics-based analyses of EVs derived from various cell types and body fluids have identified several thousands of different vesicular components.

EV secretion and EV-mediated intercellular communication are evolutionarily conserved (Biller *et al*., 2014; Deatherage and Cookson, 2012; Lee *et al*., 2008, 2009). Researchers in this field have coined dozens of different names for EVs, especially for more complex eukaryotic cell-derived EVs as listed in Box ('Extracellular Vesicles: Diverse Nomenclature') (Choi *et al*., 2014; Gould and Raposo, 2013; Kim *et al*., 2013). Nevertheless, there is progress toward a single nomenclature, since the different names in use make it difficult to follow the progress in the field. In addition, most vesicular components identified by multiomics-based high throughput analyses are presented in the supplementary information of published articles. Taken together, online searches for EV-related publications and vesicular components will help the community of EV research to understand various aspects of these complex extracellular organelles.

Extracellular Vesicles: Diverse Nomenclature

Prokaryotes

Archaea

Membrane Vesicles

Gram-negative Bacteria

Extracellular Vesicles, Membrane Blebs, Outer Membrane Blebs, Outer Membrane Vesicles

Gram-positive Bacteria

Extracellular Vesicles, Membrane Vesicles

Eukaryotes

Argosomes, Blebbing Vesicles, Budding Vesicles, Dexosomes, Ectosomes, Exosome-like Vesicles, Exosomes, Exovesicles, Extracellular Membrane Vesicles, Extracellular Vesicles, Matrix Vesicles, Membrane Particles, Membrane Vesicles, Microparticles, Microvesicles, Nanovesicles, Oncosomes, Prominosomes, Prostasomes, Shedding Microvesicles, Shedding Vesicles, Tolerosomes

2 Databases that store EV data

The explosion of EV data has justified the need for databases that catalog proteins, nucleic acids and lipids associated with EVs. Currently, three databases exist for EV research including ExoCarta (Simpson *et al*., 2012), EVpedia (Kim *et al*., 2013) and Vesiclepedia (Kalra *et al*., 2012). These existing databases have made large-scale bioinformatics analyses feasible and provide an ideal platform for EV-based biomarker studies. EVpedia provides additional benefits compared with ExoCarta and Vesiclepedia. EVpedia is the only resource that contains data on both prokaryotes and eukaryotes. In addition, EVpedia allows for Gene Ontology enrichment analysis, network analysis of vesicular proteins and mRNAs, and set analysis of vesicular datasets by ortholog identification. Other databases do not have any such embedded analysis tools.

3 Launch of EVpedia

EVpedia (http://evpedia.info) was first launched in January 2012 (Kim *et al*., 2013). To construct this public web-based database, we first collected publications on prokaryotic and eukaryotic EVs through a combination of NCBI PubMed searches (http://www.ncbi.nlm.nih.gov/pubmed) for text-mining solutions and manual curation using all nomenclatures assigned to EVs described in Box (see also Kim *et al*., 2013). Based on these EV-related publications, we constructed the comprehensive and integrated database of proteins, mRNAs, miRNAs, lipids and metabolites for systematic analyses of prokaryotic and eukaryotic EVs.

4 Overview of current EVpedia

Since the launch of EVpedia, we have improved this database by continually collecting additional EV-related publications and datasets, by adding more tools for systematic analyses of EVs, and by supplementing the menu bars for 'Top 100+ EV markers', 'User forum' as well as 'My EVpedia'. Through closed and open beta tests, we built an 'EVpedia Community' (about 350 world-wide EV researchers) and updated EVpedia most recently in May 2014.

The updated EVpedia has five functional modules for systematic analyses of EVs derived from prokaryotic and eukaryotic cells (Fig. 2): (i) a database of publications and principal investigators, (ii) a database of vesicular proteins, mRNAs, miRNAs, lipids and

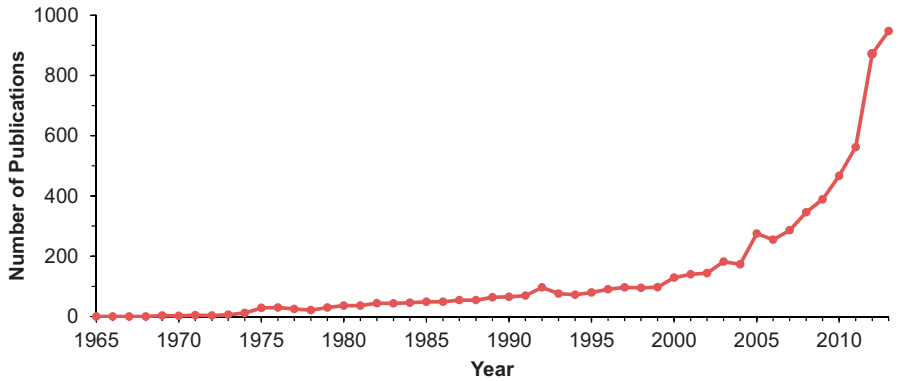

Fig. 1. Publication trend of EV studies. This graph shows the number of publications on EVs per year, indicating that the field of EVs is expanding rapidly

metabolites, (iii) identification of orthologous vesicular components, (iv) an array of tools for bioinformatic analyses including sequence search, set analysis, Gene Ontology enrichment analysis and network analysis, as well as (v) 'My EVpedia', a personalized function of EVpedia. Using 'My EVpedia', users privately store their own datasets, analysis results and publications of interest by creating their own accounts. New functions of this updated EVpedia are indicated in red texts in Figure 2.

We invite the research community to submit EV-related multiomics data and publications to EVpedia.

As of May 2014, a total of 6879 EV-related publications with 3336 principal investigators have been cataloged in EVpedia. In addition, a total of 172 080 vesicular components from 263 high-throughput datasets are listed (Table 1). All of these vesicular components could be searched by their sequences and browsed. Furthermore, in the 'Top 100+ EV markers' menu, the current vesicular components are sorted in the descending order of their identification counts, which are the numbers of datasets identifying those vesicular components or their orthologs.

5 Community participation and annotation in EVpedia

After the initial launch in January 2012, EVpedia has been globally accessed more than 65 000 times from more than 750 cities (Table 1). For community annotation of EVpedia, we built 'EVpedia Community'. About 350 members from 73 international EV research groups have joined this community, in which they can exchange EV-related information and submit their multiomics data via the 'User forum' and 'Upload' menu bars in EVpedia, respectively. In addition, non-members can easily join the 'EVpedia Community' by adding their information via clicking the 'Sign In' menu. Moreover, EVpedia has been cross-linked with the website of the 'International Society of Extracellular Vesicles' (http://www.isev.org).

6 Concluding remarks

EVpedia is a comprehensive database of EVs derived from prokaryotes and eukaryotes. Currently, a total of 6879 EV-related publications and 172 080 vesicular components (proteins, mRNAs, miRNAs, lipids and metabolites) are deposited in this public repository. For the systematic analysis of EVs, EVpedia also provides integrated systems biology research tools such as 'Experiment', 'Browse', 'Analysis', 'Top 100+ EV markers' and 'My EVpedia' menu bars. In the future, additional multiomics datasets and publications will be deposited, and we expect more researchers to join the 'EVpedia Community' and to share their research data. The community database is scheduled to be updated every 3 months. EVpedia, a community web portal for EV research, should serve as a useful resource to stimulate the emerging field of EV biology research and to help us to elucidate the fundamental roles of these complex extracellular organelles.

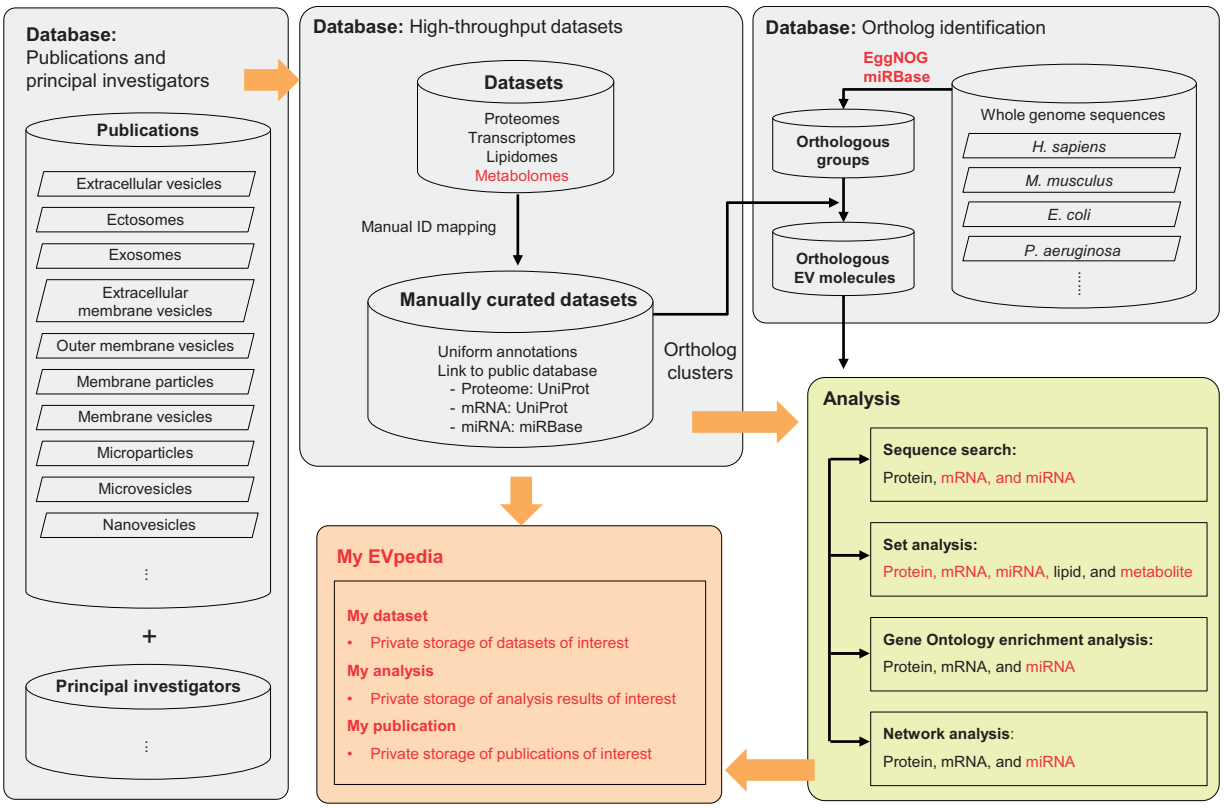

Fig. 2. Overall structure of EVpedia. EVpedia provides a comprehensive database for (i) publications and principal investigators, (ii) vesicular proteins, mRNAs, miRNAs, lipids and metabolites and (iii) identification of orthologous vesicular components. For systematic analyses of vesicular components, there is an array of tools for sequence search, set analysis, Gene Ontology enrichment analysis and network analysis. 'My EVpedia' is a personalized function of EVpedia to deposit the user's own datasets, analysis results and publications of interest. Note that red texts indicate newly included functions in the updated version of EVpedia

Table 1. EVpedia statistics

	All	Eukaryotes	Prokaryotes
Publications			
Articles	6879	6021	858
Principal investigators	3336	2886	483
Proteomes			
Studies	117	97	20
Datasets	176	148	28
Proteins	78 971	74 696	4275
Transcriptomes			
mRNA			
Studies	17	17	0
Datasets	28	28	0
mRNAs	74 430	74 430	0
miRNA			
Studies	11	11	0
Datasets	29	29	0
miRNAs	18 119	18 119	0
Lipidomes			
Studies	22	21	1
Datasets	29	28	1
Lipids	550	534	16
Metabolomes			
Studies	1	1	0
Datasets	1	1	0
Metabolites	10	10	0
Participating			
Laboratories (countries)	73 (20)		
Accesses (countries)	66 617 (73)		

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