

Databases and ontologies

EVpedia: A Community Web Portal for Extracellular Vesicles Research

Dae-Kyum Kim^{1,†,‡}, Jaewook Lee^{1,†,‡}, Sae Rom Kim^{1,‡}, Dong-Sic Choi^{1,‡}, Yae Jin Yoon^{2,‡}, Ji Hyun Kim^{1,‡}, Gyeongyun Go^{1,‡}, Dinh Nhung^{1,‡}, Kahye Hong^{1,‡}, Su Chul Jang^{1,‡}, Si-Hyun Kim^{1,‡}, Kyong-Su Park^{1,‡}, Oh Youn Kim^{1,‡}, Hyun Taek Park^{1,‡}, Ji Hye Seo^{1,‡}, Elena Aikawa³, Monika Baj-Krzyworzeka⁴, Bas W. M. van Balkom⁵, Mattias Belting⁶, Lionel Blanc⁷, Vincent Bond⁸, Antonella Bongiovanni⁹, Francesc E. Borràs¹⁰, Luc Buée¹¹, Edit I. Buzás¹², Lesley Cheng¹³, Aled Clayton¹⁴, Emanuele Cocucci¹⁵, Charles S. Dela Cruz¹⁶, Dominic M. Desiderio¹⁷, Dolores Di Vizio¹⁸, Karin Ekström^{19, 20}, Juan M. Falcon-Perez²¹, Chris Gardiner²², Bernd Giebel²³, David W. Greening²⁴, Julia Christina Gross²⁵, Dwijendra Gupta²⁶, An Hendrix²⁷, Andrew F. Hill¹³, Michelle M. Hill²⁸, Esther Nolte-'t Hoen²⁹, Do Won Hwang³⁰, Jameel Inal³¹, Medicharla V. Jagannadham³², Muthuvel Jayachandran³³, Young-Koo Jee³⁴, Malene Jørgensen³⁵, Kwang Pyo Kim³⁶, Yoon-Keun Kim³⁷, Thomas Kislinger³⁸, Cecilia Lässer³⁹, Dong Soo Lee³⁰, Hakmo Lee⁴⁰, Johannes van Leeuwen⁴¹, Thomas Lener^{42, 43}, Ming-Lin Liu^{44, 45}, Jan Löt-vall³⁹, Antonio Marcilla⁴⁶, Suresh Mathivanan²⁴, Andreas Möller⁴⁷, Jess Morhayim⁴¹, François Mullier^{48, 49}, Irina Nazarenko⁵⁰, Rienk Nieuwland⁵¹, Diana N. Nunes⁵², Ken Pang^{53, 54}, Jaesung Park⁵⁵, Tushar Patel⁵⁶, Gabriella Pocsfalvi⁵⁷, Hernando del Portillo⁵⁸, Ulrich Putz⁵⁹, Marcel I. Ramirez⁶⁰, Marcio L. Rodrigues^{61, 62}, Tae-Young Roh^{1,2}, Felix Royo²¹, Susmita Sahoo⁶³, Raymond Schiffelers⁶⁴, Shivani Sharma⁶⁵, Pia Siljander⁶⁶, Richard J. Simpson²⁴, Carolina Soekmadji⁶⁷, Philip Stahl⁶⁸, Allan Stensballe⁶⁹, Ewa Stępień⁷⁰, Hidetoshi Tahara⁷¹, Arne Trummer⁷², Hadi Valadi⁷³, Laura J. Vella⁷⁴, Sun Nyunt Wai⁷⁵, Kenneth Witwer⁷⁶, María Yáñez-Mó⁷⁷, Hyewon Youn³⁰, Reinhard Zeidler⁷⁸, Yong Song Gho^{1,†,‡,*}

¹Department of Life Sciences, Pohang University of Science and Technology, Pohang, Republic of Korea, ²Division of Integrative Biosciences and Biotechnology, Pohang University of Science and Technology, Pohang, Republic of Korea, ³Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, ⁴Department of Clinical Immunology, Polish-American Institute of Paediatrics, Jagiellonian University Medical College, Cracow, Poland, ⁵Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands, ⁶Department of Clinical Sciences, Section of Oncology, Lund University, Lund, Sweden, ⁷The Feinstein Institute for Medical Research, Manhasset, New York, United States of America, ⁸Department of Microbiology, Biochemistry, and Immunology, Morehouse School of Medicine, Atlanta, Georgia, United States of America, ⁹Institute of Biomedicine and Molecular Immunology (IBIM), National Research Council (CNR), Palermo, Italy, ¹⁰Innovation in Vesicles and Cells for Application in Therapy, Germans Trias i Pujol Research Institute, Germans Trias i Pujol University Hospital, Badalona, Spain, ¹¹Inserm, UMR837 Jean-Pierre Aubert Research Centre, Lille, France, ¹²Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary, ¹³Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Melbourne, Victoria, Australia, ¹⁴Institute of Cancer & Genetics, School of Medicine, Velindre Cancer Centre, Cardiff University, Cardiff, United Kingdom, ¹⁵Program in Cellular and Molecular Medicine at Boston Children's Hospital and Department of Cell Biology, Harvard Medical School, Boston, Massachusetts, United States of America, ¹⁶Section of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, United States of America, ¹⁷Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee, United States of America, ¹⁸Cancer Biology Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California, United States of America, ¹⁹Department of Biomaterials, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, ²⁰BIOMATCELL VINN Excellence Center of Biomaterials and Cell Therapy, Gothenburg, Sweden, ²¹Metabolomics Unit, CIC bioGUNE, CIBERehd, IKERBASQUE Research Foundation, Technology Park of

Bizkaia, Derio, Bizkaia, Spain, ²²Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom, ²³Institute for Transfusion Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, ²⁴La Trobe Institute for Molecular Science (LIMS), La Trobe University, Melbourne, Victoria, Australia, ²⁵Division of Signaling and Functional Genomics, German Cancer Research Center, Heidelberg, Germany, ²⁶Vice-Chancellor, Jai Prakash University, Chapra, Bihar, India, ²⁷Laboratory of Experimental Cancer Research, Department of Radiation Oncology and Experimental Cancer Research, Ghent University Hospital, Ghent, Belgium, ²⁸The University of Queensland Diamantina Institute, The University of Queensland, Translational Research Institute, Brisbane, Queensland, Australia, ²⁹Department of Biochemistry & Cell Biology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands, ³⁰Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea, ³¹Cellular and Molecular Immunology Research Centre, Faculty of Life Sciences and Computing, London Metropolitan University, London, United Kingdom, ³²CSIR-Centre for Cellular and Molecular Biology, Hyderabad, Andhra Pradesh, India, ³³Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota, United States of America, ³⁴Department of Internal Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea, ³⁵Department of Clinical Immunology, Aalborg University Hospital, Aalborg, Denmark, ³⁶Department of Applied Chemistry, Kyung Hee University, Yongin, Republic of Korea, ³⁷Ewha Womans University Medical Center, Seoul, Republic of Korea, ³⁸Ontario Cancer Institute, Toronto, Ontario, Canada, ³⁹Krefting Research Centre, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, ⁴⁰Biomedical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea, ⁴¹Department of Internal Medicine, Erasmus University Rotterdam Medical Centre, Rotterdam, The Netherlands, ⁴²Department of Blood Group Serology and Transfusion Medicine, University Hospital of Salzburg, Paracelsus Medical University, Salzburg, Austria, ⁴³Spinal Cord Injury & Tissue Regeneration Center Salzburg (SCI-TReCS), Paracelsus Medical University, Salzburg, Austria, ⁴⁴Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America, ⁴⁵Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania, United States of America, ⁴⁶Àrea de Parasitologia, Departamento de Biología Celular y Parasitología, Universitat de València, Burjassot, Valencia, Spain, ⁴⁷Tumour Microenvironment Laboratory, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia, ⁴⁸Hematology Laboratory, NARILIS, Namur Thrombosis and Hemostasis Center (NTHC), CHU Dinant Godinne UCL Namur, Université Catholique de Louvain, Belgium, ⁴⁹Department of Pharmacy, NARILIS, Namur Thrombosis and Hemostasis Center (NTHC), University of Namur, Namur, Belgium, ⁵⁰Institute of Environmental Health Sciences and Hospital Infection Control, Medical Center-University of Freiburg, Freiburg, Germany, ⁵¹Department of Clinical Chemistry, Academic Medical Center, Amsterdam, The Netherlands, ⁵²Laboratory of Medical Genomics, AC Camargo Cancer Center, São Paulo, Brazil, ⁵³Inflammation Division, The Walter and Eliza Hall Institute for Medical Research, Parkville, Victoria, Australia, ⁵⁴Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia, ⁵⁵Department of Mechanical Engineering, Pohang University of Science and Technology, Pohang, Republic of Korea, ⁵⁶Departments of Transplantation and Cancer Biology, Mayo Clinic, Jacksonville, Florida, United States of America, ⁵⁷Mass Spectrometry and Proteomics, Institute of Biosciences and BioResources, National Research Council of Italy, Naples, Italy, ⁵⁸ICREA, Barcelona Centre for International Health Research, Barcelona, Spain, ⁵⁹The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Victoria, Australia, ⁶⁰Laboratory of Molecular Biology of Parasites and Vectors, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, ⁶¹Paulo de Góes Microbiology Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, ⁶²Centre for Technological Development in Health (CDTS), Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, ⁶³Cardiovascular Research Institute, Icahn School of Medicine at Mount Sinai, New York, United States of America, ⁶⁴Department of Clinical Chemistry and Hematology, University Medical Center Utrecht, Utrecht, The Netherlands, ⁶⁵California Nanosystems Institute, University of California Los Angeles, Los Angeles, California, United States of America, ⁶⁶Department of Biosciences, Division of Biochemistry and Biotechnology, University of Helsinki, Helsinki, Finland, ⁶⁷Australian Prostate Cancer Research Centre-Queensland, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia, ⁶⁸Department of Cell Biology and Physiology, Washington University School of Medicine, Saint Louis, Missouri, United States of America, ⁶⁹Department of Health Science and Technology, Aalborg University, Aalborg, Denmark, ⁷⁰Department of Medical Physics, Jagiellonian University, Cracow, Poland, ⁷¹Department of Cellular and Molecular Biology, Graduate School of Biomedical Science, Hiroshima University, Hiroshima, Japan, ⁷²Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany, ⁷³Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, ⁷⁴Ludwig Institute for Cancer Research Melbourne, Austin Hospital, Heidelberg, Victoria, Australia, ⁷⁵Department of Molecular Biology, Umeå University, Umeå, Sweden, ⁷⁶Department of Molecular and Comparative Pathobiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, ⁷⁷Unidad de Investigación, Hospital Santa Cristina, Instituto de Investigación Sanitaria Princesa, Madrid, Spain, ⁷⁸University of Muenchen, Department of Otorhinolaryngology and Research Group Gene Vectors, Helmholtz-Zentrum München, Munich, Germany

Associate Editor: Prof. Yong Song Gho

ABSTRACT

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

Results: We present an improved version of EVpedia, a public database for extracellular vesicles 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 6,879 publications, 172,080 vesicular components from 263 high-throughput datasets, and has been accessed >65,000 times from >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 extracellular vesicle research.

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

Contact: ysgho@postech.ac.kr

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 20–1,000 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; Cabby *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; Lee *et al.*, 2009); 3) EVs are rich sources of biomarkers for noninvasive 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;

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, Protasomes, Shedding Microvesicles, Shedding Vesicles, Tolerosomes

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; Lee *et al.*, 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 towards 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 are currently challenging, especially for start-up researchers in this field. Therefore, a comprehensive public repository of EV-related publications and vesicular components will help the community of EV research to understand various aspects of these complex extracellular organelles.

*To whom correspondence should be addressed.

†The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

‡Only these authors are not listed alphabetically by their last name.

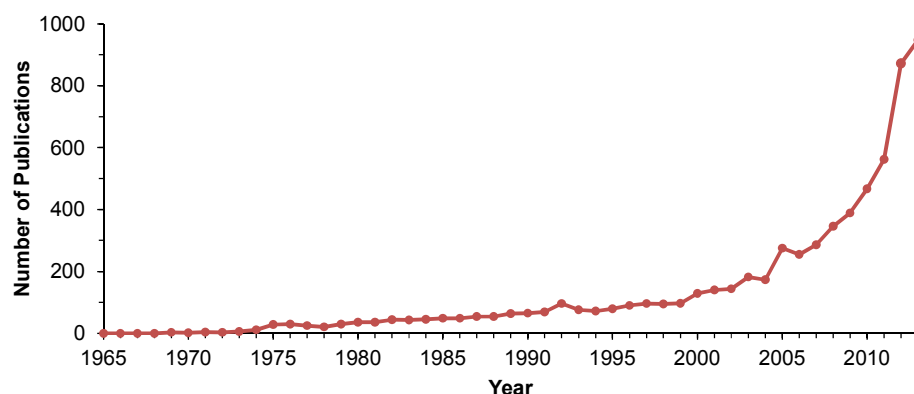


Fig. 1. Publication trend of extracellular vesicle studies. This graph shows the number of publications on extracellular vesicles per year, indicating that the field of extracellular vesicles is expanding rapidly.

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 metabolites, (iii) identification of orthologous vesicular compo-

nents, (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 Fig. 2.

Table 1. EVpedia Statistics

	All	Eukaryotes	Prokaryotes
Publications			
Articles	6,879	6,021	858
Principal investigators	3,336	2,886	483
Proteomes			
Studies	117	97	20
Datasets	176	148	28
Proteins	78,971	74,696	4,275
Transcriptomes			
<i>mRNA</i>			
Studies	17	17	0
Datasets	28	28	0
mRNAs	74,430	74,430	0
<i>miRNA</i>			
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)		

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

As of May, 2014, a total of 6,879 EV-related publications with 3,336 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, respec-

tively. 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 6,879 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 three 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.

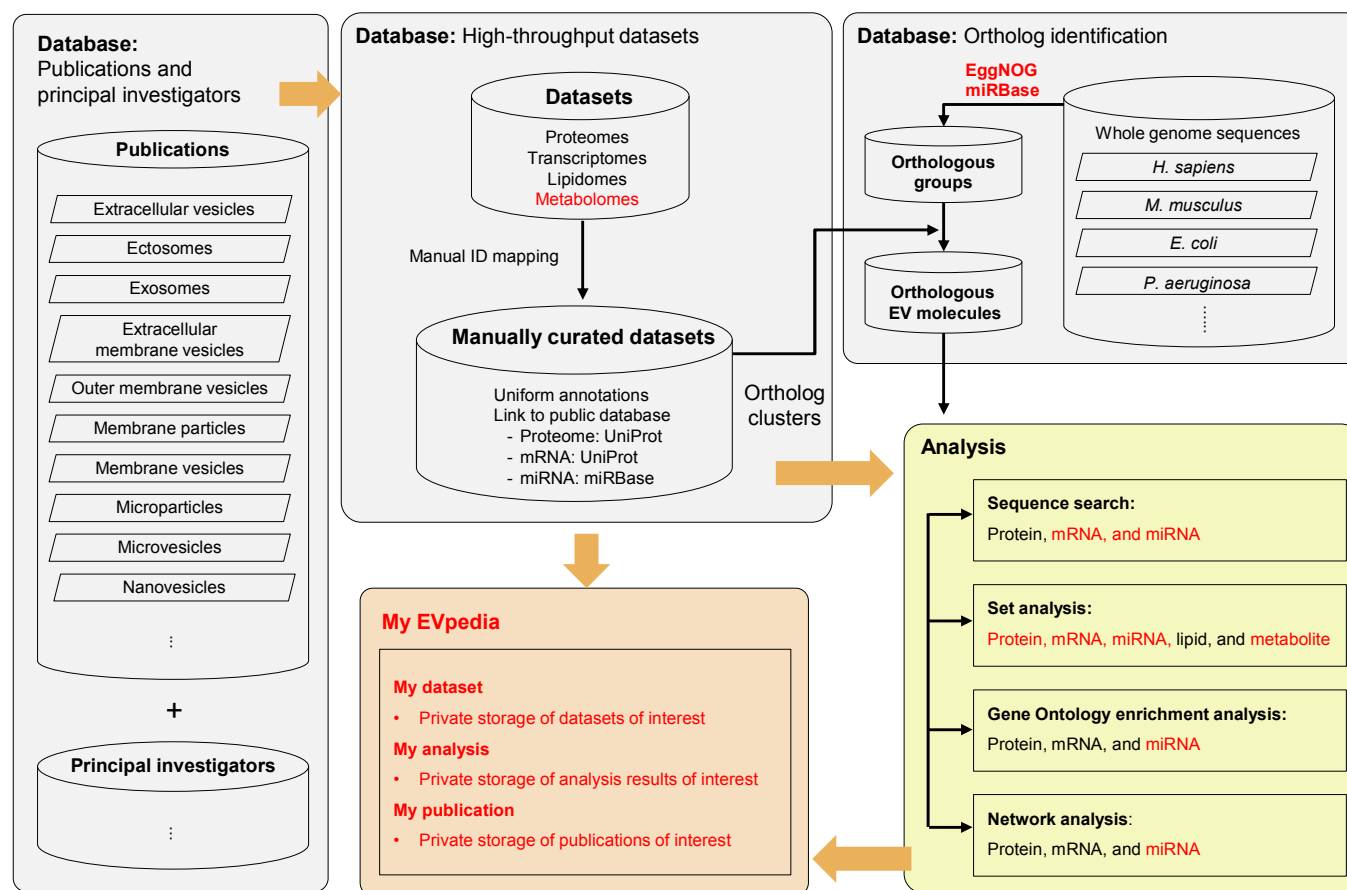


Fig. 2. Overall structure of EVpedia. EVpedia provides a comprehensive database for (i) publications and principal investigators, (ii) vesicular proteins, mRNAs, miRNAs, lipids, and metabolites, and (iii) identification of orthologous vesicular components. For systematic analyses of vesicular components, 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.

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2014-023004), the Ministry of Health and Welfare grant funded by the Korea government (No. A120273), and a grant from KRIBB Research Initiative Program. D.-K. K is supported by a National Junior Research Fellowship (No. 2013-055705) and Y. J. Y by BK21 PLUS program (10Z20130012243) funded by Ministry of Education, Science and Technology, Republic of Korea.

Conflict of Interest: none declared.

REFERENCES

- Alvarez-Erviti, L. *et al.* (2011) Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat. Biotechnol.*, **29**, 341-345.
- Asea, A. *et al.* (2008) Heat shock protein-containing exosomes in mid-trimester amniotic fluids. *J. Reprod. Immunol.*, **79**, 12-17.
- Barry, O.P. *et al.* (1997) Transcellular activation of platelets and endothelial cells by bioactive lipids in platelet microparticles. *J. Clin. Invest.*, **99**, 2118-2127.
- Bellingham, S.A. *et al.* (2012) Exosomes: vehicles for the transfer of toxic proteins associated with neurodegenerative diseases? *Front. Physiol.*, **3**, 124.
- Biller, S.J. *et al.* (2014) Bacterial vesicles in marine ecosystems. *Science*, **343**, 183-186.
- Caby, M.P. *et al.* (2005) Exosomal-like vesicles are present in human blood plasma. *Int. Immunol.*, **17**, 879-887.
- Chaput, N. *et al.* (2005) The potential of exosomes in immunotherapy. *Expert Opin. Biol. Ther.*, **5**, 737-747.
- Cheng, L. *et al.* (2014a) Exosomes provide a protective and enriched source of miRNA for biomarker profiling compared to intracellular and cell-free blood. *J. Extracell. Vesicles*, **3**, 23743.
- Cheng, L. *et al.* (2014b) Characterization and deep sequencing analysis of exosomal and non-exosomal miRNA in human urine. *Kidney Int.*, **86**:434-444.
- Choi, D.S. *et al.* (2013a) Circulating extracellular vesicles in cancer diagnosis and monitoring: an appraisal of clinical potential. *Mol. Diagn. Ther.*, **17**, 265-271.
- Choi, D.S. *et al.* (2013b) Proteomics, transcriptomics and lipidomics of exosomes and ectosomes. *Proteomics*, **13**, 1554-1571.
- Choi, D.S. *et al.* (2014) Proteomics of extracellular vesicles: Exosomes and ectosomes. *Mass Spectrom. Rev.*, (in press)
- Cocucci, E. *et al.* (2009) Shedding microvesicles: artefacts no more. *Trends Cell Biol.*, **19**, 43-51.
- D'Souza-Schorey, C. and Clancy, J.W. (2012) Tumor-derived microvesicles: shedding light on novel microenvironment modulators and prospective cancer biomarkers. *Genes Dev.*, **26**, 1287-1299.
- Dai, S. *et al.* (2008) Phase I clinical trial of autologous ascites-derived exosomes combined with GM-CSF for colorectal cancer. *Mol. Ther.*, **16**, 782-790.
- de Jong, O.G. *et al.* (2012) Cellular stress conditions are reflected in the protein and RNA content of endothelial cell-derived exosomes. *J. Extracell. Vesicles*, **1**, 18396.
- Deatherage, B.L. and Cookson, B.T. (2012) Membrane vesicle release in bacteria, eukaryotes, and archaea: a conserved yet underappreciated aspect of microbial life. *Infect. Immun.*, **80**, 1948-1957.
- Duperthuy, M. *et al.* (2013) Role of the *Vibrio cholerae* matrix protein Bap1 in cross-resistance to antimicrobial peptides. *PLoS Pathog.*, **9**, e1003620.
- Ellen, A.F. *et al.* (2009) Proteomic analysis of secreted membrane vesicles of archaeal *Sulfolobus* species reveals the presence of endosome sorting complex components. *Extremophiles*, **13**, 67-79.
- George, J.N. *et al.* (1982) Isolation of human platelet membrane microparticles from plasma and serum. *Blood*, **60**, 834-840.
- Gould, S.J. and Raposo, G. (2013) As we wait: coping with an imperfect nomenclature for extracellular vesicles. *J. Extracell. Vesicles*, **2**, 20389.
- Jang, S.C. *et al.* (2013) Bioinspired exosome-mimetic nanovesicles for targeted delivery of chemotherapeutics to malignant tumors. *ACS nano*, **7**, 7698-7710.
- Kalra, H. *et al.* (2012) Vesiclepedia: a compendium for extracellular vesicles with continuous community annotation. *PLoS Biol.*, **10**, e1001450.
- Kim, D.K. *et al.* (2013) EVpedia: an integrated database of high-throughput data for systemic analyses of extracellular vesicles. *J. Extracell. Vesicles*, **2**, 20384.
- Koh, W. *et al.* (2010) Analysis of deep sequencing microRNA expression profile from human embryonic stem cells derived mesenchymal stem cells reveals possible role of let-7 microRNA family in downstream targeting of hepatic nuclear factor 4 alpha. *BMC Genomics*, **11 Suppl 1**, S6.
- Kordelas, L. *et al.* (2014) MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease. *Leukemia*, **28**, 970-973.
- Lai, R.C. *et al.* (2010) Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. *Stem Cell Res.*, **4**, 214-222.
- Lässer, C. *et al.* (2011) Human saliva, plasma and breast milk exosomes contain RNA: uptake by macrophages. *J. Transl. Med.*, **9**, 9.
- Lee, E.Y. *et al.* (2008) Proteomics in Gram-negative bacterial outer membrane vesicles. *Mass Spectrom. Rev.*, **27**, 535-555.
- Lee, E.Y. *et al.* (2009) Gram-positive bacteria produce membrane vesicles: proteomics-based characterization of *Staphylococcus aureus*-derived membrane vesicles. *Proteomics*, **9**, 5425-5436.
- Lee, E.Y. *et al.* (2012) Therapeutic effects of autologous tumor-derived nanovesicles on melanoma growth and metastasis. *PLoS One*, **7**, e33330.
- Mayr, M. *et al.* (2009) Proteomics, metabolomics, and immunomics on microparticles derived from human atherosclerotic plaques. *Cir. Cardiovasc. Genet.*, **2**, 379-388.
- Mullier, F. *et al.* (2013) Platelet microparticle generation assay: A valuable test for immune heparin-induced thrombocytopenia diagnosis. *Thromb. Res.*, **133**, 1068-1073.
- Poliakov, A. *et al.* (2009) Structural heterogeneity and protein composition of exosome-like vesicles (prostasomes) in human semen. *Prostate*, **69**, 159-167.
- Raimondo, F. *et al.* (2011) Advances in membranous vesicle and exosome proteomics improving biological understanding and biomarker discovery. *Proteomics*, **11**, 709-720.
- Raj, D.A. *et al.* (2012) A multiplex quantitative proteomics strategy for protein biomarker studies in urinary exosomes. *Kidney Int.*, **81**, 1263-1272.
- Sarlon-Bartoli, G. *et al.* (2013) Plasmatic level of leukocyte-derived microparticles is associated with unstable plaque in asymptomatic patients with high-grade carotid stenosis. *J. Am. Coll. Cardiol.*, **62**, 1436-1441.
- Shedden, K. *et al.* (2003) Expulsion of small molecules in vesicles shed by cancer cells: association with gene expression and chemosensitivity profiles. *Cancer Res.*, **63**, 4331-4337.
- Simons, M. and Raposo, G. (2009) Exosomes--vesicular carriers for intercellular communication. *Curr. Opin. Cell Biol.*, **21**, 575-581.
- Simpson, R.J. *et al.* (2008) Proteomic profiling of exosomes: current perspectives. *Proteomics*, **8**, 4083-4099.
- Simpson, R.J. *et al.* (2012) ExoCarta as a resource for exosomal research. *J. Extracell. Vesicles*, **1**, 18374.
- Simpson, R.J. *et al.* (2009) Exosomes: proteomic insights and diagnostic potential. *Expert Rev. Proteomics*, **6**, 267-283.
- Subra, C. *et al.* (2007) Exosome lipidomics unravels lipid sorting at the level of multivesicular bodies. *Biochimie*, **89**, 205-212.
- Sun, D. *et al.* (2010) A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. *Mol. Ther.*, **18**, 1606-1614.
- Théry, C. *et al.* (2009) Membrane vesicles as conveyors of immune responses. *Nat. Rev. Immunol.*, **9**, 581-593.
- Utlög, A.G. *et al.* (2003) Proteomic analysis of human prostasomes. *Prostate*, **56**, 150-161.
- Valadi, H. *et al.* (2007) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat. Cell Biol.*, **9**, 654-659.
- Wai, S.N. *et al.* (2003) Vesicle-mediated export and assembly of pore-forming oligomers of the enterobacterial ClyA cytotoxin. *Cell*, **115**, 25-35.
- Witwer, K.W. *et al.* (2013) Standardization of sample collection, isolation and analysis methods in extracellular vesicle research. *J. Extracell. Vesicles*, **2**, 20360.