

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Kalra, H;Simpson, RJ;Ji, H;Aikawa, E;Altevogt, P;Askenase, P;Bond, VC;Borràs, FE;Breakefield, X;Budnik, V;Buzas, E;Camussi, G;Clayton, A;Cocucci, E;Falcon-Perez, JM;Gabrielsson, S;Gho, YS;Gupta, D;Harsha, HC;Hendrix, A;Hill, AF;Inal, JM;Jenster, G;Krämer-Albers, EM;Lim, SK;Llorente, A;Lötvall, J;Marcilla, A;Mincheva-Nilsson, L;Nazarenko, I;Nieuwland, R;Nolte-'t Hoen, ENM;Pandey, A;Patel, T;Piper, MG;Pluchino, S;Prasad, TSK;Rajendran, L;Raposo, G;Record, M;Reid, GE;Sánchez-Madrid, F;Schiffelers, RM;Siljander, P;Stensballe, A;Stoorvogel, W;Taylor, D;Thery, C;Valadi, H;van Balkom, BW;Vázquez, J;Vidal, M;Wauben, MHM;Yáñez-Mó, M;Zoeller, M;Mathivanan, S

Title:

Vesiclepedia: A Compendium for Extracellular Vesicles with Continuous Community Annotation

Date:

2012-12-01

Citation:

Kalra, H., Simpson, R. J., Ji, H., Aikawa, E., Altevogt, P., Askenase, P., Bond, V. C., Borràs, F. E., Breakefield, X., Budnik, V., Buzas, E., Camussi, G., Clayton, A., Cocucci, E., Falcon-Perez, J. M., Gabrielsson, S., Gho, Y. S., Gupta, D., Harsha, H. C., ... Mathivanan, S. (2012). Vesiclepedia: A Compendium for Extracellular Vesicles with Continuous Community Annotation. *Plos Biology*, 10 (12), <https://doi.org/10.1371/journal.pbio.1001450>.

Persistent Link:

<https://hdl.handle.net/11343/265302>

License:

CC BY

Vesiclepedia: A Compendium for Extracellular Vesicles with Continuous Community Annotation

Hina Kalra^{1†}, Richard J. Simpson^{1†}, Hong Ji^{1†}, Elena Aikawa², Peter Altevogt³, Philip Askenase⁴, Vincent C. Bond⁵, Francesc E. Borràs⁶, Xandra Breakefield⁷, Vivian Budnik⁸, Edit Buzas⁹, Giovanni Camussi¹⁰, Aled Clayton¹¹, Emanuele Cocucci^{12,13}, Juan M. Falcon-Perez^{14,15}, Susanne Gabrielsson¹⁶, Yong Song Gho¹⁷, Dwijendra Gupta¹⁸, H. C. Harsha¹⁹, An Hendrix²⁰, Andrew F. Hill²¹, Jameel M. Inal²², Guido Jenster²³, Eva-Maria Krämer-Albers²⁴, Sai Kiang Lim²⁵, Alicia Llorente²⁶, Jan Lötvall²⁷, Antonio Marcilla²⁸, Lucia Mincheva-Nilsson²⁹, Irina Nazarenko³⁰, Rienk Nieuwland³¹, Esther N. M. Nolte-’t Hoen³², Akhilesh Pandey^{19,33,34,35}, Tushar Patel³⁶, Melissa G. Piper³⁷, Stefano Pluchino³⁸, T. S. Keshava Prasad¹⁹, Lawrence Rajendran³⁹, Graca Raposo⁴⁰, Michel Record⁴¹, Gavin E. Reid⁴², Francisco Sánchez-Madrid⁴³, Raymond M. Schiffelers⁴⁴, Pia Siljander⁴⁵, Allan Stensballe⁴⁶, Willem Stoorvogel⁴⁷, Douglas Taylor⁴⁸, Clotilde Thery^{49,50}, Hadi Valadi⁵¹, Bas W. M. van Balkom⁵², Jesús Vázquez⁵³, Michel Vidal⁵⁴, Marca H. M. Wauben⁵⁵, María Yáñez-Mó⁵⁶, Margot Zoeller⁵⁷, Suresh Mathivanan^{1†*}

1 Department of Biochemistry, La Trobe Institute for Molecular Science, La Trobe University, Melbourne, Victoria, Australia, **2** Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, **3** Tumor Immunology Programme, German Cancer Research Center, Heidelberg, Germany, **4** Department of Medicine, Yale Medical School, New Haven, Connecticut, United States of America, **5** Department of Microbiology, Biochemistry, and Immunology, Morehouse School of Medicine, Atlanta, Georgia, United States of America, **6** IVECAT, LIRAD-BST, Institut d'Investigació Germans Trias i Pujol, Dept de Biologia Cel·lular, Fisiologia i Immunologia, Universitat Autònoma de Barcelona, Badalona, Spain, **7** Department of Neurology, Massachusetts General Hospital, and Neuroscience Program, Harvard Medical School, Boston, Massachusetts, United States of America, **8** Department of Neurobiology, University of Massachusetts Medical School, Worcester, Massachusetts, United States of America, **9** Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary, **10** Department of Internal Medicine, Centre for Molecular Biotechnology and Centre for Research in Experimental Medicine, Torino, Italy, **11** Institute of Cancer & Genetics, School of Medicine, Cardiff University, Velindre Cancer Centre, Whitchurch, Cardiff, United Kingdom, **12** Department of Cell Biology, Harvard Medical School, Boston, Massachusetts, United States of America, **13** Immune Disease Institute and Program in Cellular and Molecular Medicine at Boston Children's Hospital, Boston, Massachusetts, United States of America, **14** Metabolomics Unit, CIC bioGUNE, CIBERehd, Technology Park of Bizkaia, Derio, Bizkaia, Spain, **15** IKERBASQUE, Basque Foundation for Science, Bilbao, Spain, **16** Translational Immunology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden, **17** Department of Life Science, Pohang University of Science and Technology, Pohang, Republic of Korea, **18** Center of Bioinformatics, Institute of Interdisciplinary Studies, University of Allahabad, Allahabad, India, **19** Institute of Bioinformatics, Bangalore, India, **20** Laboratory of Experimental Cancer Research, Department of Radiation Oncology and Experimental Cancer Research, Ghent University Hospital, Ghent, Belgium, **21** Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville, Australia, **22** Cellular and Molecular Immunology Research Centre, Faculty of Life Sciences, London Metropolitan University, London, United Kingdom, **23** Department of Urology, Erasmus Medical Centre, Rotterdam, The Netherlands, **24** Department of Molecular Cell Biology, Johannes Gutenberg University Mainz, Mainz, Germany, **25** A*STAR Institute of Medical Biology and Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, **26** Department of Biochemistry, Institute for Cancer Research, Oslo University Hospital-The Norwegian Radium Hospital, Oslo, Norway, **27** Krefting Research Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, **28** Àrea de Parasitologia, Departamento de Biologia Celular y Parasitologia, Universitat de València, Burjassot (Valencia), Spain, **29** Department of Clinical Microbiology/Clinical Immunology, Umeå University, Umeå, Sweden, **30** Department of Environmental Health Sciences, University Medical Center Freiburg, Freiburg, Germany, **31** Department of Clinical Chemistry, Academic Medical Center, Amsterdam, The Netherlands, **32** Department of Biochemistry & Cell Biology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands, **33** McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, **34** Department of Biological Chemistry, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, **35** Department of Oncology and Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, **36** Mayo Clinic, Jacksonville, Florida, United States of America, **37** Department of Internal Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Davis Heart & Lung Research Institute, The Ohio State University, Columbus, Ohio, United States of America, **38** Center for Brain Repair and Wellcome Trust-MRC Stem Cell Institute, Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom, **39** Systems and Cell Biology of Neurodegeneration, Division of Psychiatry Research, University of Zurich, Zurich, Switzerland, **40** Institut Curie, Paris, France, **41** Cancer Researaud, Toulouse, France, **42** Department of Chemistry, Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, Michigan, United States of America, **43** Servicio de Inmunología, Hospital de la Princesa, Universidad Autonoma Madrid, Madrid, Spain, **44** Laboratory of Clinical Chemistry and Haematology, University Medical Center Utrecht, Utrecht, The Netherlands, **45** Department of Biosciences, Division of Biochemistry and Biotechnology, University of Helsinki, Finland, **46** Institute for Biotechnology, University of Aalborg, Denmark, **47** Department of Biochemistry and Cell Biology, Faculty of Veterinary Medicine and Institute of Biomembranes, Utrecht University, Utrecht, The Netherlands, **48** Department of Obstetrics, Gynecology and Women's Health and James Graham Brown Cancer Center, University of Louisville School of Medicine, Louisville, Kentucky, United States of America, **49** Institut Curie Centre de Recherche, Paris, France, **50** INSERM U932, Paris, France, **51** Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, **52** Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands, **53** Cardiovascular Proteomics Laboratory, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain, **54** UMR 5235 CNRS-University Montpellier II, Montpellier, France, **55** Department of Biochemistry & Cell Biology, Faculty of Veterinary Medicine, Life Sciences, Utrecht University, Utrecht, The Netherlands, **56** Unidad de Investigación, Hospital Santa Cristina, Instituto de Investigación Sanitaria Princesa, Madrid, Spain, **57** Department of Tumor Cell Biology, University Hospital of Surgery, Heidelberg, Germany

Abstract: Extracellular vesicles (EVs) are membraneous vesicles released by a variety of cells into their microenvironment. Recent studies have elucidated the role of EVs in intercellular communication, pathogenesis, drug, vaccine and gene-vector delivery, and as possible reservoirs of biomarkers. These findings have generated immense interest, along with an exponential increase in molecular data pertaining to EVs. Here, we describe Vesiclepedia, a manually curated compendium of molecular data (lipid, RNA, and protein) identified in different classes of EVs from more than 300 independent studies published over the past several years. Even though databases are indispensable resources for the scientific community, recent studies have shown that more than 50% of the databases are not regularly updated. In addition, more than 20% of the database links are inactive. To prevent such database and link decay, we have initiated a continuous community annotation project with the active involvement of EV researchers. The EV research community can set a gold standard in data sharing with Vesiclepedia, which could evolve as a primary resource for the field.

Introduction

A growing body of research has implicated extracellular vesicles (EVs), membraneous sacs released by a variety of cells, in diverse physiological and patho-physiological conditions [1–9]. They can be detected in body fluids including blood plasma, urine, saliva, amniotic fluid, breast milk, and pleural ascites [10–13], and contain proteins, lipids, and RNA representative of the host cell [14–18]. Though a definitive categorization is yet to be achieved [19], EVs can be broadly classified into three main classes, based on the mode of biogenesis: (i) ectosomes (also referred to as shedding microvesicles), (ii) exosomes, and (iii) apoptotic bodies (ABs) (see Box 1).

Recent studies have highlighted the role of EVs in intercellular communication [20–22], vaccine and drug delivery [23–25], and suggested a potential role in gene

vector therapy [26] and as disease biomarkers [27]. More than three decades of research has advanced our basic understanding of these extracellular organelles and has generated large amounts of multidimensional data [14,17]. Whilst most of the data are presented in the context of the biological findings/technical development and are mentioned in the inline text of the published article, a vast majority are often placed as supplementary information or not provided [28,29]. Importantly, none of the molecular data in published articles is easily searchable [28]. With the immense interest in EVs and advances in high-throughput techniques, the data explosion will only increase. An online compendium of heterogeneous data will help the biomedical community to exploit the publicly available datasets and accelerate biological discovery [30].

ExoCarta and Need for an EV Database

Existing databases are not comprehensive. For example, ExoCarta (<http://www.exocarta.org>), a database for molecular data (proteins, RNA, and lipids) identified in exosomes, catalogs only exosomal studies (as reported by the authors) [31]. Described initially in 2009 [32], the database has been visited by more than 16,000 unique users [33]. However, only exosomal studies (as reported by the authors) are catalogued in ExoCarta. With the confusion in terminologies and inefficiency of the purification protocols to clearly segregate each class of EVs [1,19], it is critical to build a repository with data from all classes of EVs to understand more about the molecular repertoire of the various classes of EVs and their biological functions. This was the rationale for starting the Vesiclepedia online compendium for EVs.

Vesiclepedia

Vesiclepedia (<http://www.microvesicles.org>) is a manually curated compendium that contains molecular data identified in all classes of EVs, including AB, exosomes, large dense core vesicles, microparticles, and shedding microvesicles. The main criterion for manual curation was the presence of these vesicles in the extracellular microenvironment (EVs) as approved by the investigators who undertook the research. At this juncture, the EVs are named as per the curated article or submitting author, as the nomenclature is yet to be standardized [19]. Vesiclepedia was built using ZOPE, an open source content management system. Python a portable, interpreted, object oriented programming language was used in the three-tier system to connect the web interface with a MySQL database. Users can query or browse through proteins, lipids, and RNA molecules identified in EVs. Selecting a gene of interest directs the user to a gene/molecule page with information on the gene, its external references to other primary databases, experiment description of the study that identified the molecule, gene ontology based annotations, protein-protein interactions, and a graphical display of such network with relevance to molecules identified in EVs. Gene ontology annotations of molecular functions, biological process, and subcellular localization were retrieved from Entrez Gene [34] and mapped onto the proteins/mRNA identified in EVs. Under the experiment description, the sample source including the tissue name or cell line name, EV isolation procedures, and floatation gradient density as reported in the study are provided to the users. EV proteins are mapped onto their protein physical interactors along with the protein interaction identification method and PubMed identifier. Protein-protein interaction data was obtained from HPRD

Citation: Kalra H, Simpson RJ, Ji H, Aikawa E, Altevogt P, et al. (2012) Vesiclepedia: A Compendium for Extracellular Vesicles with Continuous Community Annotation. *PLoS Biol* 10(12): e1001450. doi:10.1371/journal.pbio.1001450

Published: December 18, 2012

Copyright: © 2012 Kalra et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This work was supported by a NH&MRC fellowship (1016599) and LIMS fellowship to SM. Part of tool development for data upload into Vesiclepedia was funded by the eResearch Office at La Trobe University with programming support from the Victorian eResearch Strategic Initiative (VeRSI). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: AB, apoptotic body; EV, extracellular vesicle

* E-mail: S.Mathivanan@latrobe.edu.au

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

The Community Page is a forum for organizations and societies to highlight their efforts to enhance the dissemination and value of scientific knowledge.

Box 1. Categories of EVs Based on the Mode of Biogenesis

Ectosomes or shedding microvesicles: Ectosomes are large EVs ranging between 50–1,000 nm in diameter [1]. They are shed from cells by outward protrusion (or budding) of a plasma membrane (PM) followed by fission of their membrane stalk [3,5]. Ectosomes are released by a variety of cells including tumour cells, polymorphonuclear leucocytes, and aging erythrocytes [5]. The expression of phosphatidylserine (PS) on the membrane surface has been shown to be one of the characteristic features of ectosomes [1,5].

Exosomes: Exosomes are small membranous vesicles of endocytic origin ranging from 40–100 nm in diameter [1,42]. The density of exosomes varies from 1.10–1.21 g/ml and the commonly found markers of exosomes are Alix, TSG101, tetraspanins, and heat shock proteins [10]. The biogenesis of exosomes begins with the internalisation of molecules via endocytosis [42]. Once internalised, endocytosed molecules are either recycled to the PM or trafficked to multivesicular bodies (MVBs) [3]. The “exocytic” fate of MVBs results in their exocytic fusion with the PM, resulting in the release of intraluminal vesicles into the extracellular microenvironment as exosomes [43].

Apoptotic bodies: ABs are released from fragmented apoptotic cells and are 50–5,000 nm in diameter [1]. ABs are formed about during the process of programmed cell death or apoptosis, and represent the fragments of dying cells [3]. Similar to ectosomes, the expression of PS on the membrane surface has been shown to be a key characteristic of ABs [1,5].

[35,36], BioGRID [37], and Human Proteinpedia [38].

Database Issues and Community Annotation

Though biological databases are indispensable resources for effective scientific research, it has to be noted that more than 20% of the database links are non-existent after their initial publication [39–41]. More than 50% of the databases are never updated reducing their usability [39], primarily due to the lack of continuous funding to maintain and update these resources. At this juncture, funding for databases is largely non-existent in many parts of the world. To overcome funding-related limitations and to keep the database updated, it is essential to involve the scientific community in annotating the data. Community annotation will significantly ease the burden of the curators who maintain and update the databases. Whilst community annotation is the permanent solution to keep the database updated, it seldom happens without a clear and transparent mechanism. In addition, the system has to ensure continuous deposition of data and “not just once” uploads. It has to be noted that data annotation can be regulated at two levels: (i) principal investigators voluntarily contributing data and (ii) peer-reviewed journals mandating data deposition before publication. Currently available community annotation tools don't have a continuous data deposition arrangement with an investigator. Additionally, only few journals mandate

the deposition of data to public repositories before acceptance of a manuscript. To this end, we have initiated a community annotation project through Vesiclepedia that involves members of the EV research community (53 laboratories from 20 countries: Table 1).

Community annotation via Vesiclepedia happens through the founding members who agree to the conditions listed in Box 2. All of the members are listed in the credits page (<http://www.microvesicles.org/credits>).

On the basis of the agreement of community participation, members will submit their data automatically to Vesiclepedia before or after publication (Figure 1). Non-members submitting their research findings for peer-review through international journals might find the Vesiclepedia members as referees who will request/mandate the authors to submit the data to Vesiclepedia. By instituting this mechanism the datasets will be continuously deposited to Vesiclepedia. However, a non-member can also be appointed as a

Box 2. Conditions to Become a Member of Vesiclepedia Community Annotation

- 1, Agree to submit datasets pertaining to EVs to Vesiclepedia before or after publication on a continuous basis
- 2, When reviewing articles, mandate/request investigators to submit datasets on EVs to Vesiclepedia

Table 1. Vesiclepedia statistics.

Statistics	<i>n</i>
EV studies	341
Protein entries	35,264
mRNA entries	18,718
miRNA entries	1,772
Lipid molecules	342
Participating laboratories	53
Countries	20

doi:10.1371/journal.pbio.1001450.t001

referee in which case the data might not be submitted to Vesiclepedia. The Vesiclepedia-data capture team will work along with the researchers to make the data submission as easy as possible. Detailed information on the format of data required for submission is provided in the Vesiclepedia webpage (http://www.microvesicles.org/data_submission). Currently, Vesiclepedia comprises 35,264 protein, 18,718 mRNA, 1,772 miRNA, and 342 lipid entries (Table 1). All of these data were obtained from 341 independent studies that were published over the past several years.

Conclusions and Future Directions

ExoCarta will be active even after the release of Vesiclepedia and will become a primary resource for high-quality exosomal datasets. Data deposited to ExoCarta can also be accessed through Vesiclepedia; however, only high quality exosomal datasets deposited to Vesiclepedia can be accessed through ExoCarta. With the launch of Vesiclepedia, we expect to have an organised data deposition mechanism. We expect active participation from the EV research community, along with the addition of new members and numerous heterogeneous datasets. All datasets submitted by EV researchers will be listed in the credits page along with the investigator details.

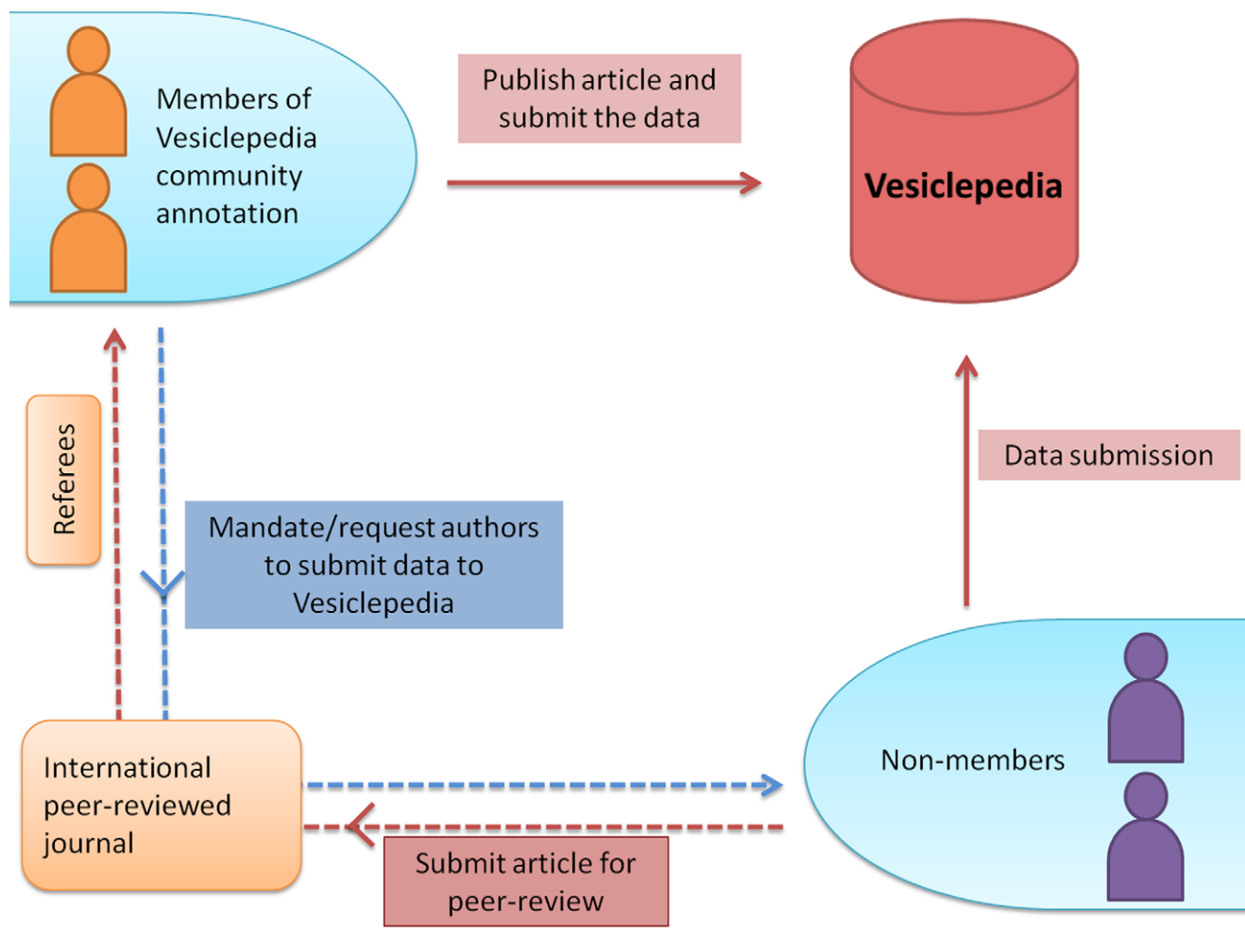


Figure 1. A schematic of Vesiclepedia community annotation. Based on the agreement of community participation, members will submit their data automatically to Vesiclepedia before and after publication. Non-members submitting their research findings for peer-review through international journals might find some of the Vesiclepedia members as referees who will request/mandate the authors to submit the data to Vesiclepedia. Alternatively, a non-member can also be appointed as a referee in which case the data might not be submitted to Vesiclepedia. A non-member can also submit data directly to Vesiclepedia.
doi:10.1371/journal.pbio.1001450.g001

References

1. Thery C, Ostrowski M, Segura E (2009) Membrane vesicles as conveyors of immune responses. *Nat Rev Immunol* 9: 581–593.
2. Keller S, Sanderson MP, Stoeck A, Altevogt P (2006) Exosomes: from biogenesis and secretion to biological function. *Immunol Lett* 107: 102–108.
3. Mathivanan S, Ji H, Simpson RJ (2010) Exosomes: Extracellular organelles important in intercellular communication. *J Proteomics* 73: 1907–1920.
4. Ratajczak J, Wysoczynski M, Hayek F, Janowska-Wieczorek A, Ratajczak MZ (2006) Membrane-derived microvesicles: important and underappreciated mediators of cell-to-cell communication. *Leukemia* 20: 1487–1495.
5. Cocucci E, Racchetti G, Meldolesi J (2009) Shedding microvesicles: artefacts no more. *Trends Cell Biol* 19: 43–51.
6. Stoorvogel W, Kleijmeer MJ, Geuze HJ, Raposo G (2002) The biogenesis and functions of exosomes. *Traffic* 3: 321–330.
7. van Niel G, Porto-Carreiro I, Simoes S, Raposo G (2006) Exosomes: a common pathway for a specialized function. *J Biochem (Tokyo)* 140: 13–21.
8. Johnstone RM (2006) Exosomes biological significance: A concise review. *Blood Cells Mol Dis* 36: 315–321.
9. Rajendran L, Honsho M, Zahn TR, Keller P, Geiger KD, et al. (2006) Alzheimer's disease beta-amyloid peptides are released in association with exosomes. *Proc Natl Acad Sci U S A* 103: 11172–11177.
10. Simpson RJ, Lim JW, Moritz RL, Mathivanan S (2009) Exosomes: proteomic insights and diagnostic potential. *Expert Rev Proteomics* 6: 267–283.
11. Lasser C, Alikhani VS, Ekstrom K, Eldh M, Paredes PT, et al. (2011) Human saliva, plasma and breast milk exosomes contain RNA: uptake by macrophages. *J Transl Med* 9: 9.
12. Admyre C, Johansson SM, Qazi KR, Filen JJ, Lahesmaa R, et al. (2007) Exosomes with immune modulatory features are present in human breast milk. *J Immunol* 179: 1969–1978.
13. Mincheva-Nilsson L, Baranov V (2010) The role of placental exosomes in reproduction. *Am J Reprod Immunol* 63: 520–533.
14. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, 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.
15. Thery C, Zitvogel L, Amigorena S (2002) Exosomes: composition, biogenesis and function. *Nat Rev Immunol* 2: 569–579.
16. Al-Nedawi K, Meehan B, Rak J (2009) Microvesicles: messengers and mediators of tumor progression. *Cell Cycle* 8: 2014–2018.
17. Mathivanan S, Lim JW, Tauro BJ, Ji H, Moritz RL, et al. (2010) Proteomics analysis of A33 immunoaffinity-purified exosomes released from the human colon tumor cell line LIM1215 reveals a tissue-specific protein signature. *Mol Cell Proteomics* 9: 197–208.

18. Al-Nedawi K, Meehan B, Micallef J, Lhotak V, May L, et al. (2008) Intercellular transfer of the oncogenic receptor EGFRvIII by microvesicles derived from tumour cells. *Nat Cell Biol* 10: 619–624.
19. Simpson RJ, Mathivanan S (2012) Extracellular microvesicles: the need for internationally recognised nomenclature and stringent purification criteria. *J Proteomics Bioinform* 5: ii–ii.
20. Hood JL, San RS, Wickline SA (2011) Exosomes released by melanoma cells prepare sentinel lymph nodes for tumor metastasis. *Cancer Res* 71: 3792–3801.
21. Peinado H, Aleckovic M, Lavotshkin S, Matei I, Costa-Silva B, et al. (2012) Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. *Nat Med* 18: 883–891.
22. Mittelbrunn M, Gutierrez-Vazquez C, Villarroya-Beltri C, Gonzalez S, Sanchez-Cabo F, et al. (2011) Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells. *Nat Commun* 2: 282.
23. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhali S, et al. (2011) Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat Biotechnol* 29: 341–345.
24. Sun D, Zhuang X, Xiang X, Liu Y, Zhang S, 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.
25. Lakhali S, Wood MJ (2010) Exosome nanotechnology: an emerging paradigm shift in drug delivery: exploitation of exosome nanovesicles for systemic in vivo delivery of RNAi heralds new horizons for drug delivery across biological barriers. *Bioessays* 33: 737–741.
26. Maguire CA, Balaj L, Sivaraman S, Crommentuijn MH, Ericsson M, et al. (2012) Microvesicle-associated AAV vector as a novel gene delivery system. *Mol Ther* 20: 960–971.
27. Skog J, Wurdinger T, van Rijn S, Meijer DH, Gainche L, et al. (2008) Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nat Cell Biol* 10: 1470–1476.
28. Santos C, Blake J, States DJ (2005) Supplementary data need to be kept in public repositories. *Nature* 438: 738.
29. Mathivanan S, Ahmed M, Ahn NG, Alexandre H, Amanchy R, et al. (2008) Human Proteinpedia enables sharing of human protein data. *Nat Biotechnol* 26: 164–167.
30. Vizcaino JA, Foster JM, Martens L (2010) Proteomics data repositories: providing a safe haven for your data and acting as a springboard for further research. *J Proteomics* 73: 2136–2146.
31. Mathivanan S, Fahner CJ, Reid GE, Simpson RJ (2012) ExoCarta 2012: database of exosomal proteins, RNA and lipids. *Nucleic Acids Res* 40: D1241–D1244.
32. Mathivanan S, Simpson RJ (2009) ExoCarta: A compendium of exosomal proteins and RNA. *Proteomics* 21: 4997–5000.
33. Simpson RJ, Kalra H, Mathivanan S (2012) ExoCarta as a resource for exosomal research. *Journal of Extracellular Vesicles* 1: 18374.
34. Maglott D, Ostell J, Pruitt KD, Tatusova T (2007) Entrez Gene: gene-centered information at NCBI. *Nucleic Acids Res* 35: D26–31.
35. Mishra GR, Mathivanan S, Kumaran K, Kannabiran N, Suresh S, et al. (2006) Human protein reference database—2006 update. *Nucleic Acids Res* 34: D411–414.
36. Keshava Prasad TS, Goel R, Kandasamy K, Keerthikumar S, Kumar S, et al. (2009) Human Protein Reference Database—2009 update. *Nucleic Acids Res* 37: D767–772.
37. Breitkreutz BJ, Stark C, Reguly T, Boucher L, Breitkreutz A, et al. (2008) The BioGRID Interaction Database: 2008 update. *Nucleic Acids Res* 36: D637–640.
38. Mathivanan S, Pandey A (2008) Human Proteinpedia as a resource for clinical proteomics. *Mol Cell Proteomics* 7: 2038–2047.
39. Wren JD (2008) URL decay in MEDLINE—a 4-year follow-up study. *Bioinformatics* 24: 1381–1385.
40. Ducut E, Liu F, Fontelo P (2008) An update on Uniform Resource Locator (URL) decay in MEDLINE abstracts and measures for its mitigation. *BMC Med Inform Decis Mak* 8: 23.
41. Wren JD (2004) 404 not found: the stability and persistence of URLs published in MEDLINE. *Bioinformatics* 20: 668–672.
42. Fevrier B, Raposo G (2004) Exosomes: endosomal-derived vesicles shipping extracellular messages. *Curr Opin Cell Biol* 16: 415–421.
43. Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding CV, et al. (1996) B lymphocytes secrete antigen-presenting vesicles. *J Exp Med* 183: 1161–1172.