

# Exosome-like vesicles of helminths: implication of pathogenesis and vaccine development

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Helminthes are multicellular parasitic pathogens including nematodes (roundworms), cestoda (tapeworms) and trematoda (flukes) (1). These parasites cause hosts' weakness and diseases by living in and feeding on living hosts, by receiving nourishment (1). Deep understanding of mechanism between parasites and hosts may help to develop a novel and effective intervention against parasitic diseases.

Extracellular vesicles (EVs) are small membrane bounded vesicles that formed via the invagination of endocytic compartments generating multivesicular bodies (MVBs) and then released to the extracellular space after fusion of the MVBs with the plasma membrane. Consequently, various proteins, lipids, and nucleic acids are capsulated into EVs. It has been demonstrated that exosomes not only contribute to importantly biological functions such as tissue repair, neural communication, immunological response and the transfer of pathogenic proteins (2) but also regulate cellular functions, including motility and polarization, immune responses and development, and contribute to diseases such as cancer and neurodegeneration (3). In parasites, the pioneering study of parasitic exosomes was determined in *Trypanosoma brucei* in 2001 (4). Subsequently, several protozoa such as *Trichomonas vaginalis*, *T. cruzi*, *Leishmania spp.*, and helminths can also found to secrete EVs into living hosts (5). In helminths, secreted EVs have important roles in establishing and maintaining infection. There are two groups of EVs associated with parasitic infection: EVs secreted from

extracellular pathogens and EVs produced by host cells infected by parasitic pathogens. Accumulated evidences indicated that pathogenic EVs can act as signal molecules both in parasite-parasite inter-communication as well as in parasite-host interactions for maintaining normal parasitic physiology and leading to the pathogenesis of host (6,7).

Firstly, Marcilla and co-worker demonstrated that two trematodes, *Echinostoma caproni* (*E. caproni*) and *Fasciola hepatica* (*F. hepatica*) can secrete exosome-like vesicles and these EVs can be taken up by host cells, suggesting their potential role in the communication between the parasites and the host (6). In addition, Cwiklinski *et al.* characterize the EVs that involved in pathogenesis and migration of parasite through host tissue, from *F. hepatica* (8). This was one of the first studies to compare soluble and vesicular secretome of *F. hepatica* and describe the EV biogenesis, cargo sorting, and membrane trafficking and cytoskeleton regulation in *F. hepatica*. EVs secreted from *F. hepatica* are enriched in miRNAs and are associated with immune regulatory function (9). In flatworm, earlier study examining the glycocalyx of *Schistosoma mansoni* (*S. mansoni*) cercariae indicated the potential presence of structures similar to MVBs around schistosomula tegument (10). Recent studies in *S. japonicum* demonstrated that adult schistosomes secrete exosome-like vesicles that are able to uptake by mammalian cells and their miRNA cargos could potentially regulate

the expression of host's genes (11,12). Similarly, studies in *S. mansoni* also demonstrated that schistosomes can secrete EVs enriching small non-coding RNAs and proteins that some of them are similar to vaccine candidate (13,14). In nematodes, Buck and coworker demonstrated that *Heligmosomoides polygyrus* (*H. polygyrus*) secretes exosomes that are internalized by host cells. These are enriched in specific proteins, including those associated with exosome biogenesis (e.g., alix, enolase, HSP70), as well as many proteins of unknown function and contain miRNAs and other classes of non-coding RNA. In addition, they further demonstrated that the *H. polygyrus* exosomes could suppress immunological response *in vivo* (15). Overall, EVs from helminths could play important roles in the regulation of host immunological responses to tolerate the parasitic living in a final host.

As EVs carry proteins, lipids and nucleic acids from originating cells, these parasitic exosomes or exosome-like vesicles may express numerous proteins of their originating pathogen, and also release several molecules that involved in origination of these vesicles (16). These proteins and molecules could be potential biomarkers for diagnosis of helminths. Meanwhile, the concept for the use of exosomes as vaccine was first begun in the field of cancer where exosomes released from dendritic cells (DC) were used to mobilize immune system (17). Recent advances in disease control making scientists more confident for the use of antigen origin exosomes in vaccine progress. For instance, *Toxoplasma gondii* (*T. gondii*) infected DC-derived exosomes were used to protect against *T. gondii* infection in mice (18). DC derived exosomes from cells infected with the parasite *Eimeria* were found to convey protection in a poultry model (19). Furthermore, DC derived exosomes were also found to confer protective immunity against *Leishmania* in mice (20). In addition, exosome associated protein, CD63-like tetraspanins, from cestode *Echinococcus granulosus* has been implicated for the targeting of recipient cells and considering the use of exosomal protein as a promising tool for vaccination against alveolar echinococcosis (21). Moreover, mice immunized with purified exosomes from *E. caproni* reduced the symptom severity and mortality and increase the level of IFN- $\gamma$ , IL-4 and TGF- $\beta$  (22). Cumulative evidence suggests that exosomes based vaccine may be an important strategy for developing novel vaccine against parasitic diseases.

Although current studies of helminths EVs significantly expand our knowledge of host-pathogen interaction, and our general understanding for roles of EVs involved

in biogenesis and pathogenesis of helminths is steadily increasing. By deeply characterizing the functions of EVs may result in the identification of novel biomarkers and therapeutic strategies against neglected tropical diseases.

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## Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

## References

1. Hotez PJ, Brindley PJ, Bethony JM, et al. Helminth infections: the great neglected tropical diseases. *J Clin Invest* 2008;118:1311-21.
2. Bobrie A, Colombo M, Raposo G, et al. Exosome secretion: molecular mechanisms and roles in immune responses. *Traffic* 2011;12:1659-68.
3. Maas SL, Breakefield XO, Weaver AM. Extracellular Vesicles: Unique Intercellular Delivery Vehicles. *Trends Cell Biol* 2017;27:172-88.
4. Estévez AM, Kempf T, Clayton C. The exosome of *Trypanosoma brucei*. *EMBO J* 2001;20:3831-9.
5. Marcilla A, Martin-Jaular L, Trelis M, et al. Extracellular vesicles in parasitic diseases. *J Extracell Vesicles* 2014;3:25040.
6. Marcilla A, Trelis M, Cortés A, et al. Extracellular vesicles from parasitic helminths contain specific excretory/secretory proteins and are internalized in intestinal host cells. *PLoS One* 2012;7:e45974.
7. Barteneva NS, Maltsev N, Vorobjev IA. Microvesicles and intercellular communication in the context of parasitism. *Front Cell Infect Microbiol* 2013;3:49.
8. Cwiklinski K, de la Torre-Escudero E, Trelis M, et al. The Extracellular Vesicles of the Helminth Pathogen, *Fasciola hepatica*: Biogenesis Pathways and Cargo Molecules Involved in Parasite Pathogenesis. *Mol Cell Proteomics* 2015;14:3258-73.
9. Fromm B, Trelis M, Hackenberg M, et al. The revised microRNA complement of *Fasciola hepatica* reveals

- a plethora of overlooked microRNAs and evidence for enrichment of immuno-regulatory microRNAs in extracellular vesicles. *Int J Parasitol* 2015;45:697-702.
10. Samuelson JC, Caulfield JP. The cercarial glycocalyx of *Schistosoma mansoni*. *J Cell Biol* 1985;100:1423-34.
  11. Wang L, Li Z, Shen J, Liu Z, et al. Exosome-like vesicles derived by *Schistosoma japonicum* adult worms mediates M1 type immune- activity of macrophage. *Parasitol Res* 2015;114:1865-73.
  12. Zhu L, Liu J, Dao J, et al. Molecular characterization of *S. japonicum* exosome-like vesicles reveals their regulatory roles in parasite-host interactions. *Sci Rep* 2016;6:25885.
  13. Sotillo J, Pearson M, Potriquet J, et al. Extracellular vesicles secreted by *Schistosoma mansoni* contain protein vaccine candidates. *Int J Parasitol* 2016;46:1-5.
  14. Nowacki FC, Swain MT, Klychnikov OI, et al. Protein and small non-coding RNA-enriched extracellular vesicles are released by the pathogenic blood fluke *Schistosoma mansoni*. *J Extracell Vesicles* 2015;4:28665.
  15. Buck AH, Coakley G, Simbari F, et al. Exosomes secreted by nematode parasites transfer small RNAs to mammalian cells and modulate innate immunity. *Nat Commun* 2014;5:5488.
  16. Schorey JS, Cheng Y, Singh PP, et al. Exosomes and other extracellular vesicles in host-pathogen interactions. *EMBO Rep* 2015;16:24-43.
  17. Viaud S, Théry C, Ploix S, et al. Dendritic cell-derived exosomes for cancer immunotherapy: what's next? *Cancer Res* 2010;70:1281-5.
  18. Beauvillain C, Juste MO, Dion S, et al. Exosomes are an effective vaccine against congenital toxoplasmosis in mice. *Vaccine* 2009;27:1750-7.
  19. del Cacho E, Gallego M, Lillehoj HS, et al. Tetraspanin-3 regulates protective immunity against *Eimeria tenella* infection following immunization with dendritic cell-derived exosomes. *Vaccine* 2013;31:4668-74.
  20. Schnitzer JK, Berzel S, Fajardo-Moser M, et al. Fragments of antigen-loaded dendritic cells (DC) and DC-derived exosomes induce protective immunity against *Leishmania major*. *Vaccine* 2010;28:5785-93.
  21. Dang Z, Yagi K, Oku Y, et al. A pilot study on developing mucosal vaccine against alveolar echinococcosis (AE) using recombinant tetraspanin 3: Vaccine efficacy and immunology. *PLoS Negl Trop Dis* 2012;6:e1570.
  22. Trelis M, Galiano A, Bolado A, et al. Subcutaneous injection of exosomes reduces symptom severity and mortality induced by *Echinostoma caproni* infection in BALB/c mice. *Int J Parasitol* 2016;46:799-808.

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