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In vivo immunomodulatory properties of *Edwardsiella piscicida* challenged olive-flounder plasma exosomes

Jayathilaka E.H.T.T., Dias M.K.H.M., De Zoysa M., Nikapitiya C.*

College of Veterinary Medicine and Research Institute of Veterinary Medicine, Chungnam National University, Daejeon 34134, Republic of Korea

Edwardsiella piscicida (Gram-negative bacteria), the major causative agent of Edwardsiellosis frequently affects aquatic animals including olive flounder (*Paralichthys olivaceus*) resulting in huge economic losses to the industry. Extracellular vesicles (EVs) including exosomes play an important role in transferring genetic information to cells from healthy or diseased states, and their potential roles in clinical diagnosis and therapeutics have been identified. Exosomes (30-150 nm) that originate from cell endocytosis secrete from both pathogens and host cells and contain pathogen-related molecules and host factors (RNAs, miRNAs, proteins, lipids, etc.) of different cellular origins. Exosomes can be utilized by both pathogens and host, hence could regulate the infection to either increase or suppress. In this study, immunomodulatory properties of the exosomes from *E. piscicida*-infected flounder plasma were investigated to search for their anti-infective role. Fish were challenged with *E. piscicida*, and exosomes (Ep-Exo) from plasma were isolated (at 72 hours post-challenge) by ultracentrifugation. Ep-Exo was characterized and its immunomodulatory effect on zebrafish and flounder was compared with non-infected exosomes (PBS-Exo). The higher number of Ep-Exo than PBS-Exo indicates that upon infection, exosome content varies due to host cellular alterations, but cup-shaped membrane-bound morphology has remained. The upregulated genes in zebrafish (*tlr2, tlr4b*, *il1β, tnfα, il6*, *cat)* and flounder (*TLR2*, *TLR5a*, *TLR5b*, *TNFα*, *IL2*) kidneys upon Ep-exo treatment demonstrated its immunostimulatory activity. It was further confirmed by upregulated zebrafish TNFα, IL10, IFNγ, and TGFβ protein expression. In conclusion, Ep-Exo could be utilized as a novel target for developing an immunostimulant/ modulatory agent for enhancing the immune protection of the fish.

Keywords: Edwardsiella piscicida; extracellular vesicles; exosomes; immunomodulation; Paralichthys olivaceus

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*Corresponding author: chamilani14@gmail.com