Interspecies Communication via Extracellular Vesicles: A Promising Strategy for Treating Respiratory Allergy

Abstract

Extracellular vesicles (EVs) releassed by parasitic organisms represent a fascinating frontier in interspecies communication, serving as nanoscale couriers that deliver regulatory cargo to modulate host immune responses and ensure parasite survival. Across diverse phyla, from protozoans deploying EVs to evade innate immunity, to trematodes using them to dampen inflammation, EVs exploit conserved uptake pathways in mammalian cells, reprogramming signaling in recipient cells which can lead to tolerance and alleviate pathology.

Among helminth parasites, nematodes such as *Trichinella spiralis* employ EVs derived from the excretory-secretory products of their muscle larvae (TsEVs), which encapsulate immunomodulatory glycoproteins, miRNAs, and lipids. These vesicles not only shield the parasite from host immune responces but also mitigate concomitant hypersensitive immune responses in the host, including allergic disorders.

Building on our *in vitro* findings that TsEVs induce a stable tolerogenic phenotype in human monocyte-derived dendritic cells, which release anti-inflammatory cytokines and stimulate regulatory T cell expansion we translated this cross-kingdom dialogue to an *in vivo* model of ovalbumin (OVA)-induced allergic airway inflammation in BALB/c mice. Intranasal TsEVs administration lead to reductions in bronchoalveolar lavage eosinophils, serum OVA-specific IgE, and lung infiltrates of macrophages and NK cells. Treated mice had increased presence of $CD103^{+}$ tolerogenic dendritic cells, CD4+Foxp3+ regulatory T cells and decreased $CD11b^{+}Ly6C^{+}$ inflammatory monocytes in the lungs,. *Ex vivo* analyses from lung and spleen isolates confirmed suppressed Th2 cytokine production (IL-4, IL-5, IL-13) and elevated IL-10, highlighting a shift from a Th2-dominated response to a more regulatory profile.

Collectively, these insights position parasitic EVs as evolutionary blueprints for future bioengineered therapeutics, harnessing interspecies EVs signaling to mitigate respiratory allergies and provide precision immunomodulation.