Heligmosomoides polygyrus extracellular vesicles as modulators of the host immune system and platforms for multivalent vaccines

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Recent reports demonstrate that vaccinating mice with EVs from the mouse parasite *Heligmosomoides polygyrus* induces strong antibody titres which confer protection against infection. This suggests that *H. polygyrus* EVs (or their components) could be used as an effective anthelminthic vaccine. Pulldown experiments have identified the most immunogenic *H. polygyrus* EV proteins. Since vaccines for clinically and economically relevant helminths (such as *Haemonchus contortus*, *Ancylostoma ceylanicum* and *Necator americanus*) are in urgent need, this list of candidate antigens has been triaged based on their conservation across orthologues of these species. AlphaFold structure predictions of these proteins have been used to decipher whether the most highly conserved sequences can fold independently. Vaccination with these highly conserved independently-expressed domains and full-length antigen candidates protect against *H. polygyrus* infection with varying degrees of success. Studies are ongoing to improve this efficacy by refining domain selection and exploring antigen combinations. Furthermore, in order to elucidate the mechanism of action of an EV-based vaccine, the immunomodulatory activity of EVs *in vivo* has been studied. Upon EV injection, CD68 and MHC-II expression on peritoneal macrophages decreases indicating reduced antigen uptake and presentation; this means fewer T-cells can be activated leading to a dampened immune response. Moreover, EVs inhibit the Type 2 immune response, responsible for helminth clearance, through reduced alternative activation of macrophages (fewer M2 cytokines, YM1 and IL-1RA, in the peritoneal cavity) along with downregulation of the co-stimulatory molecule OX40L on peritoneal macrophages (leading to reduced Th2 activation). Simultaneous CD86 upregulation on peritoneal macrophages suggests Th1 cells will be activated preferentially to Th2 cells, steering the immune response away from Type 2. Contributions to a reduced Th2 response may also originate from the lymph nodes where cytokines which induce other T-cell subsets (IL-12, IL-6, TGFβ) are upregulated, suggesting that Th1 and Treg cells outgrow Th2 cells. These data support a role of EVs in shifting the immune response away from Type 2, potentially towards Type 1. Studies are now under way to determine whether immunisation with candidate antigens is able to prevent EV-mediated inhibition of the Type 2 response.