BSP Abstract

Title

Gastrointestinal organoids as *in vitro* platforms for vaccine development against helminth parasites

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Abstract body

Mucosal vaccination offers a powerful and often underutilised approach to inducing protective immunity at mucosal surfaces such as the gastrointestinal (GI), respiratory and urogenital tracts. Many parasites infect their hosts via ingestion; infecting GI mucosal surfaces. There are currently very few licensed nematode vaccines and whilst these stimulate circulating IgG antibodies and systemic T-cell responses, there is no stimulation of mucosal surfaces which is crucial to GI nematode infections.

Mucosal vaccination can induce epithelial-driven immune responses via the activation of pattern recognising receptors (PRRs) which lead to secretory IgA and the activation of tissue resident T cells. Whilst mucosal vaccines are highly valuable tools, there is a lack of physiologically relevant *in vitro* models available to test candidate mucosal vaccine adjuvants and antigens prior to *in vivo* animal trials. Therefore, the development of an efficient, species-specific *in vitro* screening platform for such vaccine candidates could be a major step forward for the ethical and efficient development of novel mucosal vaccines. Here we report the development of rectal organoids from both ovine and bovine primary rectal stem cells and there application as physiologically relevant mucosal screening platforms. Veterinary helminths are an increasing problem as a result of anthelmintic resistance and increasing survival and spread of parasite free-living stages due to climate change, making the development of effective vaccines a priority.

Organoid cultures from multiple individual animals were characterized by bulk RNA-sequencing to confirm that they retain important properties of primary rectal epithelium including diverse epithelial cell type markers. Importantly, we find that these organoids express PRRs at a relatively high level, similar to expression levels in tissue. Moreover, these receptors can be treated with specific ligands to induce a pro-inflammatory NF-kB response. We also demonstrate that conjugation of a helminth vaccine candidate antigen to a specific Toll Like Receptor (TLR) ligand does not abrogate the receptor binding activity of the ligand or the integrity of the antigen. Our findings demonstrate the utility of the ruminant rectal organoid model for assessing vaccine potential *in vitro*. We are now aiming to develop this model into a reporter-based system that can be used as a screening tool to test adjuvant performance at inducing epithelial-driven immune responses *in vitro* for multiple novel ligands.

Disclosures- funders, affiliations
My PhD is an industrial partnership project between The Moredun Research Institute and The University of Glasgow and is part of a larger scour worm vaccine project co-funded by Meat and Livestock Australia and The Moredun Research Institute.