MODULATORS OF INNATE GUT IMMUNITY TO ENTERIC VIRAL INFECTIONS: MURINE NOROVIRUS (MNV) AS A MODEL

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ABSTRACT

Challenged by a huge and diverse antigenic stimulus, the intestinal mucosa has developed a unique immune system that mainly functions to maintain tolerance to innocuous antigens while retaining the ability to respond swiftly to pathogenic threats. Central to this specialised immune system are the Intraepithelial Lymphocytes (IELs). These cells are uniquely located between Intestinal Epithelial Cells (IECs) ready to respond to exogenous antigens in the intestinal lumen. The intestinal immune system is constantly influenced, not only by the commensal microbiota, but also by the nutritional status of the host and the availability of certain essential micronutrients that are derived from a healthy-balanced diet. Additionally, age has a significant impact on the efficiency of gut immunity in responding to infectious pathogens, as reflected by the increased burden of gastrointestinal infections at the extremes of age.

In this thesis, using the Murine Norovirus (MNV) oral infection model, I aimed to characterize intestinal mucosal antiviral-responses with specific focus on the role of IELs, the impact of aging and the influence of certain micronutrients whose effects are mediated through the Aryl Hydrocarbon Receptor (AhR). Employing different knock-out and adoptive transfer experiments, I concluded that, at least in our experimental conditions and in a viral strain-

specific manner, the activated IELs are not essential and may play a minor role in the protective response against MNV infection. This work also demonstrated that various MNV virus strains activate IELs differentially and for the first time (to our knowledge) revealed distinct abilities of these different Norovirus variants to infect IECs. Recognising an impaired response in old (2-year) mice, we were also able to identify a specific defect in the IFN-λ response of aged IECs. Furthermore, using the model of MNV infection to investigate the role of AhR signalling, the data I generated suggested a direct link between constitutive AhR signalling and innate interferon-mediated responses. These findings have uncovered a potential preventive/therapeutic targets for enhancing anti-viral responses.