Name of Student: Ganive Bhinder

Research Supervisor: Dr. Bruce Vallance

Title of Presentation: Intestinal epithelial MyD88 signalling controls early susceptibility to enteric infection

Abstract

Intestinal epithelial cells (IECs), which form an essential physical barrier separating the vast bacteria in the gut lumen from host tissues, are common targets of enteric bacterial pathogens. Early host responses to infection are mediated by innate receptors such as TLRs, most of which require the MyD88 adaptor protein. MyD88 signaling has been found to be essential in conferring protection during several models of intestinal inflammation, including infection with the naturally occurring murine specific pathogen *Citrobacter rodentium*, with many of its protective effects involving changes to the intestinal epithelial cell (IEC) layer. To address the role of MyD88 signaling during enteric infection specifically in IECs, we infected mice lacking MyD88 signaling solely in IECs (IEC-MyD88 -/-) with the bacterial pathogen *Salmonella Typhimurium*. Infection with *S. Typhimurium* led to accelerated tissue damage and barrier disruption in IEC-MyD88 -/- mice, with goblet cell specific responses being significantly altered. To examine the physiological effects of these alterations on bacterial survival, we performed crypt killing assays to determine bactericidal activity against *S. Typhimurium* and found that crypts from IEC-MyD88 -/- were severely impaired in their antibacterial capacity. Immunostaining revealed that *S. Typhimurium* were found in much closer proximity to the epithelial surface in IEC-MyD88 -/- mice, unlike in WT mice where they were sequestered to the lumen. To address whether this susceptibility was unique to only this one potent pathogen, we infected mice with another enteric pathogen: *C. rodentium.* We found that IEC-MyD88 -/- mice were again highly susceptible to accelerated tissue damage during early infection with impaired goblet cell specific responses and altered *C. rodentium* localization. These results demonstrate that MyD88 signaling within IECs plays an important role during early enteric infection in potentiating tissue protective responses.