Gut Microbiota Drives Tonic Toll-like Receptor (TLR) Signaling in the Intestine

Nicole Narayan1, 2, Amir Ardeshir2, David Merriam1, 2, Ellen Sparger1, Dennis Hartigan-O’Connor1, 2, 3

1UC Davis, CA 95616
2California National Primate Research Center, UC Davis, CA 95616
3UC San Francisco, CA 94143

Background: The détente between inflammatory components of the commensal gut microbiota and the host immune system is sensitive. Disturbance of the balance may lead to an inflammatory tendency or even inflammatory bowel disease. Toll-like receptor (TLR) signaling, including aberrant responses to commensal bacteria, can contribute to inflammation in the gut. Specific bacteria may also contribute to aberrant TLR signaling, contributing to chronic inflammation seen in IBD. However, relatively little is known about the specific relationships between commensal bacteria and TLR signaling.

Methods: We examined twelve healthy adult rhesus macaques, collecting stool, cytobrush samples, and tissue biopsies. Cytobrush sampling uses a brush to sample the intestinal wall, allowing collection of microbes that are associated with the mucosal surface. We assessed TLR signaling pathway gene expression in the intestinal wall (biopsy samples) by PCR array (QIAGEN). The microbiotas associated with the mucosal surface or the lumen were assessed by 16S rRNA sequencing of cytobrush and stool samples, respectively. Statistical analysis was performed in R.

Results: Gut microbiota composition was associated with TLR signaling pathway gene expression. That is, position of an individual along the spectrum of gut microbiota composition was associated with the extent of TLR-related gene expression. Furthermore, linear regressions showed that specific commensal bacteria were associated with specific components of the TLR signaling pathway. For example, increased Faecalibacterium was associated with decreased TLR5 expression. Bacteria that have been associated with IBD (whether increased or decreased) were also found to be associated with expression of inflammatory and anti-inflammatory cytokines resulting from TLR signaling.

Conclusions: Commensal gut microbes are significant contributors to TLR signaling in the gut. A shift in the gut microbiota, as seen in IBD, could contribute to chronic inflammation. Understanding more about how commensal gut bacteria interact with TLR signaling pathways will likely be important for understanding the pathogenesis of IBD.