Dietary L-tryptophan determines the number of colonic regulatory T-cells and susceptibility to colitis via GPR15

Sangwon V Kim¹, Nguyen T Van¹, Karen Zhang¹, Rachel M Wigmore¹, Anne I Kennedy¹, Carolina R. DaSilva¹, Jialing Huang¹, Manju Ambeli¹, Jose H Vilagomez¹, Gerald J O’Connor¹, Michael Platten², Gerard Kasenty³, Luis J Sigal¹, George C Prendergast⁴, and Sangwon V Kim¹


Environmental factors play a prominent role in the onset of immunological disorders such as ulcerative colitis, but the mechanisms are unclear. Diet is a major environmental factor, mostly known to influence the gut microbiota, which in turn affects the host immune system. Here, we demonstrated the microbiota-independent effect of the ubiquitous dietary component, L-tryptophan (L-Trp) on mucosal immune responses. We discovered that the amount of ingested L-Trp determines the number of colonic CD4⁺ T-cells through the aryl hydrocarbon receptor (AhR), which triggers the direct transcriptional activation of the colon T-cell homing receptor, GPR15. However, the default pathway connecting L-Trp, AhR, GPR15, and T-cells is microbiota-independent and involves host IDO1 and IDO2 enzymes, selectively increasing GPR15⁺ Tregs. Consequently, two weeks of L-Trp supplementation nearly doubled the colonic GPR15⁺ Tregs and significantly decreased the future risk of colitis. Our extensive, in vitro screening of AhR ligands suggests that AhR ligand-specific variations in target gene expression may account for the Treg-selective response to L-Trp. We also identified benzo[a]pyrene, a compound enriched in cigarette smoke and grilled meat, as an AhR agonist that strongly promotes GPR15⁺FOXP3⁺ Treg generation. Thus, our findings uncover mechanisms by which routine dietary and behavioral practices have a significant impact on colonic Treg responses, suggesting a potential non-invasive therapeutic approach for colitis.