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“Indolelactic acid (ILA) as a marker of vaginal health”

Background: Indolelactic acid (ILA) is a major metabolite of tryptophan and important for maturing and preventing inflammation in the infant gastrointestinal (GI) mucosa via activation of the aryl hydrocarbon receptor (AhR) pathway. ILA is known to be produced by *Bifidobacter*, a dominant bacterium in the infant GI microbiome. *Bifidobacter* synthesize ILA by metabolizing tryptophan, which is found in high concentrations in breastmilk. Importantly, we recently also found significant concentrations of ILA in the vaginal secretions of some women, and this was strongly associated with the abundance of *Lactobacillus crispatus*, the dominant bacterium in an optimal, healthy vaginal microbiome.

Objectives: Since a dysbiotic, non-optimal microbiome, most commonly caused by bacterial vaginosis (BV), is associated with inflammation and negative reproductive health outcomes, my objectives were to determine if vaginal ILA could (1) be used as a biomarker of vaginal health and (2) play a role in modulating vaginal inflammation.

Methods: Using a de-identified clinical dataset, I set out to determine if there was a significant difference in vaginal ILA concentrations (i) in women with clinically diagnosed BV (Amsel score of 3 or 4) v no BV (Amsel score 0-2) (ii) with a positive or negative score for each of the individual Amsel criteria (pH >4.5, vaginal discharge, odor, or presence of Clue cells), and (iii) in the presence or absence of a high proinflammatory cytokine index. Using the HT29 epithelial cell line engineered to express the AhR, I am also determining if, *in vitro*, ILA (i) can block the production of inflammatory cytokines and (ii) if this is via the AhR receptor.

Preliminary Results and Conclusions: With the clinical data provided, I ran Mann-Whitney tests and found that (i) ILA concentration was significantly elevated in samples with positive Amsel criteria for pH>4.5 ($p<0.0001$) and odor ($p<0.0002$) but not for discharge ($p=0.3517$) or Clue cells ($p=0.71$). When all the Amsel criteria were taken into account for a clinical BV diagnosis (Amsel 3 or 4) I also found a strong trend for ILA to differentiate between BV positive and BV negative samples ($p=0.0581$). However, there was no significant difference in ILA concentrations in samples with a high or low inflammatory index. In my *in vitro* experiments, I have so far determined that ILA activates the AhR and its genomic signaling pathway at concentrations found in vaginal secretions. I have also established that the proinflammatory cytokine TNF α can activate my cell line to produce IL8. I am now determining if ILA can prevent IL8 secretion and if this can be blocked with a known AhR antagonist. The results of my study suggest that ILA could be used as a marker of vaginal health, may provide an insight into its role in inflammation.

