Gardnerella vaginalis induces matrix metalloproteinases in the cervicovaginal epithelium through TLR-2 activation

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OBJECTIVE: Lactobacillus-deficient cervicovaginal (CV) microbial communities, as well as select anaerobes like Gardnerella vaginalis (GV), have been associated with adverse reproductive outcomes, including spontaneous preterm birth (sPTB). GV peptidoglycan cell wall can activate TLR-2. We previously showed that high MMP-9 in CV fluid in pregnancy is associated with an anaerobic-rich CV microbiota, short cervix, and sPTB. We posit that GV induces MMPs in CV epithelial cells through TLR-2, which degrades the epithelial barrier leading to premature cervical remodeling and sPTB.

STUDY DESIGN: Ectocervical (ECTO), endocervical (ENDO), and vaginal (VK2) cells were treated with 10⁵±0.5 CFUs live GV or Lactobacillus crispus (LC), a healthy CV bacteria, for 24 hours. For TLR-2 experiments, cells were pretreated with TLR-2 blocking antibody. An MMP Luminex panel was run on cell media for three biologic and two technical replicates per condition. Data were analyzed with a five-parameter logistic curve. One-way ANOVAs with Dunnet’s multiple comparisons tests were used.

RESULTS: GV induced MMP-1 in ENDO cells (p=0.01) and MMP-9 in ECTO, ENDO, and VK2 cells (p<0.001 for all) compared to non-treated controls. LC did not induce any MMPs compared to non-treated controls (Fig. 1). Epithelial cell specific effects were noted for MMP-9 with VK2 cells expressing increased levels compared to cervical cells (p<0.0001, Fig. 1). MMP-9 was selected for TLR-2 blocking experiments given induction in all cell lines after GV treatment. TLR-2 blockade mitigated GV induction of MMP-9 in cervical and VK2 cell lines (Fig. 2).

CONCLUSION: A common anaerobic microbe implicated in several adverse reproductive outcomes, including sPTB, can induce MMPs in the CV space. Upregulation of MMP-9 by GV occurs in a TLR-2 dependent fashion. These findings unveil mechanisms by which CV microbes influence host immune response and may compromise epithelial barrier integrity and promote cervical remodeling. SMFM/AAOGF (KG); 1R01HD102318, 5R01HD098867 (ME)