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Neisseria gonorrhoeae infection in the context of health- and bacterial vaginosis-associated microbiota communities in the lower female reproductive tract.

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Background

The microbiota is a major determinant of health in the female reproductive tract (FRT). At homeostasis, the lower FRT microbial community consists predominantly of Lactobacillus species. In women suffering from bacterial vaginosis (BV), the composition of the FRT microbiota shifts to an increasingly diverse consortia of anaerobic and microaerophilic organisms. This shift causes increased pH, inflammation, and susceptibility to STIs, including gonorrhea. The mechanisms linking healthy and dysbiotic FRT microbiota and Neisseria gonorrhoeae (Ngo) infectivity are poorly understood.

Aim/Methods

We used a 3-dimensional cervical epithelial model to examine Ngo infection in the context of optimal health and BV. A2EN endocervical cells were differentiated into 3-D tissue aggregates in a rotating wall vessel bioreactor, colonized with Lactobacillus crispatus or Fannyhessea vaginae to mimic healthy and BV microenvironments, respectively, and infected with Ngo strain MS11. We then examined several parameters of Ngo infection in these aggregates.

Results

Compared to uncolonized aggregates, the presence of both L. crispatus and F. vaginae reduced Ngo adhesion, while the presence of F. vaginae promoted Ngo invasion. F. vaginae increased pro-inflammatory responses compared to either Ngo or L. crispatus, and induced cytokines including TNF-alpha, IL-8, GM-CSF and MCP-1. Aggregates colonized with L. crispatus had reduced levels of matrix metalloproteinases: MMP-1

and MMP-7; those colonized with F. vaginae produced higher levels of MMP-9 and MMP-10. Ngo microcolonies interacted with L. crispatus and F. vaginae on the apical surface of the 3D epithelia, as evidenced by Scanning Electron Microscopy and Combinatorial Labeling and Spectral Imaging Fluorescence In Situ Hybridization (CLASI-FISH). Host proteins were recruited to the plasma membrane beneath Ngo microcolonies, reminiscent of the cortical plaques formed under adherent Ngo in cervical epithelial cell monolayers. Several Ngo genes were expressed at higher levels in F. vaginae-colonized aggregates compared to uncolonized- and L. crispatus-colonized aggregates, including genes implicated in metal piracy, surface lipoprotein export, and polymorphic toxin production.

Conclusions

Taken together, our data strongly suggest that the lower FRT microenvironment created by healthy and dysbiotic microbiota differentially influences Ngo gene expression and infection behavior. Future work will examine host and bacterial factors driving susceptibility of this site to Ngo infection.