(1) Submission ID#1525915

Neisseria gonorrhoeae adaptation during vaginal colonization of CEACAM-humanized mice

Author(s)

Sophie Dyzenhaus, PhD

Postdoctoral fellow

University of Toronto

Jessica Lam, MSc

Facility Manager - CL3, Viral Core & Biobank

University of Toronto

David Curran, PhD

Research Associate

University of Toronto

Scott Gray-Owen, PhD

Professor

University of Toronto

Background

Neisseria gonorrhoeae is a human-adapted pathogen with a highly plastic genome. Genomic changes that lead to altered expression and production of virulence factors are frequent and can occur during colonization/infection, as well as through in vitro laboratory passaging. Phase variation, where changes in repetitive sequences can turn genes on/off, and antigenic variation exemplify the capacity of N. gonorrhoeae to adapt rapidly. Understanding N. gonorrhoeae adaptation in a natural niche, in this case vaginal colonization, could identify new targets to combat disease.

Aim/Methods

We aimed to identify genes important in gonococcal vaginal colonization by comparing in vitro passaged ‘lab-adapted’ with in vivo passaged ‘host-adapted’ N. gonorrhoeae. We utilized the prototype lab-adapted gonococcal MS11, as well as lower passage clinical isolates (WHO P and WHO Z) in a CEACAM-humanized murine model of gonococcal vaginal colonization. We first serially plate-passaged the WHO isolates in vitro to create lab-adapted strains. These passaged strains were used to infect mice in the lower genital tract. Mice were vaginally lavaged to monitor colonization and to collect in vivo adapted N. gonorrhoeae for subsequent re-passaging and whole genome sequencing. After 3 passages in the lower genital tract, comparative genomics was performed to identify mutations arising in host-adapted strains. The future aims of this project are to identify how such mutations are contributing to in vivo fitness.

Results

In vivo passaged N. gonorrhoeae showed increased ability to colonize mice as compared to lab-adapted

strains. Infection with lab-adapted MS11 (passage 1) lead to colonization of 17% of mice, while 88% colonization was seen in passage 3. The WHO P and WHO Z isolates also showed increased ability to colonize, however this manifested in the length of colonization, rather than the proportion of mice colonized. Mutations found in host-adapted strains included multiple instances of phase variation, where genes are turned off in lab-adapted strains and on in host-adapted strains, suggesting they are important for colonization.

Conclusions

Using comparative genomics of whole genome sequences from in vitro versus in vivo passaged isolates, we have uncovered genes that we hypothesize are contributing to the success of N. gonorrhoeae during vaginal colonization.