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Neisseria gonorrhoeae infection modulates the cytokine environment of the human cervix

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Background

Neisseria gonorrhoeae (GC) infects women primarily through the female reproductive tract (FRT). GC infections in the lower FRT are mostly asymptomatic until GC ascend through the cervix to the upper FRT, suggesting that the local immunity of the lower FRT cannot effectively detect and eliminate GC. How GC evade the local immunity of the lower FRT remains elusive.

Aim/Methods

This study examined cytokine responses in the human cervix to GC infection during the first 24 hours using the human tissue explant model. Cervical tissue explants were inoculated with MS11 GC strains expressing CEACAM-binding opacity-associated protein Opa52 (OpaCEA) or with all opa genes deleted (ΔOpa).

Results

ELISA and Luminex analysis of culture supernatants found that OpaCEA GC inoculation significantly increased the secretion of multiple inflammatory cytokines, such as IL-1β, TNFα, and TNFβ, chemokines for neutrophils, macrophages, and lymphocytes, including IL-8, CXCL1, CXCL2, and CCL3, the multi-functional cytokines IL-6, G-CSF, and GM-CSF, as well as the anti-inflammatory cytokines IL-10 and LIF, compared to no GC control. In contrast, ΔOpa GC did not induce the anti-inflammatory cytokine while increasing inflammatory cytokines and chemokines in much lower levels than OpaCEA GC. Whole cervical tissue RNAseq analysis confirmed these results at the transcriptional level. The elevated cytokine production was concurrent with increased nuclear staining of NF-κB p65 and mRNA levels of NF-κB pathway genes. Inhibition of NF-κB activation by an inhibitor reduced GC-induced secretion of inflammatory but not anti-inflammatory cytokines. Neutralizing IL-10 or blocking IL-10 receptor by antibodies enhanced OpaCEA-induced inflammatory cytokine secretion. Immunofluorescence microscopy identified ectocervical epithelial cells are the primary source of IL-6. Preliminary spatial RNAseq analysis found that GC inoculation increased the transcripts of a limited number of inflammatory cytokines and chemokines, like IL-1β and IL-8, in ectocervical epithelial cells, but a large panel of cytokines and chemokines in tissue-resident macrophages. Interestingly, OpaCEA and ΔOpa GC were more potent cytokine inducers in macrophages and epithelial cells, respectively.

Conclusions

Together these results suggest that GC infection modulates the balance of the cervical cytokine environment by regulating upstream transcript factors and that OpaCEA plays essential roles in this modulation, particularly in enhancing anti-inflammatory responses.