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INTERFERON-EPSILON, AN ESTROGEN-INDUCED TYPE I INTERFERON, EXPRESSED IN THE FEMALE GENITAL TRACT ALLOWS NEISSERIA GONORRHOEAE TO EVADE INNATE IMMUNE CLEARANCE

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Background

Clinical studies indicate that estrogen plays an important role in the susceptibility of women to Ng infection. In female mice, estrogen is essential for Neisseria gonorrhoeae (Ng) vaginal colonization. Epithelial cells in the human, as well as the mouse, genital tract produce a unique type I IFN, IFN-epsilon (IFNe), in response to estrogen.

Aim/Methods

We explored the role of IFN-epsilon (IFNe) in controlling intravaginal Ng infection.

Results

IFNe promoted intravaginal Ng colonization in estrogen-treated mice. Thus, estrogen-treated WT mice were susceptible to prolonged Ng colonization (7-12 days p.i.). In contrast, estrogen-treated IFNe KO mice cleared Ng within 3 days of intravaginal inoculation. IFNe engages the common type I IFN receptor, IFNAR, and IFNAR KOs and anti-IFNAR-treated mice phenocopied the IFNe KOs with attenuated Ng infection compared to WT mice. Importantly, recombinant IFNe delivered topically into the vaginal tract was sufficient to entirely restore susceptibility to Ng infection in IFNe KO. The cellular and molecular mechanisms of IFNe/IFNAR enhanced Ng infection were investigated. The rapid clearance of Ng from the mouse genital tract of IFNe KOs was not affected when neutrophils, T lymphocytes, or NK cells (or all three cell types together) were systemically and locally eliminated using depleting mAbs. However, clearance of Ng in IFNe KOs was dependent on cathelicidin (mCRAMP) expression, evidenced by WT-level vaginal colonization in anti-IFNAR-treated mCRAMP KO mice. Ng evade killing by cationic anti-microbial peptides and by complement by sialylating its lipooligosacharide (LOS). Ng scavenges sialic acid precursors from mammalian host cells as a substrate for Ng sialytransferease. We demonstrate that Ng sialyation (and evasion of cathelicidins) is dependent on the IFNe/IFNAR axis - wherein the LOS of Ng recovered from WT mice, and examined directly ex vivo, was sialylated, but Ng from anti-IFNAR-treated mice were almost completely devoid of sialic acid.

Conclusions

We suggest that estrogen, via the IFNe/IFNAR axis, provides a permissive niche for Ng by enhancing sialyation of Ng LOS and, thus, allows the bacteria to evade innate immune killing.