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Investigating the role of lipooligosaccharide sialylation in Neisseria gonorrhoeae-neutrophil interactions

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Background

Gonorrhea, caused by the bacterium Neisseria gonorrhoeae (Gc), is characterized by influx of neutrophils to sites of infection. Gc has developed mechanisms to resist killing by human immune components, including modifying its surface lipooligosaccharide (LOS) by sialylation. Gc scavenges sialic acid from host CMP-neuraminic acid (NANA) using LOS sialyltransferase (Lst). Gc does not synthesize sialic acid; instead, Lst is located to the Gc surface and sialylates the terminal sugars of the LOS. Sialylation enables Gc to resist complement-mediated killing in a serum-dependent manner. However, little is known about the contribution of sialylation to complement-independent, direct Gc-neutrophil interactions.

Aim/Methods

We hypothesized that sialylation enhances Gc pathogenicity by increasing Gc resistance to neutrophil killing and/or reducing neutrophil activation. To test this hypothesis, isogenic Opa+ Gc strains were generated with

and without Lst and grown with CMP-NANA or vehicle alone in bacterial growth medium, yielding Gc with or without sialylated LOS. Bacterial survival after exposure to adherent, interleukin-8 treated primary human neutrophils was measured by enumerating colony forming units. Bacterial phagocytosis by neutrophils was measured by imaging flow cytometry. The neutrophilic response to sialylated Gc was investigated by measuring the oxidative burst by luminol-dependent chemiluminescence, and granule exocytosis by spectral flow cytometry assays.

Results

Sialylated Gc resisted killing significantly better than nonsialylated or lst mutant Gc when challenged with human neutrophils for up to 30 minutes. Sialylation did not markedly affect Gc binding or phagocytosis by neutrophils. Instead, sialylation dampened the neutrophil oxidative burst and primary granule exocytosis when challenged with Opa+ Gc. Previous studies have implicated Siglecs (sialic acid-binding immunoglobulin-type lectins) in modulating neutrophil engagement with sialylated bacteria. We found that addition of blocking antibodies against neutrophil Siglecs restored neutrophil activation in response to sialylated Gc.

Conclusions

Sialylated Opa+ Gc limits neutrophil activation and antimicrobial activity via Siglecs, which counteract stimulatory signals from CEACAMs. Our findings contribute to the growing understanding of how sialylated bacteria modulate the human immune response to enhance survival in their hosts. These results help provide insight into vaccine development and therapeutic intervention for Gc, and innate immune function and dysfunction in gonorrhea.