Molecular Mechanisms Underlying Glial Inflammatory Responses to *Neisseria meningitidis*

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Abstract

Over 1.2 million cases of bacterial meningitis occur worldwide each year. The bacterial pathogen *Neisseria meningitidis* (Nm) is the leading cause of pyogenic and epidemic meningitis, a life-threatening condition with a 15% mortality rate. Additionally, up to 20% of survivors suffer long-term central nervous system (CNS) deficits due to severe neuroinflammation. Within the CNS, microglia and astrocytes are cells crucial to the initiation and regulation of these immune responses to bacterial infections. Our lab and others have demonstrated both microglia and astrocytes rapidly release proinflammatory cytokines followed by later production of anti-inflammatory cytokines in response to Nm challenge. Intriguingly, Nm has been reported to bind and import host cytokines that then drive changes in bacterial gene expression, suggesting that cytokine responses serve as environmental cues to promote virulence. This study begins to address the hypothesis that Nm pathogen-associated molecular patterns (PAMPs) initiate glial immune responses that, in turn, regulate bacterial gene expression to further exacerbate infection. Nm was grown to mid-log phase in the absence or presence of host inflammatory cytokines TNF, IL-6, and IL-1β, or anti-inflammatory cytokines IL-10 and IL-19. An RNA sequencing approach was used to compare differences in transcriptome-wide gene expression profiles for Nm. These pilot studies are an essential first step in dissecting the intimate relationship between Nm and glial cells that underlies the development of detrimental neuroinflammation. Future studies will confirm novel gene clusters or molecular pathways and genes associated with Nm immune stimulation and evasion.

Introduction

Bacterial Meningitis

- *Neisseria meningitidis* is one of the causative agents of meningitis
- 1.2 million cases of each year worldwide with a 15% mortality rate
- Up to 20% of survivors suffer long-term deficits

Study Goal

- Examine host pathogens interactions in meningitis to identify novel points of therapeutic interventions

Severe Neuroinflammation

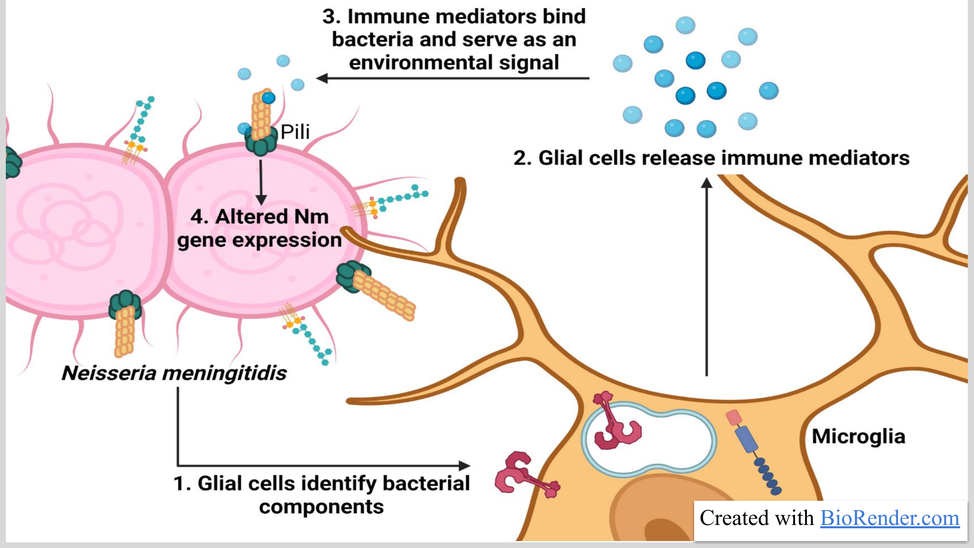
- Resident CNS cells such as microglia and astrocytes are known to initiate the inflammatory immune response to infection

Pathogen Response

- Nm has been shown to bind to host cytokines

Hypothesis

Nm stimulates glial immune responses that, in turn, regulate bacterial gene expression to further exacerbate infection.



Results

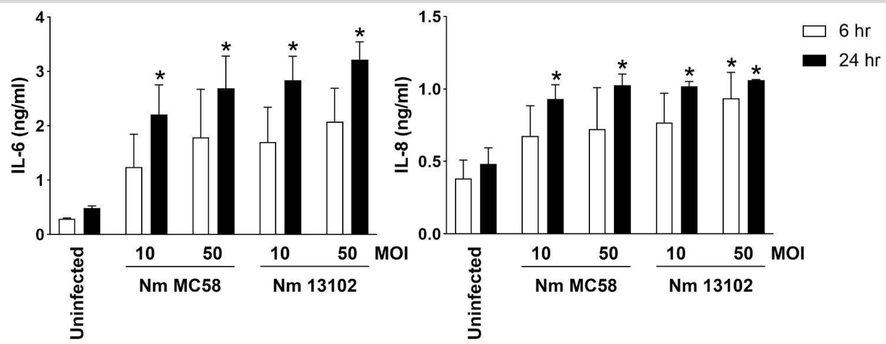


Figure 1. Human glial cells were infected *N. meningitidis* at a bacteria to microglia ratio (MOI) of 1:10 and 1:50. ELISAs were conducted for IL-6 and IL-8 using culture supernatants collected at 6 and 24 hours. The data is expressed as the mean +/- SEM (n=2). Asterisks indicate statistical significance compared to uninfected cells (two-way ANOVA with Dunnett's post hoc test, $p < 0.05$).

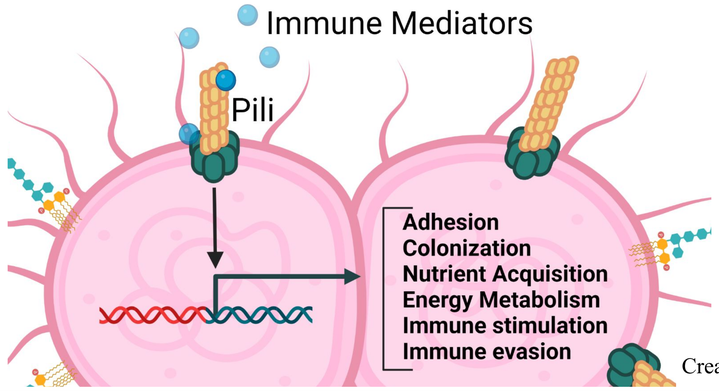
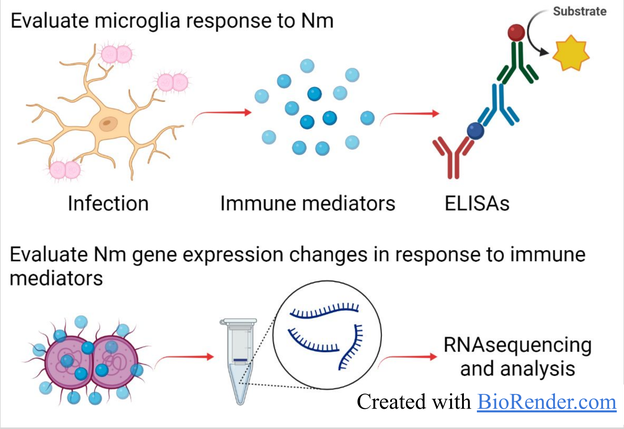


Figure 2. We hypothesize that in response to host cytokines and chemokines Nm will alter expression of genes important for adhesion, colonization, nutrient acquisition, energy metabolism, immune stimulation, and immune evasion.

Methods



Summary

- The proinflammatory cytokine, IL-6 and the chemokine, IL-8 are produced by microglia following infection with two strains of *N. meningitidis.*
- RNAsequencing experiments to examine bacterial gene expression in response to IL-6 and IL-8 production are ongoing.
- Future studies will confirm and determine the contribution of differentially expressed genes to neuroinflammation

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