Meningeal barrier breakdown and local immune response during neonatal bacterial meningitis

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OBJECTIVES

- Developing a neonatal bacterial meningitis model to study the functional role and response of the arachnoid barrier in CNS diseases.
- Investigating how leptomeningeal border-associated macrophages respond to infection and alter the arachnoid barrier integrity.

INTRODUCTION

- The central nervous system (CNS) is protected by several types of barriers, one of which is blood-cerebrospinal fluid barrier (B-CSFB).
- One component of the B-CSFB is the arachnoid barrier (AB), the outer arachnoid layer that consists of epithelial-like cells connected by extensive junctional proteins (E-cadherin/Claudin-11) and regulates cellular and molecular movement between the CSF and the periphery.
- Streptococcus agalactiae (Group B Streptococcus, GBS) is the leading cause of life-threatening meningitis in newborns and can lead to long-term neurological deficits in children who survive the initial infection during infancy.
- In the absence of AB prenatally, a significantly higher burden of GBS has been observed in the leptomeninges. Upon infection, BAMS become phagocytic and express inflammatory cytokines.
- Current gaps in the field include: 1) Investigate the cellular and molecular mechanism underlying the mislocalization of Claudin-11 expression level post-infection, but its overall expression level remains unchanged. (A) Histological result showed no difference in E-cadherin/AB junctions between the mock (top) and the GBS-infected (bottom) group. However, the localization pattern of Claudin-11 proteins appeared aberrant in the infected group with non-junctional, nuclear localization (arrowheads). (B) Example of single junction intensity quantification. A symmetrical line was drawn across a single junction (left) and the central peak, the junctional intensity, was quantified (right). (C) Line intensity analysis of Claudin-11 junctions showed no significant change in expression level post-infection. (Scale = 20 µm). 2) How do meningeal BAMS respond to GBS infection and do they contribute to the altered AB in diseased state?

METHODS

A. Acute Neonatal GBS Infection Model and Sample Collection

B. Histological Analysis of Arachnoid Barrier Post-Infection

C. Tracer Dye-Based Arachnoid Barrier Integrity Assay (ABIA)

CONCLUSIONS

- We developed a neonatal bacterial meningitis model using GBS to study the acute response at the B-CSFB, specifically the arachnoid barrier (AB).
- Infection with GBS did not alter the expression level of AB junctional proteins but resulted in altered localization pattern of Claudin-11 junctions.
- Tracer dye assay testing AB integrity showed leakage of tracer into superficial cortex post-infection, supporting a GBS infection-induced AB breakdown.
- Upon infection, the morphology of BAMS was notably altered, from a small, round form to cells with processes as seen in activated macrophages.
- Although the overall density of BAMS did not differ, the number of CD206+LYVE-1 double-positive BAMS and the expression level of LYVE-1 was significantly decreased after infection.

ACKNOWLEDGMENTS

- Siegenthaler Lab (@SiegenthalerLab) | CU Anschutz
- Doran Lab (@KdoranLab) | CU Anschutz
- Cell Biology, Stem Cells, and Development (CSD) Program | CU Anschutz
- Funding support for this project from NIH/NINDS

FUTURE DIRECTIONS

- Investigate acute and chronic local immune response during meningeal barrier breakdown following neonatal GBS infection (A: pilot flow data on mock-injected animals).
- Acute: Immune cell response (neutrophils, infiltrating monocytes) and local cytokine production.
- Chronic: Structural and functional integrity of AB and BAMS profile after meningitis resolution.
- Investigate the relevance and mechanism of LYVE-1 downregulation in BAMS during infection.
- Investigate the cellular and molecular mechanism underlying the mislocalization of Claudin-11 and potentially other AB junctional proteins (B: OB-cadherin, Type II cadherin expressed at AB cell junctions).

ARACHNOID BARRIER JUNCTIONAL PROTEIN MISLOCALIZATION POST-INFECTION

LOSS OF ARACHNOID BARRIER INTEGRITY FOLLOWING GBS INFECTION

ALTERNED LEPTOMENIGEAL BAM MORPHOLOGY AND LYVE-1 EXPRESSION POST-INFECTION

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