

Title: Meningeal barrier breakdown and local immune response during neonatal bacterial meningitis

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Abstract:

Bacterial meningitis is one of the leading infectious diseases associated with high fatality rate and long-term neurological complications in newborns. It is caused by the introduction of bacteria into the bloodstream, which subsequently invade the central nervous system (CNS) and induce inflammation of the meninges. Enveloping the outermost part of the CNS, meninges is a tri-layered structure consisting of the outer dura layer and the inner arachnoid and pia layers referred to as the leptomeninges. As a part of the blood-cerebrospinal fluid barrier (B-CSFB), the outer arachnoid layer consists of epithelial-like cells connected by junctional proteins and regulates cellular and molecular movement between the CSF and the periphery. Recently, the development of arachnoid barrier was described in perinatal mice and in its absence, a significantly higher burden of Group B *Streptococcus* (GBS) bacteria, the primary cause of bacterial meningitis in infants, was observed in the leptomeninges. This elucidated a potential role of arachnoid barrier during bacterial infection, yet the exact mechanism underlying the bacterial CNS pathogenesis via this barrier remains unknown.

Here, I utilized a neonatal bacterial meningitis model to examine how the arachnoid barrier and local meningeal immune response is altered upon GBS infection. Animals were infected at P2 (10^6 CFU of GBS) and the leptomeninges was collected from those at moribund stage (P3-P4). Histological results showed that the expression level of arachnoid barrier junctions (E-cadherin+/Claudin11+) was not significantly different between the mock and the infected groups, but the localization of Claudin11+ junctional proteins was profoundly aberrant in the infected group. The functional assay testing the arachnoid barrier integrity also showed a significant disruption of the barrier upon infection. To investigate the role of local immune cells during bacterial infection, I examined changes in the border-associated macrophages (BAMs), a specialized group of resident immune cells lining the meninges. CD206+/Lyve1+ BAMs underwent significant morphological and molecular changes in infected mice, supporting local activation and a potential proinflammatory response that may impact local barriers like the arachnoid barrier layer. Collectively, our findings suggest that neonatal bacterial infection leads to changes in the arachnoid barrier and that this may involve local meningeal immune response via the BAMs. Future work will elucidate changes in BAM and other immune profile during infection and molecular mechanism underlying the mislocalization of Claudin11+ junctions.

Keyword: Meninges, Arachnoid barrier, Bacterial meningitis, Border-associated macrophages