Göteborg, 2022

Perinatal Staphylococcus epidermidis infection and the immature brain: a neuroinflammatory link

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal **Arvid Carlsson**, Medicinaregatan 3, fredag den **17 juni 2022**, klockan **13:00**

av Giacomo Gravina

Fakultetsopponent:
Stuart Allan, professor
The Manchester University, UK

Avhandlingen baseras på följande delarbeten

I. **Gravina G**, Svedin P, Ardalan M, Levy O, Ek CJ, Mallard C and Lai JCY. Staphylococcus epidermidis Sensitizes Perinatal Hypoxic-Ischemic Brain Injury in Male but Not Female Mice. Front Immunol. 2020 Apr 21;11:516. DOI: 10.3389/fimmu.2020.00516

II. **Gravina G**, Ardalan M, Chumak T, Rydbeck H, Xiaoyang Wang, Ek CJ, Mallard C. Transcriptome network analysis link perinatal Staphylococcus epidermidis infection to microglia reprogramming in the immature hippocampus. Submitted

III. **Gravina G**, Ardalan M, Chumak T, Nilsson A, EK CJ, Danielsson H. Pekny M, Pekna M, Sävman K, Hellström A, Mallard C. Hippocampal proteomics analysis links lipocalin2 with astrocyte reactivity and vascular alteration following perinatal Staphylococcus epidermidis infection. *In Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

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Perinatal Staphylococcus epidermidis infection and the immature brain: a neuroinflammatory link

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Abstract
Preterm birth and its associated complications are among the most serious global health issues that modern society faces. Due to the prolonged medical care and immature immune system, preterm infants have a higher susceptibility to infections, which puts them at a higher risk of developing neurological impairments as well as neurodevelopmental diseases. S. epidermidis is one of the most common nosocomial infections in preterm infants. Despite being considered a harmless commensal for a long time, S. epidermidis has emerged as the predominant pathogen of neonatal sepsis, leading to inflammation-related morbidities. Moreover, the incomplete maturation of the preterm infants´ organs might lead to an increased risk of episodes of hypoxia and it is believed that the ongoing infection can worsen the effects of cerebral hypoxia-ischemia (HI), further increasing the risk for perinatal brain injury. The hypothesis of this doctoral thesis is that systemic inflammation induced by S. epidermidis infection leads to immune reactions in the periphery and the brain, which increases vulnerability to brain injury, leading to neurological impairments. Thus, the overall aim of this thesis was to explore the different aspects of the pathogenesis associated with S. epidermidis infection, ranging from its sensitizing effects to the neuroinflammatory responses. Using our established animal model for S. epidermidis infection and Hypoxia-ischemia (HI), in Paper I we induced HI 24 hours or 5 days after S. epidermidis infection, demonstrating a sex-dependent sensitization 24 hours after infection in male, but not female mice. We also found a dramatic upregulation of peripheral cytokines, brain Chemokine ligand 2 (CCL2) together with decreased plasma levels of Complement protein 5a. As neuroinflammation contributes to perinatal brain injury, in Paper II we analyzed hippocampal microglia activation both at morphological and transcriptional levels. We found that S. epidermidis induced significant changes in microglial morphology as well as in their transcriptional programs. We also found that microglial inflammasome activation might act in synergy with blood-brain barrier alterations as well as leukocyte infiltration into the brain. To further characterize the neuroinflammatory response in the hippocampus of S. epidermidis infected mice, in Paper III we carried out hippocampal global protein expression analysis, revealing astrocytic activation as well as vascular changes. These alterations were associated with increased lipocalin 2 levels in both plasma and brain. We also demonstrated that a similar pattern of events might occur in a cohort of preterm infants with signs of infection by analyzing plasma levels of lipocalin 2. To conclude, this thesis clearly highlights a previously unrecognized and important contribution of S. epidermidis in triggering neuroinflammation in the developing brain. Overall, the findings in this thesis shed new light on how S. epidermidis affects the immature brain, representing a suitable platform for the development of novel treatment or preventative strategies in babies who experience S. epidermidis infection.

Keywords: *S. epidermidis*, neonatal brain injury, hypoxia-ischemia, microglia, neuroinflammation

ISBN 978-91-8009-823-6 (PRINT)
ISBN 978-91-8009-824-3 (PDF)
http://hdl.handle.net/2077/70947