

The role of neonatal immunity in preterm brain injury

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i Nils Nilsson, Medicinaregatan 3, onsdagen den 14 december 2016, klockan 09.00

av Anna-Maj Albertsson

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Avhandlingen baseras på följande delarbeten

- I. Albertsson A-M, Bi D, Duan L, Zhang X, Leavenworth J W, Qiao L, Zhu C, Cardell S, Cantor H, Hagberg H, Mallard C, and Wang X. The immune response after hypoxia-ischemia in a mouse model of preterm brain injury. *J. Neuroinflammation*. 2014; 11:153.
- II. Albertsson A-M, Zhang X, Vontell R, Bi D, Xu Y, Bronson R, Baburamani A A, Supramaniam V, Xia L, Song J, Zhu D, Shang Q, Hua S, Nazmi A, Cardell S, Mallard C, Hagberg H, Xing Q, Zhu C, Cantor H, Leavenworth J, and Wang X. Preterm brain injury is gamma/delta T-cell dependent and IL-17/IL-22 independent. *Manuscript in preparation*.
- III. Albertsson A-M, Zhang X, Leavenworth J W, Bi D, Nair S, Qiao L, Hagberg H, Mallard C, Cantor H, and Wang X. The effect of osteopontin and osteopontin-derived peptides on preterm brain injury. *J. Neuroinflammation*. 2014; 11:197.
- IV. Bi D, Qiao L, Bergelson I, Ek C. J, Duan L, Zhang X, Albertsson A-M, Pettengill M, Kronforst K, Ninkovic J, Goldmann D, Janzon A, Hagberg H, Wang X, Mallard C, and Levy O. *Staphylococcus epidermidis* Bacteremia Induces Brain Injury in Neonatal Mice via Toll-like Receptor 2-Dependent and -Independent Pathways. *J. Infect. Dis*. 2015; 212:1480–90.

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH
FYSIOLOGI**



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Abstract

Perinatal brain injury is an important cause of mortality and morbidity and is associated with neurological disabilities such as those seen in cerebral palsy. Prematurity, especially in combination with very low birth weight, is associated with elevated risks for developing brain injuries, and the leading causes of perinatal brain injury are hypoxia-ischemia (HI) and infection/inflammation. The aims of this thesis were to establish a mouse model of HI-induced preterm brain injury, to determine the immune response after preterm brain injury, to explore the role of $\gamma\delta$ T-cells and the immune regulatory protein osteopontin (OPN) in preterm brain injury, and to evaluate the impact of *Staphylococcus epidermidis* bacteremia on the developing mouse brain.

We found that HI-induced preterm brain injury elicited a Th1/Th17-skewed immune response in the mouse brain, but in contrast to adult ischemic brain injury, the inflammatory cytokine IL-17 did not contribute to injury. Furthermore, we showed that $\gamma\delta$ T-cells are found in the mouse brain after HI, in the brains of asphyxiated fetal sheep, and in postmortem brains of human preterm infants with white matter injury. Genetic depletion of $\gamma\delta$ T-cells reduced the HI-induced preterm brain injury in mice, suggesting that $\gamma\delta$ T-cells contribute to preterm brain injury. We also showed that administration of OPN immediately before HI or the genetic depletion of OPN do not affect the outcome of brain injury in the mouse model of HI, while administration of the OPN-derived peptides N134-153 and C154-198 aggravate brain injury, which contrasts to what has been seen in adult ischemic brain injury. Finally, we showed that *S. epidermidis* bacteremia impair gray and white matter development in the mouse brain even without entry of bacteria into the central nervous system (CNS), providing evidence that systemic infections in the neonate can affect brain development.

In our studies, several findings indicate that the developmental state of the CNS and immune system is of great importance for the outcome of injury as well as for possible therapeutic strategies. Thus identifying specific therapeutic targets for different age groups is of great importance.

Keywords: preterm brain injury, hypoxia-ischemia, immature brain, inflammation, neonatal immunity, $\gamma\delta$ T-cells, osteopontin, *Staphylococcus epidermidis*

ISBN: 978-91-628-9973-8 (TRYCK)
ISBN: 978-91-628-9974-5 (PDF)

<http://hdl.handle.net/2077/47400>