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Characterization of immune cell profiles in meninges and brain parenchyma following injury in the developing mouse brain

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i hörsal **Arvid Carlsson, Medicinaregatan 3, torsdagen den 25 februari 2021 kl. 09:00.**

av Aura Zelco

Fakultetsopponent:

Ulrika Ådén, Professor

Karolinska Universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Nazmi A., Albertsson AM., Rocha-Ferreira E., Zhang X., Vontell R., **Zelco A.**, Rutherford M., Zhu C., Nilsson G., Mallard C., Hagberg H., Lai J.C.Y., Leavenworth J.W., Wang X. "Lymphocytes contribute to the pathophysiology of neonatal brain injury", *Front. Neurol., doi: 10.3389/fneur.2018.00159*

II. **Zelco A.,** Rocha-Ferreira E., Nazmi A., Ardalan M., Chumak T., Nilsson G., Hagberg H., Mallard C., Wang X. "Type 2 Innate Lymphoid Cells Accumulate in the Brain After Hypoxia-Ischemia but Do Not Contribute to the Development of Preterm Brain Injury". *Front. Cellular Neuroscience, 14. doi: 10.3389/fncel.2020.00249*

III. **Zelco A.,** Börjesson V., de Kanter J., Lebrero-Fernández C., Lauschke V.M., Rocha-Ferreira E., Nilsson G., Nair S., Svedin P., Bemark M., Hagberg H., Mallard C., Holstege F.C.P., Wang X. "Single-cell atlas reveals meningeal leukocyte heterogeneity in the developing mouse brain". *Submitted*

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Characterization of immune cell profiles in meninges and brain parenchyma following injury in the developing mouse brain

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ABSTRACT

Preterm newborns are particularly susceptible to complications such as hypoxia-ischemia (HI), which can result in brain injury and subsequent cognitive and/or motor function disabilities, including cerebral palsy. Immune cells have been shown to be involved in the development of perinatal brain damage, commonly with detrimental effects. There is recent evidence that the membranes around the brain parenchyma, the meninges, might also have important roles in the immune response after injury in the adult brain, for example, by being a site of peripheral immune cell infiltration into the brain parenchyma. However, the role of the meninges in preterm brain injury is not known. Thus, the aim of this doctoral thesis was to identify the roles of immune cells in the meninges and brain parenchyma after preterm brain injury using a mouse model of HI-induced preterm brain injury.

In **Paper I** we found that T and B cells accumulate in post-mortem brains and meninges in preterm infants with brain injury. Similarly, in mouse experiments we found that T and B cells respond to the HI injury and infiltrate into the parenchyma. Additionally, genetic deletion of T and B cells resulted in reduced white matter tissue loss 7 days after HI. **Paper II** shows that innate lymphoid cells subtype 2 (ILC2s) also accumulate in the meninges 7 days after HI, but ILC2-impaired mice show no differences in inflammatory response, tissue loss, or glial immunoreactivity compared to wild type mice after HI, demonstrating a non-essential role for this immune cell subtype after preterm brain injury. Using single cell RNA sequencing, **Paper III** presents the cellular composition and the unique transcriptional identities of meningeal immune cells in neonatal mice such as border-associated macrophages, monocytes, and microglia. We also identify the possible involvement of neutrophils in the injury process 6 hours after HI.

To conclude, the findings of this thesis reveal the participation of immune cells in the brain parenchyma and in the meninges to the development of HI injury. We provide insights into the unique single cell profile in the meninges in the immature mouse brain and thus contribute to the understanding of immune cell involvement in the injury process and the inflammatory reactions after preterm brain injury.

Keywords: preterm brain injury, hypoxia-ischemia, immune response, neonatal meninges

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