Repair after injury: unveiling the role of NG2-glia, the major progenitor population in the adult brain, in different injury paradigms

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Short title

Role of NG2-glia in traumatic brain injury Role of NG2-glia in traumatic brain injury

Research Training Group

X Neurobiology

☐ Aging and Degeneration

☐ Oncology and Endocrinology

☐ Virology, Microbiolgy, Biotechnology and Systems Biology

☐ Development and Regeneration

X Trauma, Regeneration and Immune Modulation

☐ Pulmosens

Project description

Project background

NG2-glia, also known as oligodendrocyte progenitor cells, are a highly abundant population in the adult brain. They are the only proliferating cells outside the neurogenic niches and they continuously generate mature, myelinating oligodendrocytes in a region depending manner, well after the end of the major myelination process. However, despite their high numbers and detailed characterization it is still widely unknown if and how NG2-glia react to injury. We have used stab wound injury (SWI) as a model of acute, invasive lesion and followed the reaction of NG2-glia by repetitive live 2-photon *in vivo* imaging. We could show that NG2-glia respond to injury not only with changes in cell morphology but also with an increase in cell number by recruitment of quiescent NG2-glia into the cell cycle and shortening of its length. The NG2-glia reaction takes place very fast and is very heterogeneous, leading to an accumulation of these cells in the injury core and a transient loss of the homeostatic control of their density. Interestingly, physiological

conditions are restored within 14-28 days after the injury. Genetic ablation of proliferating NG2-glia after injury leading to the lack of their increase in number resulted into strong effects in wound closure. To identify molecular mechanisms by which NG2-glia react to injury, we have performed comparative genomic-wide expression profiling and revealed candidate genes that we are currently analyzing.

Project Proposal

We are planning to study the reaction of NG2-glia after a more broad and diffuse traumatic brain injury (TBI) and compare it to their reaction after an invasive SWI. Therefore, we will perform TBI on transgenic mice that we have generated -labeling the oligodendrocyte lineage or NG2-glia and their progeny- and distinguish between animals showing or not a hematoma and/or bone fracture. As it has been speculated (but never analyzed) that NG2-glia react differently depending on the disruption of the blood brain barrier, this would be of great interest. We also intend to study the reaction of NG2-glia after repetitive injury by combining several mild TBIs and SWIs. We will combine the above-described experiments with NG2-glia depletion studies, to analyze the role of these cells in the regeneration and wound closure properties of the brain. As we could also show that NG2-glia and microglia can affect each other under physiological (Hagemeyer et al., 2017) and pathological conditions (unpublished data), the behavior and interaction between NG2-glia and microglia/immune system after SWI/TBI will be studied in more detail.

Keywords (max. five)

- oligodendrocyte progenitor cells (OPCs)
- brain injury
- repair
- knockout and transgenic mice
- oligodendrocyte differentiation