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DISSERTATION

"Pediatric Murine Neural Progenitor Cell Proliferation Following a Mild Traumatic Brain Injury"

by

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Wednesday, November 18th, 2020
1:00 pm.

Meeting link:
https://rutgers.webex.com/rutgers/j.php?MTID=m2445b53272815fd8e8c8473d82c49b9b
Meeting number: 120 015 0604
Password: 020304

Abstract

Pediatric traumatic brain injury (TBI) is a significant problem that affects ~500,000 children each year. As injuries stimulate the production of cytokines that alter cell proliferation, a central goal of this project was to determine how a closed head injury (CHI) would affect the progenitors of the subventricular zone (SVZ), a germinal zone responsible for producing the majority of those brain cells made postnatally. Leukemia Inhibitory Factor (LIF) is a key cytokine increased after TBI; therefore, we evaluated the function of LIF in pediatric TBI using LIF heterozygous mice (LIF Het). CHI's were performed on postnatal day 20 LIF Het and wild type (WT) mice. Two days post injury, cell proliferation within the SVZ increased ~250% in injured LIF Het mice compared to a 30% increase in WT mice. Using a 7-color flow cytometry panel, three distinct multipotential progenitors were more active in the LIF Het SVZ compared to WT SVZ. Surprisingly, early oligodendrocyte progenitor cells (OPC) proliferated 6-fold more, as revealed using flow cytometry and there were 3-fold more proliferating Olig2 expressing cells in the SVZ. By contrast, LIF had a minimal effect on neuronal progenitor proliferation. To establish that LIF was directly exerting an inhibitory effect on the neural progenitors, SVZ derived neurospheres were treated with LIF and cell proliferation measured. LIF treatment decreased overall proliferation and exerted a strong negative effect on late OPC proliferation. Within the OPCs, LIF stimulated phosphorylation of Akt and phosphorylation of S6 ribosomal protein, consistent with the view that the mammalian target of Rapamycin (mTOR) pathway is downstream of LIF receptor activation.

LIF deficiency had the opposite effect on SVZ astrocyte progenitors, whose proliferation increased 2.5-fold in WT injured mice when compared to sham controls, whereas the astrocyte progenitors were quiescent in the LIF Het injured mice. When applied to neurospheres, LIF increased astrocyte progenitor proliferation. To rule out the involvement of other cytokines in neural progenitor cell proliferation homeostasis, a multiplex qPCR array was performed, as well as targeted qPCR analyses on injured LIF Het vs. WT neocortex. Of the 105 cytokines analyzed, only Prokineticin-2 required LIF signaling. However, when Prokineticin-2 was applied to neurospheres, it decreased both OPC and astrocyte progenitor cell proliferation. Altogether, these data reinforce the view that LIF is a key injury-induced cytokine. Importantly, these studies demonstrate that LIF exerts opposite effects upon the oligodendrocyte and astrocyte progenitors of the SVZ, which has important ramifications for understanding how brain development is affected after a pediatric TBI and for producing novel therapeutics for regenerative medicine.