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PreImplantation Factor promotes Neuroprotection by modulating Long non-coding RNA H19 of the Neuronal Stem Cells

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Introduction: Premature infants face multiple challenges including periventricular leukomalacia (PVL) and successful therapies are lacking. Neural stem cells (NSCs) from the subventricular zone give rise to myelin producing cells during brain development. Post-injury, activation of dormant NSCs represents an attractive strategy and long non-coding RNA H19 is a potential candidate to regulate cell differentiation. Since synthetic PreImplantation factor (sPIF) protects against multiple neuronal disorders, we posit that sPIF activates NSCs after injury by modulating H19 and therefore modulates myelin.

Methods: Cell lines (Immature oligodendrocytes MO13.13) were treated with sPIF (200nM; 48h), and evaluated by quantitative RT-PCR and H19 silencing was performed. We used a mouse model of PVL (LPS and hypoxia-ischemia; n=20) to test specific effects on NSCs. All animals were electroporated with a pCAG-Cre plasmid to permanently label NSCs at P0. Injury group was subjected to brain injury and received NaCl as treatment; Sham animals served as healthy controls. sPIF (0.75 mg/kg sc twice daily) treatment was started from P0 until P7. As a proof of concept we used a constitutively active plasmid encoding H19 (pCMV-H19CA) to increase H19 activity in NSCs. We evaluated animals by MRI, immunohistochemistry, and in-situ hybridization at P7 with special focus on labeled NSCs. Two-tailed Student's t-test and Mann- Whitney tests were used in analysis with level of significance set at $p < 0.05$.

Results: We detected myelin loss by reduced fractional anisotropy (FA), diffusion tensor imaging and myelin basic proteins (MBP) intensity post- injury. Both sPIF and H19CA ameliorated this loss significantly, increasing both FA and MBP intensity. Furthermore, sPIF and H19CA resulted in increased NSCs differentiation. In cell lines, sPIF increased mRNA expression of immature (OLIG2) and mature (MBP) oligodendrocyte markers in H19-dependent manner. sPIF also increased H19 expression in the brain, as detected by in-situ hybridization.

Conclusion: sPIF activates NSCs and prevents myelin loss after injury by modulating H19 of the NSCs. Given the FDA Fast Track designation and safety data of sPIF in First in Human Clinical Trial (ClinicalTrials.gov Identifier: NCT02239562), clinical trials to prevent or treat PVL can be envisioned.

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