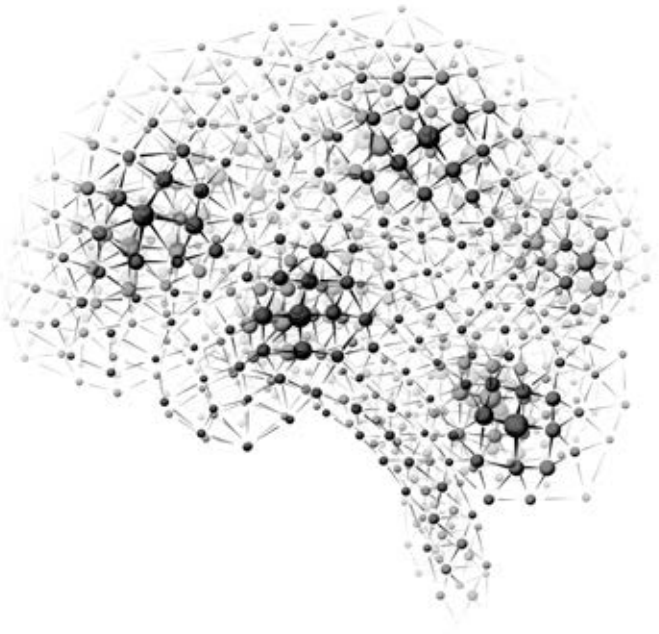
Cell-based therapy for hypoxic-ischemic injury in the preterm brain

Chapter 7
Summary



Cell-based therapy for hypoxic-ischemic injury in the preterm brain

Introduction

Preterm infants are prone to hypoxic-ischemic encephalopathy. Unfortunately, no therapy exists to treat this brain injury. The objective of this translational research project was (1) to study the role of the cerebral and peripheral inflammatory response in the etiology of preterm brain injury following global hypoxia-ischemia, and (2) to assess the neuroprotective effect of exogenous administration of stem cells and the mobilization of endogenous stem cells in the preterm brain after global hypoxia-ischemia.

Methods

Instrumented preterm sheep were subjected to global hypoxia-ischemia by 25 minutes of umbilical cord occlusion at a gestational age of 104 (term is 150) days (± 32 weeks of human gestation). One hour after global hypoxia-ischemia animals were either treated with (1) exogenous mesenchymal stem cells (MSCs) or (2) mobilization of endogenous stem cells using granulocyte-colony stimulating factor (G-CSF). The study consisted of the treatmentgroups with appropriate controle groups. During a 7 day reperfusion period, all vital parameters, including (amplitude-integrated) electroencephalogram, were recorded. At the end of the experiment, the preterm brain was assessed using histology and diffusion tensor imaging (DTI). The effect of MSCs on the peripheral immune system was assessed in a splenocyte proliferation assay.

Results

Our findings showed that global hypoxia-ischemia induced marked activation and proliferation of microglia in the preterm brain. Furthermore, we observed mobilization of immune effector cells (T-cells and neutrophils), most likely originating from the spleen, that invaded the preterm brain. These pro-inflammatory changes were associated with loss of pre-oligodendrocytes and hypomyelination. Moreover, global hypoxia-ischemia caused persistent suppression of brain activity and a pronounced increase in the number of seizures.

Administration of exogenous mesenchymal stem cells (MSCs) reduced cerebral inflammation and white matter injury. MSCs induced T-cell tolerance, which was paralleled with diminished mobilization and invasion of these cells in the preterm brain. In addition, MSCs established functional improvement, as shown by decreased number of seizures after global hypoxia-ischemia.

Similarly, mobilization of endogenous stem cells using systemic granulocyte-colony stimulating factor (G-CSF) reduced cerebral inflammation and white matter injury. However, G-CSF did not reduce the number of seizures after global hypoxia-ischemia.

Conclusion

We have shown in a translational animal model that cell-based therapy is effective in protecting the preterm brain against the cerebral and peripheral inflammatory responses that are involved in the etiology of white matter injury in the preterm brain after global hypoxia-ischemia. Our findings indicated that the administration of exogenous MSCs in particular is an effective method to reduce hypoxic-ischemic injury in the preterm brain. Our studies form the basis for future clinical trials, which will study feasibility of cell-based therapy in preterm infants with hypoxic-ischemic encephalopathy, creating an eligible chance to improve the life of many preterm infants that suffer from hypoxic-ischemic brain injury.