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Mariya Hristova

University College London, UK

Neonatal hypoxic ischemic brain damage: New pathways, new challenges and new treatments

Neonatal Hypoxic-Ischemic Encephalopathy (HIE) is a leading cause of neonatal mortality and morbidity, affecting 1-3 per 1000 live-births in developed countries with rates about 5-10 times higher in low-income setting. About 40% of the affected children die in the neonatal period and further 30% develop life-long neurological disabilities. Therapeutic hypothermia is the only clinically approved care for moderate to severe neonatal Hypoxic-Ischemic (HI) brain injury; however it reduces death and disability only by 11% with about 40% of the treated infants still developing neurological incapacities. Therefore, it is necessary to establish simple, safe and effective supplementary therapies to add to the current therapeutic strategy for HIE. Signal Transducer and Activator of Transcription 3 (STAT3) is strongly up-regulated by HI in the immature brain. Data obtained in our lab suggests that STAT3 removal in neurons or astrocytes and to some extent, systemic STAT3 inhibition reduces inflammation and tissue loss. Exploring the role of Extracellular signal-Regulated Kinase (ERK) isoforms in neonatal HI at cellular level we observed a cell-specific and time-dependent role of ERK, with a predominant, neurotoxic effect of neuronal ERK2, which was counteracted by neuroprotection by ERK1 and astrocytic ERK2. We observed time- and cell-dependent ERK phosphorylation (pERK), with strongly up-regulated pERK first in periventricular white matter axons, followed by forebrain astrocytes and neurons. Overall, global pharmacological inhibition of pERK is strongly neuroprotective. Stem cell therapy decreases brain injury either by replacing lost cells, promoting the differentiation of host progenitors and/or modulating the host immune system. We demonstrated that a single contralateral injection of human amniotic fluid stem cells into the neonatal HI mouse brain decreased the brain lesion, reduced cell death and microglial activation, prevented demyelination and reduced TGFβ1 levels. Thus, STAT3 and ERK inhibition, as well as stem cell therapy have potential as supplementary therapies for neonatal HIE.

Biography

Mariya Hristova is a Senior Research Associate and leads the Perinatal Brain Repair Group at the Institute for Women's Health, University College London, UK. She has her expertise in neuroimmunology and in the hypoxia-ischemia model, therapeutic hypothermia and brain analysis investigating the role of post-translational modifications, transcription factors (STAT3), cytokines (TNFa) and pH changes following neonatal hypoxia-ischemia. She has been studying the combination of xenon and therapeutic hypothermia and melatonin and therapeutic hypothermia in a neonatal piglet model of transient birth asphyxia.

m.hristova@ucl.ac.uk

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