Research

Immune-Neurovascular Interactions in Stroke ? Effects of CNS immaturity.

We recently discovered that both the structural and functional aspects of the BBB are markedly more intact after acute neonatal focal stroke than after adult stroke. Such distinctly different and somewhat surprising vascular resistance in neonates is associated with a different ?signature? of upregulated and downregulated endothelial genes (endothelial transcriptome), different composition of key barrier structural proteins, collagens and laminins, and tight junction proteins between injured adults and neonates. To identify the underlying mechanisms of the functional intactness of the BBB in injured neonates, we focus on interactions between endothelial cells, microglial cells and the extracellular matrix, and communication with peripheral immune signaling, and use an array of in vivo imaging technics, in combination with genetic and pharmacologic tools, to examine the role of immune signals as modifiers of neurovascular integrity and angiogenesis after stroke. We also study the role of the blood-CSF barrier system in immune-neurovascular interactions in perinatal stroke.

Microglial cells, the main cell type that provides immuno-surveillance and serves to remove cellular debris in the brain, have been seen as purely toxic after stroke. Data are emerging, including ours, that the heterogeneity of the microglial pool, the timing of activation and the presence of other stimuli?excitotoxic, infectious, inflammatory, or anti-inflammatory?critically affect an array of microglial effects. We recently discovered that depletion of microglia before neonatal stroke does not limit neuroinflammation or protect and that in fact microglial cells contribute to endogenous defense mechanisms. We explore how pharmacological alteration of the microglial phenotypes or genetic modification of microglial receptors affect short-term and long-term injury after experimental stroke and examine the role of microglial-derived microvesicles and exosomes instroke pathophysiology. Considering that many mediators play more than one role and affect phagocytosis and the associated reduction of neuroinflammation, as well as neurogenesis, we use an array of biochemical techniques to define the microglial phenotypes. We are developing several *non-invasive* approaches to image immune responses in *living* injured brains using bioluminescence, tagged ultrasound and novel ?vessel painting? techniques.