ImmunoTools *special* Award 2014

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MOLECULAR BASIS OF SELECTIVE VULNERABILITY OF NEURONAL CIRCUITS TO BRAIN DAMAGE

The molecular basis of selective vulnerability of different brain regions to the hypoxic/ischemic stress is not known, but what is interesting to note is that the areas of transient synaptic connections like neuronal subplate zone seems to be the most sensitive. The fact that cells with highest proliferation rate are those most sensitive to die upon stress exposure, implies that changes at the DNA level are responsible for such vulnerability. Poly (ADP-ribose) polymerase (PARP-1) is an enzyme activated in response to DNA injury in the nucleus of eukaryotic cells and its basic function is to sense DNA damage that occurs at the highest rate at the transcriptional active genes. As such it has been implicated in cell dysfunction in stressful situations like injury or inflammation. Its crucial role in the regulation of stress induced is confirmed by the finding that mice deficient in PARP-1 enzyme are basically resistant to stroke and inflammation.

That inflammatory cytokines play an important roles both in normal CNS development and response of the brain to divers forms of CNS injury and inflammation is well documented by observation that in the same brain areas where glutamate release causes neuronal cell death after focal cerebral ischemia, like in hippocampal CA1 and CA3 regions and dentate gyrus, TNFα deprivation causes morphological and functional abnormalities.Using TNFα KO mice it has been clearly demonstrated that TNF in the brain regulates a hippocampal development indirectly via nerve growth factor (NGF) and brain derived neurotrophic growth factor (BDNF) but also, directly, acting on its own as a neurotrophic factor upon binding to p75 type of its receptor. Abnormal development of the hypocampal dentate gyrus has also been reported in mice lacking CXCR4 chemokine receptor. High level of CXCR4mRNA expression is detected in Cajal-Retzius (CR) cells which are glutamate immunoreactive, in marginal zone cells and suplate neurons.

The aim of this study is to elucidate the molecular basis of the selective vulnerability of brain regions containing Cajal-Ratzius cells, marginal zone neurons and sublate neurons to common form of perinatal brain injury, hypoxia/ischemia and the contribution of the meditaors of an immune system to such vulnerability. We hypothesize that cells of subplate zone could act as a developmental sensor to monitor the level of the immune response mediators having a function of morphogen or neurotrophic factor in brain development. As such they are already present at significant level in brain and even a slight change in their expression level could potentially cause a serious alteration of brain development. So, in order to avoid potentially hamrful effect of locally induced an immune response, shortly after its initiation, the process of temporaraly shutting down cytokine expression is activated almost in parallel. Better understanding of molecular interactions between glutamate as a major neurotransmitter in a brain and mediators of the innate and adoptive immune response could be potentially promising in the finding new prognostic markers and therapeutic approaches to cure cognitive, physiogenic and neurologic deficits developed following brain injury.

Mice deficient in PARP-1 enzyme which are basically resistant to stroke and inflammation will be used to better understand the mechanism of negative control of apoptotic cell death upon inflammatory stress. In order to identify molecule which would carry out resistance to inflammation induced by brain damage, hippocampal slices cultures from PARP-1 deficient mice exposed to hypoxia and LPS will be analysed by immunohistochemistry for the sublate zone markers to trace its cellular composition (p73, CXCR4, Reelin), chemokine/cytokine production in situ (TNFα, IFNγ, TGF-β, IL-2, IL-10. Also, the level of proinflammatory cytokines IL-1-β, TNF–α, IL-6, and antiinflammatory cytokines IL-10, TGF-β in sera of PARP-1 deficient mice will be evaluated by ELISA. At this point we are interested in getting ImmunoTools reagents.

ImmunoTools *special* AWARD for **Ljijana Poljak** includes 17 reagents

FITC - conjugated anti-mouse CD11b, CD25, CD29, CD117, CD247, isotype control IgG2b,

PE - conjugated anti-mouse CD3e, CD44, isotype control IgG2b,

mouse IL-6 ELISA-set (for one 96 plate, ELISA set contain 3 reagents)

recombinant mouse cytokines: IL-1 alpha, IL-1beta, NGF beta, IL-6, TNF alpha

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