

## Euro Neuropharmacology 2018 - Targeting the splenic response to brain ischemia as a treatment for stroke - Keith Pennypacker - University of Kentucky

**Keith Pennypacker**

University of Kentucky, USA

Stroke, a cerebrovascular injury, is the leading cause of disability and recent reports shows that inhibiting the inflammatory response to stroke enhances neurosurvival and limits expansion of the infarction. The immune response which is initiated in the spleen linked to the systemic inflammatory response to stroke, contributes to neurodegeneration. Removal of the spleen significantly reduces neurodegeneration after ischemic insult. The spleen is a highly vascularized secondary peripheral lymphoid organ and is organized into the white pulp and the red pulp. The white pulp consists of T cell zones, or periarteriolar lymphoid sheaths, and B cell follicles; while the red pulp consists B cells, natural killer cells (NK cells), and macrophages which are in close proximity to the vasculature. This allows macrophages to filter the blood for dying red blood cells, hemoglobin, and antibody covered bacterial pathogens. Plasma cells and antibody producing B cells, are the particular type of B cells found in the red pulp. This location in the spleen allows for rapid delivery of antibodies into circulation. Natural killer cells in the red pulp resemble NK cells found in circulation. Splenectomy resulted in decreased numbers of activated microglia, macrophages, and neutrophils present in the brain tissue. Peripheral immune response as mediated by the spleen is a major contributor to the inflammation that enhances neurodegeneration after stroke. Protecting neurons and blunting the inflammatory response are key components for developing new treatments to alleviate the cerebral damage, disability, and ultimately death caused by stroke. After the initial ischemic injury, a compromised blood-brain barrier coupled with expression of adhesion molecules by the vascular endothelial cells permits an influx of peripheral immune cells including macrophages, neutrophils, leukocytes, T cells, and B cells. This influx of peripheral immune cells into the brain exacerbates the local brain inflammatory response, which is leading to enhanced neurodegeneration. Ischemia produces a hypoxic and glucose deprived environment that leads to cell death through necrosis or apoptosis. In an attempt to keep up with the high energy demands in the brain, neural cells switch to anaerobic cellular respiration. Cell membranes get damaged from the resulting build up of reactive oxygen and nitrogen free radicals, which leads to cellular edema and necrosis. The leaky BBB contributes to increased neuronal injury by increasing edema, as intracranial pressure builds from the influx of excess fluid. This BBB damage allows the peripheral immune system which comes in contact with these neural antigens and generate an immune response to the brain, which results in injury. Monocytes have been shown to play a detrimental role in ischemic pathology in many other organs. As the spleen contains a majority of the monocytes in the body, these cells responsible for IR organ damage. This has lead to the conclusion that the spleen is an important mediator of post IR injury tissue

damage. Additionally, blocking Kupffer cell activation with gadolinium chloride was as efficacious as splenectomy in renal and intestinal IR. Studies indicate that the spleen activates Kupffer cells to a pro-inflammatory state resulting in increased tissue damage following IR injuries. permanent middle cerebral artery occlusion The spleen has been found to decrease in size following pMCAO in rats and tMCAO in mice . The spleen transiently decreases in size from 24 to 72 h following pMCAO in rats. A catecholamine (CA) surge occurs following damage to the insular cortex, an area mainly perfused by the MCA, which may be responsible for this reduction in size. Activation of the  $\alpha 1$  adrenergic receptors on the splenic smooth muscle capsule results in contraction of the splenic capsule, which leads to the decrease in spleen size. Administration of prazosin, an  $\alpha 1$  adrenergic receptor antagonist, prevents the decrease in spleen size following pMCAO . Spleen size has also been inversely correlated with infarct volume in rats following pMCAO, with smaller spleen sizes correlating with larger infarcts. The splenic response in mice following tMCAO appears to be different from the response observed in rats following pMCAO. The spleens of mice continually decrease in size following tMCAO out to 96 h. This decrease in spleen size appears to be due to apoptosis of the spleen and a loss of the germinal B cell centers. The only immune cell population that has been shown to decrease in number following tMCAO in mice is B cells. Another study in mice with tMCAO found the spleen continues to decrease in size out to 7 days post tMCAO. Cytokines extensively studied following experimental stroke, as well as in stroke patients. As some cytokines have dual roles in the immune response and can be either protective or detrimental depending on the circumstances. Some cytokines are inflammatory early after a stroke, but provide trophic support to cells at delayed time points. Other cytokines can have survival or inflammatory effects depending on the receptor to which they bind. Even, some cytokines are elevated very early following stroke. The two TNF $\alpha$  receptors activated, results in different cellular responses depending on the cell type or the presence of both receptors on the same cell. TNF $\alpha$  can initiate response resulting the production of cytokines, or be protective by preventing apoptosis. The two different receptors, TNF $\alpha$ R1 and TNF $\alpha$ R2, results in a combination of different cellular responses. TNF $\alpha$ R1 has an intracellular death domain that divert the cellular response to TNF $\alpha$  in a Fas-associated protein with a death domain (FADD) towards apoptosis, or the binding of TNF-receptor associated protein 2 (TRAP2), which leads to the transcription of anti-inflammatory factors. Removal of the spleen proven that inflammatory response originating from this organ to stroke is responsible for delayed neurodegeneration. IFN $\gamma$  levels are increased as part of this splenic inflammatory

response and resulting in delayed activation of microglia/macrophages in the brain that is detrimental to the survival of compromised neural cells.  $\text{IFN}\gamma$  is also known to induce several proteins, many of which are chemokines. IP-10 is of particular interest as it plays a role in influencing the differentiation of naïve Th cells to become Th1 cells, and is a strong chemoattractant for Th1 cells while subsequently blocking the activation of Th2 cells.