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Targeting the splenic response to brain ischemia as a treatment for stroke

Many studies have recently demonstrated that the spleen plays a central role in the immune response to stroke, yet few have been successful in describing the precise splenic mechanisms leading to neurodegeneration. Our laboratory was the first to demonstrate that splenectomy decreases infarct volume. Importantly, we have spent the past decade elucidating the inflammatory signals and cell types involved. We have identified the splenic immune cells (monocytes, NK and T) that migrate to the injured hemisphere following experimental stroke. We have also shown that systemic administration of the pro-inflammatory cytokine IFNγ abolished the protective effects of splenectomy, and administration of IFNγ blocking antibodies reduced injury. Moreover, IFNγ activates and induces expression of IP-10 in microglia. IP-10 attracts IFNγ-expressing T cells to the injured hemisphere and drives a Th1 response while inhibiting the Th2 one. The spleen-derived neurodestructive signaling involves IFNγ-associated activation of microglia, which leads to a feed forward signal through IP10 to attract more IFN-γ. This leads to the additional expression of IP-10 in M1 microglia to further exacerbate stroke-induced neurodegeneration. This splenic response provides a therapeutic target for novels treatments to reduce stroke-induced neurodegeneration.

Biography

Keith Pennypacker has completed his PhD from Penn State University and Postdoctoral studies from National Institute of Environmental Sciences. He is a Professor in the Department of Molecular Pharmacology and Physiology. He has published more than 100 papers in peer-reviewed journals and has been serving as an Editorial Board Member on *Translational Stroke Research* and *Toxicology and Applied Pharmacology.*

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