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Inhibition of system Xc- transporter attenuates autoimmune inflammatory demyelination

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T cell infiltration into the central nervous system (CNS) is a significant underlying pathogenesis in autoimmune inflammatory demyelinating diseases. Several lines of evidence suggest that glutamate dysregulation in the CNS is an important consequence of immune cell infiltration in neuroinflammatory demyelinating diseases; yet, the causal link between inflammation and glutamate dysregulation is not well understood. A major source of glutamate release during oxidative stress is the system Xc^- transporter, however, this mechanism has not been tested in animal models of autoimmune inflammatory demyelination. We find that pharmacological and genetic inhibition of system Xc^- attenuates chronic and relapsing-remitting experimental autoimmune encephalomyelitis (EAE). Remarkably, pharmacological blockade of system Xc^- seven days after induction of EAE attenuated T cell infiltration into the CNS, but not T cell activation in the periphery. Mice harboring a Slc7a11 (xCT) mutation that inactivated system Xc^- were resistant to EAE, corroborating a central role for system Xc^- in mediating immune cell infiltration. We next examined the role of the system Xc^- transporter in the CNS after immune cell infiltration. Pharmacological inhibitors of the system Xc^- transporter administered during the first relapse in a SJL animal model of relapsing-remitting EAE abrogated clinical disease, inflammation, and myelin loss. Primary co-culture studies demonstrate that myelin-specific $CD4^+$ T helper type 1 (Th1) cells provoke microglia to release glutamate via the system Xc^- transporter causing excitotoxic death to mature myelin-producing OLs. Taken together these studies support a novel role for the system Xc^- transporter in mediating T cell infiltration into the CNS as well as promoting myelin destruction after immune cell infiltration in EAE.

Biography

Tara DeSilva, Assistant Professor, recently joined the faculty at the University of Alabama at Birmingham after her postdoctoral fellowship at Harvard Medical School and Children's Hospital Boston. The research in Dr. DeSilva's laboratory focuses on understanding demyelinating diseases such as Multiple Sclerosis and Transverse Myelitis. Dr. DeSilva's research has been awarded grants from the National Multiple Sclerosis Society, National Science Foundation, and the National Institutes of Health. The goal of Dr. DeSilva's research is to understand 1) how activity-dependent mechanisms stimulate glutamatergic signaling between axons and oligodendrocyte progenitor cells (OPCs) to turn on transcriptional programs necessary for myelination; and 2) how immune cell inflammatory mediators prevent newly proliferated OPCs, as a consequence of neuroinflammation, from forming normal mature myelin. The goal of these studies is to understand how to reprogram newly proliferated OPCs to remyelinate, which has important implications in neural regeneration in demyelinating diseases like multiple sclerosis as well as neurodegenerative diseases. To elucidate these mechanisms Dr. DeSilva's laboratory uses conditional knockout mice in developmental models of myelination, animal models of experimental autoimmune encephalomyelitis, and co-culture models of immune cells and glia cells.

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