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Targeting toll-like receptors to reduce brain injury

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Toll-like receptors (TLRs), a family of innate immune receptors, play a critical role in mediating inflammation in response to both pathogens and non-pathogen stimuli, so called sterile inflammation, such as cerebral hypoxia-ischemia. We have studied the contribution of TLRs to injury in the developing brain and showed that TLRs are regulated in the newborn brain following both systemic inflammation and after neonatal cerebral hypoxia-ischemia. LPSa TLR-4 agonist, given to fetal sheep at midgestation, results in brain injury similar to that observed in preterm infants. Chronic systemic exposure of either LPS or a TLR-1/2 agonist (Pam_3CSK_4) during the early neonatal period impairs both grey and white matter development in mice and genetic inhibition of TLR-2 protects against neonatal hypoxia-ischemia. Stimulation of TLRs can also increase the vulnerability to subsequent insults and thereby exaggerate brain injury in the neonate. We showed that stimulation of TLR-3 or TLR-4 renders newborn rodents highly susceptible to hypoxia-ischemia and that the increased vulnerability is dependent on the TLR adaptor proteins MyD88 and TRIF. In a recent study we have further explored the neuroprotective potential of a novel class of immunomodulation peptides following LPS-induced brain injury. In summary, there is convincing data to show that inflammatory mechanisms contribute to perinatal brain injury. TLRs seem to play an important role in mediating these neurotoxic effects on the developing brain.

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Interleukin-27 is locally produced and triggers responses in the inflamed human CNS

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The mechanisms whereby CNS cells locally modulate immune responses are not fully elucidated. Our goal is to determine whether interleukin-27 (IL-27), a cytokine with both pro- and anti-inflammatory properties, contributes to the pathogenesis of multiple sclerosis (MS), the prototypic neuroinflammatory disease. IL-27 is composed of two subunits: EBI3 and p28 whereas its receptor (IL-27R) consists of two chains: TCCR and gp130. We observed that IL-27 is up-regulated in MS brains compared to controls and that astrocytes (GFAP+) and microglia/macrophages (Iba1+) are important sources of this cytokine. We demonstrated that pro-inflammatory cytokines (e.g. TNF) up-regulate IL-27 production by human astrocytes. Human pro-inflammatory macrophages and microglia (M1 cells) also produce high levels of IL-27, whereas anti-inflammatory (M2 cells) do not. Moreover, we detected that most CNS infiltrating CD8 T lymphocytes express the IL-27R, supporting the notion that these infiltrating immune cells are susceptible to the local IL-27-mediated effects. We have previously shown that IL-27 promotes the activation of human CD8 T-lymphocytes into Tc1 cells, thus CNS sources of IL-27 could locally increase cytotoxic function of these infiltrating T cells. Finally, IL-27 triggers signaling into human astrocytes suggesting that these CNS cells are also receptive to this cytokine. Overall, our data demonstrate that IL-27 and its receptor are elevated in the CNS of MS patients and that several cells (T lymphocytes, astrocytes) present in such inflamed CNS are susceptible to this cytokine. We are currently investigating whether elevated IL-27 levels within the CNS are beneficial or detrimental in the context of MS..

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