The brain has been traditionally regarded as an immune-privileged organ because the blood-brain barrier restricts the access of immune cells and mediators from blood. However, recent studies indicate that the brain can offer an environment for innate immune responses and that a considerable bi-directional communication takes place between the nervous and the immune system in both health and disease. Growing evidence shows that innate immune cells including microglia, macrophages and neutrophils are implicated not only in infectious brain diseases but also in neurological disorders. Despite extensive researches, the roles of innate immune cells in non-infectious brain diseases have not been well elucidated.

In chapter 1, the in vivo role of microglia activation in kainic acid (KA)-induced neurodegeneration was investigated using IkkYα conditional knockout mice (LysM-Cre/IkkYαF/F) in which the IkkYα gene is specifically deleted in cells of myeloid lineage including microglia in the brain. This deletion resulted in the reduction of IKK activity in cultured primary microglia by up to 40% compared to wild-type (WT, IkkYαF/F), and LPS-induced proinflammatory gene expression was also compromised. KA-induced hippocampal neuronal cell death was reduced by 30% in LysM-Cre/IkkYαF/F mice compared to WT mice. Reduced neuronal cell death was accompanied by decreased KA-induced glial cell activation and subsequent expression of proinflammatory genes such as TNF-α and IL-1β. Similarly, neurons in organotypic hippocampal slice cultures (OHSCs) from LysM-Cre/IkkYαF/F mouse brain were less susceptible to KA-induced excitotoxicity compared to WT OHSCs, due in part to decreased TNF-α and IL-1β expression. Collectively, the data demonstrate that IKK/NF-κB-dependent microglia activation contributes to KA-induced hippocampal neuronal cell death in vivo through induction of inflammatory mediators.

In chapter 2, the role of TLR2 in excitotoxic hippocampal cell death was studied using TLR2 knock-out (KO) mice. TLR2 expression was up-regulated in microglia in the ipsilateral hippocampus of KA-injected mice. KA-mediated hippocampal cell death was reduced in TLR2 KO mice compared to WT mice. Similarly, KA-induced glial activation and proinflammatory gene expression in the hippocampus were compromised in TLR2 KO mice. These effects were accompanied by reduced macrophage recruitment to the hippocampus. In addition, neurons in OHSCs from TLR2 KO mouse brains were less susceptible to KA excitotoxicity than WT OHSCs. This protection is partly due to decreased expression of proinflammatory genes, such as TNF-α and IL-1β in OHSCs from TLR2 KO mice. These data demonstrate that TLR2 signaling in microglia contributes to KA-mediated innate immune responses and hippocampal excitotoxicity.

In chapter 3, the in vivo role of TLR2 in brain injury after Intracerebral hemorrhage (ICH) was characterized using TLR2 KO mice. TLR2 expression was upregulated in the ipsilateral hemorrhagic brain tissue after collagenase injection. Brain injury volume and neurological deficits following ICH were reduced in TLR2 KO mice compared to WT mice, although the brain water content was not significantly different. Neutrophil infiltration after ICH was attenuated in TLR2 KO mice compared to WT mice. The decrease in neutrophil infiltration in TLR2 KO mice was accompanied by reduced neutrophil-attracting chemokine gene expression in injury sites and compromise in the migration ability of TLR2 KO neutrophils. Likewise, decreased brain damage in TLR2 KO mice post-ICH was accompanied by the reduced gelatinolytic activity and MMP-9 gene expression in the hematoma. In addition, primary hippocampal neurons from TLR2 KO mice were less vulnerable to thrombin than that from WT mice. Taken together, these data show that TLR2 have a detrimental role in brain injury after ICH and may be utilized as a new therapeutic target for the treatment of ICH.

In conclusion, the present study demonstrates that microglial activation via TLR2 and IKK/NF-κB signaling pathway contributes to KA-induced hippocampal neuronal cell death. In addition, TLR2 have a detrimental role in brain injury after ICH. These results suggest that targeting TLR2- and/or IKK-dependent innate immune response may be an effective therapeutic treatment in delayed neuronal cell death due to excitotoxic stimuli and ICH.
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