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Inflammation and cytokine production in experimental neuroinflammatory disorders

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ABSTRACT

Glutamate excitotoxicity is involved in the pathogenesis of a variety of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). Kainic acid (KA), an analogue of excitotoxic glutamate, can elicit selective neuronal death in the brain of rodents, of which the pathological changes partially mimic the neurodegenerative disorders in humans. Experimental autoimmune neuritis (EAN) is an immune-mediated acute inflammatory disease of peripheral nervous system (PNS) and shares many characteristics of human Guillain-Barré syndrome (GBS). Thus EAN is considered to represent as an animal model to study pathogenesis and therapy of human GBS.

Cytokines play a key role in neuroinflammatory disorders. In our studies, we attempted to explore the possible roles of tumor necrosis factor (TNF)-α and interferon gamma (IFN-γ) in experimental neurodegenerative and neuroinflammatory disorders.

In **Paper I**, the role of TNF-α in KA-induced hippocampal neurodegeneration was studied by comparing TNF-α knockout (KO) mice with C57BL/6 wild type (WT) mice. After KA treatment, TNF-α KO mice showed more sensitivity to KA-induced neurotoxicity than WT mice, as demonstrated by more severe seizures, measurable behavior changes, greater neuronal degeneration and enhanced glial cell activation, as well as nitric oxide (NO) production. Additionally, KA-treatment up-regulated the expression of nuclear factor kappa B (NFκB) in TNF-α KO mice to a greater degree as compared to that in KA-treated WT mice. In **Paper II**, we aimed to further clarify the protective role of TNF-α in KA-induced hippocampal neuronal death in vitro and elucidated the potential signaling pathways. After 24-hours treatment with KA, comparing with WT mice, TNF-α KO mice showed more susceptibility to KA-induced neurotoxicity, as demonstrated by higher expression of lactate dehydrogenase (LDH) and lower neuronal survival rates, as well as elevated NO production. It is also evidenced that pretreated with anti-TNF-α antibody increased the production of LDH and NO, and decreased the neuronal survival rate. In contrast, neurons from WT mice pretreated with recombinant TNF-α were more resistant to KA induced neurotoxicity. TNF-α deficiency induced down-regulation of phospho-IκBα, total AKT and phospho-AKT, as well as up-regulation of phospho-p38 MAPK expressions after KA treatment. The reverse results can be achieved in WT hippocampal neurons with TNF-α treatment, i.e. up-regulation of phospho-IκBα and AKT. In **Paper III,** to further explore the role of TNF-α in the pathogenesis of neuroinflammation, the animal model-EAN was introduced. TNF-α deficiency significantly attenuated the clinical signs of EAN. Further, anti-TNF-α receptor 1 (TNFR1) antibodies markedly suppressed the clinical severity of EAN. TNF-α deficiency down-regulated the production of interleukin (IL)-12 and NO, as well as enhanced the production of IL-10 in macrophages. In **Paper IV,** the role of IFN-γ in the pathogenesis of EAN was investigated. The clinical signs of IFN-γ KO EAN mice were aggravated when compared with WT EAN mice. At the peak of EAN course, the IL-17A expressing cells in cauda equine (CE) and the levels of IL-17A in sera were elevated in IFN-γ KO mice. The proportions of MHC II, macrosialin, and IL-12 expressing cells, relative to total CE infiltrating cells were correspondingly higher in IFN-γ KO than WT mice with EAN.

In summary, TNF-α may play a protective role in KA-induced excitotoxic neurodegeneration, while TNF-α exacerbates EAN via TNFR1 by inducing the proinflammatory phenotype of macrophage. IFN-γ deficiency enhanced the clinical severity of EAN via upregulating of IL-17A and Th2 cytokines production. These findings have relevance for future studies on pathogenesis and treatment of neurodegenerative and neuroinflammatory disorders in humans.

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