論文要約　藤川理沙子

EP4 Receptor-Associated Protein in Microglia Promotes Inflammation in the Brain

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The American Journal of Pathology, Vol. 186, No. 8, August 2016

Microglial cells play a key role in neurodegenerative disorders. Over-activated microglia induce detrimental neurotoxic effects through the excess production of pro-inflammatory cytokines; however, the mechanisms of microglial activation are poorly understood. We focused on prostaglandin E_2 type 4 receptor-associated protein (EPRAP), which suppresses inflammation in macrophage[1,2]. We demonstrated that EPRAP exists in microglia in the brain. EPRAP deficiency markedly decreased the expression of TNF-α and MCP-1 in primary microglial cells after LPS stimulation. Accordingly, EPRAP deficient mice showed less microglial accumulation and reduced expression of TNF-α and MCP-1 mRNA in the cortex after intraperitoneal administration of LPS, compared to wild-type mice. In addition, EPRAP deficiency decreased microglial activation and neuronal cell death in the hippocampus induced by intraventricular injection of kainic acid. EPRAP deficiency impaired the LPS-induced phosphorylation of c-jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38) in microglia. The phosphorylation level of mitogen-activated protein kinase kinase 4 (MKK4), which phosphorylates JNK and p38, were also decreased in EPRAP-deficient microglia. Although EPRAP in macrophages suppresses inflammation, EPRAP promotes pro-inflammatory activation of microglia through MKK4-mediated signaling. EPRAP in microglia may be key to deteriorating neuronal damage brought on by brain inflammation.

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2) Nakatsuji M, Minami M, Seno H, Yasui M, Komekado H, Higuchi S, Fujikawa R, Nakanishi Y, Fukuda A, Kawada K, Sakai Y, Kita T, Libby P, Ikeuchi H, Yokode M, Chiba T: EP4 receptor-associated protein in macrophages ameliorates colitis and colitis-associated tumorigenesis. PLoS Genet 2015, 11:e1005542