Toll like receptor 4 (TLR4)

Toll-like receptor 4 is a protein that in humans is encoded by the TLR4 gene.

TLR 4 is a toll-like receptor that is responsible for activating the innate immune system. It is most well-known for recognizing lipopolysaccharide (LPS), a component of Gram-negative bacteria, but its ligands also include several viral proteins, polysaccharides, and a variety of endogenous proteins such as low-density lipoprotein, beta-defensins, and heat shock protein.

TLR 4 has also been designated as CD284 (cluster of differentiation 284). The molecular weight of TLR 4 is approximately 95 kDa.

Eupatilin has a therapeutic effect on inflammation caused by intracerebral hemorrhage. The underlying mechanism may be related to TLR4/MyD88, which brings new hope for clinical patients to improve symptoms and prognosis [1)].

Tang et al. identify endothelial Toll-like receptor 4 (TLR4) and the gut microbiome as critical stimulants of cerebral cavernous malformation formation. Activation of TLR4 by Gram-negative bacteria or lipopolysaccharide accelerates CCM formation, and genetic or pharmacologic blockade of TLR4 signalling prevents CCM formation in mice. Polymorphisms that increase expression of the TLR4 gene or the gene encoding its co-receptor CD14 are associated with higher CCM lesion burden in humans. Germ-free mice are protected from CCM formation, and a single course of antibiotics permanently alters CCM susceptibility in mice. These studies identify unexpected roles for the microbiome and innate immune signalling in the pathogenesis of a cerebrovascular disease, as well as strategies for its treatment [2)].

A single treatment of hyperbaric oxygen (HBO) therapy immediately after middle cerebral artery occlusion (MCAO) followed by 24 h' reperfusion significantly reduces edema and may improve perfusion. TLR4 knockout protects mice from MCAO damage, but to a lesser extent than HBO treatment [3)].

Cerebral ischemia-reperfusion injury in rats can be alleviated via the inhibition of the TLR4/NF-κB signaling pathway [4)].

Toll-like receptor 4 (TLR4), predominantly expressed by microglia, recognizes damage-associated molecular patterns (DAMPs) and regulates inflammatory processes. Interestingly, the switch of microglial M1/M2 phenotypes after TBI is highly important regarding damage and restoration of neurological function. Therefore, we investigated the role and mechanisms of the TLR4 signalling pathway in regulating microglial M1/M2 phenotypes. Using a controlled cortical impact (CCI) model, we found that TLR4 knockout (KO) mice exhibited decreased infarct volumes and improved outcomes

in behavioural tests. In addition, mice lacking TLR4 had higher expression of M2 phenotype biomarkers but lower expression of M1 phenotype biomarkers. Compared with microglia derived from wild-type (WT) mice, increased expression of M2 phenotype biomarkers and decreased expression of M1 phenotype biomarkers were also noted in primary cultures of microglia from TLR4 KO mice. In TLR4 KO mice, the expression levels of downstream signalling molecules of TLR4, such as active Rac-1 and phospho-AKT, were higher, while MyD88 and phospho-NF-κB p65 expression levels were lower than in WT mice. Our results demonstrate that the absence of TLR4 induces microglial polarization toward the M2 phenotype and promotes microglial migration and, in turn, alleviates the development of neuroinflammation, which indicates potential neuroprotective effects in the TBI mouse model. Furthermore, up-regulation of IL-4 expression in TLR4 KO mice could contribute to anti-inflammatory functions and promote microglial polarization toward the M2 phenotype, which might be mediated by active Rac-1 expression. Taken together, TLR4 deficiency contributes to regulating microglia to switch to the M2 phenotype, which ameliorates neurological impairment after TBI [5].

1)
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