Contrasting roles of IL-9 and IL-21 in modulating microglial activation and neuroinflammation.

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Outline

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2. Interleukin-9 protects from microglia- and TNF-mediated synaptotoxicity in experimental multiple sclerosis
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Abstract

Neuroinflammation is a major pathogenic mechanism underlying various central nervous system (CNS) diseases, in which microglia play a crucial role. Microglia help maintain neural homeostasis under normal conditions but can cause neuronal damage when excessively activated. Cytokines are critical regulators of microglial activity. This report compares the effects of the cytokines IL-9 and IL-21 on neuroinflammation. In an experimental autoimmune encephalomyelitis (EAE) mouse model, IL-9 was found to suppress the pro-inflammatory cytokine TNF signaling pathway and reduce synaptic hyperexcitability-induced inflammatory synaptopathy, thereby alleviating neuroinflammation and improving clinical symptoms, demonstrating its neuroprotective effects. In contrast, IL-21 induces extensive neuroinflammatory responses and promotes lipid accumulation in microglia, accompanied by upregulation of lipid metabolism–related genes such as CD36, TREM2, and ApoE, ultimately leading to microglial dysfunction and neurodegeneration. These two studies indicate that within the CNS, IL-9 and IL-21 represent neuroprotective and pro-inflammatory cytokines, respectively, and exert opposing regulatory effects on microglial phenotype and neural function. In summary, enhancing IL-9 signaling or inhibiting IL-21 pathways may serve as potential therapeutic strategies to rebalance CNS immunity and preserve neuronal function.

Reference

Oyamada, H., Ying, Y., Agrawal, S. *et al*. Chronic IL-21 drives neuroinflammation and promotes lipid accumulation in microglia. *Immun Ageing* 22, 15 (2025). doi: 10.1186/s12979-025-00510-2

Guadalupi, L., Vanni, V., Balletta, S. *et al.* Interleukin-9 protects from microglia- and TNF-mediated synaptotoxicity in experimental multiple sclerosis. *J Neuroinflammation 21*, 128 (2024). doi: 10.1186/s12974-024-03120-9