Interleukin 18

Interleukin-18 (IL18, also known as interferon gamma inducing factor) is a protein which in humans is encoded by the IL18 gene.

The protein encoded by this gene is a proinflammatory cytokine.

IL-18 is a cytokine that belongs to the IL-1 superfamily and is produced by macrophages and other cells. IL-18 works by binding to the interleukin-18 receptor, and together with IL-12 it induces cell-mediated immunity following infection with microbial products like lipopolysaccharide (LPS). After stimulation with IL-18, natural killer (NK) cells and certain T cells release another important cytokine called interferon-γ (IFN-γ) or type II interferon that plays an important role in activating the macrophages or other cells.

The combination of this cytokine and IL12 has been shown to inhibit IL-4 dependent IgE and IgG1 production, and enhance IgG2a production in B cells. IL-18 binding protein (IL18BP) can specifically interact with this cytokine, and thus negatively regulate its biological activity.

Clinical significance

Apart from its physiological role, IL-18 is also able to induce severe inflammatory reactions, which suggests its role in certain inflammatory disorders.

Endometrial IL-18 receptor mRNA and the ratio of IL-18 binding protein to interleukin 18 are significantly increased in adenomyosis patients in comparison to normal people, indicating a role in its pathogenesis.

IL-18 has been implicated as an inflammatory mediator of Hashimoto's thyroiditis, the most common cause of autoimmune hypothyroidism. IL-18 is up regulated by interferon-gamma.

IL-18 has also been found to increase the Alzheimer's disease-associated amyloid-beta production in human neuron cells.

Rashad et al., from Sendai, Japan showed the intense activation of immune cells, particularly the microglia, along with the increase in macrophage activity and NLRP3 inflammasome activation that is indicated by NLRP3, Interleukin 1 beta (IL-1β), and Interleukin 18 gene and caspase 1 upregulation and cleavage as well as pyroptosis.

Leukocytes were observed in the brain parenchyma, indicating a role in cerebral venous thrombosis (CVT)-induced inflammation. In addition, astrocytes were activated, and they induced glial scar leading to parenchymal contraction during the subacute stage and tissue loss. MMP9 was responsible primarily for the BBB breakdown after CVT and it is mainly produced by pericytes. MMP9 activation was observed before inflammatory changes, indicating that BBB breakdown is the initial driver of the pathology of CVT. These results show an inflammation driven pathophysiology of CVT that follows MMP9-mediated BBB breakdown, and identified several targets that can be targeted by pharmaceutical agents to improve the neuroinflammation that follows CVT, such as MMP9, NLRP3,

and IL-1β. Some of these pharmaceutical agents are already in clinical practice or under clinical trials indicating a good potential for translating this work into patient care [1)].

1)
Rashad S, Niizuma K, Sato-Maeda M, Fujimura M, Mansour A, Endo H, Ikawa S, Tominaga T. Early BBB breakdown and subacute inflammasome activation and pyroptosis as a result of cerebral venous thrombosis. Brain Res. 2018 Jul 4. pii: S0006-8993(18)30362-7. doi: 10.1016/j.brainres.2018.06.029. [Epub ahead of print] PubMed PMID: 29981290.