# Interleukin-1

There are two genes for Interleukin 1 (IL-1): IL-1 alpha and IL-1 beta (this gene). IL-1β precursor is cleaved by cytosolic caspase 1 (interleukin 1 beta convertase) to form mature IL-1β.

The fever-producing property of human leukocytic pyrogen (Interleukin 1) was purified by Dinarello in 1977 (PNAS) with a specific activity of 10-20 nanograms/kg. In 1979, Dinarello reported that purified human leukocytic pyrogen was the same molecule that was described by Igal Gery in 1972.

He named it lymphocyte-activating factor (LAF) because it was a lymphocyte mitogen. It was not until 1984 that interleukin 1 was discovered to consist of two distinct proteins, now called interleukin-1 alpha and interleukin-1 beta.

IL-1β is a member of the interleukin 1 family of cytokines. This cytokine is produced by activated macrophages as a proprotein, which is proteolytically processed to its active form by caspase 1 (CASP1/ICE). This cytokine is an important mediator of the inflammatory response, and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. The induction of cyclooxygenase-2 (PTGS2/COX2) by this cytokine in the central nervous system (CNS) is found to contribute to inflammatory pain hypersensitivity. This gene and eight other interleukin 1 family genes form a cytokine gene cluster on chromosome 2.

The molecular weight of the proteolytically processed IL1B is 17.5 kDa. IL1B has the following amino acid sequence:

APVRSLNCTL RDSQQKSLVM SGPYELKALH LQGQDMEQQV VFSMSFVQGE ESNDKIPVAL GLKEKNLYLS CVLKDDKPTL QLESVDPKNY PKKKMEKRFV FNKIEINNKL EFESAQFPNW YISTSQAENM PVFLGGTKGG QDITDFTMQF VSS The physiological activity determined from the dose dependent proliferation of murine D10S cells is 2.5 x 108 to 7.1 x 108 units/mg.

Increased production of IL-1B causes a number of different autoinflammatory syndromes, most notably the monogenic conditions referred to as CAPS, due to mutations in the inflammasome receptor NLRP3 which triggers processing of IL-1B.

Intestinal Dysbiosis has been observed to induce Osteomyelitis through a IL-1β dependent manner.

Canakinumab is a human monoclonal antibody targeted at IL-1B, and approved in many countries for treatment of cryopyrin-associated periodic syndromes.

---

As a major producer of the inflammatory cytokine interleukin-1 (IL-1), peripheral macrophages can augment IL-1 expression via type 1 IL-1 receptor (IL-1R1) mediated autocrine self-amplification. In the CNS, microglial cells are the major producers of inflammatory cytokines, but express negligible levels of IL-1R1.

In a study, Zhu et al., showed CNS IL-1 induced microglial proinflammatory cytokine expression was mediated by endothelial, not microglial, IL-1R1. This paracrine mechanism was further dissected in vitro. IL-1 was unable to stimulate inflammatory cytokine expression directly from the microglial cell line BV-2, but it stimulated the brain endothelial cell line bEnd.3 to a produce factor(s) in the culture supernatant, which was capable of inducing inflammatory cytokine expression in BV-2. We termed this factor IL-1-induced microglial activation factors (IMAF). BV-2 cytokine expression was inducible by

extracellular ATP, but IL-1 did not stimulate the release of ATP from bEnd.3 cells. Filtration of IMAF by size-exclusion membranes showed IMAF activity resided in factors larger than 50 kd and incubation of IMAF at 95°C for 5 minutes did not alter its activity. Microglial inhibitor minocycline was unable to block IMAF activity, even though it blocked LPS induced cytokine expression in BV-2 cells. Adding NF-κB inhibitor to the bEnd.3 cells abolished IL-1 induced cytokine expression in this bi-cellular system, but adding NF-κB inhibitor after IMAF is already produced failed to abrogate IMAF induced cytokine expression in BV-2 cells. RNA sequencing of IL-1 stimulated endothelial cells revealed increased expression of genes involved in the production and processing of hyaluronic acid (HA), suggesting HA as a candidate of IMAF. Inhibition of hyaluronidase by ascorbyl palmitate (AP) abolished IMAF-induced cytokine expression in BV-2 cells. AP administration in vivo also inhibited ICV IL-1-induced IL-1 expression in the hippocampus and hypothalamus. In vitro, either TLR2 or TLR4 inhibitors blocked IMAF induced BV-2 cytokine expression. In vivo, however, IL-1 induced cytokine expression persisted in either TLR2 or TLR4 knockouts. These results demonstrate IL-1 induced inflammatory cytokine expression in the CNS requires a bi-cellular system and HA could be a candidate for IMAF [1)].

1)

Zhu L, Liu X, Nemeth DP, DiSabato DJ, Witcher KG, Mckim DB, Oliver B, Le X, Gorantla G, Berdysz O, Li J, Ramani AD, Chen Z, Wu D, Godbout JP, Quan N. Interleukin-1 causes CNS inflammatory cytokine expression via endothelia-microglia bi-cellular signaling. Brain Behav Immun. 2019 Jun 19. pii: S0889-1591(18)30762-1. doi: 10.1016/j.bbi.2019.06.026. [Epub ahead of print] PubMed PMID: 31228609.