# Interleukin 6

**Interleukin 6** (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the *IL6* gene.[1]

IL-6 is secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, especially burns or other tissue damage leading to inflammation. IL-6 also plays a role in fighting infection, as IL-6 has been shown in mice to be required for resistance against bacterium *Streptococcus pneumoniae*.[2]

In addition, osteoblasts secrete IL-6 to stimulate osteoclast formation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6's role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL-1ra and IL-10.

## 1 Function

IL-6 is an important mediator of fever and of the acute phase response. It is capable of crossing the blood-brain barrier[3] and initiating synthesis of $PGE_2$ in the hypothalamus, thereby changing the body's temperature setpoint. In muscle and fatty tissue, IL-6 stimulates energy mobilization that leads to increased body temperature. IL-6 can be secreted by macrophages in response to specific microbial molecules, referred to as pathogen-associated molecular patterns (PAMPs). These PAMPs bind to an important group of detection molecules of the innate immune system, called pattern recognition receptors (PRRs), including Toll-like receptors (TLRs). These are present on the cell surface and intracellular compartments and induce intracellular signaling cascades that give rise to inflammatory cytokine production.

IL-6 is also essential for hybridoma growth and is found in many supplemental cloning media such as briclone. Inhibitors of IL-6 (including estrogen) are used to treat postmenopausal osteoporosis. IL-6 is also produced by adipocytes and is thought to be a reason why obese individuals have higher endogeneous levels of CRP.[4] Intranasally administered IL-6 has been shown to improve sleep-associated consolidation of emotional memories.[5]

IL-6 is responsible for stimulating acute phase protein synthesis, as well as the production of neutrophils in the bone marrow. It supports the growth of B cells and is antagonistic to regulatory T cells.

## 2 Role as myokine

IL-6 is also considered a myokine, a cytokine produced from muscle, which is elevated in response to muscle contraction.[6] It is significantly elevated with exercise, and precedes the appearance of other cytokines in the circulation. During exercise, it is thought to act in a hormone-like manner to mobilize extracellular substrates and/or augment substrate delivery.[7]

IL-6 has extensive anti-inflammatory functions in its role as a myokine. IL-6 was the first myokine that was found to be secreted into the blood stream in response to muscle contractions.[8] Aerobic exercise provokes a systemic cytokine response, including, for example, IL-6, IL-1 receptor antagonist (IL-1ra), and IL-10. IL-6 was serendipitously discovered as a myokine because of the observation that it increased in an exponential fashion proportional to the length of exercise and the amount of muscle mass engaged in the exercise. It has been consistently demonstrated that the plasma concentration of IL-6 increases during muscular exercise. This increase is followed by the appearance of IL-1ra and the anti-inflammatory cytokine IL-10. In general, the cytokine response to exercise and sepsis differs with regard to TNF-α. Thus, the cytokine response to exercise is not preceded by an increase in plasma-TNF-α. Following exercise, the basal plasma IL-6 concentration may increase up to 100-fold, but less dramatic increases are more frequent. The exercise-induced increase of plasma IL-6 occurs in an exponential manner and the peak IL-6 level is reached at the end of the exercise or shortly thereafter. It is the combination of mode, intensity, and duration of the exercise that determines the magnitude of the exercise-induced increase of plasma IL-6.[9]

IL-6 had previously been classified as a proinflammatory cytokine. Therefore, it was first thought that the exercise-induced IL-6 response was related to muscle damage.[10] However, it has become evident that eccentric exercise is not associated with a larger increase in plasma IL-6 than exercise involving concentric "nondamaging" muscle contractions. This finding clearly demonstrates that muscle damage is not required to provoke an increase in plasma IL-6 during exercise. As a matter of fact, eccentric exercise may result in a delayed peak and a much slower decrease of plasma IL-6 during recovery.[11]

Recent work has shown that both upstream and downstream signalling pathways for IL-6 differ markedly between myocytes and macrophages. It appears that unlike IL-6 signalling in macrophages, which is dependent upon

activation of the NFκB signalling pathway, intramuscular IL-6 expression is regulated by a network of signalling cascades, including the Ca2+/NFAT and glycogen/p38 MAPK pathways. Thus, when IL-6 is signalling in monocytes or macrophages, it creates a pro-inflammatory response, whereas IL-6 activation and signalling in muscle is totally independent of a preceding TNF-response or NFκB activation, and is anti-inflammatory.[12]

IL-6, among an increasing number of other recently identified myokines, thus remains an important topic in myokine research. It appears in muscle tissue and in the circulation during exercise at levels up to one hundred times basal rates, as noted, and is seen as having a beneficial impact on health and bodily functioning when elevated in response to physical exercise.[13] IL-6 was the first myokine that was found to be secreted into the blood stream in response to muscle contractions.[14]

# 3 Receptor

Main article: Interleukin-6 receptor

IL-6 signals through a cell-surface type I cytokine receptor complex consisting of the ligand-binding IL-6Rα chain (CD126), and the signal-transducing component gp130 (also called CD130). CD130 is the common signal transducer for several cytokines including leukemia inhibitory factor (LIF), ciliary neurotropic factor, oncostatin M, IL-11 and cardiotrophin-1, and is almost ubiquitously expressed in most tissues. In contrast, the expression of CD126 is restricted to certain tissues. As IL-6 interacts with its receptor, it triggers the gp130 and IL-6R proteins to form a complex, thus activating the receptor. These complexes bring together the intracellular regions of gp130 to initiate a signal transduction cascade through certain transcription factors, Janus kinases (JAKs) and Signal Transducers and Activators of Transcription (STATs).[15]

IL-6 is probably the best-studied of the cytokines that use gp130, also known as IL-6 signal transducer (IL6ST), in their signalling complexes. Other cytokines that signal through receptors containing gp130 are Interleukin 11 (IL-11), Interleukin 27 (IL-27), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), leukemia inhibitory factor (LIF), oncostatin M (OSM), Kaposi's sarcoma-associated herpesvirus interleukin 6-like protein (KSHV-IL6).[16] These cytokines are commonly referred to as the *IL-6 like* or *gp130 utilising* cytokines [17]

In addition to the membrane-bound receptor, a soluble form of IL-6R (sIL-6R) has been purified from human serum and urine. Many neuronal cells are unresponsive to stimulation by IL-6 alone, but differentiation and survival of neuronal cells can be mediated through the action of sIL-6R. The sIL-6R/IL-6 complex can stimulate neurites outgrowth and promote survival of neurons and, hence, may be important in nerve regeneration through remyelination.

# 4 Interactions

Interleukin 6 has been shown to interact with interleukin-6 receptor.[18][19][20] and glycoprotein 130.[21]

# 5 Role in disease

IL-6 stimulates the inflammatory and auto-immune processes in many diseases such as diabetes,[22] atherosclerosis,[23] depression,[24] Alzheimer's Disease,[25] systemic lupus erythematosus,[26] multiple myeloma,[27] prostate cancer,[28] Behçet's disease,[29] and rheumatoid arthritis.[30]

Hence, there is an interest in developing anti-IL-6 agents as therapy against many of these diseases.[31][32] The first such is tocilizumab, which has been approved for rheumatoid arthritis,[33] Castleman's disease[34] and systemic juvenile idiopathic arthritis.[35] Others are in clinical trials.[36]

## 5.1 Rheumatoid arthritis

The first FDA approved anti-IL-6 was for RA.

## 5.2 Cancer

Recently, Anestakis *et al.* outlined the interleukin mechanisms in cancer progression and possibilities in application for cancer immunotherapy in their systematic review.[37] IL-6 was seen to have roles in tumor microenvironment regulation,[38] production of breast cancer stem cell-like cells,[39] metastasis through down-regulation of E-cadherin,[40] and alteration of DNA methylation in oral cancer.[41]

Advanced/metastatic cancer patients have higher levels of IL-6 in their blood.[42] One example of this is pancreatic cancer, with noted elevation of IL-6 present in patients correlating with poor survival rates.[43]

## 5.3 Infectious diseases

### 5.3.1 Enterovirus 71

High IL-6 levels are associated with the development of encephalitis in children and immunodeficient mouse models infected with Enterovirus 71; this highly contagious virus normally causes a milder illness called Hand,

foot, and mouth disease but can cause life-threatening encephalitis in some cases. EV71 patients with a certain gene polymorphism in IL-6 also appear to be more susceptible to developing encephalitis.

### 5.4 Epigenetic modifications

IL-6 has been shown to lead to several neurological diseases through its impact on epigenetic modification within the brain.[44][45][46][47] IL-6 activates the Phosphoinositide 3-kinase (PI3K) pathway, and a downstream target of this pathway is the protein kinase B (PKB) (Hodge et al., 2007). IL-6 activated PKB can phosphorylate the nuclear localization signal on DNA methyltransferase-1(DNMT1).[48] This phosphorylation causes movement of DNMT1 to the nucleus, where it can be transcribed.[48] DNMT1 recruits other DNMTs, including DNMT3A and DNMT3B, which, as a complex, recruit HDAC1.[47] This complex adds methyl groups to CpG islands on gene promoters, repressing the chromatin structure surrounding the DNA sequence and inhibiting transcriptional machinery from accessing the gene to induce transcription.[47] Increased IL-6, therefore, can hypermethylate DNA sequences and subsequently decrease gene expression through its effects on DNMT1 expression.[46]

#### 5.4.1 Schizophrenia

The induction of epigenetic modification by IL-6 has been proposed as a mechanism in the pathology of schizophrenia through the hypermethylation and repression of the GAD67 promoter.[47] This hypermethylation may potentially lead to the decreased GAD67 levels seen in the brains of people with schizophrenia.[49] GAD67 may be involved in the pathology of schizophrenia through its effect on GABA levels and on neural oscillations.[50] Neural oscillations occur when inhibitory GABAergic neurons fire synchronously and cause inhibition of a multitude of target excitatory neurons at the same time, leading to a cycle of inhibition and disinhibition.[50] These neural oscillations are impaired in schizophrenia, and these alterations may be responsible for both positive and negative symptoms of schizophrenia.[51]

#### 5.4.2 Depression

The epigenetic effects IL-6 have also been implicated in the pathology of depression. The effects of IL-6 on depression are mediated through the repression of brain-derived neurotrophic factor (BDNF) expression in the brain; DNMT1 hypermethylates the BDNF promoter and reduces BDNF levels.[52] Altered BDNF function has been implicated in depression,[53] which is likely due to epigenetic modification following IL-6 upregulation.[52] BDNF is a neutrophic factor implicated in spine formation, density, and morphology on neurons.[54] Downregulation of BDNF, therefore, may cause decreased connectivity in the brain. Depression is marked by altered connectivity, in particular between the anterior cingulate cortex and several other limbic areas, such as the hippocampus.[55] The anterior cingulate cortex is responsible for detecting incongruences between expectation and perceived experience.[56] Altered connectivity of the anterior cingulate cortex in depression, therefore, may cause altered emotions following certain experiences, leading to depressive reactions.[56] This altered connectivity is mediated by IL-6 and its effect on epigenetic regulation of BDNF.[52]

## 6 References


[1] Ferguson-Smith AC, Chen YF, Newman MS, May LT, Sehgal PB, Ruddle FH (April 1988). "Regional localization of the interferon-beta 2/B-cell stimulatory factor 2/hepatocyte stimulating factor gene to human chromosome 7p15-p21". *Genomics* **2** (3): 203–8. doi:10.1016/0888-7543(88)90003-1. PMID 3294161.

[2] van der Poll T, Keogh CV, Guirao X, Buurman WA, Kopf M, Lowry SF (1997). "Interleukin-6 gene-deficient mice show impaired defense against pneumococcal pneumonia". *J. Infect. Dis.* **176** (2): 439–44. doi:10.1086/514062. PMID 9237710.

[3] Banks WA, Kastin AJ, Gutierrez EG (September 1994). "Penetration of interleukin-6 across the murine blood-brain barrier". *Neurosci. Lett.* **179** (1-2): 53–6. doi:10.1016/0304-3940(94)90933-4. PMID 7845624.

[4] Bastard J, Jardel C, Delattre J, Hainque B, et al. (1999). "Evidence for a Link Between Adipose Tissue Interleukin-6 Content and Serum C-Reactive Protein Concentrations in Obese Subjects". *Circulation* **99** (16): 2219–2222. doi:10.1161/01.CIR.99.16.2219.c.

[5] Benedict C, Scheller J, Rose-John S, Born J, Marshall L (October 2009). "Enhancing influence of intranasal interleukin-6 on slow-wave activity and memory consolidation during sleep". *FASEB J.* **23** (10): 3629–36. doi:10.1096/fj.08-122853. PMID 19546306.

[6] Febbraio MA, Pedersen BK (2005). "Contraction-induced myokine production and release: is skeletal muscle an endocrine organ?". *Exerc Sport Sci Rev* **33** (3): 114–9. doi:10.1097/00003677-200507000-00003. PMID 16006818.

[7] Petersen AM, Pedersen BK (April 2005). "The anti-inflammatory effect of exercise". *J. Appl. Physiol.* **98** (4): 1154–62. doi:10.1152/japplphysiol.00164.2004. PMID 15772055.

[8] Pedersen BK, Febbraio MA (October 2008). "Muscle as an endocrine organ: focus on muscle-derived interleukin-6". *Physiol. Rev.* **88** (4): 1379–406. doi:10.1152/physrev.90100.2007. PMID 18923185.

[9] Pedersen BK (July 2013). "Muscle as a secretory organ". Compr Physiol 3 (3): 1337–62. doi:10.1002/cphy.c120033. PMID 23897689

[10] Bruunsgaard H, Galbo H, Halkjaer-Kristensen J, Johansen TL, MacLean DA, Pedersen BK (March 1997). "Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage". *J. Physiol. (Lond.)* **499** (3): 833–41. PMC 1159298. PMID 9130176.

[11] Pedersen BK (July 2013). "Muscle as a secretory organ". *Compr Physiol* **3** (3): 1337–62. doi:10.1002/cphy.c120033. PMID 23897689.

[12] The Role of Exercise-InducedMyokines in Muscle Homeostasis and the Defense against Chronic Diseases. Claus Brandt and Bente K. Pedersen. Journal of Biomedicine and Biotechnology. Volume 2010, Article ID 520258, 6 pages. doi:10.1155/2010/520258

[13] Muñoz-Cánoves P, Scheele C, Pedersen BK, Serrano AL (September 2013). "Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword?". *FEBS J.* **280** (17): 4131–48. doi:10.1111/febs.12338. PMC 4163639. PMID 23663276.

[14] Pedersen BK, Febbraio MA. Muscle as an endocrine organ: Focus on muscle-derived interleukin-6. Physiol Rev 88: 1379-1406, 2008.

[15] Heinrich PC, Behrmann I, Müller-Newen G, Schaper F, Graeve L (1998). "Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway". *Biochem. J.* **334** (Pt 2): 297–314. PMC 1219691. PMID 9716487.

[16] Kishimoto T, Akira S, Narazaki M, Taga T (1995). "Interleukin-6 family of cytokines and gp130". *Blood* **86** (4): 1243–54. PMID 7632928.

[17] Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F (2003). "Principles of interleukin (IL)−6-type cytokine signalling and its regulation". *Biochem. J.* **374** (Pt 1): 1–20. doi:10.1042/BJ20030407. PMC 1223585. PMID 12773095.

[18] Schwantner A, Dingley AJ, Ozbek S, Rose-John S, Grötzinger J (January 2004). "Direct determination of the interleukin-6 binding epitope of the interleukin-6 receptor by NMR spectroscopy". *J. Biol. Chem.* **279** (1): 571–6. doi:10.1074/jbc.M311019200. PMID 14557255.

[19] Schuster B, Kovaleva M, Sun Y, Regenhard P, Matthews V, Grötzinger J, Rose-John S, Kallen KJ (March 2003). "Signaling of human ciliary neurotrophic factor (CNTF) revisited. The interleukin-6 receptor can serve as an alpha-receptor for CTNF". *J. Biol. Chem.* **278** (11): 9528–35. doi:10.1074/jbc.M210044200. PMID 12643274.

[20] Taga T, Hibi M, Hirata Y, Yamasaki K, Yasukawa K, Matsuda T, Hirano T, Kishimoto T (August 1989). "Interleukin-6 triggers the association of its receptor with a possible signal transducer, gp130". *Cell* **58** (3): 573–81. doi:10.1016/0092-8674(89)90438-8. PMID 2788034.

[21] Kallen KJ, zum Büschenfelde KH, Rose-John S (March 1997). "The therapeutic potential of interleukin-6 hyperagonists and antagonists". *Expert Opin Investig Drugs* **6** (3): 237–66. doi:10.1517/13543784.6.3.237. PMID 15989626.

[22] Kristiansen OP, Mandrup-Poulsen T (December 2005). "Interleukin-6 and diabetes: the good, the bad, or the indifferent?". *Diabetes*. 54 Suppl 2: S114–24. doi:10.2337/diabetes.54.suppl_2.S114. PMID 16306329.

[23] Dubiński A, Zdrojewicz Z (April 2007). "[The role of interleukin-6 in development and progression of atherosclerosis]". *Pol. Merkur. Lekarski* (in Polish) **22** (130): 291–4. PMID 17684929.

[24] Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL (March 2010). "A meta-analysis of cytokines in major depression". *Biol. Psychiatry* **67** (5): 446–57. doi:10.1016/j.biopsych.2009.09.033. PMID 20015486.

[25] Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N (November 2010). "A meta-analysis of cytokines in Alzheimer's disease". *Biol. Psychiatry* **68** (10): 930–41. doi:10.1016/j.biopsych.2010.06.012. PMID 20692646.

[26] Tackey E, Lipsky PE, Illei GG (2004). "Rationale for interleukin-6 blockade in systemic lupus erythematosus". *Lupus* **13** (5): 339–43. doi:10.1191/0961203304lu1023oa. PMC 2014821. PMID 15230289.

[27] Gadó K, Domján G, Hegyesi H, Falus A (2000). "Role of INTERLEUKIN-6 in the pathogenesis of multiple myeloma". *Cell Biol. Int.* **24** (4): 195–209. doi:10.1006/cbir.2000.0497. PMID 10816321.

[28] Smith PC, Hobisch A, Lin DL, Culig Z, Keller ET (March 2001). "Interleukin-6 and prostate cancer progression". *Cytokine Growth Factor Rev.* **12** (1): 33–40. doi:10.1016/S1359-6101(00)00021-6. PMID 11312117.

[29] Hirohata S, Kikuchi H (Dec 2012). "Changes in biomarkers focused on differences in disease course or treatment in patients with neuro-Behçet's disease". *Intern. Med.* **51** (24): 3359–65. doi:10.2169/internalmedicine.51.85834. PMID 23257520.

[30] Nishimoto N (May 2006). "Interleukin-6 in rheumatoid arthritis". *Curr Opin Rheumatol* **18** (3): 277–81. doi:10.1097/01.bor.0000218949.19860.d1. PMID 16582692.

[31] Barton BE (August 2005). "Interleukin-6 and new strategies for the treatment of cancer, hyperproliferative diseases and paraneoplastic syndromes". *Expert Opin. Ther. Targets* **9** (4): 737–52. doi:10.1517/14728222.9.4.737. PMID 16083340.

[32] Smolen JS, Maini RN (2006). "Interleukin-6: a new therapeutic target". *Arthritis Research & Therapy*. 8 Suppl 2 (Suppl 2): S5. doi:10.1186/ar1969. PMC 3226077. PMID 16899109.

[33] Emery, P.; Keystone, E.; Tony, H. P.; Cantagrel, A.; van Vollenhoven, R.; Sanchez, A.; Alecock, E.; Lee, J.; Kremer, J. (2008). "IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial". *Annals of the Rheumatic Diseases* **67** (11): 1516–1523. doi:10.1136/ard.2008.092932. ISSN 0003-4967. PMID 18625622.

[34] Nishimoto, N. (2005). "Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease". *Blood* **106** (8): 2627–2632. doi:10.1182/blood-2004-12-4602. ISSN 0006-4971.

[35] Yokota, Shumpei; Imagawa, Tomoyuki; Mori, Masaaki; Miyamae, Takako; Aihara, Yukoh; Takei, Shuji; Iwata, Naomi; Umebayashi, Hiroaki; Murata, Takuji; Miyoshi, Mari; Tomiita, Minako; Nishimoto, Norihiro; Kishimoto, Tadamitsu (2008). "Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial". *The Lancet* **371** (9617): 998–1006. doi:10.1016/S0140-6736(08)60454-7. ISSN 0140-6736. PMID 18358927.

[36] First IL-6–blocking drug nears approval for rare blood disorder, Nature Medicine, October 7, 2013

[37] Anestakis, Doxakis; Petanidis, Savvas; Kalyvas, Spyridon; Nday, Christiane; Tsave, Olga; Kioseoglou, Efrosini; Salifoglou, Athanasios (2015). "Mechanisms and Applications of Interleukins in Cancer Immunotherapy". *International Journal of Molecular Sciences* **16** (1): 1691–1710. doi:10.3390/ijms16011691. ISSN 1422-0067. PMID 25590298.

[38] Li, J.; Mo, H.-Y.; Xiong, G.; Zhang, L.; He, J.; Huang, Z.-F.; Liu, Z.-W.; Chen, Q.-Y.; Du, Z.-M.; Zheng, L.-M.; Qian, C.-N.; Zeng, Y.-X. (2012). "Tumor Microenvironment Macrophage Inhibitory Factor Directs the Accumulation of Interleukin-17-producing Tumor-infiltrating Lymphocytes and Predicts Favorable Survival in Nasopharyngeal Carcinoma Patients". *Journal of Biological Chemistry* **287** (42): 35484–35495. doi:10.1074/jbc.M112.367532. ISSN 0021-9258. PMID 22893706.

[39] Yuan, Yawei (2011). "IL-6-induced epithelial-mesenchymal transition promotes the generation of breast cancer stem-like cells analogous to mammosphere cultures". *International Journal of Oncology* **40**: 1171–9. doi:10.3892/ijo.2011.1275. ISSN 1019-6439. PMID 22134360.

[40] Miao, Jin-Wei; Liu, Li-Jiang; Huang, Jie (2014). "Interleukin-6-induced epithelial-mesenchymal transition through signal transducer and activator of transcription 3 in human cervical carcinoma". *International Journal of Oncology* **45**: 165–76. doi:10.3892/ijo.2014.2422. ISSN 1019-6439. PMID 24806843.

[41] Gasche, Jacqueline A.; Hoffmann, Jürgen; Boland, C. Richard; Goel, Ajay (2011). "Interleukin-6 promotes tumorigenesis by altering DNA methylation in oral cancer cells". *International Journal of Cancer* **129** (5): 1053–1063. doi:10.1002/ijc.25764. ISSN 0020-7136. PMID 21710491.

[42] "Cancer Patients Typically Have Increased Interleukin-6 Levels". *American Society of Clinical Oncology 2006 Annual Meeting, Abstracts 8632 and 8633*. Medscape.com. 2006-06-26.

[43] Bellone, Graziella; Smirne, Carlo; Mauri, Francesco Angelo; Tonel, Elena; Carbone, Anna; Buffolino, Alessandra; Dughera, Luca; Robecchi, Antonio; Pirisi, Mario; Emanuelli, Giorgio (2005). "Cytokine expression profile in human pancreatic carcinoma cells and in surgical specimens: implications for survival". *Cancer Immunology, Immunotherapy* **55** (6): 684–698. doi:10.1007/s00262-005-0047-0. ISSN 0340-7004. PMID 16094523.

[44] Smith SE, Li J, Garbett K, Mirnics K, Patterson PH (October 2007). "Maternal immune activation alters fetal brain development through interleukin-6". *J. Neurosci.* **27** (40): 10695–702. doi:10.1523/JNEUROSCI.2178-07.2007. PMC 2387067. PMID 17913903.

[45] Kaiser L, Fritz RS, Straus SE, Gubareva L, Hayden FG (July 2001). "Symptom pathogenesis during acute influenza: interleukin-6 and other cytokine responses". *J. Med. Virol.* **64** (3): 262–8. doi:10.1002/jmv.1045. PMID 11424113.

[46] Foran E, Garrity-Park MM, Mureau C, Newell J, Smyrk TC, Limburg PJ, Egan LJ (April 2010). "Upregulation of DNA methyltransferase-mediated gene silencing, anchorage-independent growth, and migration of colon cancer cells by interleukin-6". *Mol. Cancer Res.* **8** (4): 471–81. doi:10.1158/1541-7786.MCR-09-0496. PMID 20354000.

[47] Kundakovic M, Chen Y, Guidotti A, Grayson DR (February 2009). "The reelin and GAD67 promoters are activated by epigenetic drugs that facilitate the disruption of local repressor complexes". *Mol. Pharmacol.* **75** (2): 342–54. doi:10.1124/mol.108.051763. PMC 2684898. PMID 19029285.

[48] Hodge DR, Cho E, Copeland TD, Guszczynski T, Yang E, Seth AK, Farrar WL (2007). "IL-6 enhances the nuclear translocation of DNA cytosine-5-methyltransferase 1 (DNMT1) via phosphorylation of the nuclear localization sequence by the AKT kinase". *Cancer Genomics Proteomics* **4** (6): 387–98. PMID 18204201.

[49] Guidotti A, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR, Impagnatiello F, Pandey G, Pesold C, Sharma R, Uzunov D, Costa E, DiGiorgi Gerevini V (November 2000). "Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study". *Arch. Gen. Psychiatry* **57** (11): 1061–9. doi:10.1001/archpsyc.57.11.1061. PMID 11074872.

[50] Gandal MJ, Sisti J, Klook K, Ortinski PI, Leitman V, Liang Y, Thieu T, Anderson R, Pierce RC, Jonak G, Gur RE, Carlson G, Siegel SJ (2012). "GABAB-mediated rescue of altered excitatory-inhibitory balance,

gamma synchrony and behavioral deficits following constitutive NMDAR-hypofunction". *Transl Psychiatry* **2**: e142. doi:10.1038/tp.2012.69. PMC 3410621. PMID 22806213.

[51] Uhlhaas PJ, Singer W (February 2010). "Abnormal neural oscillations and synchrony in schizophrenia". *Nat. Rev. Neurosci.* **11** (2): 100–13. doi:10.1038/nrn2774. PMID 20087360.

[52] Sharma RP, Tun N, Grayson DR (2008). "Depolarization induces downregulation of DNMT1 and DNMT3a in primary cortical cultures". *Epigenetics* **3** (2): 74–80. doi:10.4161/epi.3.2.6103. PMID 18536530.

[53] Hwang JP, Tsai SJ, Hong CJ, Yang CH, Lirng JF, Yang YM (December 2006). "The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression". *Neurobiol. Aging* **27** (12): 1834–7. doi:10.1016/j.neurobiolaging.2005.10.013. PMID 16343697.

[54] Ethell IM, Pasquale EB (February 2005). "Molecular mechanisms of dendritic spine development and remodeling". *Prog. Neurobiol.* **75** (3): 161–205. doi:10.1016/j.pneurobio.2005.02.003. PMID 15882774.

[55] Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, Reiss AL, Schatzberg AF (September 2007). "Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus". *Biol. Psychiatry* **62** (5): 429–37. doi:10.1016/j.biopsych.2006.09.020. PMC 2001244. PMID 17210143.

[56] Somerville LH, Heatherton TF, Kelley WM (August 2006). "Anterior cingulate cortex responds differentially to expectancy violation and social rejection". *Nat. Neurosci.* **9** (8): 1007–8. doi:10.1038/nn1728. PMID 16819523.

# 7 Further reading

- De Kloet ER, Oitzl MS, Schöbitz B (1994). "Cytokines and the brain corticosteroid receptor balance: relevance to pathophysiology of neuroendocrine-immune communication". *Psychoneuroendocrinology* **19** (2): 121–34. doi:10.1016/0306-4530(94)90002-7. PMID 8190832.
- Morishita R, Aoki M, Yo Y, Ogihara T (2002). "Hepatocyte growth factor as cardiovascular hormone: role of HGF in the pathogenesis of cardiovascular disease". *Endocr. J.* **49** (3): 273–84. doi:10.1507/endocrj.49.273. PMID 12201209.
- Ishihara K, Hirano T (2003). "IL-6 in autoimmune disease and chronic inflammatory proliferative disease". *Cytokine Growth Factor Rev.* **13** (4-5): 357–68. doi:10.1016/S1359-6101(02)00027-8. PMID 12220549.
- Culig Z, Bartsch G, Hobisch A (2002). "Interleukin-6 regulates androgen receptor activity and prostate cancer cell growth". *Mol. Cell. Endocrinol.* **197** (1-2): 231–8. doi:10.1016/S0303-7207(02)00263-0. PMID 12431817.
- Rattazzi M, Puato M, Faggin E, Bertipaglia B, Zambon A, Pauletto P (2003). "C-reactive protein and interleukin-6 in vascular disease: culprits or passive bystanders?". *J. Hypertens.* **21** (10): 1787–803. doi:10.1097/01.hjh.0000084735.53355.44. PMID 14508181.
- Berger FG (2004). "The interleukin-6 gene: a susceptibility factor that may contribute to racial and ethnic disparities in breast cancer mortality". *Breast Cancer Res. Treat.* **88** (3): 281–5. doi:10.1007/s10549-004-0726-0. PMID 15609131.
- Stenvinkel P, Ketteler M, Johnson RJ, Lindholm B, Pecoits-Filho R, Riella M, Heimbürger O, Cederholm T, Girndt M (2005). "IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia--the good, the bad, and the ugly". *Kidney Int.* **67** (4): 1216–33. doi:10.1111/j.1523-1755.2005.00200.x. PMID 15780075.
- Vgontzas AN, Bixler EO, Lin HM, Prolo P, Trakada G, Chrousos GP (2005). "IL-6 and its circadian secretion in humans". *Neuroimmunomodulation* **12** (3): 131–40. doi:10.1159/000084844. PMID 15905620.
- Jones SA (2005). "Directing transition from innate to acquired immunity: defining a role for IL-6". *J. Immunol.* **175** (6): 3463–8. doi:10.4049/jimmunol.175.6.3463. PMID 16148087.
- Copeland KF (2005). "Modulation of HIV-1 transcription by cytokines and chemokines". *Mini Rev Med Chem* **5** (12): 1093–101. doi:10.2174/138955705774933383. PMID 16375755.
- Mastorakos G, Ilias I (2006). "Interleukin-6: a cytokine and/or a major modulator of the response to somatic stress". *Ann. N. Y. Acad. Sci.* **1088**: 373–81. doi:10.1196/annals.1366.021. PMID 17192581.

# 8 External links

- IL-6 expression in various cancers

# 9 Text and image sources, contributors, and licenses

## 9.1 Text

- **Interleukin 6** *Source:* https://en.wikipedia.org/wiki/Interleukin_6?oldid=700117837 *Contributors:* Selket, Diberri, Jfdwolff, Delta G, Discospinster, Arcadian, Fawcett5, Mindmatrix, G.hartig, Ketiltrout, Rjwilmsi, YurikBot, DRosenbach, SmackBot, GaiJin, NCurse, Flipperinu, Novangelis, JoeBot, Vanisaac, Fvasconcellos, Klement, Cydebot, Mvilchez, Red Director, Anthonyhcole, Anupam, Headbomb, Nafeh9, Gcm, Barek, Sedmic, Ciar, Emw, Boron11, R'n'B, Nbauman, Boghog, Rod57, Mikael Häggström, Belovedfreak, MetsFan76, STBotD, Lrunge, Andrew Su, Guillaume2303, GeneralBelly, Epgui, AlleborgoBot, ProteinBoxBot, Xenobiologista, NickCT, Lhuntkenora, DumZiBoT, MystBot, Addbot, DOI bot, Luckas-bot, Yobot, Citation bot, Xqbot, LucienBOT, Citation bot 1, Sctechlaw, Yeast2Hybrid, Trappist the monk, Radio89, RjwilmsiBot, Johnnytucf, Hazard-SJ, AManWithNoPlan, Kinkreet, Scien801, JOJ1001, Alternateuniverse6457, BattyBot, Ossip Groth, Luckydhaliwal, Aestin, Randykitty, BMBS2011, Cbavley, NyascaB, Brainiacal, Uno Nano D. Picto, Lkears11, Monkbot, Sam.park44 and Anonymous: 40

## 9.2 Images

- **File:IL6_Crystal_Structure.rsh.png** *Source:* https://upload.wikimedia.org/wikipedia/commons/e/e7/IL6_Crystal_Structure.rsh.png *License:* Public domain *Contributors:* Created from PDB 1ALU and rendered by me using Pymol *Original artist:* Ramin Herati
- **File:PDB_1alu_EBI.jpg** *Source:* https://upload.wikimedia.org/wikipedia/commons/e/e9/PDB_1alu_EBI.jpg *License:* Public domain *Contributors:* http://www.ebi.ac.uk/pdbe-srv/view/images/entry/1alu600.png, displayed on http://www.ebi.ac.uk/pdbe-srv/view/entry/1alu/summary *Original artist:* Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute
- **File:PDB_1il6_EBI.jpg** *Source:* https://upload.wikimedia.org/wikipedia/commons/2/2e/PDB_1il6_EBI.jpg *License:* Public domain *Contributors:* http://www.ebi.ac.uk/pdbe-srv/view/images/entry/1il6600.png, displayed on http://www.ebi.ac.uk/pdbe-srv/view/entry/1il6/summary *Original artist:* Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute
- **File:PDB_1p9m_EBI.jpg** *Source:* https://upload.wikimedia.org/wikipedia/commons/f/f6/PDB_1p9m_EBI.jpg *License:* Public domain *Contributors:* http://www.ebi.ac.uk/pdbe-srv/view/images/entry/1p9m600.png, displayed on http://www.ebi.ac.uk/pdbe-srv/view/entry/1p9m/summary *Original artist:* Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute
- **File:PDB_2il6_EBI.jpg** *Source:* https://upload.wikimedia.org/wikipedia/commons/8/82/PDB_2il6_EBI.jpg *License:* Public domain *Contributors:* http://www.ebi.ac.uk/pdbe-srv/view/images/entry/2il6600.png, displayed on http://www.ebi.ac.uk/pdbe-srv/view/entry/2il6/summary *Original artist:* Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute

## 9.3 Content license

- Creative Commons Attribution-Share Alike 3.0