JCP Online First, published on July 16, 2014 as 10.1136/jclinpath-2014-202493

Gene of the month: Interleukin 6 (IL-6)

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Received 17 June 2014
Accepted 18 June 2014

To cite: Ataie-Kachoie P, Pourgholami MH, Richardson DR, *et al*. *J Clin Pathol* Published Online First: [*please include* Day Month Year] doi:10.1136/jclinpath-2014-202493

ABSTRACT

The *Interleukin 6 (IL-6)* gene encodes the classic proinflammatory cytokine IL-6. It is also known as interferon-β2 (IFN-β2), B cell stimulatory factor-2 and hybridoma/plasmacytoma growth factor. IL-6 is a multifunctional cytokine with a central role in many physiological inflammatory and immunological processes. Due to its major role in initiation as well as resolving inflammation, deregulation of IL-6 is a mainstay of chronic inflammatory and autoimmune diseases. Additionally, IL-6 has been shown to be implicated in pathogenesis of many human malignancies. Thus, a better understanding of IL-6 and its role in various pathological conditions could enable the development of strategies to use it as a therapeutic target. This short review focuses on the structure, regulation and biological activities of IL-6. In addition we discuss the role of IL-6 in diseases with inflammatory background and cancer and also the therapeutic applications of anti-IL-6 agents.

STRUCTURE AND REGULATION OF INTERLEUKIN 6

The human gene for *Interleukin 6 (IL-6)* was cloned and reported by Hirano *et al* in 1986. It is mapped to 7p15–p21 chromosome and consists of five exons and four introns.[1] The *IL-6* gene encodes the 212 amino acid length IL-6 precursor protein including a 28 amino acid signal sequence and a 184 amino acid mature segment.[1 2] Mature IL-6 is a single-chain glycoprotein characterised with a typical four-helix bundle structure made up of four long α-helices arranged in an up-up-down-down topology. IL-6 molecular masses vary from 21 kDa to 28 kDa depending on the cellular source and also post-translational modification such as N-/O-glycosylation and phosphorylation.[3]

Due to the rapid plasma clearance, IL-6 levels are largely regulated at the expression level.[4] IL-6 is also regulated through activation of transcription factors nuclear factor (NF)-kB, NF-IL-6 (also known as CCAAT-enhancer-binding proteins or C/EBP), activator protein-1, cyclic Adenosine 3',5'-monophosphate (cAMP) response element binding protein, Fos/Jun and glucocorticoid receptor.[5 6] IL-6 transcription can be inducted by second messengers, bacterial lipopolysaccharides, viruses, cytokines such as IL-1 and TNF-α and growth factors such as epidermal growth factor, platelet-derived growth factor and transforming growth factor-β.[7–9] Polymorphisms in the promoter region of *IL-6* gene may also result in variation of transcription and expression of this cytokine. Available data support the role of a G/C single nucleotide polymorphism (replacement of a nucleotide with another one) at the promoter 174 of the *IL-6* gene in controlling the *IL-6* gene transcription rate and consequently its circulating levels.[10–12] Two phenotypes for this polymorphism have been identified: the 174 G/G and 174 G/C genotypes as the high-producer phenotype; and the 174 C/C genotype as the low-producer phenotype.[10 12] The 174 G/C phenotype has been reported to be associated with the diseases with inflammatory background such as juvenile chronic arthritis,[10] Alzheimer disease,[13] type 2 diabetes,[14] atherosclerosis,[15] osteoporosis,[16] cardiovascular diseases,[17 18] and also multiple cancers including hepatocellular,[19] colorectal,[20] prostate,[21] ovarian[22] and breast cancer[23] as well as Hodgkin's lymphoma[24] and neuroblastoma.[25]

INTERLEUKIN 6 BIOLOGICAL ACTIVITIES

IL-6 is a classic proinflammatory cytokine produced by a variety of cells, such as T and B lymphocytes, fibroblasts, monocytes, keratinocytes, mesangial and endothelial cells; and several tumour cells.[26] It regulates various physiological processes, including acute phase response, inflammation, immune response, host defence mechanisms, haematopoiesis and cellular growth.[27] *IL-6* induces production of a number of positive acute phase proteins such as serum amyloid A, C reactive protein, leading to a strong pyrogenic activity.[27] It is involved in initiation and maintenance of inflammation by facilitating neutrophil trafficking to the inflammation site,[28] leading to production of a number of inflammatory mediators, such as cytokines, prostaglandins, reactive oxygen species and proteases.[29] It also regulates T lymphocytes activation and differentiation.[30] Besides, by promoting B lymphocytes maturation, *IL-6* stimulates the synthesis and secretion of immunoglobulins including IgM, IgG and IgA.[27 31] In haematopoiesis, *IL-6* along with IL-3 induce the formation of blast cell colonies. Moreover, it supports the differentiation of macrophage and megakaryocyte.[32] *IL-6* is known as a positive growth regulator, which along with IL-1, IL-3, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, stimulates the proliferation and differentiation of myeloid cells.[33] It induces the production of vascular endothelial growth factor (VEGF) and is involved in neoangiogenesis.[34]

INTERLEUKIN 6 RECEPTOR SYSTEM AND SIGNALLING CASCADES

IL-6 transmits its signals through interacting with a receptor complex consisting of the ligand-binding glycoprotein termed IL-6R (also called CD126) and the signal-transducing component gp130 (also called CD130). There are two types of IL-6R, that is, cell membrane IL-6 receptor (IL-6Rα) with low affinity that forms a complex with gp130 after binding with IL-6 to start the intracellular signal

(classical signalling), and a soluble IL-6 receptor (sIL-6R) which binds with IL-6 and then with the membrane receptor β chain—gp130 leading to the signal transduction (trans-signalling).[26 35] Under normal conditions, IL-6R is only expressed by selected cells including T and B lymphocytes, monocytes, macrophages, neutrophils and hepatocytes.[36] However gp130 which is shared between all members of the IL-6 superfamily including oncostatin M, IL-11, leukaemia inhibitory factor, ciliary neurotrophic factor and cardiotrophin-1,[37] exists ubiquitously on all cells.[38] sIL-6R is generated by shedding from membrane-bound IL-6R via limited proteolysis of the ADisintegrin and Metalloproteinases (ADAM) gene family members and also by mRNA alternative splicing.[39] sIL-6R mediates IL-6 signalling in cells only harbouring gp130 on their surfaces.[40]

The signal transduction of IL-6 involves phosphorylation and activation of Janus kinase (JAK) intracellular kinase family members. JAKs phosphorylate the tyrosine residues of the IL-6 receptor, thus allowing the phosphorylation of signal transducer and activator of transcription (STAT3) which possess phosphotyrosine-binding SH2 domains. After phosphorylation, STAT3 forms a dimer which is then translocated to the nucleus to regulate the expression of several genes leading to the induction of cell growth, differentiation and survival.[41] The termination of this signalling pathway is mediated by endogenous inhibitors including the suppressor of cytokine signalling and protein inhibitor of activated STAT proteins. These proteins are induced by activated STAT3 in normal cells under normal physiological conditions. In addition to STAT3, phosphorylation of tyrosine 759 of cytokine receptor by JAKs leads to engagement of SH2 domain in PI3K enzyme. Following phosphorylation, this enzyme modifies certain phosphatidylinositides to phosphorylate phosphatidylinositol-4,5-bisphosphate into phosphatidylinositol-3,4,5-trisphosphate. Phosphatidylinositol-3,4,5-trisphosphate in turn phosphorylates and activates serine/threonine kinase Protein kinase (Pk)B/AKT which is recruited to the plasma membrane.[42] Activated AKT regulates the activities of several downstream targets to mediate cell growth, differentiation and survival via various signalling pathways.[43] IL-6 also activates the small G protein Ras. Ras activation leads to hyperphosphorylation of Raf (MAPKKK) and an increase in its serine/threonine kinase activity. Raf then phosphorylates and activates Mek (MAPKK) and ERK1/2 (MAPK). Activated ERK1/2 has a variety of nuclear and cytoplasmic substrates which mediate diverse effects depending on cell type, including cell growth stimulation, acute phase protein synthesis and immunoglobulin synthesis.[44]

INTERLEUKIN 6 ABNORMALITIES

Interleukin 6 in autoimmune and inflammatory diseases

IL-6 is regarded as a central mediator in many autoimmune and chronic inflammatory human diseases including rheumatoid arthritis, multiple sclerosis, Crohn's disease,[30] Castleman's disease, adult onset Still's disease,[45] Alzheimer disease,[46] juvenile idiopathic arthritis[47] and multiple sclerosis.[48] Overproduction of IL-6 is also documented in many inflammatory-mediated neurodegenerative[49] and cardiovascular diseases.[50]

IL-6 is the chief stimulator of acute phase proteins which are increased in acute and chronic inflammatory diseases.[27] IL-6 elicits acute phase reactions and induces differentiation of B cells into antibody-producing cells thus stimulating immunoglobulin secretion and promoting autoantibody production.[1] Besides, IL-6 controls T cell proliferation, differentiation and activation to promote a proinflammatory environment.[51–53] IL-6 also contributes to acute inflammation via attraction of neutrophils to the site of inflammation.[28] Invading neutrophils, in turn, drive IL-6 trans-signalling in resident tissue cells through proteolytic processing of IL-6R. This will lead to a switch from neutrophil to monocyte recruitment via upregulating monocyte-attracting chemokines such as monocyte chemoattractant protein 1 and 2.[54–56] Since, recruitment of monocytes to the area of inflammation is the main switch from acute to chronic inflammation, IL-6 is known as a major stimulus of this transition. IL-6 trans-signalling also controls leucocyte infiltration by enhancing the expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 on endothelial cells, as well as L-selectin on lymphocytes.[57 58] Furthermore, IL-6 trans-signalling induces differentiation of monocytes to macrophages via stimulating the expression of macrophage colony-stimulating factor (M-CSF) receptor.[59] The induction of neutrophil apoptosis by IL-6 also supports its role in subsiding acute neutrophil infiltration.[55] Therefore, IL-6 controls the intermediary factors that are involved in resolving inflammation. A disruption in this control, for example, by persistent production of IL-6, may thus be crucial at the onset of chronic inflammation. Moreover, by inducing mononuclear cell accumulation, angioproliferation and antiapoptotic functions on T cells, IL-6 contributes to an amplifying loop for chronic inflammatory process.[60]

Interleukin 6 in cancer

Chronic inflammation is often linked with malignant transformation. IL-6 as a mainstay of chronic inflammation is upregulated in most common human tumours including lung, prostate, breast, pancreatic, renal, gastrointestinal and ovarian cancer; as well as melanoma, lymphomas and multiple myeloma. Elevated serum IL-6 levels is known as an indicator of poor prognosis in most malignancies.[61]

As the positive regulator and also target of inflammation amplifier, IL-6 gene is coexpressed with many oncogenic genes showing its potential significance in tumour development.[62] In fact, IL-6 plays a central role in modifying various tumour behaviours including proliferation and differentiation of tumour cells, apoptosis,[63] angiogenesis,[64] migration,[65] invasion[66] and tumour cell attachment thus promoting tumour growth and metastasis.[65 66] Moreover, by modulating the immune system, IL-6 inhibits the immunogenic response to tumour.[67] IL-6 has also been linked with chemotherapy resistance. It is known as a resistance factor in multidrug resistant breast, ovarian and prostate cancer.[68] Besides, IL-6 has been implicated in aetiology of cancer related anorexia, cachexia[69] and anaemia.[70]

IL-6 contributes to tumour initiation and progression through activation of several oncogenic pathways including JAK/STAT3, Ras/MAPK and PI3K/AKT signalling pathways (figure 1).[71]

Aberrant activation of STAT3 leads to modification of the expression of various genes which are regulated by this transcription factor. These include apoptotic-regulatory genes such as *Mcl-1, Bcl-2, Bcl-xl, survivin*,[72] *Fas*[73] and *X-linked inhibitor of apoptosis protein (XIAP)*;[74] cell survival genes including *cyclins D1, D2 and B1*,[75] *myc*[76] and cyclin dependent kinase inhibitor *p21*.[75] Persistently activated STAT3 also upregulates the expression of *MMPs*,[74] which mediate tumour invasion and metastasis.[77] It also enhances the transcription of *VEGF*[34] and *basic fibroblast growth factor (BFGF)* thus promoting tumour angiogenesis.[78] Besides, activated STAT3 induces the expression of numerous cancer-promoting proinflammatory cytokines and chemokines including IL-1β, IL-6 and cyclooxygenase 2.[79]

In addition to STAT3, activation of PI3K/AKT pathway by IL-6 is also known as a crucial oncogenic stimulus in various types of

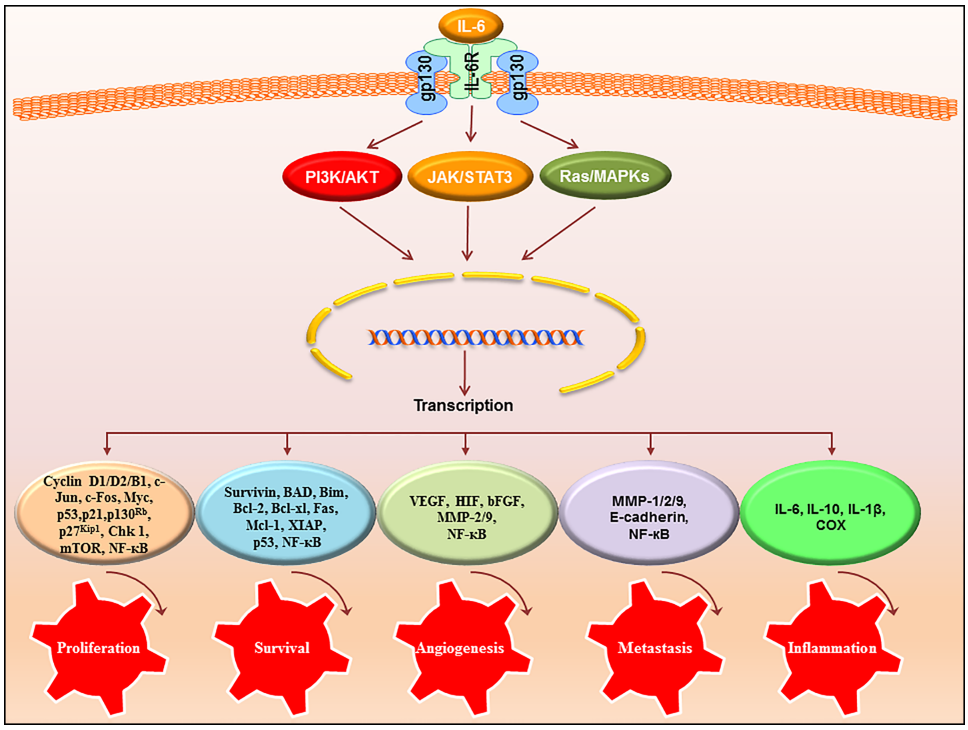

Figure 1 Interleukin 6 (IL-6) and its contribution to tumour development. IL-6 activates oncogenic pathways; JAK/STAT-3, Ras/MAPK and PI3K/AKT resulting in the modification of the transcription of various genes which in turn modify cell behaviours such as proliferation, survival, migration, invasion, angiogenesis and cancer-promoting inflammation causing tumorigenic effects.

cancer. It promotes tumour cell proliferation and survival through suppression of proapoptotic proteins Bcl-2, BAD (Bcl-XL/Bcl-2-associated death promoter), Mcl-1,[80] Bcl-xl, Bim (bcl-2-interacting mediator of cell death), Fas Ligand and p53[81] as well as modulation of cell cycle regulatory proteins cyclin D1, myc, checkpoint kinase 1, $p27^{Kip1}$ and $p130^{Rb2}$.[82] PI3K/AKT also enhances cell growth through activation of mammalian target of rapamycin, a Ser/Thr kinase which promotes protein synthesis through phosphorylation and activation of 4E-BP1 and $p70^{S6Kinase}$.[83] Moreover, PI3K/AKT pathway contributes to activation of NF-κB pathway via phosphorylation of IκB kinase. NF-κB pathway is known as a major regulator of cell survival, angiogenesis and invasiveness.[84] The PI3K/AKT signalling pathway induces angiogenesis by upregulating the expression of VEGF in tumour and endothelial cells in a hypoxia inducible factor (HIF)-1-dependent manner.[85]

Similarly, Ras/MAPK cascade activated by IL-6 regulates a variety of cellular processes including tumour cell proliferation, differentiation, survival and apoptosis.[86] Continuously activated MAPK pathway affects cell cycle via modulation of the expression of cyclin D1,[87] myc, c-Jun, c-Fos[88] and $p27^{Kip1}$.[89] It also influences the activation of the key regulators of apoptosis including Bcl-2, Mcl-1, BAD, Bim and caspase-9.[90] Activated ERK also enhances cell migration through rendering epithelioid to fibroblastoid morphological changes in tumour cells via reducing membranous E-cadherin expression.[77] Furthermore, Ras/MAPK pathway induces angiogenesis by upregulating VEGF expression.[85] Collectively these events lead to tumour cell survival and proliferation, followed by angiogenesis, growth and dissemination of tumours. Recent research has shed light on the importance of interfering with IL-6 as a valuable tool in therapeutics.

THERAPEUTIC IMPLICATIONS OF TARGETING INTERLEUKIN 6

The huge body of evidence linking IL-6 to various diseases provides a biological rationale for targeted therapeutic investigations. A number of conventional drugs with proved inhibitory effects on IL-6 expression and signalling have been used with much success in IL-6 mediated disorders.[26] These include corticosteroids, non-steroidal anti-inflammatory agents and

Table 1 Potential therapeutic implications of anti-IL-6 agents

Agent	Disorders where beneficial effects have been observed
Corticosteroids	A range of autoimmune and inflammatory diseases,[26] multiple myeloma,[92] prostate cancer[93] and advanced renal cell carcinoma.[93 94]
NSAIDS	Inflammatory and pyrogenic diseases,[26] hepatocellular[95] and oral squamous cell carcinoma,[96] melanoma,[97] breast,[98] colorectal,[99] ovarian,[100] prostate,[101] lung,[102] gastric,[103] oesophageal[104] and pancreatic cancer.[105]
Tetracyclines	Rosacea and periodontitis,[106] melanoma,[107] ovarian,[108–110] breast,[111] and prostate cancer.[112]
BE-8	Lymphoproliferative diseases, multiple myeloma.[79]
CNTO 136	Systemic lupus erythematosus, rheumatoid arthritis.[90]
ALD 518	Systemic lupus erythematosus, rheumatoid arthritis,[90] non-small cell lung cancer,[113] multiple myeloma.[114]
Sirukumab	Systemic and cutaneous lupus erythematosus,[115] rheumatoid arthritis.[116]
Siltuximab	Castleman's disease,[117] multiple myeloma,[118–120] prostate,[121–123] ovarian,[124] metastatic renal[125] and non-small-cell lung cancer.[126]
Tocilizumab	Systemic lupus erythematosus,[127] rheumatoid arthritis,[128–130] systemic and polyarticular juvenile idiopathic arthritis,[131–133] Takayasu arteritis,[134 135] systemic sclerosis,[136] Crohn's disease,[137] Castleman's disease,[138] oral squamous cell carcinoma,[139] glioma,[140] multiple myeloma,[141] mesotheliomas.[142]

IL, interleukin; NSAID, non-steroidal anti-inflammatory drug.

tetracyclines. Besides, monoclonal antibodies (mAbs) directed against IL-6 and IL-6R, are now widely investigated as targeted biological options for the treatment of autoimmune and chronic inflammatory diseases and cancer. Initial studies date back to early 1990s with BE-8 (a mouse mAb to IL-6) in multiple myeloma which was associated with many problems such as short half-life and neutralisation by human antimouse responses.[91] Since then several human or humanised mAbs against IL-6 or IL-6R have been developed to overcome these problems. CNTO 136, ALD 518, mAb 1339, CNTO 136 (sirukumab), CNTO 328 (siltuximab) and tocilizumab are among the list. So far, promising results have been obtained using these agents in numerous preclinical and clinical investigations on different autoimmune, chronic inflammatory diseases or cancer (table 1).

SUMMARY

IL-6 is a pleiotropic protein which is the regulator of various physiological processes. It is involved in initiation and termination of an inflammatory response under physiological conditions. Hence, aberrant expression of IL-6 results in manifestation of uncontrolled inflammatory responses leading to chronic inflammation. This makes IL-6 a major contributing factor to autoimmune and chronic inflammatory diseases. It is also implicated in initiation and progression of many human cancers. Inhibitors of IL-6 and IL-6 signalling pathways are thus the subject of increasing investigations in the treatment of many inflammatory disorders and cancer.

Take home messages

- IL-6 gene encodes the pleotropic cytokine IL-6 which is a central mediator of various physiological inflammatory and immunological responses.
- IL-6 orchestrates acute inflammation through stimulation of acute phase reaction and chemokine-directed leukocyte trafficking and directs transition from acute to chronic inflammation through regulation of leukocyte activation, differentiation, and apoptosis.
- IL-6 activates the oncogenic signalling pathways JAK/STAT3, Ras/MAPK and PI3K/AKT that together promote tumour cell survival and proliferation, angiogenesis, metastasis and drug resistance.
- IL-6-targeted therapies have shown promising results in a variety of human disorders ranging from autoimmune and chronic inflammatory diseases to cancer.

Contributors PA-K contributed to conception, design and writing the manuscript. MHP, DRR and DLM contributed to conception, revising and final approval of the manuscript. All authors are equally responsible for the overall content.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

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Gene of the month: Interleukin 6 (IL-6)

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J Clin Pathol published online July 16, 2014