

Anti-inflammatory Cytokines List

The principal anti-inflammatory cytokines and cytokine inhibitors are listed in Tables 1, 2. The functional definition of an anti-inflammatory cytokine is the ability of the cytokine to inhibit the synthesis of IL-1, tumor necrosis factor (TNF), and other major proinflammatory cytokines.

Table 1: Cytokines with anti-inflammatory activities

Cytokines	Major Activities
IL-1ra	Specific inhibitor of IL-1 α and IL-1 β mediated cellular activation at the IL-1 cellular receptor level
IL-4	Promotes Th2 lymphocyte development; inhibition of LPS-induced proinflammatory cytokines synthesis
IL-6	Inhibition of TNF and IL-1 production by macrophages
IL-10	Inhibition of monocyte/macrophage and mrtrophil cytokine production and inhibition of TH1-type lymphocyte responses
IL-11	Inhibits proinflammatory cytokines response by monocyte/macrophages and promotes Th2 lymphocyte response
IL-13	Shares homology with IL-4 and shares IL-4 receptor; attenuation of monocyte/macrophage function
TGF- β	Inhibition of monocyte/macrophage MHC, class II expression and proinflammatory cytokines synthesis

Table 2: Soluble Cytokin Receptors With Anti-inflammatory Activities

Solube receptor	Major Activities
Solube TNF receptor p55 (sTNFR1 or sTNFRp55)	Binds to TNF trimers in the circulation, preventing membrane-bound TNF receptor-TNF ligand interactions

Soluble TNF receptor p75(sTNFRII or sTNFRP75)	Binds to TNF trimers in the circulation, preventing membrane-bound TNF receptor-TNF ligand interactions
Soluble IL-1 receptor type 2 (sIL-1RII)	Binds to circulating IL-1 ligands in the plasma, preventing IL-1 β from binding to the IL-1 receptor type 1
Membrane-bound IL-1 receptor type 2 (mIL-1RII)	Decoy receptor that lacks intracellular signaling function and competes with type 1 IL-1R for IL-1 ligand binding at the cell membrane
IL-18 binding protein (IL-18BP)	Soluble extracellular domain of IL-18 receptor that function as a decoy receptor and binds circulating IL-18

Anti-inflammatory cytokines list 1: IL-1ra

IL-1ra is a 152-amino-acid protein that functions as a specific inhibitor of the two other functional members of the IL-1 family, IL-1a and IL-1 b. IL-1ra blocks the action of IL-1a and IL-1b functional ligands by competitive inhibition at the IL-1 receptor level. IL-1ra binds with equal or greater affinity than does IL-1a and IL-1 b to the type 1 (80 kd) membrane-bound IL-1 receptor. IL-1ra does not bind with high affinity to the type II (68 kd) IL-1 receptor.

IL-1ra is produced by monocytes and macrophages and is released into the systemic circulation in >100-fold excess than either IL-1a or IL-1 b after lipopolysaccharide (LPS) stimulation in human volunteers. The synthesis of IL-1ra and IL-1 b are differentially regulated at their own promoter sites. Although bacterial LPS stimulates the synthesis of both IL-1b and IL-1ra, other stimuli cause differential release of IL-1ra and IL-1 b. The anti-inflammatory cytokines IL-4, IL-6, IL-10, and IL-13 inhibit the synthesis of IL-1 b, yet they stimulate the synthesis of IL-1ra.

Because IL-1 is such a prominent proinflammatory cytokine in a multitude of systemic inflammatory states, IL-1ra has been extensively studied in clinical trials as a specific IL-1 inhibitor. Despite convincing evidence that IL-1 plays an important role in the pathogenesis of bacterial sepsis, the results of IL-1ra therapy in large phase III clinical trials for severe sepsis have been disappointing. Nonetheless, IL-1ra continues to be a promising new treatment for the management of patients with refractory forms of rheumatoid arthritis.

Anti-inflammatory cytokines list 2: IL-4

IL-4 is a highly pleiotropic cytokine that is able to influence Th cell differentiation. Early secretion of IL-4 leads to polarization of Th cell differentiation toward Th2-like cells. Th2-type cells secrete their own IL-4, and subsequent autocrine production of IL-4 supports cell proliferation. The Th2-

cell secre-infections is not adequately defined and will necessitate additional clinical investigation. IL-4 is able to affect a variety of structural cells. It can potentiate proliferation of vascular endothelium and skin fibroblasts yet decrease proliferation of adult human astrocytes and vascular smooth muscle cells. In addition, IL-4 induces a potent cytotoxic response against tumors. In a study of 63 patients with stage IV non-small cell lung cancer, data on treatment with recombinant human IL-4 seemed to suggest a possible dose-related response. IL-4 may act by stabilizing disease and modifying tumor growth rates in addition to inducing tumor shrinkage and cell death without causing severe side effects, suggesting a possible adjuvant role for IL-4 in the treatment of malignant diseases.

Anti-inflammatory cytokines list 3: IL-6

IL-6 has long been regarded as a proinflammatory cytokine induced by LPS along with TNF- α and IL-1. IL-6 is often used as a marker for systemic activation of proinflammatory cytokines. Like many other cytokines, IL-6 has both proinflammatory and anti-inflammatory properties. Although IL-6 is a potent inducer of the acute-phase protein response, it has anti-inflammatory properties as well. IL-6, like other members of the gp130 receptor ligand family, acts predominantly as an anti-inflammatory cytokine. IL-6 down-regulates the synthesis of IL-1 and TNF.

IL-6 attenuates the synthesis of the proinflammatory cytokines while having little effect on the synthesis of anti-inflammatory cytokines such as IL-10 and transforming growth factor- β (TGF- β). IL-6 induces the synthesis of glucocorticoids and promotes the synthesis of IL-1 α and soluble TNF receptor release in human volunteers. At the same time, IL-6 inhibits the production of proinflammatory cytokines such as GM-CSF, IFN- γ , and MIP-2. The net result of these immunologic effects place IL-6 in the anti-inflammatory cytokine group.

Anti-inflammatory cytokines list 4: IL-10

IL-10 is the most important anti-inflammatory cytokine found within the human immune response. It is a potent inhibitor of Th1 cytokines, including both IL-2 and IFN- γ . This activity accounts for its initial designation as cytokine synthesis inhibition factor. In addition to its activity as a Th2 lymphocyte cytokine, IL-10 is also a potent deactivator of monocyte/macrophage proinflammatory cytokine synthesis. After engaging its high-affinity 110-kD cellular receptor, IL-10 inhibits monocyte/macrophage-derived TNF- α , IL-1, IL-6, IL-8, IL-12, granulocyte colony-stimulating factor, MIP-1 α , and MIP-2 α .

Anti-inflammatory cytokines list 5: IL-11

IL-11 has been shown to attenuate IL-1 and TNF synthesis from macrophages by up-regulating inhibitory NF- κ B (inhibitory NF- κ B) synthesis in monocyte/macrophage cell lines. Inhibitory NF- κ B prevents NF- κ B from translocating to the nucleus where NF- κ B functions as a transcriptional activator for the proinflammatory cytokines. IL-11 has also been shown to inhibit the synthesis of IFN- γ and IL-2 by CD41 T cells. IL-11 functions as a Th2-type cytokine, with induction of IL-4 and inhibition of Th1-type cytokines. IL-11 does not induce the synthesis of IL-10 or TGF- β . This indicates that IL-11 is a direct inhibitor of Th1 lymphocytes and does not act indirectly through induction of IL-10.

Anti-inflammatory cytokines list 6: IL-13

IL-13 and IL-4 share a common cellular receptor (IL-4 type 1 receptor), and this accounts for many of the similarities between these two anti-inflammatory cytokines. IL-4 and IL-13 share only 20% to 25% primary amino acid homology, but the major α -helical regions that are essential for their activity are highly homologous. IL-13 can down-regulate the production of TNF, IL-1, IL-8, and MIP-1 α by monocytes and has profound effects on expression of surface molecules on both monocytes and macrophages.

Anti-inflammatory cytokines list 6: TGF- β

Like many cytokines, TGF- β has both pro- and anti-inflammatory effects. It functions as a biological switch, antagonizing or modifying the action of other cytokines or growth factors. The presence of other cytokines may modulate the cellular response to TGF- β , and the effect may differ depending on the activation state of the cell. TGF- β is capable of converting an active site of inflammation into one dominated by resolution and repair. TGF- β often exhibits disparate effects with immune-enhancing activity in local tissues and immune-suppressive activity in the systemic circulation. TGF- β 1 suppresses the proliferation and differentiation of T cells and B cells and limits IL-2, IFN- γ , and TNF production. TGF- β 1 acts as a monocyte/macrophage deactivator in a manner similar to IL-10. However, TGF- β 1 is less potent an inhibitor than IL-10 and has little or no effect on IL-1 production. The severe and uncontrolled inflammatory reactions observed in the TGF- β 1 knockout mouse attests to the physiologic role of TGF- β as an endogenous anti-inflammatory cytokine.

There are also many soluble cytokine receptors as anti-inflammatory molecules. Such as: type 1 (p55) and type 2 (p75) receptors for human TNF- α .

Anti-inflammatory cytokines related reference

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Growth Factors Regulating Different Stem Cells

Hematopoietic stem cells

Hematopoietic stem cell therapy growth factors (cytokines) are responsible for the regulation of the multiple fates of hematopoietic stem cells – including quiescence, self-renewal, differentiation, apoptosis, and mobilization from the niche – requires the cooperative actions of several growth factors and other hormones that bind to receptors on these cells.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are the non-haematopoietic, multipotent stem cells with the capacity to differentiate into mesodermal lineage. Growth factors regulate mesenchymal stem cell functions more than any other molecule and they play an important role in the proliferation, differentiation, or other properties of mesenchymal stem cells, either alone or in combination of other growth factors (cytokines).

Embryonic / pluripotent stem cells

Embryonic / pluripotent stem cells are ideal candidates for novel stem cell therapy because it can differentiate into any cell type. Many Growth Factors (Cytokines) have overlapping, pleiotropic effects on a variety of different cell types and activate target genes involved in survival, apoptosis, proliferation and differentiation, as well as suppression of differentiation.

Neural stem cells

Growth factors (cytokines) play an important role in determining the inflammatory microenvironment and have also been shown to have effects on the differentiation, proliferation,

migration and survival of Neural stem cells. These growth factors have been shown to alter neural stem cell self-renewal and progenitor cell division and differentiation

Vital Stem Cell Therapy Growth Factors & Cytokines Involved With Inflammation Modulation

IL-3

The human interleukin-3 (hIL-3) is a glycoprotein, which served as a key modulation factor of primitive hematopoietic cell proliferation and differentiation. It was also demonstrated that IL-3 enhances human osteoblast differentiation and bone formation in both in vitro and in vivo conditions

SCF

Stem cell factor (SCF, also called Steel factor or Kit ligand) is a growth factor that exists both as a membrane-bound and soluble form. It is expressed by fibroblasts and endothelial cells throughout the body, promoting proliferation, migration, survival, and differentiation of hematopoietic progenitors, melanocytes, and germ cells.

IL-6

IL-6 was originally identified as a T cell-derived factor, which induced the final maturation of B lymphocytes into antibody-forming plasma cells. IL-6 functions neural stem/progenitor cells by binding to the soluble form of IL-6R and then bind directly to the gp130 receptor.

GM-CSF

Granulocyte-macrophage colony stimulating factor (GM-CSF) is a hematopoietic growth factor involved in the generation of granulocytes, macrophages, and dendritic cells from hematopoietic stem cells. It was also identified as a neuronal growth factor in the brain and a factor involved in arteriogenesis after brain ischemia.

LIF

LIF is capable of maintaining embryonic stem (ES) cells in a pluripotent state through promoting self-renewal or suppressing stem cell differentiation. It has become a standard protocol to use LIF to maintain murine embryonic stem cell pluripotency, whereas withdrawal of LIF allows embryonic stem cells to undergo cell differentiation

G-CSF

The ability to mobilize hematopoietic stem cells from the bone marrow into the blood of G-CSF changes the face of hematopoietic stem cell transplantation. It was among the first growth factors to be identified and rapidly transitioned into clinical medicine.

EPO

Erythropoietin (EPO) is a glycoprotein that regulates the growth and differentiation of erythroid

progenitor cells. In addition, Erythropoietin (EPO) was reportedly to mediate the proliferation and apoptosis of a variety of non-hematopoietic cells through the erythropoietin receptor (EPOR).

Flt3-ligand

Flt3-Ligand has an effect on early B cell development as well as on T cell development, at least in the embryo. It was shown that intracellular Flt3 receptors have been found to exist in human mesenchymal stem cells and expansion of human mesenchymal stem cells is highly dependent on the time, duration and concentration of Flt3-Ligand.

TPO

TPO augmented survival and proliferation of CD34+ hematopoietic stem or progenitor cells, especially when used in combination with IL3 or SCF. TPO also plays a role in hematopoietic stem cell maintenance in humans. TPO can augment ex vivo expansion of hematopoietic stem cells to increase the pool available for transplantation

M-CSF

M-CSF acts on hematopoiesis by promoting the growth of monocyte/macrophage colonies from human blood CD34+ progenitor cells and high proliferation colony-forming cells.. It was also shown that M-CSF can directly induce the myeloid master regulator PU.1 and instruct myeloid cell-fate change

FGF-2

FGF-2 is expressed mostly in tissues of mesoderm and neuroectoderm origin, and is thought to play an important role in the mesoderm induction. In recent years, a number of studies have identified fibroblast growth factors FGF-2 as key regulator of a variety of stem cell types.

TGF beta

In most cell types, TGF-beta signaling additionally controls the expression of a plethora of homeostatic genes whose activity determines cell proliferation, extracellular matrix production, paracrine factor secretion, cell-cell contacts, immune function, and tissue repair.

VEGF

VEGF has the role of cellular survival during bone and cartilage development. In contrast to the paracrine functions of VEGF in vascular development and angiogenesis, the survival of endothelial cells, hematopoietic stem cells and tumor cells has been linked to intracrine/autocrine functions of VEGF.

Activin A

Using the embryoid body differentiation model of mouse embryonic stem cells, first studies showed that endoderm cells could be induced by treatment with activin A. , In human embryonic stem cells activin A at low concentration is also able to maintain the undifferentiated pluripotent state.

BMP4

BMP4 belong to the transformation growth factor beta (TGF β) superfamily. is involved in

regulation of cell proliferation, differentiation, and apoptosis of stem cells, including Embryonic Stem (ES) cells, hematopoietic Stem (ES) cells, Mesenchymal Stem (ES) cells and Neural Stem (ES) cells. So BMP4 play an essential role in stem cell therapy.

BMP-2

Bone morphogenetic protein-2 (BMP-2) is a member of the transforming growth factor beta superfamily implicated by gene ablation studies in several critical processes in early mouse development. BMP-2 plays an essential role not only in embryonic stem cell differentiation, but also in mesenchymal stem cell differentiation and bone formation.