

Cytokine Receptors (Hematopoietin Receptor Family)

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Overview

A broad array of molecules can be functionally termed cytokines. These secreted or membrane-bound regulatory factors control myriad of developmental, metabolic and host defense processes in cells that display the correct assortment of surface receptors. Cytokine ligands and cellular receptors then form specific binding complexes that trigger intracellular signaling cascades to recast the fate of the cell. The rules of engagement between cytokines and receptors are highly structural in nature; cytokine and receptor families have distinct domain architectures that are employed in specific and highly conserved three-dimensional interactions.

The largest and most divergent family of cytokines are the hematopoietic factors that comprise around 50 distinct lymphokines, growth hormones, hemopoietins, neuropoietins and interleukins. In spite of minimal sequence homology, these hematopoietic cytokines have a singular four- α -helix protein fold that has been evolutionarily honed to interact with approximately 45 receptors that sport a distinctive pair of fibronectin-type-3 (Fn3) modules. As a number of receptor crystal structures reveal, these Fn3 modules fold as β -sheet sandwiches (reminiscent of Ig domains) with a characteristic "bent" hinge that forms a loop-rich binding site for their helical cytokine ligands. This conserved protein-protein interaction mode is capable of granting both high specificity or perplexing promiscuity to ligand binding, since both dedicated (or 'private') and shared receptors are found in the hematopoietic family. The latter type includes critical molecules such as $R\gamma_c$ (a common chain in IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 receptor complexes), $R\beta_c$ (likewise for IL-3, IL5 and GM-CSF), gp130 for the IL-6-like cytokine clan, and IL-10R2 for the IL-10-like factors.

Though hematopoietic cytokines all share a common fold topology, sequence divergence has given rise to differences in the length and packing of their core α -helices, variations in loop geometry and extracore adornments such as short β -strands or α -helices nestled against the α -helical bundle core. These divergent architectural themes underlie the current classification of hematopoietic cytokines into three types, Short-chain (like the aforementioned ligands of $R\gamma_c$ and $R\beta_c$), Long-chain (comprising the IL-6-like cytokines, growth hormones, EPO and TPO) and Interferon-like (IFNs- $\alpha/\beta/\gamma$ and the IL-10-like cytokines). This structural division of cytokine ligands mirrors an evolutionary split of their respective receptors into Class 1 (or classically hematopoietic) Receptors for either Short- or Long-chain cytokines, and Class 2 (or Interferon-like) Receptors for Interferon-like cytokines.

The most recent structural investigations have uncovered a greater complexity of ligand/receptor interactions than was first revealed in the paradigmatic framework of the growth hormone (GH) receptor complex where the cytokine was cradled between two receptor subunits that formed a face-to-face dimer. The majority of Class 1 and 2 hematopoietic cytokines utilize this scheme, driving association of a receptor homodimer (like GH, PRL, EPO and TPO) or heterodimer (all of the Short-chain and Interferon-like factors) to create an active signaling complex. The IL-6-like cytokines of the Class 1, Long-chain group, including IL-6, IL-11, IL-12, IL-23, IL-27, IL-31, CLC, CNTF, CT-1, G-CSF, Leptin, LIF and OSM, have evolved an additional (non-GH-like) receptor-binding epitope that captures an N-terminal Ig domain of their second critical hematopoietic receptor signaling chain. This more elaborate choreography

of gp130-like receptors assembling around IL-6-like cytokines is reflected in the subunit composition of the particular receptor complexes (see Table). However, exceptions exist in the form of three membrane-tethered Short-chain cytokines, namely FLT3L, MCSF and SCF, that are obligate dimers that appear to have escaped the confines of the hematopoietic cytokine receptor family and bind to three tyrosine-kinase receptors of the PDGFR class, FLT-3, FMS and KIT, respectively.

The hematopoietic cytokine/receptor system, which funnels its signals through conserved JAK/STAT intracellular pathways, is arguably the key regulator of the developmental fates and functional roles of blood cell types. As such, this system is critical in helping marshal and shape effective immune responses to pathogen attack. Dysregulation of this molecular network by mutation or pathogen deception, can contribute to a variety of human immunodeficiencies or cancers. Nevertheless, efforts are underway to develop small molecule drugs that either augment or suppress hematopoietic receptor signaling by targeting critical points of interaction between cytokines and their receptors, or receptors and intracellular effectors.

Cytokine Receptors (Hematopoietin Receptor Family)

Cytokine Receptors – Class 1 (Short Chain) Hematopoietin Receptor Family

RECEPTOR FOR ^a	IL-2 (I0779 , I0904 , I1029)	IL-3	IL-4 (I6021)	IL-5	IL-7	IL-9	IL-13
CURRENTLY ACCEPTED NAME	IL-2 Receptor	IL-3 Receptor	IL-4 Receptor	IL-5 Receptor	IL-7 Receptor	IL-9 Receptor	IL-13 Receptor
ALTERNATIVE NAME	TCGF	Multi-CSF, MCGF	BCGF, BSF-1	EDF	PreBCGF	—	—
SUBUNIT COMPOSITION	IL2R α (I0779)/IL2R β (I0904)/R γ c (I1029)	IL3R α /Rbc	IL4R/R γ c	IL5R α /R β c	IL7R2/R γ c	IL9R/R γ c	IL13R α 1/IL4R α . IL13R α 2=decoy
SELECTIVE AGONISTS ^{a,b}	IL-2 (I2644 , I7908 (h), I0523 (m), T0892 (r)), (IL-4 (I4269 (h), I1020 (m), I3650 (r)) IL-7 (I5896 (h), I4892 (m)), IL-15 (I8648)	IL-3 (I1646 , I7389 (h), I4144 (m))	IL-4 (I4269 (h), I1020 (m), I3650 (r))	IL-5 (I5273 (h), I1145 (m))	IL-7 (I5896 (h), I4892 (m))	IL-9 (I3394 (h), I3269 (m))	IL-13 (I1771 (h), I1896 (m)), IL-7 (I5896 (h), I4892 (m)), IL-15 (I8648)
SIGNAL TRANSDUCTION MECHANISMS	JAK/STAT lyn lck	JAK/STAT	JAK/STAT IRS-1	JAK/STAT 4PS lyn	JAK/STAT	JAK/STAT	JAK/STAT lyn lck
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-IL-2	[¹²⁵ I]-IL-3	[¹²⁵ I]-IL-4	[¹²⁵ I]-IL-5	[¹²⁵ I]-IL-7	[¹²⁵ I]-IL-9	[¹²⁵ I]-IL-13
TISSUE EXPRESSION	Thymus	Activated T cells, mast cells, eosinophils	Th2-cells, NK-T cells, mast cells	T cells, mast cells	Bone marrow stromal cells, T cells	Th2 cells	Activated Th2 cells
PHYSIOLOGICAL FUNCTION	Hematopoiesis, proliferation of T- and B-cells	Growth and proliferation of immune cells	Proliferation and development of Th2 cells, B-cell proliferation, activation of monocytes-macrophages	Growth and differentiation of B cells and eosinophils	Early B and T cell development	Eosinophil differentiation, mast cell proliferation	B cell maturation and differentiation, downregulates macrophages
DISEASE RELEVANCE	Therapeutic for many cancers	Myeloid leukemias	Allergy, asthma	Asthma, allergy	Psoriasis	Asthma	Asthma

Cytokine Receptors – Class 1 (Short Chain) Hematopoietin Receptor Family (continued)

RECEPTOR FOR ^a	IL-15	IL-21	GMCSF	TSLP	FLT3L	MCSF	SCF
CURRENTLY ACCEPTED NAME	IL-15 Receptor	IL-21 Receptor	GMCSF Receptor	TSLP Receptor	FLT3/FLK2 RTK	c-FMS RTK	c-KIT RTK
ALTERNATIVE NAME	—	—	CSF2	—	—	CSF-1	MGF, Steel
SUBUNIT COMPOSITION	IL15R α /IL2R β /R γ c	IL21R/R γ c	GMCSFR α /R β c	TSLPR/IL7R α	(FLT3)2	(FMS)2	(KIT)2
SELECTIVE AGONISTS ^{a,b}	IL-15 (I8648), IL-2 (I2644 , I7908), IL-4 (I4269), IL-7 (I5896)	IL-21	GMCSF (G5035)	TSLP, (IL-7)	Not known	Not known	Not known
SIGNAL TRANSDUCTION MECHANISMS	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT	Tyrosine Kinase	Tyrosine Kinase	Tyrosine Kinase
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-IL-15	[¹²⁵ I]-IL-21	[¹²⁵ I]-GMCSF	[¹²⁵ I]-TSLP	[¹²⁵ I]-FLT3L	[¹²⁵ I]-MCSF	[¹²⁵ I]-SCF
TISSUE EXPRESSION	Placenta, skeletal muscle	Activated CD4 ⁺ T-cells	Immune cells	Spleen, thymus, kidney, lung, bone marrow	Immune cells	Immune cells	Immune cells

Cytokine Receptors (Hematopoietin Receptor Family)

PHYSIOLOGICAL FUNCTION	T cell stimulation	NK cell proliferation and maturation, B and T cell function, inhibition of dendritic cells	Hemopoietic progenitor growth and differentiation	Myeloid stimulation, dendritic cell and B cell development	Stem cell growth factor	Stem cell growth factor, macrophage development, immune defense, bone metabolism	Stem cell growth factor, mast cell development
DISEASE RELEVANCE	Arthritis	Psoriasis	Therapeutic myeloid reconstitution	Not known	Leukemia	Leukemia	Mast cell leukemia, piebaldism, gastrointestinal stromal tumor

Cytokine Receptors – Class 1 (Long Chain) Hematopoietin Receptor Family

RECEPTOR FOR	EPO	TPO	GH *	PRL	CLC	CNTF	CT-1
CURRENTLY ACCEPTED NAME	EPO Receptor (E0643)	TPO Receptor	GH Receptor	PRL Receptor	CLF and CNTF Receptor	CNTF Receptor	CNTF Receptor
ALTERNATIVE NAME	—	MegCSF, MGDF, MPL ligand	Somatotropin	Placental Lactogen (L4759)	BSF3, NNT1	—	—
SUBUNIT COMPOSITION	(EPOR) ₂	(TPOR) ₂	(GHR) ₂	(PRLR) ₂	CLF/NR6 for secretion, CNTFR α /gp130/LIFR	CNTFR α /gp130/LIFR	CNTFR α /gp130/LIFR
SELECTIVE AGONISTS ^{a,b}	EPO (E5627)	TPO (T1568)	GH/CS, PRL (L4021)	PRL (L4021), GH/CS	CLC, CNTF (C3710)	LIF (L5283), OSM (O9635), CT-1, IL-6 (I1395 , I3268), IL-11 (I2406), CNTF (C3710), IL-11 (I2406)	CT-1, LIF (L5283), OSM (O9635), CNTF (C3710), IL-6 (I1395 , I3268)
SIGNAL TRANSDUCTION MECHANISMS	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-EPO	[¹²⁵ I]-TPO	[¹²⁵ I]-GH	[¹²⁵ I]-PRL	[¹²⁵ I]-CLC, [¹²⁵ I]-CNTF, [¹²⁵ I]-LIF, [¹²⁵ I]-OSM	[¹²⁵ I]-CNTF, [¹²⁵ I]-LIF, [¹²⁵ I]-OSM	[¹²⁵ I]-CT-1, [¹²⁵ I]-LIF, [¹²⁵ I]-OSM
TISSUE EXPRESSION	Kidney, liver	Liver	Pituitary gland	Placenta	Lymph nodes, spleen, PBLs, bone marrow, fetal liver	Central nervous system	Heart, skeletal muscle, prostate, liver
PHYSIOLOGICAL FUNCTION	Regulator of erythropoiesis	Regulator of thrombopoiesis, megakaryocyte development, platelets	Growth control, differentiation and proliferation of myoblasts	Promotes lactation by mammary gland	B cell stimulation, neuronal regeneration	Neuronal regeneration	Cardiac myocyte development
DISEASE RELEVANCE	Therapeutic for treatment of anemia	Therapeutic for platelet reconstitution; thrombocytopenia	Dwarfism	Not known	Not known	Treatment for obesity, amyotrophic lateral sclerosis	Not known

Cytokine Receptors (Hematopoietin Receptor Family)

RECEPTOR FOR	GCSF	Leptin	LIF	OSM	IL-6	IL-11	IL-12p35
CURRENTLY ACCEPTED NAME	GCSF Receptor	Leptin Receptor	LIF Receptor	LIF Receptor and OSM Receptor	IL-6 Receptor IL-6 (I5771)	IL-11 Receptor	IL-12 Receptor
ALTERNATIVE NAME	CSF3, pluripoietin	Obese, OB	HILDA	—	IFN- β 2, BSF2	AGIF	NKSF1, IL-12A
SUBUNIT COMPOSITION	(GCSFR)2	(LepR)2	gp130/LIFR	gp130/LIFR, gp130/OSMR	IL6R α /(gp130)2	IL11R/yp130	p40/IL12R β 1/ IL12R β 2
SELECTIVE AGONISTS ^{a,b}	GCSF (G0407)	Leptin (L4146)	LIF (L5283), OSM (O9635), IL-6 (I1395), CT, IL-11 (I2406), CNTF (C3710)	LIF (L5283), OSM (O9635), CT, IL-6 (I1395), IL-11 (I2406), CNTF (C3710)	IL-6 (I1395), (OSM (O9635), LIF (L5283), IL-11 (I2406), CNTF (C3710), CT)	IL-11 (I2406), (OSM (O9635), CT, IL-6 (I1395), LIF (L5283), CNTF (C3710))	IL-12p35/p40 (I2276)
SIGNAL TRANSDUCTION MECHANISMS	JAK/STAT SH-PTPase	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-GCSF	[¹²⁵ I]-Leptin	[¹²⁵ I]-LIF	[¹²⁵ I]-LIF, [¹²⁵ I]-OSM	[¹²⁵ I]-IL-6, [¹²⁵ I]-OSM	[¹²⁵ I]-IL-11	[¹²⁵ I]-IL- 12p35/p40
TISSUE EXPRESSION	Immune cells	Adipocytes, stem cells	Immune cells	Activated leukocytes	Immune cells	Stromal cells	Monocytes, T cells, B cells
PHYSIOLOGICAL FUNCTION	Regulates granulocyte proliferation and maturation	Early hematopoiesis, regulation of obesity and metabolism, bone development	Hematopoietic, neuronal and endothelial cell development	Liver development, hematopoiesis regulation	Proinflammatory, bone resorption control, hematopoiesis regulation, plasma cell development	T cell proliferation and regulation, stimulates platelet production	Promotes Th1 immune response, NK cell cytotoxicity, proinflammatory
DISEASE RELEVANCE	Therapeutic against neutropenia	Obesity	Arthritis	Not known	Therapeutic for cancers	Therapeutic for psoriasis	Chronic inflammatory diseases

Cytokine Receptors – Class 1 (Long Chain) Hematopoietin Receptor Family (continued)

RECEPTOR FOR ^a	IL-23p19	IL-27p28	IL-31
CURRENTLY ACCEPTED NAME	IL-23 Receptor	IL-27 Receptor	IL-31 Receptor
ALTERNATIVE NAME	IL-23A	TCCR, WSX-1	GLMRL
SUBUNIT COMPOSITION	p40/IL12R β 1/IL23R	EBI3/TCCR/yp130	IL-31R/OSMR
SELECTIVE AGONISTS ^a	IL-23p19/p40	IL-27p28/EBI3	IL-31
SIGNAL TRANSDUCTION MECHANISMS	JAK/STAT	JAK/STAT	JAK/STAT
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-IL-23p19/p40	[¹²⁵ I]-IL-27p29/EBI3	[¹²⁵ I]-IL-31
TISSUE EXPRESSION	Monocytes, dendritic cells, T cells, NK-cells	Monocytes, dendritic cells	Activated Th2 cells

Cytokine Receptors (Hematopoietin Receptor Family)

PHYSIOLOGICAL FUNCTION	Promotes Th1 immune response, IFN- γ inducer, proliferation of memory and naive T cells	Promotes Th1 immune response, proliferation of naive CD4 ⁺ T cells	Immune response
DISEASE RELEVANCE	Chronic inflammation	Chronic inflammation	Epithelial skin disorders, asthma and allergy

Cytokine Receptors – Class 2 Hematopoietin Receptor Family

RECEPTOR FOR	IFN- α/β **	IFN- γ	IL-10	IL-19	IL-20
CURRENTLY ACCEPTED NAME	IFN- α Receptor-2	IFN- γ Receptor-1	IL-10 Receptor-1	IL-20 Receptor	IL-20 Receptor
ALTERNATIVE NAME	—	—	CSIF	—	—
SUBUNIT COMPOSITION	IFN α R2/IFN α R1	IFN γ R1/IFN γ R2	(IL10R1)2/(IL10R2)2	IL20R1/IL20R2	IL20R1/IL20R2, IL22R1/IL20R2
SELECTIVE AGONISTS ^{a,b}	IFN- α ** (I4401, I4276), IFN- β (I4151)	IFN- γ (I1520, I3265)	IL-10 (I9276)	IL-20, IL-24, IL-26	IL-20, IL-19, IL-22, IL-24, IL-26
SIGNAL TRANSDUCTION MECHANISMS PI3K, NFKB, MAPK, PRMT1	JAK/STAT PI3K, MAPK, NFKB	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-IFN- α/β	[¹²⁵ I]-IFN- γ	[¹²⁵ I]-IL-10	[¹²⁵ I]-IL-19	[¹²⁵ I]-IL-20
TISSUE EXPRESSION	Dendritic cells	Th1 cells	Th2 cells, B cells	Monocytes, B cells	Immune cells
PHYSIOLOGICAL FUNCTION	Immune response against viral infection, antiviral, antiproliferative	Immune response, triggers cytokine release	Immunosuppressive functions, blocking cytokine production	Immune response	Immune response
DISEASE RELEVANCE	Lupus, rheumatoid arthritis; treatment of Hepatitis-B and -C, multiple sclerosis	Chronic inflammatory disease	Asthma, allergy	Chronic inflammatory skin disease (e.g. psoriasis)	Psoriasis

Cytokine Receptors (Hematopoietin Receptor Family)

RECEPTOR FOR ^a	IL-22	IL-24	IL-26	IL-28 α / β ***	IL-29
CURRENTLY ACCEPTED NAME	IL-22 Receptor	IL-22 Receptor	IL-20 Receptor	IL-28 Receptor	IL-28 Receptor
ALTERNATIVE NAME	IL-TIF	MDA7, FISP	AK155	IFN-I2/I3	IFN-I1
SUBUNIT COMPOSITION	IL22R1/IL10R2, IL22bp=Decoy	IL22R1/IL20R2, IL20R1/IL20R2	IL20R1/IL10R2	IL28R1/IL10R2	IL28R1/IL10R2
SELECTIVE AGONISTS ^{a,b}	IL-22, IL-20	IL-24, IL-19, IL-20, IL-26	IL-26, IL19, IL-20, IL-24	IL-28 α / β , IL-29	IL-29, IL-28 α / β
SIGNAL TRANSDUCTION MECHANISMS	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT	JAK/STAT
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-IL-22	[¹²⁵ I]-IL-24	[¹²⁵ I]-IL-26	[¹²⁵ I]-IL-28 α / β	[¹²⁵ I]-IL-29
TISSUE EXPRESSION	T cells, mast cells, thymus, brain	Immune cells, PBLs, melanocytes	T cells, monocytes, NK-cells, B cells	T cells	T cells
PHYSIOLOGICAL FUNCTION	Immune response	Immune response apoptosis inducing in tumor cells	Immune response	Immune response, antiviral, antiproliferative	Immune response, antiviral, antiproliferative
DISEASE RELEVANCE	Allergy	Melanoma	Upregulated in T cells by Herpes virus infection, stimulation of cytotoxic activity of immune cells	Not known	Not known

Abbreviations

4PS: IL-4-induced phosphotyrosine substrate

AGIF: Adipogenesis inhibitory factor

BCGF: B cell growth factor

BSF: B cell stimulatory factor

CLC: Cardiotrophin like cytokine

CLF: Cytokine-like factor

CNTF: Ciliary neurotrophic factor

CS: Chorionic somatotropin

CSF: Colony stimulating factor

CSIF: Cytokine synthesis inhibitory factor (CSIF).

CT: Cardiotrophin

EDF: Eosinophil differentiation factor

EPO: Erythropoietin

FISP: IL4 induced secreted protein

FLT-3: Fms-like tyrosine kinase 3

FLT3L: Fms-related tyrosine kinase 3 ligand)

FMS: formerly McDonough feline sarcoma viral (v-fms) oncogene homolog

GH: Growth Hormone

GHR: Growth hormone receptor

GMCSF: Granulocyte macrophage colony stimulating factor

GSCF: Granulocyte colony stimulating factor

IFN: Interferon

IL: Interleukin

IL-TIF: IL-10-related T-cell-derived inducible factor

IRS-1: Insulin receptor substrate-1

Jak: Janus kinase

KIT: V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog

LIF: Leukemia inhibitory factor

Lck: Lymphocyte-specific protein tyrosine kinase

Lyn: V-yes-1 Yamaguchi sarcoma viral related oncogene homolog

MCSF: Macrophage colony stimulating factor

MDA7: Melanoma differentiation-associated protein 7

MGDF: megakaryocyte growth and development factor

MGF: Mast cell growth factor

NKSF1: NK cell stimulatory factor chain 1

NNT1: Novel neurotrophin 1

OSM: Oncostatin M

PBLs: Peripheral blood leukocytes

PDGF: Platelet-derived growth factor

PRL: Prolactin

RTK: Protein tyrosine kinase

SCF: Stem cell growth factor

SH-PTPase: Src homology domain 2-containing protein tyrosine phosphatase

STAT: Signal transducer and activator of transcription

TCCR: Type I T-cell cytokine receptor

TPO: Thrombopoietin

TSLP: Thymic stromal lymphopoietin

FOOTNOTES

a Product numbers refer to the human cytokine. For other species, please visit our website at www.sigma-aldrich.com and use our Product Search.

b Agonists not in parentheses are primary agonists for the receptor.

* GH and four closely related chorionic somatotropin homologs.

**IFN α , β , δ , ϵ , κ , τ , ω and limitin.

*** IL28 α and IL28 β are two closely related cytokines.