Chapter

# A World of Wonders: Interleukin-1 (IL-1) and IL-2 Families

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## Abstract

Human interleukins (ILs) are a collection of different biological molecules belonging to the group of cytokines, associated with various immune and non-immune systems and different signaling pathways. ILs contribute to the function of different tissues, organs and systems in the human body. They are involved in homeostasis, infectious diseases, autoimmune diseases, cancers and even therapeutics. Due to this knowledge, this chapter aims to summarize the importance of the IL-1 and IL-2 superfamilies.

**Keywords:** immune system, cytokines, interleukins, interleukin-1, interleukin-2

## 1. Introduction

Human cytokines are consisted of a wide range of proteins (and/or glycoproteins) known as immune molecules with different properties that affect both immune and non-immune cells. Based on different characteristics, cytokines are classified into several groups including interleukins (ILs), interferons (IFNs), chemokines and lymphokines [1–4].

In 1979 at the cytokinologists' meeting of "the Second International Lymphokine Workshop" in Switzerland, the term of *Interleukin* was officially proposed for the first time. The proposed term of "*Interleukin*" was published in a letter to the editor by the *Journal of Immunology* [2, 5–7].

However, this term is not entirely correct, because the ILs are not only limited to leukocytes but they also involve other cells other than leukocytes [4]. The majority of IL glycoproteins are produced by endothelial cells, monocytes, macrophages (MΦs) and T helper (CD4+) lymphocytes [3].

There are several nomenclature systems, which may be applied for the categorization of ILs. However, interleukins are recognized through the capital letters IL followed immediately by a dash and a number e.g. IL-17 [3, 5, 8]. One of these nomenclature systems was approved by the subcommittee of the nomenclature committee of the International Union of Immunological Societies (IUIS) and the World Health Organization (WHO). Functional characteristics, structural properties, amino acid sequences and related homology, types of receptors (among other things) may be recognized as important criteria for ILs' classification [2, 9].

The authors try to discuss general characteristics, structures, classifications, and genomic maps of ILs throughout this chapter.

## 2. General characteristics and structure of interleukins

ILs as a group of cytokines, which are involved in immune and non-immune cell activation, cell adhesion, cell differentiation, cell maturation and cell migration; in other words, these proteins act like signaling molecules that induce different pathways in the human body. Although ILs encompass a wide range of functions and structures, they participate in immunomodulatory activities and also contribute to pro-inflammatory and anti-inflammatory responses. These processes initiate through the attachment of the IL biomolecules to their specific receptors onto the cells, which may lead to induction of immune responses. However, the efficacy and specificity of these responses is associated with the related receptors, ligands and signaling pathways [2, 3, 10, 11].

In addition, IL proteins have pivotal role in cancers. Indeed, these biomolecules are produced and secreted by tumor- and immune cells within the tumors. Due to these facts, ILs affect the processes of angiogenesis, invasion, growth and immune responses related to tumors. Because of the presence of ILs in different cells, tissues and organs, they have recognized as invaluable biomarkers in diagnostics and therapeutic planning [11, 12].

Up to date, more than 40 ILs have been identified with a wide range of subtypes. The structural characteristics of cytokines, including IL proteins, are effective criteria for their categorization. In this regard, some IL glycoproteins are divided into two groups: type I (class I) and type II (class II) cytokines. Type I cytokines bear a general structure comprising four compact α-helices within tensed packages. The arrangement of the related α-helices involves a four-helix bundle with an antiparallel (up-up-down-down) configuration. Type II cytokines obey the same structure as described for type I cytokines. However, type II cytokines bear the compact packages of six to seven-helix bundles with the configuration of antiparallel arrangement [2, 3, 11, 13–15].

Furthermore, in accordance with the length of bundles made of α-helices, type I cytokines are classified into short- and long-chains subclasses. The members of long-chain subclass pertaining to type I cytokines encompass bundle peptides with more than 165 amino acids, while the members of short-chain subclass belonging to type I cytokines possess bundle peptides with less than 165 amino acids [3, 16]. Interleukins are classified into the families of IL-1 family, IL-2 family, IL-6 family (including ILs 6, 11, 31, cardiotrophin-like cytokine (CLC), cardiotrophin-1 (CT-1), ciliary neurotrophic factor (CTNF), leukemia inhibitory factor (LIF), and oncostatin M (OSM)) [17]; IL-10 family (composed of ILs 10,19, 20, 22, 24, 26) [18]; IL-12 superfamily (comprising ILs 12, 23, 27, 35) [19]; and IL-17 family (containing ILs 17 A-D and IL-25 (IL-17E)) [20]. IL-8 belongs to the CXC-chemokines and is classified along with them [21].

## 3. The IL-1 superfamily and the related members

IL-1 superfamily members (IL1-like cytokines) involve functionally quite distinct molecules composed of IL-37, as the single member anti-inflammatory cytokine, IL-1Ra, IL-36Ra and IL-38 as three well-known receptor blockers or antagonists, and IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ as

seven ligands with agonistic functions [2, 3, 22, 23]. The IL-1 is known as the pioneer member of the IL-1 superfamily and its receptor was recognized as IL-1R. Interestingly, the IL-1R encompasses a molecule of Toll-IL-1 receptor (TIR) domain in its structure. The TIR domain – which is identified in both structures of IL-1R and toll-like receptor (TLR) glycoproteins – has pivotal roles in transduction of internal signals by different stimulators e.g. recognition of pathogen/microbe-associated molecular patterns (PAMPs/MAMPs) and danger/damage-associated molecular patterns (DAMPs) by ectodomain structures of TLRs to strengthen the immune responses and inflammation [22, 24–27]. The gene clusters of IL-1 superfamily members, excluding ILs 18 and – 33, map within chromosome 2 in humans (**Table 1**) [2, 3, 22].

IL was identified for the first time in 1979. IL-1α and IL-1β proteins (**Figure 1**) have the same biological characteristics but the lowest homology in their sequences. Moreover, the nature of IL-1α subunit makes it active with effective biological functions, while the IL-1β is produced as a pro-subunit which the enzyme of caspase-1 should be activated [3, 12, 22, 29, 34].

The IL-1 superfamily members are produced by different of immune and non-immune cells such as chondrocytes, dendritic cells (DCs), epithelial- and endothelial cells, keratinocytes, lymphocytes, fibroblasts, MΦs, monocytes, neutrophils and smooth muscle cells [2, 35–37].

As presented on **Figures 1** and **2** each subunit whether IL-1α or IL-1β, encompasses 11 loops and 12 β-strands which appear as a typical configuration of β-trefoil. The two ILs 1α and 1β have no specific binding to the IL-1 receptor type I and II, respectively; they both can bind both types, but, in case of type I receptor (CD 121a), with stimulatory action and pathway signaling, and, in case of the type II receptor, (decoy receptor that lacks the TIR domain) with inhibitory effect similar to the IL1Ra binding. The connections between the ligands and receptors are supported by the presence of IL-1R accessory co-receptor proteins (IL-1RAcP) to prepare proper conformational changes [3, 22].

| IL-1 superfamily member | | Gene | | Active form | Molecular weight (active structure) | Chromosome | References |
|---|---|---|---|---|---|---|---|
| IL-1α/IL-1F1 | | *IL-1α/IL1F1* | | Heterodimer; β-trefoil fold | 17 kDa | 2q14 | [2, 22, 28, 29] |
| IL-1β/IL-1F2 | | *IL-1β/IL-1F2* | | | 17 kDa | 2q14 | [2, 22, 28, 29] |
| IL-1Ra/IL-1F3 | | *IL-1Ra/IL-1F3* | | | 22 kDa | 2q14.2 | [2, 22, 28, 29] |
| IL-18/IL-1F4 | | *IL-18/IL-1F4* | | Homodimer; β-trefoil fold | 18 kDa | 11q22.2-11q22.3 | [2, 22, 28, 29] |
| IL-33/IL-1F11 | | *IL-33/IL-1F11* | | β-trefoil fold | 18 kDa | 9p24.1 | [2, 22, 28, 29] |
| IL-36/ IL-1F | α/6 | *IL-36/ IL-1F* | *A/6* | β-trefoil fold | 35 kDa | 2q12-2q14.1 | [2, 22, 23, 28] |
| | β/8 | | *B/8* | | | 2q14 | |
| | γ/9 | | *G/9* | | | 2q12-2q21 | |
| | Ra/5 | | *Ra/5* | | 17 kDa | 2q14 | [2, 22, 28, 30] |
| IL-37/IL-1F7 | | *IL-37/IL-1F7* | | β-trefoil fold | 17–24 kDa | 2q12-2q14.1 | [2, 22, 28, 31] |
| IL-38/IL-1F10 | | *IL-38/IL-1F10* | | β-trefoil fold | 17 kDa | 2q14 | [2, 22, 28, 32] |

**Table 1.**
*IL-1 superfamily members, related genes, molecular weight and loci.*

**Figure 1.**
*The IL-1α structure including an α-helix, β-sheets and loops (shown in green color) (PDB ID 5UC6) [33].*

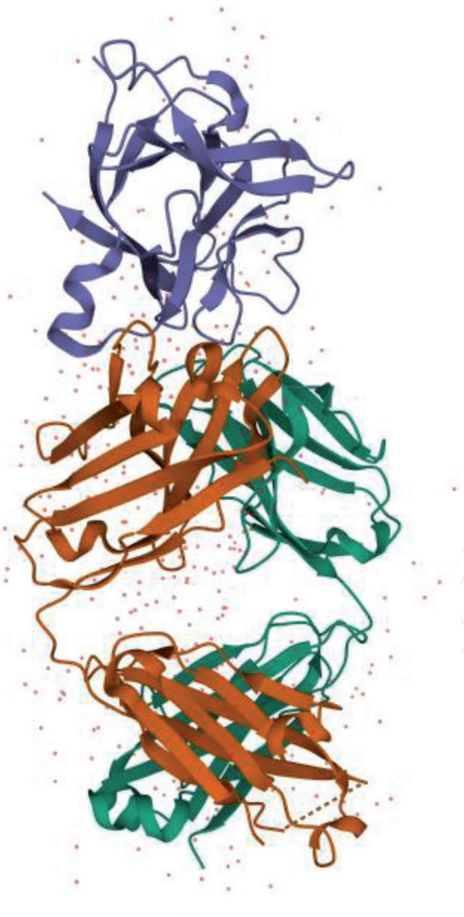

**Figure 2.**
*The IL-1β structure including an α-helix, β-sheets and loops (shown in violet color) (PDB ID 7CHZ) [38].*

The heterodimers of IL-1α and IL-1β activate the inflammatory pathway via the employment of MyD88, which may lead to expression of the nuclear factor κB (NF-κB) and consequently, to expression of inflammatory products. Thus, the

IL-1 is known as endogenous pyrogen. The IL-1 functional properties are modulated by IL-1Ra. However, the IL-1RAcP binding domain is absent in IL-1Ra. Thus, the IL-1 signaling pathway cannot be induced via the IL-1Ra molecule [3, 22, 29, 39].

IL-1 is also involved in tumor biology through the processes of angiogenesis, invasion and proliferation. The expression of IL-1 proteins increase within a wide range of cancers e.g., melanoma, lung, breast, neck, colon, head among others [11, 40].

IL-18 is another member of IL-1 superfamily, which was identified in 1989 and introduced as the triggering factor of interferon-γ (IFN-γ). IL-18, resembling IL-1β is produced as an inactive protein and should be activated by the cleavage done via caspase-1. IL-18 is the ligand of the double stranded and heterodimeric receptor of IL-18R complex. The combined complex of IL-12 and IL-18 may lead to significant expression of IFN-γ. The expression of IFN-γ resulted from IL-18 and IL-12 combination has anti-tumoral effects. The expression of IL-18 increases in breast-, hepatocellular-, lung-, esophageal-, ovarian- and renal carcinomas [2, 11, 22, 29, 34, 41–43]. The immune and non-immune cells (e.g. astrocytes, DCs, keratinocytes, Kupffer-cells, MΦs and osteoblasts) are important resources for IL-18 expression and secretion [29, 44].

IL-33 as another IL-1 superfamily member contributes to type 2 immunity and inflammation. Indeed, the IL-33/ST2 pathway has pivotal roles in activation of type 2 immunity through triggering of those T helper 2 (Th2) cells which produce suppression of tumorigenicity 2 (ST2) molecules [3, 45–47]. The main resource cells that produce IL-33 include keratinocytes, mucosal tissues, fibroblasts, endothelial- and epithelial cells [3, 22, 45, 48]. IL-33 binds to the related receptor of IL-1RL1 (or ST2). Furthermore, the related co-receptor is IL-1RAcP [45]. The precursor of the alarmin cytokine IL-33 is inactivated by caspase-1, while the enzymes of neutrophil elastase and serine proteases cathepsin G cleave the IL-33 precursor into active mature structures. However, the 30 kDa precursor of IL-33 is functional upon necrotic cell death and cell damage [3, 22, 34, 45, 49]. The IL-33 receptor, ST2 mediates activation of the MyD88-dependent signaling pathway. The ST2 molecules are produced by different innate and adaptive immune cells. The ST2 molecule participates in type 2 cytokines expressions which are involved in inflammatory and allergic responses [3, 22, 29]. IL-33 supports the homeostasis of intestinal microbiota through the induction of Immunoglobulin A (IgA) in adaptive immune B cells. In addition, the IL-33 receptor of ST2 is capable to inhibit the colorectal cancer via reduction of regulatory T cells ($T_{reg}$) infiltration and enhancement of CD8+ T cells [12, 45, 50].

IL-36 cytokines belong to the subfamily members of IL-1 superfamily. The subfamily of IL-36 is comprised of three IL-36 receptor (IL-36R) agonists of IL-36α, IL-36β, and IL-36γ and an IL-36R antagonist of IL-36Ra. The IL-36α, IL-36β, and IL-36γ have 24%, 27% and 20% similar homology with IL-1Ra, respectively and 30%, 31% and 31% similarity with IL-1β, respectively [23, 51, 52]. The IL-36α, IL-36β, and IL-36γ bind to IL-36R through the co-receptor IL-1RAcP. The IL-36α, IL-36β, and IL-36γ are expressed as biologically inactive precursors which should be activated by proteases of elastase/Cat G, Cat G, proteinase3/elastase/CatG, respectively [23]. The IL-36α, IL-36β, and IL-36γ are recognized as inflammatory cytokines which activate the related signaling pathway via activation of NF-κB, while the antagonist of IL-36Ra as the anti-inflammatory cytokine inhibits the inflammatory signaling pathway through inactivation of L-36R [23, 53]. The expression of IL-36γ cytokine is observed in cancers of colorectal, esophageal, melanoma, lung and neck and squamous cell carcinoma [11, 54].

IL-37, which is the anti-inflammatory member of the IL-1 superfamily was identified in 2000. IL-37 cytokines consist of five isoforms including IL-37a (isoform 5), IL-37b (isoform 1), IL-37c (isoform 4), IL-37d (isoform 2) (expressed only

in the testes and the bone marrow) and IL-37e (isoform 3) (expressed only in the testes and the bone marrow). The isoform of IL-37a is the only that is expressed in the brain (along with the heart and kidney, like the IL-37b and IL-37c, —and also in lymph nodes, bone marrow, placenta, lung-; IL-37a is brain-specific between the three), IL-37b is kidney-specific between the three, and, finally, IL-37c is heart-specific (the only of them expressed in the heart). Moreover, the IL-37b or isoform 1 is the largest member of the IL-37 isoforms with a length of 218 amino acids. The IL-37 isoforms are produced as precursors which should be biologically activated by protease enzymes e.g. caspase-1 [55, 56]. The IL-37b has considerable sequence similarity with IL-18 and therefore the isoform 2 of IL-37 is capable to bind to the α-chain of IL-18 receptor (IL-18Rα) [29, 55]. The IL-37 prevents the progression of colon cancer through inhibition of β-catenin [12].

IL-38 is known as bioinformatic cytokine, because it was detected by *in silico* studies. This cytokine was discovered in 2001, and has 41% sequence similarity with IL-1Ra, 43% with IL-36Ra and 29% with IL-1β. Interestingly similar to IL-36Ra, the IL-38 behaves as an antagonist and binds to IL-36R [3, 22, 57]. The *IL-38* gene maps to chromosome 2, situated within a gene cluster containing *IL-1*α*-IL-1*β*-IL-37-IL-36*γ*-IL-36*α*-IL-36*β*-IL-36Ra-IL-38-IL-1Ra* that spans from the centromere to the telomere [57]. In accordance with previous studies, IL-38 enhances the pro-inflammatory immune responses against LPS and inhibits the expression of IL-17 triggered by *Candida albicans* and IL-22 [11, 22, 57–59].

## 4. The IL-2 superfamily and related members

The IL-2 superfamily is known as the $\gamma_c$ family of cytokines [2, 3, 29, 60]. The IL-2 superfamily or $\gamma_c$ family of cytokines comprise six members including IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 (**Table 2**); the members of this superfamily are classified as type I cytokines bearing four α-helical bundle. $\gamma_c$ (CD132) is the pivotal protein portion of IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 receptors. The first recognized member of this family, IL-2 was identified in 1976 as a T-cell growth factor [3, 60–62]. The IL-2 superfamily members contribute to a wide range of immune cells' activities such as regulation of B cell development, innate lymphoid cells, natural killer (NK) and T cells, differentiation, proliferation and survival of immune cells [60].

The IL-2 cytokine is expressed by a wide range of innate and adaptive immune cells, including DCs, NK cells, NK T (NKT) cells, active $CD4^+$ and $CD8^+$ T cells. Interestingly, the IL-2 cytokine targets the B immune cells, NK and $CD4^+$ and $CD8^+$ T. IL-2Rα (known as $T_{ac}$ antigen or CD25), IL-2Rβ (known as CD122) and IL-2Rγ (known as CD132 or $\gamma_c$) together form a three-segmented receptor for IL-2

| IL-2 superfamily member | Gene | Active form | Molecular weight (active structure) | Chromosome | References |
|---|---|---|---|---|---|
| IL-2 | *IL-2* | monomer | 15.5 kDa | 4q26-4q27 | [2, 29] |
| IL-4 | *IL-4* | monomer | 15 kDa | 5q23-5q31 | [2, 29] |
| IL-7 | *IL-7* | monomer | 25 kDa | 8q12-8q13 | [2, 29] |
| IL-9 | *IL-9* | monomer | 14 kDa | 5q31-5q35 | [2, 29] |
| IL-15 | *IL-15* | monomer | 14–15 kDa | 4q31 | [2, 29] |
| IL-21 | *IL-21* | monomer | 15 kDa | 4q26-4q27 | [2, 29] |

**Table 2.**
*IL-2 superfamily members, related genes, molecular weight and loci.*

[3, 29, 60, 61]. The IL-2 cytokine has therapeutic application for some cancers, e.g., melanoma and renal carcinoma. IL-2 alone or together with related vaccines and/or cytokines can be considered as therapeutic options [11, 63].

IL-4, another member of the IL-2 superfamily, is secreted by activated basophils, eosinophils, mast cells, NKT cells, T helper 2 ($T_{h2}$) cells and γδ T cells [29, 64]. It participates in the differentiation of $T_{h2}$ and $T_{h9}$, mediates allergic conditions, triggers expression of IgE in B cells, and protects the human body from infectious diseases caused by extracellular parasites and helminths. However, it was shown that rather than IL-4, the ILs of 1, 2, 25, and 33 enhance the process of $T_{h9}$ differentiation [60, 65]. IL-4 and IL-13 – with 25% sequence similarity – cooperate with each other in some functional activities [3, 29, 60, 64].

IL-4 has 2 groups of receptors: type I (composed of IL-4Rα or CD124 and the $\gamma_c$ or CD132) and type II (involves IL-4Rα and IL-13Rα1). The type I IL-4R is able to bind only to IL-4 while the type II IL-4R is capable to bind to the both of IL-4 and IL-13 [29, 66]. High levels of IL-4Rs are detected in tumors. The IL-4 participates in tumorigenesis through prevention of $T_{h1}$ activation and activation of $T_{h2}$. The expression of IL-4 increases in different types of cancers including urinary bladder, breast, colon, lung ovary, pancreas and the prostate [11, 67].

IL-7 is a critical cytokine in B- and T-lymphocyte development and maturation. The main expression resources of IL-7 are immune and non-immune cells, such as B cells, DCs, epithelial cells, keratinocytes, MΦs and monocytes. IL-7 is the ligand of the complex structured IL-7R which is composed of IL-7Rα or CD127 and the $\gamma_c$ or CD132 [29, 66]. IL-7 is significantly involved in homeostatic regulation of the both groups of immature and mature T cell types [2, 60]. In addition, IL-7 triggers the anti-tumoral immune responses and prevents the growth of tumors [11].

IL-9 is expressed by the immune cells of eosinophils, mast cells and T cells of $T_{h2}$ and $T_{h9}$. IL-9 triggers the expression of IgE by the adaptive B immune cells and the secretion of mucosal production and chemokines in the bronchi. IL-9 is involved in helminth infectious diseases, allergies and asthma. The IL-9R is composed of two subunits of IL-9Rα and the $\gamma_c$ or CD132 [3, 29]. Moreover, the IL-9 acts as a double-edged sword. In melanoma, IL-9 acts as tumor inhibitor while in acute leukemia, it acts as a tumorigenetic cytokine [11].

IL-15 is expressed by a wide range of immune and non-immune cells consisting CD4+ T cells (functional), monocytes, keratinocytes and skeletal muscle cells. IL-15 and IL-2 have significant similarities in their structures. The IL-15R involves three subunits of IL-15Rα, IL-2Rβ and the $\gamma_c$ or CD132. IL-15 participates in proliferation of NK cells and the homeostasis of memory $CD8^+$ T cells [3, 29, 60]. Additionally, IL-15 has anti-tumoral effects [11]. IL-15, unlike IL-2, does not stimulate $LT_{reg}$, that can be useful in cancer therapy. Treg stimulation is one of the negative sides of IL-2 that IL-15 does not share [68–70].

IL-21 is expressed by immune cells such as NKT, T and mainly by $T_{h17}$ and T follicular helper ($T_{fh}$) [29, 60]. Similarly to IL-4, IL-21 enhances the expression of IgG1; on the other hand, conversely from IL-4, IL-21 prevents the expression of IgE [60, 71]. The IL-21 receptor is composed of two subunits of IL-21R and the $\gamma_c$ or CD132. IL-21 has anti-tumoral effects on some groups of cancers which may lead to recuperate melanoma and renal carcinoma; while the IL-21 is tumorigenic in colorectal cancer [3, 11].

## 5. Conclusion

Cytokines involve a wide range of molecules with different structural characteristics, functional properties and biological activities. Identification and recognition

of these characteristics help us to understand their classification and categorization. Each group of these biomolecules has its massive importance and huge application prospects. Indeed, ILs have pivotal roles in different parts of the human body, particularly associated with the innate and adaptive immune system. A complete understanding of ILs characteristics and properties will improve the successful outcomes against infectious and autoimmune diseases, as well as cancers.

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## Conflict of interest

The authors declare no conflicts of interest.

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