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# Emerging Role of Interleukins in Cancer Treatment

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### Abstract

Interleukins as a part of immune system were first represented in 1977. However, advancing knowledge of immune system and its role in pathogenesis of different diseases from allergic reactions to autoimmune disorders and even cancer makes these immune mediators an attractive target among different available treatment modalities. This article discusses the role of interleukins in cancer treatment.

**Keywords:** Interleukins; Inflammation; Autoimmune disorders; Allergic reaction; Cancer immunotherapy

#### Introduction

The immune system is a network of cells, tissues and mediators that work together, distinguishing self from foreign organisms and elaborating in keeping the body healthy through removal of the invaders. Any particle that stimulates the immune system is called an antigen. The main cellular components of the immune system are T lymphocytes and B lymphocytes. These cells are involved in recognizing antigens, antibody production and cell mediated cytotoxity leading to antigen removal and immune response that might last from days to years after antigen exposure.

Apart from different cells that are involved in immune response, cytokines are supposed to be a major component of the immune system. They are considered chemical communicators of different parts of the immune system and consist of interleukins, interferons and growth factors. Complement system is also a chemical part of the immune system that is made up of about 25 proteins that work together to destroy antibody covered organisms or remove them through other cellular components of the immune system. Each component of the complement system activates one another leading to a cascade that remove the invaders. They also act as a part of the inflammatory response system.

Discovery of Interleukins began in 1950s, but it took about 2 decades to precise structure and function of them to be identified. The first described members of this family were interleukin 1 (IL-1), interferon and nerve growth factors. Nowadays, more than 35 types of Interleukins have been identified. Table 1 summarizes known types of Interleukins.

# Interleukin 1

Il-1 was primarily discovered as a pyrogenic; fever causing, factor during sepsis and bacterial infections. However, there are different functions associated with this cytokine such as induction of vascular permeability, and activation and boosting of the secretion of other interleukins especially during the inflammatory response. It also has an endocrine function through the production of pituitary hormones. Production of prostaglandins and collagenase are also some other roles of IL-1.

From a structural point of view, the IL-1 family contains 3 different protein structures, IL-1 alfa and beta that is considered to be an agonist of each other, and IL-1 receptor antagonist (IL-1ra) [1-3]. The two former structures, despite their different encoding genes share similar structure and biological function, both bind to the same receptor.

However, their secretion and processing is different; Il-1 alfa is mostly localized in cytosol and cell membrane and regulates intracellular microenvironment, while IL-1 beta needs first to be enzymatically activated through its cleavage by Interleukin 1 beta converting enzyme (ICE) followed by its extracellular secretion [2,3].

Similarly, there are two different types of Interleukin 1 receptors, IL-1 receptor type I and II. Although they both share similarities such as being members of Immunoglobulin superfamily and similar IL-1 binding sites, from a functional point of view they act as antagonists. IL-1RI is expressed in most cell types and prefers to bind to IL-1 alfa and is responsible for IL-1 signal transduction. IL-1RII is mostly present on monocytes, B lymphocytes and neutrophils, preferably binds to IL-1 beta and decrease IL-1 signal transduction. Due to its antagonist effect, IL-1RII is also referred as "decoy IL\_1 receptor" [2,4]. There is also an Interleukin 1 receptor accessory protein (IL\_1RACP). that facilitates signal transduction via activation of intracellular kinases. Without this accessory protein, signal transduction would not be possible [5-7] (Figure 1).

Cancer cells are able to produce Interleukin 1 beta in animal models and human cancer cell lines including sarcoma, ovarian cancer and transitional cell carcinoma [3]. Up-regulation of IL-1 beta has also been reported in different types of solid tumors such as breast, lung, colon, head and neck cancers as well as malignant melanoma. It is also considered as a poor prognostic feature in solid tumors [4,9,10].

IL-1 also plays an important role in tumor promotion and metastasis through various mechanisms of action, such as expression of metastatic genes namely matrix metalloproteinases (MMP), excretion of angiogenic proteins, growth factors like VEGF, IL-8, IL-6, TNF $\alpha$ , and tumor growth factor beta [TGF $\beta$ ] from adjacent cells [3,11-13]. Angiogenesis plays a key role in tumor promotion and metastasis and Interleukin 1 indirectly induces neovascularization and angiogenesis through its effect on increasing levels of Vascular Endothelial Growth Factor (VEGF0 [1,3].

Due to its role in tumor proliferation, angiogenesis and

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Cytokine	Structure	Size molecular weight	Receptors	Cell Sources	Cell Targets	Major functions	Disease Associations
IL-1α, IL-1β	Heterodimer	17 kd	IL-1RI, IL-1RII	Macrophages Monocytes Lymphocytes Keratinocytes Microglia Megakaryocytes Neutrophils Fibroblasts	T cells Fibroblasts, epithelial and endothelial cells	Induction of proinflammatory proteins, hematopoiesi, Differentiation of T17 cells	Wide range of autoimmune and inflammatory diseases, RA
IL-1Ra (antagonist)	Heterodimer	16.1-20 kd	IL-1RI, IL-1RII	Monocytes Macrophages Fibroblasts Neutrophils epithelial and endothelial cells Keratinocytes	T cells Fibroblasts, epithelial and endothelial cells	Induction of proinflammatory proteins, hematopoiesis, Differentiation of T17 cells	Wide range of autoimmune and inflammatory diseases, RA
IL-2	Monomer	15.5 kd	IL-2R	CD4 <sup>+</sup> and CD8 <sup>+</sup> activated T cells, DC, NK cells, NKT cells	CD4⁺ and CD8⁺ T cells, NK and B cells	Proliferation of effector T and B cells	T-cell mediated autoimmune and inflammatory diseases, X-linked severe combined immunodeficiency I
IL-3	Monomer	15 kd	IL-3Rα + β (CD131)	T cells, Macrophages, NK cells	Erythroid Progression, granulocytes, macrophages progenitors, CD34 <sup>+</sup>	Hematopoietic growth factor, activation of basophils and eosinophils	Role of allergic diseases, different types of cancers, lymphocytic and active myeloid leukemias
IL-4	Monomer	15kd	IL-4R type I, IL- 4R type II	T2 cells, basophils, eosinophils, NKT cells	T and B cells	Induction of T 2 differentiation, IgE class switch, upregulation of class II MHC expression on B cells, upregulation of CD23 and IL-4R, survival factor, for B and T cells, role in tissue adhesion and inflammation	Inflammatory and autoimmune diseases (allergy/asthma/diabetes mellitus), chronic lymphocytic leukemia diseases
IL-5	Dimer	15kd	IL-5R	T2 cells, activated eosinophils, NK and NKT cells, CD 4 <sup>-</sup>	Eosinophils, basophils, mast cells	Differentiation and function of myeloid cells, increment of chemotactic activity and adhesion capacity on eosinophils, remodeling and wound healing	Allergy/ Asthma/hypereosino- philic Syndrome
IL-6	Homodimer	19-26kd	IL-6R (IL-6R) gp 130	Endothelial cells, fibroblasts, monocytes/macrophages	Hepatocytes, leukocytes, T cells, B cells, hematopoietic cells	Liver: Synthesis of acute phase proteins; leukocytes trafficking, activated T cell; differentiation production of IgG, IgM, IgA hematopoiesis	Autoimmune diseases, chronic inflammatory disease, B-cell malignancy, SLE, Castleman disease, Multiple myeloma
IL-7	Monomer	25kd	IL-7R	Epithelial cells, keratinocytes, DCs, B cells, and Monocytes/ macrophages	B,T and NK cells	Proliferation of cells (mice), megakaryocytes, maturation, recombination, naïve T cell survival, Synthesis induction of inflammatory mediators in monocytes	Allergy/autoimmunity
IL-8	Homodimer	16kd	CXCR1 and CXCR2	Monocytes, macrophages, neutrophils, lymphocytes,endothelial cells, epithelial cells, fibroblasts, keratinocytes,	Neutrophils, NK cells, T cells, basophils, eosinophils, endothelial cells	NK cells, T cells, basophils, eosinophils, mobilization of hematopoetic stem cells, angiogenesis	Increased levels during inflammatory diseases (RA, Psoriasis, bacterial and viral infection)
IL-9	Monomer	14kd	IL-9R	T, 2, T, 9 mast cells and eosinophils	B, T and mast cells	T and mast cells growth factor, inhibition of T1 cytokines, proliferation of CD8 <sup>+</sup> T cells and mast cells, IgE production, chemokine	Helminth infection, Hodgkin, lymphoma, asthma, food allergy

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IL-10	Homodimer	20.5 kd Predicted size of precursor proteins; 18.6 kd, predicted size mature proteins, monomer	IL-10R1/IL-10R2 complex	T cells, B cells, monocytes, macrophages, DCs	Macrophage, monocytes	Immune suppression	Cancer, autoimmunity, allergy
IL-11	Monomer	19kd	IL-11Rα	Stromal cells, fibroblasts, epithelial cells, endothelial cells, vascular smooth muscle cells,	Myeloid	Growth factor for myeloid	Increased during allergic Asthma
IL-12 (p35/ p40)	Heterodimer	IL-12a p35, 35 kd, IL-12b p40, 40 kd	IL-12Rb1 and 12 Rb2	Monocytes, macrophages, neutrophils, microglia, DCs, B cells	T cells (Th1 cells), NK cells	Induced T cell differentiation and cytotoxicity	Impaired T1 exposed with higher susceptibility to intracellular pathogens, use as anticancer agents
IL-13	Monomer	10 kd	IL-13R1α1 and IL-13R1α2	T, NKT and mast cells, basophils and eosinophils	B cells, Mast cells, epithelial cells, eosinophils, smooth muscle cells, and macrophages	Switching to IgG4	Ashtma, allergic , rhinitis, fibrosis
IL-14	Monomer	53kd	IL-14R	T cells, T-cell clones, B-lineage and T-lineage lymphoma cell lines	B-cells contain leukemia cells	Proliferation of activated B cells	Autoimmunity, Lymphoma genetics
IL-15	Monomer	14-15 kd	IL-15R	Monocytes, activated CD4 <sup>+</sup> T cells, keratinocytes, skeletal muscle cells	T, NK and NKT cells	T cell activation proliferation and activation of NK cells, differentiation of T cells, Suppression of IL-2 induced, NK and NKT cells	Autoimmune and inflammatory diseases
IL-16	Heterodimer	56 kd	CD4	T cells, Eosinophils, mast cells, monocytes, DCs, fibroblasts, epithelial cells	T cells, monocytes, macrophages eosinophils	Chemotaxis, Modulation of T-cell response	Increased during various inflammatory and infectious diseases
IL-17A	Cytokine knot, Homodimer or heterodimer	35kd	IL-17RA	CD8 <sup>+</sup> , T cells, NK cells, NKT cells, neutrophils	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages	Induction of proinflammatory cytokines, chemokines	RA, MS, IBD, Psoriasis, allergic asthma, atopic dermatitis, contact hypersensitivity
IL-17B,C,D	Cytokine knot, Homodimer	41 kd, 40 kd, 52 kd	For IL-17B, IL- 17RB, (-IL-17H1, IL 25R) for IL- 17Cand D not known	IL-17B: neuronal cells, chondrocytic IL-17C, immune cells under certain conditions, IL-17D, resting B and T cells	Monocytes, endothelial cells, myofibroblasts	Induction of preinflammatory cytokines, chemokines, and metalloproteases; IL-17B Chondrogenesis and osteogenesis	RA, allergic asthma, inflammatory cardiomyopathy
IL-17F	Cytokine knot, Homodimer or heterodimer	44 kd	IL 17RA (-IL 17R) and IL- 17RC	T <sub>k</sub> 17 cells, CD8 <sup>+</sup> , T cells, NK cells, NKT cells, neutrophils	Endothelial/epithelial cells, fibroblasts, osteoblasts, monocytes, macrophages	Induction of proinflammatory cytokines, chemokines,	HBD, Psoriasis, allergic asthma
IL-18	Heterodimer	22.3 kd	IL-18R	Wide range of cells, mainly macrophages, kupffer cells, keratinocytes, osteoblasts, astrocytes, DCs	Variety of cells, T cells, NK cells, macro- phagesepithelial cells, chondrocytes	Induction of IFN- $\gamma$ in presence of IL-12, enhances NK cells cytotoxicity, promoting $T_{a}^{1}$ or $T_{a}^{2}$ - cell responses	Autoimmune diseases or inflammatory disorders, RA, Psoriasis, MS, type diabetes
IL-19	Monomer	20.5 kd Predicted size of precursor; 17 kd; predicted size of mature protein; 35-40 kd, found in transfected cells, glycoxylated	IL 20R1/IL-20R2	Monocytes, keratinocytes, airway epithelial cells and B cells	Keratinocytes	Unknown	Psoriasis

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IL-20	Monomer	20 kd, predicted size of precursor; 17.5 kd, predicted size of mature protein	IL-20RI/II 20 R2 and II-22R1/IL	Monocytes, Keratinocytes Epithelial and endothelial cells	KeratinocytesMono- cytes	Role in skin biology	Psoriasis, RA
IL-21	4-Helix bundle, monomer	15 kd	IL-21R	T cells, NKT cells	CD4 <sup>+</sup> T cells, CD8 <sup>+</sup> T cells, B cells, DCs, MacrophagesKerati- nocytes	Regulation of proliferation, differentiation, apoptosis, antibody isotype balance, cytotoxic activity	Cancer, SLE, RA
IL-22	6-Antiparallel α-helices, Monomer	23 kd	IL-10R2 Chain and IL-22R1 chain	Activated T cells, NKT cells (NK-22)	Tissue cells like keratinocytes subepithelial myofibroblast	Pathogen defense, wound healing, tissue regonization	Psoriasis, IBD, Cancer
IL-23 (P19⁺)	Heterodimer	IL-12b p40, 40 kd; IL-23 p19, 19 kd	IL-12Rb1 and IL-23R	Macrophages, activated DCs	T cells and macrophages	Stimulate production of proinflammatory IL-17 and promote memory T cell Proliferation	Susceptibility to extracellular pathogen, Organ specific autoimmune inflammation
IL-24	Homodimer and monomer	23.8 kd, pre- dicted size of unprocessed precursor; 18 kd; unglycox- ylated mature protein	IL20R1/IL 20R2 and IL-22R1/IL 20R2	Melanocytes, T cells, Monocytes	Cancer cells	Tumor suppression	Melanoma, Psoriasis
IL-25 (IL-17E)	Homodimer	17kd	IL-17RA and IL-17RB	T <sub>a</sub> 2 cells, mast and epithelial cells, eosinophils and basophils from atopic individuals	$T_{a}^{2}$ memory cells	Induction of T <sub>a</sub> 2 responses, IgE, IgG, IL-4, IL-5, IL-13 and IL-9 production	Gastrointestinal disorders, Asthma
IL-26	6α-Helices, homodimer	38 kd	IL-10R2 chain and IL-20R1 chain	Activated T cells, NKT cells	Epithelial cells	Activation and regulation of epithelial cells	IBD
IL-27 P28+EB13)	Heterodimer	IL-27a p28, 28 kd; IL-27b, EB13, 25.4 kd	WSX-1	Activated DCs, macrophages, epithelial cells	T cells, NK cells	Induction of the promoting $T_{\alpha}$ 1-cell differentiation, inhibition of $T_{\alpha}$ 17-cell response via STAT1	Immune pathology because of uncontrolled inflammatory response
IL-28A/B/ IL-29	Monomer	IL-28A, 22.3 kd, IL-28B, 22.2 kd; IL-29; 21.9 kd	II-28R1/IL-10R2	Monocyte derived DCs	Most cell types	Antiviral immunity	Role in allergic and autoimmune diseases
IL-30 (p28 subunit of IL-27)							

Table 1: Known Cytokines, their old names and equivalent abbreviations and their gene location [16].

metastasis, anti-interleukin -1 agents are theoretically considered to be effective in cancer treatment. However, animal model just shows partial tumor regression in response to anti IL-1 treatments and long term benefit of antagonizing IL-1 in cancer is questionable. Some challenging facts against its therapeutic role in cancer include the rapid regeneration potential of IL-1 receptors and presence of these receptors in all different cells throughout the body except for red blood cells [1,12]. Kineret, an IL-1 receptor antagonist that is structurally similar to IL-1Ra has been successfully used as a treatment modality for inflammatory disorders such as severe rheumatoid arthritis in selected cases [14].

# Interleukin 2

IL-2 is a single chain peptide structure that is produced by T lymphocytes and to a less extent by natural killer (NK) and dendritic (DC) cells [15]. When a helper T cell binds to APC through CD28 and B7, CD4<sup>+</sup> cells produce IL-2. This cytokine itself supports the proliferation and differentiation of any cell that has high-affinity IL-2 receptors [16]. There are several factors enhancing the IL-2 driven T

cell activation such as IL-2 concentration, IL-2 receptor density and duration of this IL-2 /IL-2receptor interaction [17].

Interleukin 2 receptor contains three different subunits; the ligand specific alfa chain or IL-2R alfa (CD25), the beta chain or IL-2R beta (CD 122 That is also a part of IL- 15 receptor complex), and the common gamma and based on the arrangement of these subunits the affinity of the IL-2 receptor would be different [18]. The monomeric IL-2R possesses low affinity, the dimeric IL-2R has an intermediate affinity and the trimeric IL-2R has high affinity. IL-2R beta and common gamma subunits are also members of the hematopoietic superfamily of interleukin receptors and are involved in cytokine signaling pathway of other members of the interleukin family, including IL-4, IL-7, IL-9, IL-15 and IL-21 [19-22]. Alfa subunit of the IL-2 receptor which is also called TAC (T cell activator) receptor is just expressed on active and not resting lymphocytes. The presence of both beta and gamma subunits of the IL-2 receptor are necessary for signal transduction via receptor [23-25].

Activation of T cells in the absence of IL-2 might not be possible.

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Resting T lymphocytes (unstimulated) belonging to either the CD4<sup>+</sup> or the CD8<sup>+</sup> subsets possess few high- affinity IL-2 receptors, but following stimulation with specific antigens, there is a substantial increase in the number of these receptors leading to increase population as well as activation of both CD 4<sup>+</sup> and CD 8<sup>+</sup> T lymphocytes. IL-2 also increases the effector function of NK cells.

IL-2 enhances the ability of the immune system to kill tumor cells and may also interfere with the blood flow to the tumors. Interestingly, IL-2 knockout mice produce a wide range of autoantibodies and many die of autoimmune hemolytic anemia, which suggests that it plays a role in immune tolerance. This role is supposed to be the effect of IL-2 on T regulatory cells similar to activation of helper and cytotoxic T lymphocytes [19-21].

Figure 2 shows the correlation between subunits of the IL-2 receptor and its signaling pathway. Both IL-2Rbeta and gamma subunits are activated through phosphorylation. IL-2 stimulation leads to binding of Jak3 to the gamma chain, phosphorylation of the gamma chain, and the subsequent phosphorylation of tyrosine kinase residues in the beta chain by the gamma chain [26-28]. These newly phosphorylated sites on the beta chain act as docking sites for the signal transducers and activators of transcription (Stat) proteins, which then either homo- or 1 dimerize and translocate to the nucleus to induce gene transcription [29]. This is a common occurrence in Stat activation via cytokine receptors. Studies show that other anti-apoptotic survival pathways such as Ras/Raf/Mek/Erk and PI3K/Akt are also activated in a similar way through IL-2 beta and gamma subunits [30,31].

Studies have shown a correlation between soluble interleukin 2 receptor (sIL-2R) levels that is a circulating form of membrane receptor expressed on the surface of lymphocytes and cancer cells with chronic inflammatory and infectious diseases like Tuberculosis and Autoimmune disorders [32,33]. Similar studies in various solid tumor cases have also shown sIL-2R to be an adverse prognostic feature, especially in patients with nasopharyngeal cancer [34,35], colorectal cancer [36,37], breast cancer [38], ovarian cancer [39-41], gastric cancer [42,43], lung cancer [44,45] and leukemia [46,47], respectively.

IL-2 has been introduced as a cancer treatment since 1992. It was first administered for malignant melanoma and renal cell carcinoma with approximately 7% long lasting reported complete response rate. However, this treatment modality, although effective has significant adverse events resulting from cytokine release and activation of immune response and needs to be administered in specialized centers supervised by trained medical professionals [48,49].

Other clinical application of IL-2 is the monoclonal antibody targeting alfa subunit of IL- 2R. Daclizumab is a humanized form of this antibody and Basiliximab is the chimeric mouse- human form that are both used as a therapeutic option in selected cases of autoimmune disorders, multiple sclerosis and prevention of graft rejection in solid organ transplant [50,51].

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Combining cancer vaccines with interleukin 2 has also been applied in some clinical trials, especially in cases of metastatic/recurrent malignant melanoma due to enhanced activity of the immune system resulting from interleukin 2. However, long term added benefits of these combination modalities need to be evaluated in large phase III clinical trials with adequate duration of follow up [52].

# Interleukin 3

Interleukin 3 that is also named as multi lineage colony stimulating factor is produced by activated T lymphocytes as well as mast cells. Similar to other growth factors, IL-3 induces growth and differentiation of nearly all hematopoietic cells from multi potential stem cells to differentiated neutrophils, eosinophils, megakaryocytes, macrophages as well as lymphoid and erythroid cells [53].

Interleukin 3 receptor has also two subunits; alfa chain and beta chain. These subunits, while activated, induce JAK2/STAT5, c-myc [cell-cycle progression and DNA synthesis]., and the Ras pathway (suppression of apoptosis), similar to the proposed function of GM-CSF [54]. The beta subunit of IL-3 receptor also shares similar structure with GM-CSF and IL-5 that might partially explain the similar

function of GM-CSF and IL- 3 as a growth and differentiation factor in hematopoietic cells [55].

Based on these similarities as well as the key role of IL-3 as a growth factor, after it's cloning in 1986, various clinical trials have been designed to validate in vivo potential of recombinant human (rhIL-3). Preliminary data from phase I/II studies of IL-3 at a dose of 5-10  $\mu$ g/kg subcutaneously daily for 5-10 days in patients with both hematologic malignancies as well as solid tumors such as lymphoma, small-cell lung cancer, breast cancer and ovarian cancer showed that post-chemotherapy administration of IL-3 reduces chemotherapy delays with resultant earlier hematological recovery after combination chemotherapy. However, these results were not confirmed in phase III studies. The role of IL-3 alone in the treatment of marrow failure or dysfunction syndromes such as Myelodysplastic syndromes (MDS), aplastic anemia (AA) was not found to be effective and successful [55].

As a hematopoietic and non- hematopoietic growth factor, IL-3 stimulation has been reported to induce proliferation of tumor cells in colorectal adenocarcinomas, bladder, and lung cancers. It has also been detected on the surface of malignant B cells in 40% of patients with B-cell acute lymphocytic leukemia or acute myeloid leukemia. In these

patients, the increased expression of IL-3R $\alpha$  has been associated with enhanced proliferation of malignant clone, increased cellularity, and poor prognosis [56].

## Interleukin 4

Interleukin 4 is a monomer peptide mainly produced and secreted by type 2 of T helper lymphocytes, basophils, mast cells and eosinophils. It also has 2 different receptors; IL- 4 RI which contains two chains and binds specifically to IL-4 and IL-4 RII which is able to bind to both IL-4 and IL-13. Interleukin 4 receptor type I contains two chains; alfa chain (IL-4R alfa) and the common gamma chain that is a common part in all IL-2 family members. Interleukin 4 receptor type II on the other hand, contains alfa chain and IL- 13R alfa chain that explains its ability to bind to both IL-4 and IL-13, respectively [15].

IL-4 is considered as a regulating cytokine in proliferation, differentiation, and apoptosis of different haematopoietic and non-haematopoietic cell lineages, including myeloid, mast, dendritic, endothelial, muscular, and neuronal cells [57-59]. Th2 cell differentiation that is induced by IL-4 is an essential step of immune responses against parasitic infections [60]. IL- 4 and its associated pathway is also important in the development of allergic [62] and autoimmune diseases [62].

Similar to other members of interleukins such as interleukin 2, exposure of cells to IL-4 results in the activation of JAK1 and JAK3 [31,32] that is shown to be resulted from their association with IL-4R chains; JAK1 associates with the IL-4R $\alpha$  chain while JAK3 associates with the common gamma chain [63]. The process of JAK activation also is accompanied with their cross phosphorylation that in turn would lead to phosphorylation of specific tyrosine residues within IL-4 receptor alfa and initiating intracellular activation. The final step is the activation of STAT6 that migrates into the nucleus [64,65]. Figure 3 shows the mechanism of activation of STAT [Signal Transducer and Activator of Transcription]. 6 mediated by IL-4.

From a clinical point of view, interleukin 4 has been considered to play an important role in asthma and other allergic reactions. This fact is based on the crucial role of type 2 helper T lymphocytes and STAT 6 allergic reactions such as asthma, atopic dermatitis and systemic anaphylaxis [61]. Unlike allergic reactions, IL-4 is supposed to act as an anti-inflammatory cytokine in autoimmune disorders. The main reason for this suggested anti-inflammatory role comes from the fact that autoimmune disorders are generally based on abnormal activation of type 1 helper T lymphocytes and IL-4 inhibits T h type 1 formation through induction of proliferation and maturation of T0 helpers toward type 2 helper T cells. Another possible inhibitory role of IL-4 in autoimmune disorders also comes from its ability to decrease the production of pro inflammatory cytokines from monocytes as well as induction of anti-inflammatory mediators such as IL-1R antagonists and TNF alfa soluble receptors [66].

Role of interleukin 4 in cancer is more complicated. IL-4 is known as a potent anti- apoptotic agent based on studies in colon, breast, lung, fibrosarcoma, prostate and bladder cancer models [57,59]. Similar data suggest that IL-4 is produced by many cultured tumor cell lines, and its interaction with IL4-R\_ leads to the up-regulation of antiapoptotic molecules such as cFLIP, PED, FLAME-1 and Bcl-x (L). This anti-apoptotic effect can be abrogated by neutralizing IL-4 antibodies, and is dependent upon downstream STAT-6 signaling [67-70]. On the contrary, there is some experimental evidence that show addition of IL-4 at high concentrations to breast and colorectal cancer cell lines results in inhibition of growth [73]. Despite this observation, clinical studies with interleukin-4 in indolent B cell lymphoproliferative disorders was not shown to be beneficial for most cancer patients [72].

# Interleukin 5

IL-5 was first described as eosinophil and B-cell growth factor in 1987 [73]. It has a major role in maturation, proliferation, and activation of eosinophils and most of tissue damage caused by as asthma as well as other eosinophilia related disorders is believed to be resulted from





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Il-5 [74]. Similar to other members of interleukin family, IL-5 receptor contains two subunits of alfa and beta. Alfa subunit contains an extracellular (soluble) domain, is IL-5 specific and has the capability of binding to IL-5 independently without the need for beta unit. Beta chain, on the contrast, shares similar structure with beta unit of other cytokines namely GM-CSF and interleukin 3 but it is necessary for activation of signal transduction [75,76].

Similar to other interleukins, IL-5 signaling contains Jak/STAT, MAPK, and PI3K pathways. Activation of STAT1 and 5 has a key role in the proliferation and differentiation mediated by IL-5. This step is activated following Jak/STAT phosphorylation of Jak1 and Jak2 after heterodimerization of the IL-5 receptor, respectively. Similarly, activation of TCF/ERK/ MAPK pathway, leads to cytokine-induced proliferation and preventing apoptosis of eosinophils by upregulation of genes encoding for bcl-2 and bcl-x. Other signaling pathways that are activated by IL-5 include JNK pathway as well as PI3K- mediated signaling via Akt/PKB. Anti-apoptotic role of IL-5 has been suggested in the latter pathway [77-79].

There are reports in bladder cancer cell lines suggesting IL-5 increase migration and MMP-9 expression via activation of transcription factors NF- $\kappa$ B and AP-1 [80].

Considering the role of eosinophils in asthma and other allergic reactions and IL-5 as a potent activator of eosinophil proliferation and differentiation suggests a therapeutic role for IL-5 antagonists in severe allergic asthma and other eosinophilic associated pathologies such as hypereosinophilic syndrome and eosinophilic vasculitis. To date, two anti-IL-5 monoclonal antibodies have been developed; Mepolizumab and Reslizumab. Both are under phase I /II clinical trials for allergic asthma and other hyper eosinophilic disorders such as hypereosinophilic syndrome and Churg Strauss vasculitis [81-83].

#### Interleukin 6

IL-6 was primarily supposed to have interferon like activity and was named as B cell differentiation factor, but further studies showed its role as a multifunctional cytokine that regulates immune responses, the acute-phase response of the liver, hematopoiesis, and inflammation. Interleukin 6 is a member of a family which contains other cytokines namelyIL-11, leukemia inhibitory factor (LIF), ciliary neurotrophic factor, oncostatin-M [OSM] and neurotrophin-1/B cell-stimulating factor-3 [84].

IL-6 is produced by many cells, such as T cells, B cells, granulocytes, smooth muscle cells, eosinophils, chondrocytes, osteoblasts, mast cells, glial cells, and keratinocytes in response to stimulation. However, during systemic inflammation various stimuli are able to trigger other cells, such as to act as the main source of this cytokine. Bacterial lipopolysaccharides, and other cytokines like IL-1 alfa, TNF alfa, Interferon gamma and GM-CSF is also considered to be stimulators of monocytes/macrophages in IL-6 production and corticosteroids are able to inhibit its release. Human fibroblasts secrete IL-6 on stimulation with IL-1 $\alpha$ , bacteria/yeast, TNF alfa, and IFN alfa. The main cellular targets of IL-6 are hepatocytes, leukocytes, T cells, B cells, and hematopoietic cells [15].

Similar to other members of interleukin family, interleukin 6 receptor contains two different parts; IL-6 alfa chain receptor and gp 130. IL-6 binds first to its cognate alfa- chain receptor (IL-6R). with low affinity, and then the complex binds to the signal- transducing molecule gp130 to form a high-affinity, functional hexameric receptor complex of two IL-6, IL-6R, and gp130 hetero-trimers [85]. Figure



Figure 4: IL-6 signaling is mediated by a unique receptor system that consists of two functional membrane proteins: an 80 kDa ligand-binding IL-6R together with a 130 kDa signal-transducing chain, gp130. A soluble form of IL-6R that lacks the cytoplasmic domain is also observed in normal serum. This soluble receptor is an agonist that is capable of transmitting signals via trans-signaling. The binding of IL-6 to either the membrane-anchored or soluble form of IL-6R can mediate IL-6 signaling into cells, as long as gp130 is expressed (which occurs ubiquitously in vivo). In chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, IL-6 trans-signaling is critically pathologically involved. Receptor activation facilitates transphorylation and activation of JAKs. Subsequently, the gp130 tails are phosphorylated, which mediates the recruitment of the STAT3 proteins. Dimerization of activated (phosphorylated) STAT3 is followed by nuclear entry. Within the nucleus, STAT3 can enhance the transcription of many genes, including those that encode acute-phase proteins.STAT3 also upregulates the transcription of genes encoding the SOCS3 proteins—intracellular negative-feedback factors that inhibit the JAK–STAT pathway [88].

4 summarizes the structure of the IL-6 receptor and its signaling pathway [86].

Once homodimerization of gp 130 into IL-6R and IL-6 has been established, intracellular signaling is subsequently activated through gp130-associated cytoplasmic tyrosine kinases (JAK1, JAK2, and TYK2) and phosphorylation of STAT1 and STAT3. Interleukin 6 also activates the Ras-Raf signaling cascade, which regulates phosphorylation of MAP-kinase and ultimate activation of the transcription factors NF-IL-6 (a C/EBP family member) and AP-1 (c-Jun and c- Fos) [87,88].

One of the essential roles of IL-6 is the promotion of inflammatory reactions through the expansion and activation of T cells, differentiation of B cells, and the induction of acute-phase reactants by hepatocytes. However, there are studies that have shown an anti-inflammatory role for IL-6 acting as a protective mechanism during disease. The suppressive effect of IL-6 on acute neutrophil accumulation during septic shock is an example of this anti-inflammatory response. One explanation for this anti-inflammatory response might be supporting the findings of studies showing that IL-6 down-regulates pro-inflammatory cytokine expression while simultaneously inducing the expression of IL-1 receptor antagonist and the soluble p55 tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) receptor [89-92].

Based on the wide spectrum of the cells that produce IL-6 and cells that has been affected by this cytokine, IL-6 plays an important role in many inflammatory and autoimmune disorders, even myocardial infarction and Alzheimer disease. Moreover, there are several studies that show over-activity of IL-6 in almost all different types of cancer. Aberrant activation of IL-6 pathway has been reported in several types of solid tumors such as prostate, breast, ovarian and lung cancer as well as hematologic malignancies like multiple myeloma, leukemia and lymphoproliferative disorders, respectively [93-96]. Figure 5 represents the different roles of IL-6 [97].

Multipotential nature of IL-6 may attribute several roles in cancer promotion such as cancer cell development, proliferation, and differentiation, as well as migration, invasion, apoptosis, and angiogenesis in tumors. For example, IL-6 aids tumor growth by inhibiting cancer cell apoptosis and inducting tumor angiogenesis, and contributes to the proliferation of colorectal cancer cells and other cancers, especially at the advanced stage of development. IL-6 has also enhanced endothelial cell migration, which is basically the cornerstone of angiogenesis, and sequentially dissemination of solid tumors. The direct stimulating role of IL-6 in hematological malignancies has been studied in specific T cell and B cell lymphoproliferative disorders as well as multiple myeloma, and AIDS associated Kaposi sarcomas [98-103]. Studies on both solid tumors and hematological malignancies have shown a correlation between increased interleukin 6 levels and active disease states as well as poor prognosis, advanced clinical stage and shorter duration of survival [97]. These observations suggest a potential therapeutic role for anti-IL-6 based treatments such as monoclonal antibodies. Interestingly, there are other studies that suppose anticancer activity of IL-6 through promotion of the antitumor activity in macrophages, production and activation of lymphokine-activated killer cells, and anti-apoptosis activity in neutrophils that may increase their cytotoxic effect on tumor cells. Increased IL-6 mediated production may also indirectly influences the binding of this protein to phospholipids on tumor cells, activating C1q of the complement system, and complement mediated tumor lysis. However, the tumor promoting activity of IL-6 has been shown to be more potent than its anti-tumoral role [97].



Based on the role of IL-6 in both solid tumors and hematologic malignancies, monoclonal antibodies against IL-6 have been investigated for the past two decades on cancer patients through phase I and II clinical trials. Although these monoclonal antibodies showed to be active by reducing levels of IL-6 and CRP in patients, their clinical benefit in providing clinical remission/response was limited. However, cancer patients might benefit from their effect on subsiding inflammatory mediators that are responsible for cancer associated symptoms such as fatigue and anorexia that may indirectly have a negative impact in survival and quality of life [97].

Siltuximab, a chimeric human- murine anti-IL-6 monoclonal antibody has recently been approved for treatment of Castleman's disease in HIV negative and HHV-8 negative patients and a phase II clinical trial on its efficacy and safety in smoldering multiple myeloma is still ongoing [104].

### Other interleukins

Apart from the interleukins discussed above, there are other members of interleukin family that are involved in cancer development and promotion namely interleukin 9, 10, 12, 15, 21, 22 and 24.

Interleukin 9 is a T cell derived cytokine with proliferative effect on activated and transformed T lymphocytes. It also promotes the immunoglobulin production by B cells and shows proliferative and differentiation effect on mast cells and erythroid progenitors [105-108]. Interleukin 9 receptor, similar to interleukin 2 receptor has 2 components, interleukin 9 receptor alfa chain and common gamma chain. Moreover, cross phosphorylation of Janus kinase 1 (Jak 1) and 3 through the IL-9 receptor leads to activation of STAT 1, STAT 3 and 5 with resultant final gene transcription induction in a similar way with other interleukins [110]. Insulin like growth factors, RAS-mitogen activated protein kinase (MAP kinase) activation are subsequently triggered by STATs although physiological requirements for this activation are not fully understood [110].

There are several investigations suggesting a correlation between poor prognostic features in Hodgkin's Lymphoma such as advanced stage, presence of B symptoms [including fever plus either more than 10% weight less or drenching night sweats], low hemoglobin level and elevated erythrocyte sedimentation rate and interleukin 9 levels [111]. Similarly, there are studies representing the role of IL-9 overexpression in thymic lymphomas in mice, and the association between IL-9 production and HTLV-I transformed T cells in humans [112].

IL-9 has shown to play an important role in pathogenesis of allergic reactions and asthma through several mechanisms. These mechanisms include activation of mast cells. IL-9 also induces the release of Th2-associated chemokines in cultured human airway smooth muscle cells [113] and enhanced the stem cell factor-dependent growth of human mast cell progenitors, particularly those of children with asthma.

MEDI-528 is a humanized immunoglobulin G1 monoclonal antibody that binds to IL-9, and hence reduces the activity of a variety of cell types implicated in asthma pathogenesis [113,114]. Despite available phase I and II clinical trials on safety and efficacy of this anti-IL-9 antibody in severe uncontrolled asthma, its clinical application and benefit in hematologic malignancies was not identified.

Interleukin 10 is a cytokine with known anti-inflammatory properties that is supposed to act as a potent suppressor preventing against autoimmune disorders [115]. It is produced by many cells, but macrophages are considered its main source. IL-10 regulates

differentiation and proliferation of immune cells, such as T and B lymphocytes, Natural Killer cells, Antigen presenting cells, mast cells and neutrophils. Despite its effectiveness as a main anti-inflammatory cytokine, recent studies suggest an immune stimulatory role for IL-10 augmenting in eradication of infections [116]. IL-10 receptor is composed of two different chains, alfa and  $\beta$  (CRFB4) both chains are members of the class II cytokine receptor family. The IL-10/IL-10R interaction activates the tyrosine kinases Jak1 and Tyk2, which are associated with the IL-10R1 and IL-10R2, respectively. The receptor engagement and tyrosine phosphorylation activates the cytoplasmically localized inactive transcription factors STAT 1, 3, and 5, resulting in translocation and gene activation [117].

Anti-inflammatory role of interleukin 10 analogues has clinically been evaluated in patients with autoimmune disorders such as psoriasis, rheumatoid arthritis, chronic hepatitis and AIDS, inflammatory bowel disease as well as a cytokine release control agent in solid organ transplant recipients after anti T lymphocyte treatments [116].

The role of IL-10 in cancer is even more complicated. Dual effects of immune suppression and immune stimulation of this cytokine has been observed in different studies. To date, no clinical indication for interleukin 10 analogues has been proposed in cancer [118].

Interleukin 12 is produced by antigen presenting cells, dendritic cells and macrophages. It is the most potent known stimulus for IFNgamma production by resting and activated T cells and NK cells. It also enhances proliferation of activated T cell and NK cells and their cytolytic activity. Several cytokines, including tumor necrosis factor a (TNF-a), IL-1, IL-2 and IL-15, can act synergistically with IL-12 to stimulate IFN-gamma secretion [119,120]. IL-12 has been shown to stimulate in vitro anti tumoral activity of lymphocytes from cancer patients and shows in-vivo anti tumoral activity in murine models [121]. Clinical responses to IL-12 treatment have been reported in many types of tumors, such as cutaneous T cell lymphoma, non-Hodgkin's lymphoma, melanoma, renal cell carcinoma, and gastrointestinal carcinoma [122-127]. However, the IL-12 clinical application has been complicated with severe systemic toxicity caused by this cytokine [128,129]. Alternative approaches, including local administration of recombinant IL-12, application of IL-12 gene-modified tumors, fibroblasts, or dendritic cells, or local injection of recombinant viruses expressing IL-12, have been proposed to enhance the IL-12 activity to the tumor site, with the goal of reducing systemic toxicity [130-136]. Anti-tumoral activity of IL-12 is mediated through its role in interferon gamma production as well as inhibition of angiogenesis. This anti-angiogenesis has been mediated through down- regulation of pro-angiogenic gene vascular endothelial growth factor (VEGF)-C, as well as the pro-angiogenic proteins, VEGF and basic fibroblast growth factor (BFGF) on tumor cells and supporting fibroblast cells. CD8+ T lymphocytes and NK cells have shown to contribute to this anti-angiogenesis effect on some models, especially by direct endothelial cell directed toxicity and cytolysis [137,138].

Both human and murine recombinant IL-12 are available and has been tried in phase I and II clinical trials in different types of solid tumors and hematologic malignancies both as single agents and as a part of combination treatment. Breast cancer, epithelial ovarian cancer and gastrointestinal malignancies are among the tumors that IL-12 has been tried either alone or combined with other chemotherapeutic agents. Both indolent and aggressive lymphoproliferative disorders were also investigated. However, adverse events such as constitutional symptoms, fever, heart and liver dysfunction and gastrointestinal toxicities are among the important reported toxicities in phase I/II clinical trials, respectively.

Interleukin 15 is known as T cell growth factor and it shares many common properties with IL-2. Both IL-15 and IL-2 receptors contain common gamma chain as well as IL-2R beta chain and JAK 1/JAK3/STAT5 acts as a common signaling pathway for both of these cytokines. Their function shares some similarities; they stimulate T cell proliferation, induce cytotoxic T cells and NK cells, and stimulate immunoglobulin production of B lymphocytes [139-140]. IL-15 also acts as an anti-apoptotic agent in neutrophils and mast cells, modulates their phagocytosis and stimulates the secretion of IL-8 and IL-1R antagonist [142].

Apart from hematologic cell lines, IL-15 has also been shown to affect non- hematological cells, including myocytes, adipocytes, endothelial and neural cells. IL-15 has an anabolic effect on muscle and may support muscle cell differentiation. Similarly IL-15 induces growth and survival in microglial cell. This effect might reduce or even stop the process of muscle wasting secondary to cancer cachexia. IL-15 also stimulates angiogenesis [143-145].

IL-15 is a potent stimulator of both T cells and B cells, which is able to start and maintain inflammation. It also stimulates angiogenesis, halt apoptosis and specifically induces proliferation of NK, T and B lymphocytes. Animal studies have shown proliferation of CD8+ T cell lymphoma cell lines to be enhanced by L-15. These facts suggest that IL-15 may act as a cancer development stimulator in leukemia and lymphomas originating from B cell, T cell and NK cell. Observations such as activated of expression of IL-15 and IL-15R alfa by viral Tax protein in HTLV 1 associated T cell leukemia/lymphoma as well as association of IL-15 expression with mediastinal lymphadenopathy in acute lymphoblastic leukemia (ALL) and poor prognosis and inferior 5 year survival in B cell type ALL and higher risk of CNS relapse in pediatric ALL further supports that IL-15 may act as a cancer development cytokine in hematological malignancies originating from lymphoid cell lines [146,147]. However, observations in solid tumor and cancer cell lines did not show any direct effect of IL-15. Moreover, pro-inflammatory and immune stimulating effects of IL-15 might potentiate immunotherapeutic effects of these treatments such as cancer vaccines and anti PD-1 antibodies [148-150].

From clinical point of view ALT 803 as an IL-15 agonist has been tried in phase I and II clinical trials, both as a single agent and combined with chemotherapeutic agents or vaccines in different types of advanced solid tumors such as malignant melanoma, bladder cancer, and renal cell carcinoma. It has also been under clinical investigation in relapsed hematological malignancies after allogeneic stem cell transplantation.

Interleukin 21 is mainly produced by stimulated CD4<sup>+</sup> T lymphocytes. Moreover, NK cells are also considered another source of this cytokine. IL-21 shares similar structure with both IL-2 and IL-15. Its receptor also contains common gamma chain like other members of this family and activates JAK/STAT signalling pathway in a similar way. B lymphocytes express the highest number of IL-21 receptors. Il-21 has a dual effect on B lymphocytes; it mainly inhibits B cell proliferation and induces apoptosis in the absence of co-stimulatory signals while augments extensive B cell proliferation and differentiation into immunoglobulin G producing plasma cells in the presence of cross linking of both B cell receptor and CD40 [151-153]. IL-21 also co-stimulates antigen-dependent and independent proliferation, expansion, survival, and cytotoxicity of CD8<sup>+</sup> T cells. Furthermore, IL-21 maintains CD8<sup>+</sup> T cell expression of CD28 and increases their IFN-y and IL-2 production, creating a more robust and independent CD8<sup>+</sup> T cell response. IL-21 affects other members of the immune system in different ways; it activates NK cells and macrophages and inhibits dendritic cells [153].

Considering immune activating role of IL-21 and observations in tumor cell lines and animal studies it is concluded that the most anti tumoral activity of this cytokine is believed to be the result of cell mediated cytotoxicity development through NK cells and CD8<sup>+</sup> T lymphocytes as well as B cell induced antibodies directed against tumor antigens. Interferon gamma production also shows anti-tumor effects, however, this role is not supposed to be as strong as cell mediated cytotoxicity [154-156].

Monotherapy with IL-21 has been tried in phase I/II clinical trials in advanced solid tumors such as malignant melanoma, and renal cell carcinoma. It has also showed a synergy effect in combination with other cancer treatments such as monoclonal antibodies, tyrosine kinase inhibitors and even chemotherapeutic agents. However, anti tumoral effects of IL-21 therapy are delayed compared to chemotherapy [153,157,158]. From a safety point of view, IL-21 is well tolerated and the most encountered adverse events have been flue like symptoms such as fever, fatigue and malaise, hematologic toxicity presenting with lymphocytopenia, neutropenia and thrombocytopenia and increased liver enzymes [158].

Interleukin 22 is another member of the interleukin 10 family. It is mainly secreted by helper T lymphocytes, CD8<sup>+</sup> lymphocytes, innate lymphoid cells and NK cells, but during inflammatory process it can be induced by both lymphoid and myeloid cells such as dendritic cells, macrophages and neutrophils. These myeloid sources of IL-22 are suggested as the main source of the cytokine during pathological and regenerative processes in non-hematopoietic tissues such as intestines, lung, kidney, and liver [159-163].

Similar to other members of interleukin family, IL-22 receptor contains two different subunits; IL-22R1 and IL- 10R2. Activation of the IL-22 receptor leads to STAT 1,3,5 signalling followed by nuclear factor kb, MAPK and PI3K-AKT-mTOR pathway activation [160]. Although IL-22 is produced by immune cells, IL-22R1 is selectively expressed on non-immune cells especially smooth muscle cells, thymic epithelial cells, liver stellate cells and myofibroblasts of colonic submucosa [164-166]. IL-22 is a pro inflammatory cytokine with rapid effects on mucosal surfaces against invading pathogens. It also causes proliferation in hepatocytes, and intestinal and respiratory epithelium in response to injury and tissue damage through cell cycle related molecule induction such as Cyclin D 1, Cyclin-dependent kinase 1 (CDK1), BCL-2, and BCL-x [167-171].

The correlation between IL-22 and different types of solid tumors and hematological malignancies have been addressed in different studies. Observations on gastric, colon and pancreas cancer have shown correlation between increased number of IL-22producing T lymphocytes and advanced stage of cancer and its negative impact on patients' overall survival. IL-22 level was also elevated in chemoresistant colon cancer cases [172-174]. Similar observations have been reported in liver cancer, and non-small cell lung cancer [168,175]. Among hematologic malignancies, Mantle cell lymphoma, primary CNS lymphoma and anaplastic large cell lymphoma show a positive correlation between IL-22 level and proliferation index of lymphoma cells along with a negative impact in prognosis [176].

Based on the available basic and observational information anti-IL-22 might be suggested as a targeted therapy in both solid tumors as well as hematologic malignancies. Fezakinumab (ILV 094) is an IL-22 directed human monoclonal antibody that has been tried in phase I/II clinical trials against autoimmune diseases (rheumatoid arthritis and psoriasis) but not in hematologic malignancies or solid tumors.

Interleukin 24 is a member of the interleukin 10 family and primarily known as melanoma differentiation antigen 7 (mda-7). It is mainly produced by activated monocytes and type 2 helper T lymphocytes. Skin, lung, testicle and ovaries are considered as target organs for this cytokine. Proliferation of dermal cells is induced by IL-24 in physiological states. Wound healing is supposed to be the result of this physiologic activity of IL-24. Abnormal activation of migrating monocytes that infiltrate dermal layer and act as a source of IL-24 on the other hand, leads to persistent receptor activation and cell proliferation of keratinocytes and development of psoriasis as a pathology [177-179].

IL-24 shares common receptors with both IL-22 and IL-20. While IL-24 binds to either IL-20R1/R2 or IL-22R1/R2 the signal transduction mediated by JAK/STAT is activated similar to other interleukins. Based on available studies several roles for IL-24 has been proposed and observed. IL-24 can induce other cytokines such as TNF- alfa, Interferon gamma and interleukin 6. These cytokines are considered as a part of inflammation cascade and have specific effects on cancer cells as well as hematologic cell lines [180]. It can also inhibit angiogenesis through its effect on endothelial cells although no receptor expression was clearly demonstrated in these cells [181]. There are also some controversial observations on both anti-apoptosis and proliferative role of IL-24 on IL-3 dependent murine pro B cells vs. its apoptotic and growth inhibitory role in cultured cell lines, respectively [182]. Main proposed anti-tumoral mechanism of IL-24 is inducing apoptosis through several intracellular mechanisms which is independent from IL-24 receptors and JAK/STAT signaling pathways [183].

Unlike other interleukins, the recombinant form of IL-24 doesn't show the apoptotic property of this cytokine, gene engineering technic using adenovirus vectors are the most applicable method that has been applied in preclinical studies [184].

# Conclusion

Advanced knowledge of the immune system and its different aspects has led to extensive basic and clinical studies in immunological based treatment modalities in many inflammatory, malignant and even infectious diseases. As a leading cause of death and morbidity, cancer gains special attention among these different pathologies. Many active and passive immunotherapies for both solid tumors and hematologic malignancies have been proposed and applied. Cancer patients may also benefit from adding interleukins to both conventional and immunologic based treatments due to the variety of their biological functions [185-192]. Interleukins have been tried, both as a single anticancer treatment and as an immunomodulatory for active and passive immunotherapies applying dendritic cells and cancer vaccines. Table 2 summarizes the active clinical trials on interleukins in cancer treatment [193-197].

Interleukins are a heterogeneous family of cellular products that are mainly produced by immune cells, and may affect potentially all types of cells in the body. Their role is not limited to immune reactions and immune cells and proliferation, differentiation as well as angiogenesis and regeneration are mediated by them. Despite differences in their origin and target, most of them follow the similar intracellular activation through JAK/STAT signaling pathway. Immune-modulatory role of interleukins as well as their direct and indirect role in angiogenesis, apoptosis and other cancer development and progression pathways makes them attractive targets for cancer treatment. However, interaction between different molecular pathways, dual action of cytokines, technical problems in the production of interleukins and severe immunological adverse events are the potential problems that would be faced. These limitations as well as the proper sequence or combination of different treatment modalities such as chemotherapy, monoclonal antibodies, cancer vaccines and interleukin based treatments and long term effect of these immunological treatments are among the questions that are not answered yet and need more basic and clinical studies.

ID	Title	IL type	Phase	Age Group
NCI-2009-01064	Isotretinoin With or Without Dinutuximab, Aldesleukin, and Sargramostim Following Stem Cell Transplant in Treating Patients With Neuroblastoma	IL-2	ш	Less than 30
NCI-2012-02900	Entinostat in Combination With Aldesleukin in Treating Patients With Metastatic Kidney Cancer	IL-2	Phase I/ II	18 and over
NCI-2011-03631	Cetuximab and Recombinant Interleukin-12 in Treating Patients With Squamous Cell Carcinoma of the Head and Neck That is Recurrent, Metastatic, or Cannot Be Removed by Surgery	IL-12	Phase I/ II	18 and over
NCT02099539	A Study of ALT-803 in Patients With Relapsed or Refractory Multiple Myeloma	IL-15	Phase I/ II	18 and over
NCI-2011-02498	Aldesleukin With or Without Ziv-Aflibercept in Treating Patients With Stage III-IV Melanoma That Cannot Be Removed by Surgery	IL-2	Phase II	16 and over
NCT01441063	Tocilizumab for KSHV-Associated Multicentric Castleman Disease	Anti IL-6 receptor monoclonal antibody	Phase II	18 and over
NCI-2013-00998	CYT107 With or Without Vaccine Therapy in Treating Patients With Metastatic Hormone-Resistant Prostate Cancer	Recombinant IL-7	Phase II	18 and over
NCI-2014-01306	High-Dose Aldesleukin, and Ipilimumab in Treating Patients With Stage III-IV Melanoma That Cannot Be Removed By Surgery	IL-2	Phase II	18 and over
NCT00072098	Interleukin-12 Gene in Treating Patients With Liver Metastases Secondary to Colorectal Cancer	IL-12 gene therapy	Phase I	Adults
NCT01572493	Continuous Infusion of rhIL-15 for Adults With Advanced Cancer	IL-15	Phase I	18 and over
NCI-2012-02205	Recombinant Interleukin-15 in Treating Patients With Advanced Melanoma, Kidney Cancer, Non-small Cell Lung Cancer, or Squamous Cell Head and Neck Cancer	IL-15	Phase I	18 and over
NCT01946789	A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803 in Patients With Advanced Solid Tumors	IL-15	Phase I	18 and over

Table 2: Active clinical trials on interleukins in cancer patients (189-200).

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