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# IL-12 FAMILY CYTOKINES: GENERAL CHARACTERISTICS, PATHOGENIC MICROORGANISMS, RECEPTORS, AND SIGNALLING PATHWAYS

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Among a wide range of cytokines, the Interleukin 12 (IL-12) family has its unique structural, functional, and immunological characteristics that have made this family as important immunological playmakers. Because of the importance of IL-12 heterodimeric cytokines in microbial infections, autoimmune diseases, and cancers, the authors of this literature discuss about the general characteristics of IL-12 family members, the interactions between IL-12 cytokines and pathogenic microorganisms, the interleukins receptors and their strategies for selecting different signalling pathways. IL-12 and IL-23 are similar in p40 subunits and both are involved in pro-inflammatory responses while, IL-27 and IL-35 contribute to anti-inflammatory activities; however, IL-27 is also involved in pro-inflammatory responses. There are some similarities and dissimilarities among IL-12 family members which make them a unique bridge between innate and adaptive immune systems. The bioactivities of IL-12 family indicate a brilliant promise for their applications in different fields of medicine. The members of IL-12 family are candidate for several therapeutics including gene therapy, cancer therapy, tumour therapy, and vaccination. To have an accurate diagnostic technique and definite treatment regarding to infectious diseases, the playmakers of IL-12 family as effective criteria together with microarray technology are the best choices for current and future applications.

**Keywords:** IL-12, IL-23, IL-27, IL-35

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## Introduction

The term Cytokine is composed of Cyt/o (Cell) and Kin/e (movement) [1]. This term involves a wide range of soluble components such as glycoproteins of monokines, lymphokines, interferon- $\gamma$  (IFN- $\gamma$ ) and interleukins (ILs) which are produced via a vast number of cell types. The secreted proteins of cytokines affect their targets throughout different immunological pathways comprised of apoptosis (programmed cell death/cell suicide), growth, development and differentiation. The activities of cytokines are directly influenced by a series of regulators and feedbacks. The nonstructural proteins of cytokines are categorized in accordance with their biological functions. The majority of cytokines are secreted when an infection/disease is trying to invade the human host and immune system. Therefore, cytokines are recognized as the body's feedback against strangers and stresses [2–7].

According to previous surveys, ILs involve a vast range of structures, functions and diversity to have a considerable role in modulating human immune system responses against undesirable conditions such as infectious diseases, autoimmune diseases and cancers. As a duty, ILs contribute to the processes of differentiation, growth, progression and production of immune cells for protecting host body's from strangers like pathogenic microorganisms including bacteria, fungi, protozoa, helminths and viruses. Besides, the anti-inflammatory and pro-inflammatory activities, allergic reactivities, induction of different types of immune regulations and secretions within the immune cells' system are dominated by ILs. The aforementioned characteristics relating to ILs indicate that, they are capable to influence different generations and types of immune system cells as a powerful defence system against pathogens. The incredible occurrence is that, cytokines are able to distinguish microbial microflora from the other pathogens. These advanced abilities of ILs, represent them as invaluable biological playmakers within the human immune system. There are over than 40 types of ILs with different properties. The IL-12 family members are known as quite distinct cytokines rather than others; because of their unique characteristics of heterodimeric structures [3, 8–13].

The processes of secretion, resolution, activation and termination of cytokines including IL-12 family members are directly in association with transcriptional, post-transcriptional, translational and post-translational factors. These factors determine and programme different regulons including transcriptional, post-transcriptional, translational and post-translational regulons. The transcriptional regulons trigger genes to express mRNA molecules encoding different immunofunctional proteins. So, the process of gene expression regulation is known as transcription. The expression of cytokines such as IL-12 family

members is performed throughout the process of DNA molecules conversion into mRNAs. This process is followed by another step that is considered as a very fine regulated procedure in which the hidden data within mRNA molecules are translated into a vast range of immunological responses such as cytokines secretion. Thus, the transcription phase involves processed mRNAs encompassing caps and polyadenylated tails. It must be considered that, the mRNA molecules are increased in parallel with cytokines secretion [14–16].

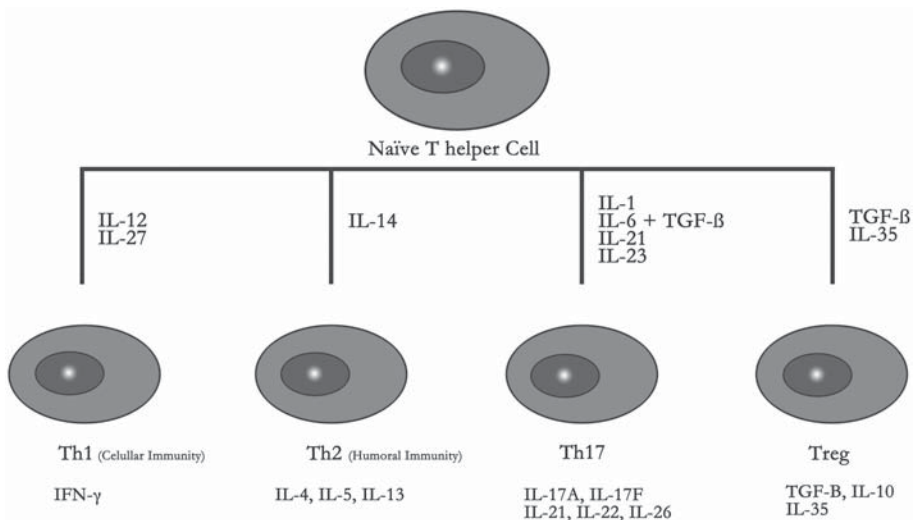
There are some important approaches which control the process of mRNA translation. The presence, and absence of mRNAs and the translation inhibition of mRNA molecules are regarded as particular factors which determine and programme post-transcriptional regulons. So, the post-transcriptional components dominate the process of genes expressions which are relating to immunological reactions. In other word, the post-transcriptional pathway regulates the running mRNA molecules from nucleus, localization of mRNAs within cellular cytoplasm, the beginning of translation step and disappearance of mRNAs [15–18].

According to recent investigations, initiation and termination of immunological reactions including expression of anti-inflammatory and pro-inflammatory ILs like IL-12 family members are also regulated by transcription and post-transcription processes. The beginning and termination of cytokines secretion may lead to occurrence of serious damages within tissues. So, aforementioned processes are achieved in a quick and fast duration. Today, our knowledge about mRNAs and the related processes has risen up via advanced molecular technology of microarray. This reliable, reproducible, rapid and accurate technique is effective for detecting and identifying DNA and RNA molecules [19–22].

Because of the noticeable properties of IL-12 family members against infectious diseases as important immunological playmakers regarding to human immune system, the main aspect of the present review literature is to focus on characteristics of the family members of IL-12.

### **IL-12 family members**

The IL-12 family members are consisted of IL-12, IL-23, IL-27, and IL-35. They contribute to regulation of immune system against infectious diseases, autoimmune diseases and cancers. The main sources of triad ILs involving IL-27, IL-23 and IL-12 are active antigen presenting cells (APCs) while the IL-35 is produced by activated and resting regulatory T (Treg) cells including thymus originated Tregs (natural Treg (nTreg) cells) and the peripheral induced Treg (iTreg) cells in high level and IL-35-producing regulatory B (Breg) cells in low level. The quadruple group of IL-12 family converts the immature CD4<sup>+</sup> T cells

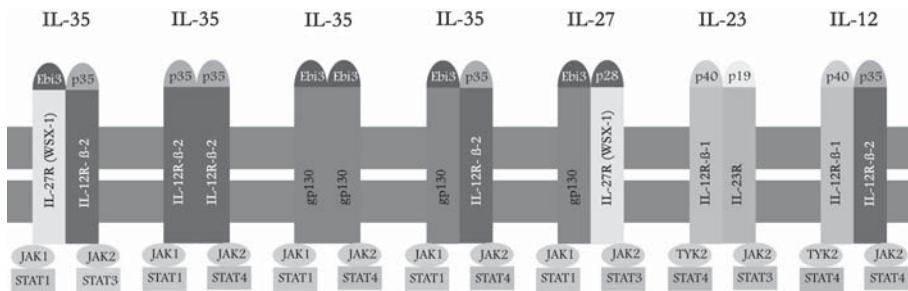


**Figure 1.** Naïve T cell differentiation into four types of Th cells and their related cytokine secretions. The naïve Th cells are able to be induced and make several Th cell subsets. IL-12 and IL-27 activities result in induction of INF- $\gamma$  producing Th1 cells. The Th1 cells are known as mediators of cellular immune system. IL-14 is Th2 cells inducer. The triggered humoral immune system mediator of Th2, is able to produce ILs-4, 5, and 13. 5 ILs including IL-1, IL-6+TGF- $\beta$ , IL-21, and IL-23 are important inducers of Th17 cells. It must be mentioned that IL-23 is known as a Th17 stabilizer rather than Th17 inducer. The Th17 cells are able to produce a wide range of ILs including IL-17A, IL-17-F, IL-21, IL-22, and IL-26. TGF- $\beta$  and IL-35 are Treg inducers. However, IL-35 is also known as a Treg production

into memory T cells and T helper (Th) cells in which the innate part of defence system links into the adaptive immunity. Actually, some IL-12 cytokines such as IL-12 and IL-23 are the main stimulators for memory T cells proliferation. However, IL-12 cytokines normally influence the duration of effectors responses. Besides, these cytokines are able to polarize the innate or native T cells [23–31].

The members of IL-12 are all involved in cytological and physiological activities in association with CD4<sup>+</sup> Th cells. Indeed, naïve Th cells are able to be differentiated into four major categories of Th1 (producing IFN- $\gamma$ ), Th2 (producing IL-4, IL-5, and IL-13), Th17 (producing IL-17A, IL-17F, IL-21, and IL-22, IL-26) and Treg (producing transforming growth factor (TGF)- $\beta$ , IL-10, and IL-35) (Fig. 1). IL-12 and IL-23 are necessary cytokines for Th1 and Th17 cells activities [12, 32–35].

The fourfold members of IL-12 family have some similarities and dissimilarities in their structures and functions. Each member of IL-12 family is individually discussed below:



**Figure 2.** The structures of IL-12 family, related receptors and signalling pathway in an immune cell.

The IL-12 family is consisted of IL-12, IL-23, IL-27 and IL-35. The IL-12 (p35/p40) sends signals through its receptor (IL-12R- $\beta$ 1/IL-12R- $\beta$ 2), TYK2/JAK2, and STAT4 molecules. The IL-23 (p19/p40) utilizes its receptor (IL-12R- $\beta$ 1/IL-23R) for sending signals through TYK2/JAK2, and STAT3/STAT4 signalling pathway.

The IL-27 (p28/Ebi3) and the related receptor (gp130/IL-27R (WSX-1)) use JAK1/JAK2, and STAT1/STAT3 molecules as a regular signalling pathway for signal casting.

IL-35 (p35/Ebi3) possesses four different receptors (gp130/IL-12R- $\beta$ 2 (heterodimers), gp130/gp130 (homodimers), IL-12R- $\beta$ 2/IL-12R- $\beta$ 2 (homodimers), and IL-27R (WSX-1)/IL-12R- $\beta$ 2 (heterodimers). The first three receptors apply JAK1/JAK2, and STAT1/STAT4 and the last receptor uses JAK1/JAK2, and STAT1/STAT3 as appropriate signalling pathways for moving the subjected signals.

## IL-12 and general characteristics

Trinchieri [82] and Gately et al. [70] are the first scientists that discovered cytokine of IL-12. IL-12 is known as one the most significant cytokines that regulates immune system responses. The 70 kDa pro-inflammatory molecule of IL-12 works as a powerful response to pathogenic microorganisms. B cells, dendritic cells (DCs) and macrophages (M $\Phi$ s) are the main resources for IL-12 cytokine. Structurally, IL-12 is consisted of two subunits of  $\alpha$  (IL-12p35) and  $\beta$  (IL-12p40) weighting 35 kDa and 40 kDa, respectively (Fig. 2). The  $\alpha$ -spiral structure subunit resembles IL-6 and the  $\beta$  is similar to IL-6 receptor. Each subunit is produced by a separate chromosome and the subunits are linked via covalent bonds [36–38].

According to the recent studies, IL-12  $\alpha$ -subunits are produced in different type of cells but in low level. On the other hand, the  $\beta$ -subunits are secreted only within limited cells that are able to produce IL-12p70 including activated DCs, M $\Phi$ s, monocytes and neutrophils. Hence, to form an active IL-12 cytokine; there is a need for simultaneous co-expression of IL-12p35, IL-12p40, and IL-12p70 within a same home cell. The level of IL-12p40 is up to 1000 rather than IL-12p35. So, always there is a high amount of unbound and free molecules of IL-12p40 within the cells [39–41].

Recent studies decipher the transcriptional and post-transcriptional regulations regarding to IL-12 family members. The combination of myeloid differentiation primary response gene 88 (MyD88) with toll-like receptors (TLRs) (excluding TLR3) activates nuclear factor- $\kappa$ B (NF- $\kappa$ B). On the other hand, the simultaneous presence of IFN-Regulatory factor 5 (IRF5) with MyD88 and NF- $\kappa$ B provides IL-12 family members producing genes to express [42–44].

The contribution of TLR ligands prepares an appropriate situation for transcriptional regulations. Hence lipopolysaccharide (LPS), a bacterial TLR ligand is able to rearrange the configuration of a particular region (nucleosome-1) relating to p40 gene promoter. The new arrangement of the region is prompt for activation of several transcription factors including CCAAT/enhancer binding protein (C/EBP). NF- $\kappa$ B is an essential factor for activating promoter during the presence of LPS. The consensus region of NF- $\kappa$ B, ETS links ETS-2 to PU.1 to make them ready for creating a complex with some other components such as c-Rel, some of IFR members, and IFN-consensus sequence binding protein (ICSB). The basis of transcriptional and translational processes of p35 and p40 genes expressions is the same with some differences in details; however, a main functional dissimilarity is distinguished regarding to p35 and p40 genes expressions. The common enzyme of extracellular signal regulated kinase mitogen activated protein kinase (ERKMAPK) between p35 and p40 genes expressions processes acts with different attitudes. ERKMAPK is known as a halter in p40 gene expression but as a restrictive agent in p35 gene expression [45–47].

The processes of post-transcriptional and post-translational in association with p35 and p40 occur within the cell milieu but in different pathways. The cleavage of p40 is performed once during the entrance into the endoplasmic reticulum (ER), while the p35 is cleaved twice within the ER milieu. The transcriptional, post-transcriptional, and post-translational processes pertaining to the other IL-12 family members subunits are as the same with some dissimilarity in details [48–50].

### **IL-12 and pathogenic microorganisms**

Several surveys show a high induction of IL-12 in the presence of microbial agents such as bacteria (Gram positive and Gram negative), fungi, helminths, protozoa, and viruses. The microbial components act as TLR ligands. The signaling process between microbial components and their related TLRs leads to induction of IL-12 via innate immune system. TLRs are recognized as important balancers for secretion of IL-12 family members. Bacterial pieces like DNA, LPS, peptidoglycan and lipoteichoic acid are important inducers of IL-12. The

adaptive system encompasses to produce IL-12 via CD40 and APCs attachments which are mediated by T cells CD40L receptors [42, 51–59].

There is a two-way positive interaction between IL-12 and IFN- $\gamma$ . The secretion of IL-12 leads to production of IFN- $\gamma$  by Natural killer (NK) and T cells. The axis of IL-12/IFN- $\gamma$  regulates immunological reactions. Moreover, IL-12 increases the cytotoxicity of cytotoxic T and NK cells and stimulates T cells differentiation into Th1 effectors. These characteristics relating to IL-12, support the importance of IL-12 in cell mediated pathways within immune system. Simultaneously, the secretion and dissemination of IFN- $\gamma$  triggers the production of IL-12; which is an appropriate mechanism against pathogenic microorganisms such as *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Candida albicans* and *Leishmania major*. In other word, IFN- $\gamma$  activates phagocytes to achieve their bactericidal activities throughout the production of more IL-12 and phagocytosis. IL-12 is known as an effective biological inhibitor for IL-4, IL-10, IL-11, and IL-13 [33, 60–66].

The absence of IL-12 predisposes human cells for invasion of intra-M $\Phi$  pathogenic microorganisms such as *Francisella tularensis*, *Klebsiella pneumoniae*, Mycobacteria, and *Salmonella*. Stimulation of TLR3 (viral ligands), TLR4 (bacterial (Gram negative bacteria) ligands) and TLR8 (viral ligands) gives rise to induction of IL-12p35. Stimulation of aforementioned TLRs and TLR2 (fungal and bacterial (Gram positive) ligands) induces IL-12p40 subunit [52, 67–69].

### IL-12 receptors and signalling pathway

IL-12 affects the immune system activities throughout binding to IL-12 receptors (IL-12Rs). The IL-12R is composed of two subunits of  $\beta$ 1 and  $\beta$ 2 which their genes are situated on two different chromosomes. The  $\beta$ 1 links to IL-12p40 and the  $\beta$ 2 binds to IL-12p35 (Fig. 2). The role of  $\beta$ 2-subunit is to convert signals received from IL-12. The highest affinity between IL-12 and IL-12R is performed when all the IL-12 and IL-12R subunits are actively present [12, 70].

Each subunit of IL-12R has its distinct biological activity. The cytoplasmic end of IL-12R- $\beta$ 1 which is missing the three tyrosine amino acids within intracellular domain, is bound to Tyrosine kinase-2 (TYK2). The mammalian Janus kinases (JAKs) involve four members including JAK1, JAK2, JAK3 and TYK2. The lack of tyrosine residues within IL-12R- $\beta$ 1 subunit prevents the contribution of  $\beta$ 1-subunit in the process of signal transducing. The key role of IL-12R- $\beta$ 1 is contributing in ligand binding process. In contrast, the IL-12R- $\beta$ 2 which binds to JAK-2 contributes in signalling transduction process throughout the three amino acid residues of tyrosine. These tyrosine amino acids are recog-

nized as a suitable binding site for signalling and triggering transcription 4 (STAT4) (Fig. 2). So, the activation of signalling pathway of JAK-STAT is done via IL-12R induction. Several investigations indicate that, signals activate related JAK(s) which may lead to phosphorylate the attached STAT molecule(s). Following the phosphorylation process of STAT molecule(s), DNA binding, nuclear movement, and dimerization will happen. It is revealed that not only IL-12 but also the majority of cytokines use JAK-STAT pathway to transmit related signals. A huge amount of signals sent from more than 50 cytokines are transmitted via seven molecules of STAT (STAT6, STAT5b, STAT5a, STAT4, STAT3, STAT2, and STAT1) among mammals. IL-12 is in association with STAT1, STAT3, STAT4, STAT5a and STAT5b. The STAT4 has the most important role in IL-12 signalling pathway. The induction of STAT4 by IL-12 may lead to promotion of IFN- $\gamma$  production. Indeed, IL-12 by triggering the expression of T-bet provides the Th1 responds and IFN- $\gamma$  secretion [36, 71–82].

Different studies show the amazing property of plasticity among Th17 cells. This characterization is appeared by some changes within transcription factors genes which produce Foxp3, ROR- $\gamma$ -t, and T-bet. Th17 cells are able to be converted into Tregs or other types of Th1 cells and vice versa. This process is mediated by the transcription factor of ROR- $\gamma$ -t which is known as an important regulator agent in association with Th17 cells. Th17 cells have positive influences on Th1 cells differentiation through IL-17 secretion. The IL-17 affects directly on DCs, which results in IL-12 upregulation. This process is applied regarding to intracellular bacterial agents like *F. tularensis* (the causative agent of tularaemia). The activation of STAT4 molecule by IL-12 may lead to generation of Th1 cells. The increase of Th1 cells results in considerable secretion of IFN- $\gamma$ . An increase in Th1 secretions can cause inflammation symptoms within a wide range of autoimmune diseases. On the other hand, Th1 cells have antagonistic manner against Th17 cells which may lead to suppression of these cells. The IL-12 plays a key role for polarizing and stabilizing Th1 phenotype against intracellular pathogenic infectious agents and the related autoimmune diseases [12, 34, 41, 69, 82–87].

### **IL-23 and general characteristics**

Ten years after identification of IL-12, IL-23 as the second member of IL-12 family was identified in 2003. Resembling to IL-12, IL-23 is a cytokine that mediates pro-inflammatory mechanism. IL-23 is composed of two subunits including IL-23p40 (as the same in IL-12) and IL-23p19. The co-production of both subunits involving IL-23p40 and IL-23p19 within a same cell and at the same



time leads to appearance of disulfide bonds between the subunits and the start of normal bioactivity of IL-23 (Fig. 2). There is a 40 percentage similarity between IL-23p19 and IL-12p35 sequences [38, 39, 88–91].

The main IL-23 secreting cells are recognized as activated skin and mucosa membranes APCs such as B cells, endothelial cells, MΦs, monocytes and DCs against pathogenic microorganisms. The main known key roles for IL-23 are: triggering IL-17 (responsible for bone erosion and tissue malignancies) via Th17 cells, IL-22, and the development of memory T cells. Secretion of IFN-γ (by T cells and NK cells), and differentiation of Th1 with low rates are known as circumstantial role for IL-23. The intensive communication between CD40 and CD40L, may lead to increase the production of IL-23, induction of IL-23R expression, and a positive circular circumstance for promoting IL-23 production. Fungal elements trigger for IL-23 secretion which this occurrence causes differentiation among Th17 cells [35, 92–99].

Recent researches indicate that, the presence of IL-23 guarantees the secretion and survival of Th17 cells [32].

### IL-23 and pathogenic microorganisms

Similar to IL-12, stimulation of TLR2, TLR3, TLR4 and TLR8 via pathogenic microbial ligands triggers the simultaneous secretion of IL-23p40 and IL-23p19. The stimulation of TLR2 via Gram positive bacteria peptidoglycan is significantly more effective than TLR4 via Gram negative bacteria LPS for expression of IL-23p19 and secretion of IL-23. The virulence factor of pertussis toxin produced by *Bordetella pertussis* promotes the secretion of IL-23. Many studies indicate that the both forms of dimorphic opportunistic fungus of *C. albicans* including yeasts and hyphae trigger the secretion of IL-23 via stimulation of Dectin-1, TLR4, and TLR2 (by yeast) or TLR2 and Dectin-2 (by hyphae) [68, 87, 100–104].

It is revealed that, microbial components and threatening signals within the human body stimulate the secretion of IL-23 throughout the exposed MΦs, monocytes, and DCs in a few hours. In consequence, IL-17 is produced and other cells are activated in a cascade pathway which finally may lead to pro-inflammation within infected or wounded anatomical site. The chronic bowel inflammation of Crohn's disease (CD) is an autoimmune disorder in association with IL-23. Thus, IL-12 and IL-23 are recognized as acute protectors for immune system surveillance. Besides, the importance of IL-23 is identified during lung infections caused by Mycobacteria, *K. pneumoniae*, candidemia caused by *C. albicans*, and salmonellosis caused by *Salmonella*. The axes of IL-23-IFN-γ and IL-23-IL-17

are the most effective pathways against extracellular opportunistic pathogenic microorganisms such as *C. albicans* (causative agent of different types of candidiasis), *Pseudomonas aeruginosa* (causative agent of wounds and urinary tract infections (UTIs), etc.), *Escherichia coli* (causative agent of different infections like UTIs) *K. pneumoniae* (causative agent of lungs, wounds and UT infections) and etc. [34, 38, 63, 64, 87, 105–113].

Furthermore, recent researches reveal that the colonization of normal flora and useful intestinal microbiota in human alimentary tract prevents the attachment of pathogenic microorganisms and balances the immunological responses. The intestinal microbiota increases production of IL-23 which may lead to induce Th17 cells for secreting IL-17. Therefore, the presence of commensal bacteria protects intestinal milieu against pathogenic microbial agents throughout IL-23/Th17 axis. Interestingly, the high increase of Th17 cells within intestines triggers epithelial cells to produce IL-25. IL-25, reduces IL-23 secretion, downregulates the expansion of Th17 cells and rebalances the intestinal homeostasis [95, 114, 115].

Investigations show that microbial productions are the major triggering factors which may lead to secret IL-12 and IL-23 via immunological innate cells system. IL-12 prevents the production of IL-23 [47, 50, 116].

Previous investigations indicate that, IL-23 is not necessary for differentiating Th17 cells. However, the presence of IL-23 is vital for polarization and stabilization of Th17 cells which leads to appearance of inflammation symptoms in different types of autoimmune diseases comprising psoriasis, multiple sclerosis, rheumatoid arthritis, CD, and Experimental autoimmune encephalomyelitis (EAE) etc. Not only IL-23, but also IL-12 has a strong inflammatory effect on autoimmune diseases with different pathways [12, 39, 69, 83, 84, 87, 89, 117, 118].

### **IL-23 receptors and signalling pathway**

IL-23 possesses a bi-subunit receptor consisted of IL-12R- $\beta$ 1 (pairing with IL-23p40) and IL-23R (matching with IL-23p19). The presence of all subunits regarding to IL-23 and its receptor guarantees the occurrence of high affinity bonds. The biological effects of IL-23 are performed via heterodimeric signalling pathways of JAK2, STAT3, STAT4, and TYK2 (Fig. 2). Surveys show that IL-6 and IL-21 are the main cytokines which control the regulation of IL-23R [4, 88, 89, 118, 119].

After linking between IL-23 subunits including IL-23p40 and IL-23p19 and their receptors, the STAT3 and STAT4 will be activated (Fig. 2). In parallel with polarization of Th17 cells, IL-23 supports the promotion of heterodimeriza-

tion of STAT3 and STAT4. Active STAT3 molecules increase the production of cytokines regarding to inflammatory activity. Moreover, STAT3 heterodimers trigger the inflammatory related subset of T cells, Th17. STAT3 is directly affects the process of Th17 differentiation [77, 78, 120].

### **IL-27 and general characteristics**

The heterodimeric IL-27 is consisted of two subunits including IL-27p28 and Epstein-Barr virus induced gene 3 (EBI3). The EBI3 which resembles IL-12p40 is a glycoprotein with a molecular weight of 34 kDa. The IL-27p28 subunit is a helical peptide with a molecular weight of 24.5 kDa. Different surveys show that, each subunit is secreted separately and the links between EBI3 and IL-27p28 are unstable because of the lack of sulphide bonds. Interestingly, EBI subunit is able to connect with IL-12p35 to create IL-35 (Fig. 2) [121–124].

APCs (such as DCs, and MΦs) are the main resources that secrete IL-27. Two functional key roles including inhibitory and pre-stimulatory have recognized for IL-27. IL-27 is able to inhibit the process of immune system responses (in both sections of innate and adaptive immunities) and to limit the progression of inflammatory. Previous investigations indicate that IL-27 operates as a functional antagonist cytokine to suppress T cells activities and responses. The suppressive functional effects of IL-27 on MΦs and neutrophils are identified in infectious sepsis. Cooperation of IL-27 and IL-12 may lead to trigger mast cells, monocytes, NK and T cells to secrete the IFN- $\gamma$ . IFN- $\gamma$  stimulates the production of IL-27 in a positive feedback loop which may lead to suppress the inflammatory responses. Moreover, the presence of IL-2 together with IL-27 prevents the proliferation of Th2, Th17 cells and production of IL-12 and IL-23. On the other hand, the upregulation of T-bet and intracellular adhesion molecule-1 (ICAM-1) gives IL-27 permission for promoting the process of Th1 differentiation. IL-27 in the presence of TGF- $\beta$  is able to produce Type 1 regulatory T (Treg1) cells that secrete anti-inflammatory IL-10. However, for differentiation of Th1 and secretion of IFN- $\gamma$ , IL-27 plays its pro-inflammatory role [122, 123, 125–127].

### **IL-27 and pathogenic microorganisms**

The anti-inflammatory characteristic of IL-27 leads to downregulation of inflammatory process in the meanwhile of acute and chronic infections. The induction of IL-10 and direct suppression of Th1, Th2 and Th17 by IL-27, subverts the efficacy of immune responses for the most; in contrast, the presence of anti-

IL-27R and IL-12 upregulates the pro-inflammatory responses throughout different cytokines such as IL-18, IFN- $\gamma$  and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ). These mechanisms are studied on *Mycobacterium tuberculosis*, *Leishmania major*, *L. donovani*, *Toxoplasma gondii*, *Plasmodium berghei*, and *Trypanosoma cruzi*. Thus, IL-27 creates a critical condition during infectious diseases for the host immune system by preventing secretion of IL-2, IL-6, and IL-17 and subverting immune responses against microbial pathogens. The inhibition of IL-2 production may happen via suppressor of cytokine signalling 3 (SOCS3) [123, 128–132].

### IL-27 receptors and signalling pathway

Similar to IL-12 and IL-23, IL-27 has receptor of IL-27R which is composed of a gp130 subunit and a WSX-1 subunit. The latter belongs to the class I cytokine receptor family (TCCR) (Fig. 2). B (activated) cells, DCs, Endothelial (activated) cells, mast cells, monocytes, naïve T cells, and NK cells are all recognized as the IL-27R producer cells. The IL-27 JAK-STAT signalling pathway varies in different immune cells including mast cells (STAT3), monocytes (NF- $\kappa$ B, STAT1, and STAT3), naïve T cells (TYK2, JAK1, JAK2, STAT1, STAT2, STAT3, STAT4, STAT5a, and STAT5b) and NK cells (JAK1, STAT1, STAT3, STAT5a, and STAT5b). STAT1 and STAT3 molecules are needed for IL-27 biological activities [123, 133–139].

### IL-35 and general characteristics

The heterodimeric cytokine of IL-35 involves two subunits of p35 and Ebi3 which are also seen in IL-12 and IL-27 (Fig. 2). IL-35 is the newest member of IL-12 family. IL-12 and IL-23 are pro-inflammatory cytokines, while IL-27 has anti-inflammatory activities for the most. However, there are some activities (such as Th1 promotion and IFN- $\gamma$  secretion) which are performed by IL-27. In the case of IL-35, this cytokine is recognized as a definite immunosuppressor with a huge potent of suppression. T cells (Th1, Th17) are suppressed via cell cycle termination in G1 phase. No apoptosis feature is used within T cell suppression process. Prior to APCs, nTregs are the main resources for IL-35 secretion. IL-35 resembling IL-10 and TGF- $\beta$ , has the capability of triggering proliferation of the iTreg of iTr35 (the CD4<sup>+</sup> Tregs induced by IL-35). iTr35 produces IL-10, Foxp3, and TGF- $\beta$ ; but suppresses via IL-35. nTregs are able to transform the suppressed T cells into iTr35. The contribution of iTr35 for regulating the envi-

ronmental parameters regarding to inflammation is identified. Moreover, the entrance of IL-35 into the inflammatory sites at the present of nTreg works for the maximal potential [8, 12, 13, 28].

### **IL-35 and pathogenic microorganisms**

Immune cells of monocytes which are activated by bacterial LPS and pro-inflammatory cytokines are able to transcribe IL-35 genes [9]. More investigations are needed relating to IL-35 activities against microbial pathogens.

### **IL-35 receptors and signalling pathway**

Unlike other members of IL-12 family, IL-35 encompasses four receptors including IL-12R- $\beta$ 2-IL-27R (WSX-1), IL-12R- $\beta$ 2-IL-12R- $\beta$ 2, IL-12R- $\beta$ 2-gp130, and gp130-gp130. Normally, IL-12R- $\beta$ 2 subunit is produced within active NK and T cells; while gp130 is secreted by the majority of immune cells. The IL-35 signalling pathway is consisted of JAK1, JAK2, STAT1, STAT3, and STAT4 molecules (Fig. 2). A group of B cells such as regulatory B cells which produce IL-35 possesses two receptor subunits of IL-12R- $\beta$ 2 and IL-27R- $\alpha$  for IL-35 for activating STAT1 and STAT3 molecules. This characteristic indicates the probable contribution of regulatory B cells in association with immune system responses in healthy people and patients. In T cells, the IL-35 signals encompass three receptor subunits comprising IL-12R- $\beta$ 2-IL-12R- $\beta$ 2, IL-12R- $\beta$ 2-gp130, and gp130-gp130 which activate STAT1 and STAT4 molecules [23, 28, 75, 140, 141].

### **The connection of IL-12 family with IL-6 family**

In addition to IL-12 cytokines, the IL-6 cytokine family belongs to type-I cytokines. The IL-12 family members excluding IL-35 (IL-35 is secreted by Tregs and some of Bregs) are secreted by APCs (DCs, monocytes, and M $\Phi$ s), whereas the IL-6 cytokines are produced by a vast range of cells including adipocytes, B cells, endothelial cell, fibroblasts, keratinocytes, mesangial cells, monocytes and T cells. These families have some similarities and dissimilarities regarding to their structural and molecular properties. The IL-12 and IL-6 super-families encompass similar structural motifs of four-helix-bundle and hematopoietin receptor domain. On the other hand, the IL-6 family members including

cardiotrophin-1 (CT-1), cardiotrophin like cytokine (CLC), ciliary neurotrophic factor (CNTF), IL-6, IL-11, leukaemia inhibitory factor (LIF), neuropoietin (NP), and oncostatin M (OSM) are single-structured monomers while the IL-12 cytokines possess a heterodimeric structure of  $\alpha$ - $\beta$ -subunits (Table I). Furthermore, the cytokines biological activities are performed via their specific receptors. In this article we just focus on IL-6 and its receptors [31, 94, 122, 142–146].

The IL-6 receptors comprising (IL-6R/IL-6R- $\alpha$ /gp80/CD126) and gp130 (IL-6R- $\beta$ /CD130) molecules have a key role in association with IL-6 biological tasks. The hexamer complex of IL-6-IL-6R- $\alpha$ -gp130 (including six molecules/two molecules per each) creates powerful signals within cells. The evolutionary scientific documents show that IL-12 cytokines  $\beta$ -subunits including p40 and Ebi3 have close relationship with IL-6R- $\alpha$  while a close homology is observed between gp130 and the both components of IL-12 receptors (IL-12R- $\beta$ 1 and 12R- $\beta$ 2), (Table I and Fig. 2). The gp130 molecule is present in receptors of IL-27 (gp130 and WSX1) and IL-6 (gp130 and IL-6R- $\alpha$ ). The glycoprotein of gp130, is the main signal transducer in association with IL-6 and IL-27 signalling pathways. Interestingly, the signalling pathway of IL-6 includes JAK1, JAK2, TYK2, STAT1, and STAT3. Moreover it is remarkable finding that, the IL-6 as well as IL-11 applies for gp130-gp130 homodimer-structures in its signalling pathway [31, 79, 94, 143, 144, 147, 148].

According to the previous studies, the 40-kDa molecule of p40 (IL-12- $\beta$ -subunit and IL-23- $\beta$ -subunit) is able to build homodimer structures of (p40)<sub>2</sub> which have antagonistic functional properties against IL-12 and IL-23. The (p40)<sub>2</sub> homodimers have a strong affinity for IL-12R- $\beta$ 1-subunits. The new iden-

**Table I.** A structural comparison between IL-6 and IL-12 family cytokines

Cytokine family	Cytokines	Structure	$\alpha$ -Subunit	$\beta$ -Subunit
IL-6	cardiotrophin-1 (CT-1), cardiotrophin like cytokine (CLC), ciliary neurotrophic factor (CNTF), granulocyte colony stimulating factor (GCSF), IL-6, IL-11, leukaemia inhibitory factor (LIF), neuropoietin (NP), oncostatin M (OSM)	monomer	Homologous to IL-12 cytokines $\alpha$ -subunits	No homology
IL-12	IL-12	heterodimer	p35	p40
	IL-23		p19	p40
	IL-27		p28	Ebi3
	IL-35		p35	Ebi3

tified homologies among IL-6 and IL-12 family members and the related receptors have shown that, the gp130 as a receptor is able to contribute to inhibit the formation of (p40)<sub>2</sub> homodimers through its high homology with IL-12R-β1 and IL-12R-β2. Moreover, the IL-23 receptors include IL-12R-β1 and IL-23R; the IL-23R has a close similarity with gp130. These characteristics may decrease the formation of (p40)<sub>2</sub> homodimers [31, 47, 141, 147, 149, 150].

### **Conclusion**

Recent investigations reveal similarities and dissimilarities among functions, structures, regulatory systems, and secretion pathways of IL-12 family members. The importance of IL-12 family is considerable in different fields such as gene therapy, cancer therapy, tumour therapy, and vaccination. Thus, the science of bioengineering is trying to use IL-12 family members as especial therapeutic tools in modern pharmacology. Besides, the members of IL-12 family are known as important biomarkers in association with infections, autoimmune diseases, and cancers.

Furthermore, the progression of advanced molecular diagnostic technology of microarray provides an appropriate opportunity for applying IL-12 family members as brilliant diagnostic playmakers in the field of infectious diseases with high accuracy, reliability, and reproducibility.

The recent decade has given us the opportunity for identifying this group of cytokines. Identification of cytokines, their receptors and signalling pathway permit us to have a much better diagnostic approach and designing definite therapeutic methods. The results from different studies confirm a variety of mechanisms in different infections. So, an individual pathway and mechanism can be used as a prompt sign for performing an accurate diagnosis and definite treatment. We conclude that, the ability of IL-12 family cytokines as significant immunological playmakers together with microarray technology can provide us a new chapter of reliable diagnostics and successful treatments now and tomorrow.

### **Conflict of Interest**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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