

# Role of interleukin-6 in immunity: A Review

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**Abstract:** Interleukin-6 is a cytokine with an extensive range of biological activities. On the immune system it has the wide range of impact and it can affect the homeostatic process by having hormone like characteristics. It is widely used in the clinical intervention because it has both anti and pro-inflammatory properties. It is activated during inflammation and maturation of B cells. It can act as pyrogen and can cause fever during infection, non-infection and autoimmune diseases. IL-6 is produced by the macrophages and monocytes in reaction to other inflammatory cytokines which contain tumor necrosis factor (TNF)-beta and interleukin-11. In resting phase the receptors of IL-6 is present on normal activated B-cells, cells in hepatic and myeloid cell lines and normal T-lymphocytes. In the host defense the acute IL-6 expression plays a main role by activates the different cell population. IL-6 initiates the wide range of acute-phase proteins such as serum amyloid A (SAA), fibrinogen, haemoglobin, C-reactive protein, hepcidin and antichymotrypsin when acting on hepatocytes and lessend the cytochrome P450, transferrin, fibronectin and albumin, its structure contains the IL-6R, Sil-6R and gp130.it has role in many diseases but major role is present in the cancer.

**Keywords:** IL-6, structure of IL-6, signaling of IL-6, role of IL-6 in diseses, IL-6 and cancer.

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## 1. INTRODUCTION

Interleukin-6 is a cytokine with an extensive range of biological activities. It is mediator for immunoglobulin class substituting and to regulate the acute phase response. It is also inflammation indicator within body. For the occurrence of bacteremia IL-6 can also use as investigative marker (Remick, *et al.*, 2005; Fuster, 2014).

IL-6 is an endogenous biochemical which is active during B cell maturation and process of inflammation. It can act as pyrogen and can cause fever during infection, non-infection and autoimmune diseases (Dalrymple *et al.*, 1996). Either inflammation chronic or acute it is produced and situation is cancers, trauma, burns and infections (Srirangan & Choy, 2010). IL-6 is also assumed to cause improved susceptibility to systemic form of juvenile rheumatoid arthritis and diabetes mellitus (Tanaka & Kishimoto, 2012).

IL-6 is produced by the macrophages and monocytes in reaction to other inflammatory cytokines which contain tumor necrosis factor (TNF)-beta and interleukin-11. In resting phase the receptors of IL-6 is present on normal activated B-cells, cells in hepatic and myeloid cell lines and normal T-lymphocytes (Kubistova *et al.*, 2012). In B-cells that are modified by the Epstein-Barr virus IL-6 is also present. Inflammatory reaction is produced by the IL-6 by initiating the transcription factors that are present on multiple inflammation pathways. Its origin occurs with protein kinase C, cAMP/protein kinase A and release of Calcium occurs. IL-6 has various function and forms on the basis of its production and also has pleiotropic activity (Maeda *et al.*, 2016).

IL-6 is produced by the macrophages and monocytes in the initial stage of infectious inflammation immediately after the stimulation of Toll-like receptors (TLRs) with separate pathogen related molecular patterns (PAMPs). When noninfectious inflammation occurs such as traumatic injury or burn then damage related molecular patterns (DAMPs) from the damages sites activates the TLRs to produce the IL-6 ( Uchiyama *et al.*, 2012) .

In the host defense the acute IL-6 expression plays a main role by activates the different cell population. IL-6 initiates the wide range of acute-phase proteins such as serum amyloid A (SAA), fibrinogen, hatoglobin, C-reactive protein, hepcidin and antichymotrypsin when acting on hepatocytes and lessend the cytochrome P450, transferrin, fibronectin and albumin (Figure 1) (Wang *et al.*, 2013).

For clinical laboratory tests CRP (C-reactive protein) is a good biomarker of inflammation and its expression is related to IL-6. If the level of hepcidin that is activated the IL-6 can block iron transporter ferroportin 1 in gut epithelial, hepatocytes and macrophages it can lead to anemia of chronic inflammation and hypoferremia. TGF-  $\beta$  with the IL-6 enhance the differentiation of IL-17 manufacturing T helper cells that have important role in initiating autoimmune tissue injury (Eto *et al.*, 2011).

Induction of CD8+ T-cells by the IL-6 is helpful to produce the T cells. Activation of hematopoietic stem cell and maturation of megakaryocytes into platelets is inducing by the IL-6 in hematopoiesis. Receptor activation of NF-kappa B ligand is activated by the IL-6 production in bone marrow stromal cells that is important for the activation and differentiation of bone resorption and osteoporosis (Grossman *et al.*, 1989; Korn *et al.*, 2008). IL-6 in inflamed lesion such as seen in synovium tissue of rheumatoid arthritis is due to the excessive vascular endothelial growth factor (VEGF) that increases the angiogenesis. Autoimmune skin disease occurs due to the collagen manufacture in dermal fibroblasts and also enhanced growth of mesangial cells and plasmacytoma occurs (Laws *et al.*, 2013).

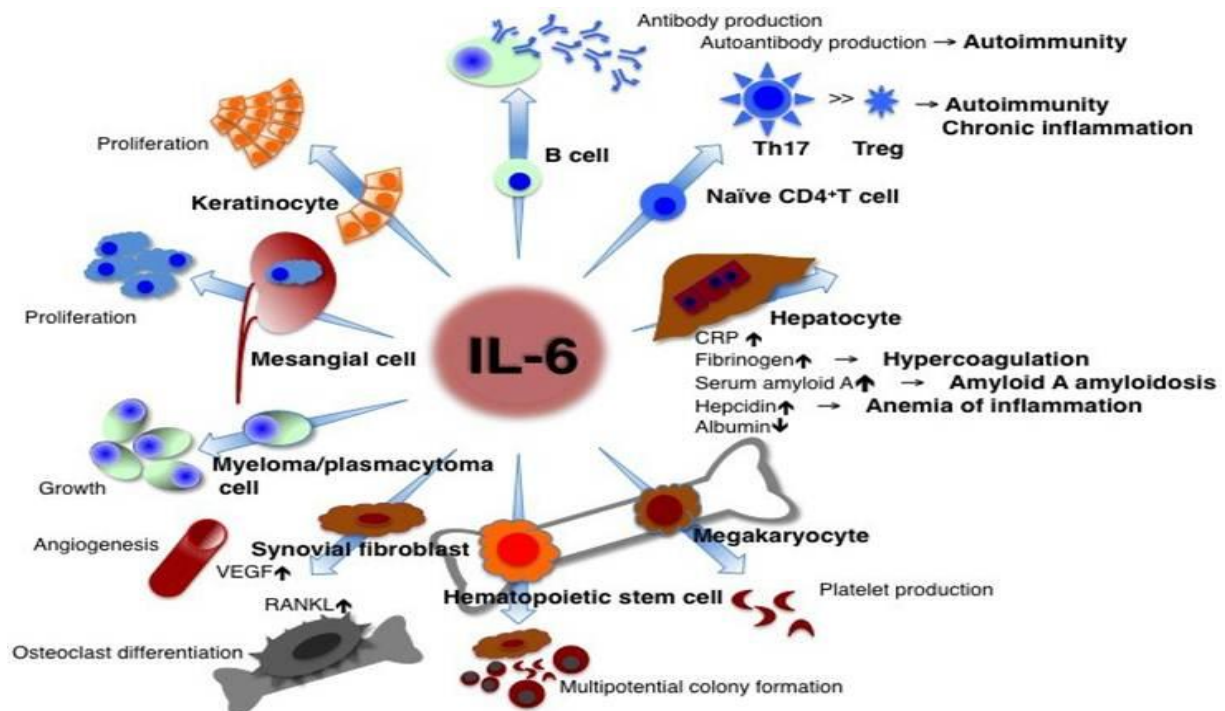


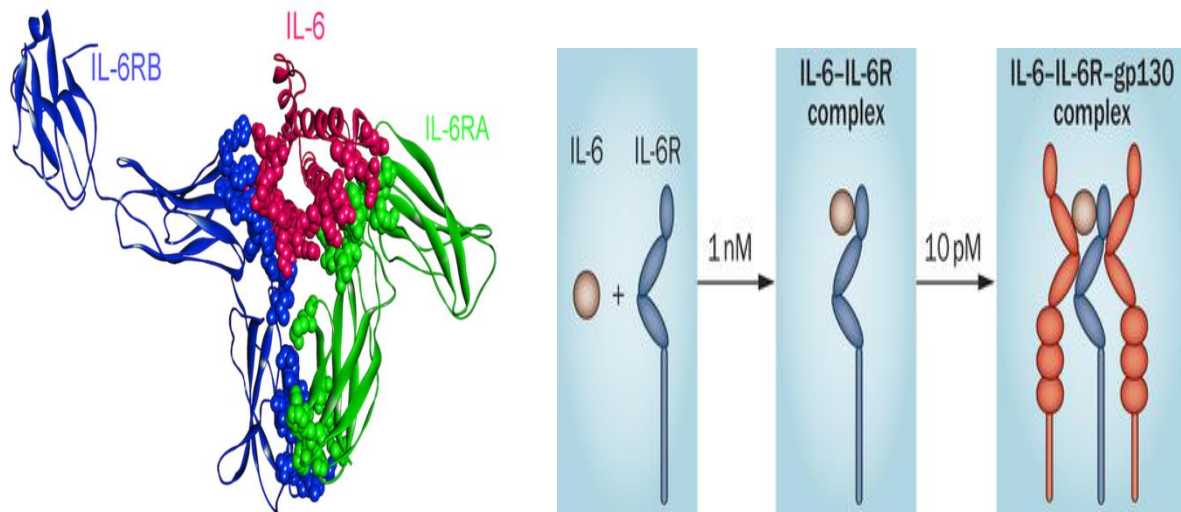
Figure.1: Functions of IL-6

## 2. STRUCTURE OF IL-6

Signaling of IL-6 is started by relation of IL-6 and IL-6R (IL6RA, CD126) with gp130 dimerization induction and gp130 protein (IL6RB, CD130) that results in a complex of hexameric structure that is capable of signaling. In the body fluids IL-6R is present in soluble form and it has the ability to bind with IL-6 that leads to trans signaling process of IL-6 so that expression of gp130 occurs (Simpson *et al.*, 1997; Gruys *et al.*, 2005).

Signaling of IL-6 activates the Ras-Raf, P3K/AKT and JAK/STAT pathways. By activation of different pathways regulation of pro-tumorigenic and anti-apoptotic activities occur (Escobar-Morreale *et al.*, 2003). It is most ubiquitously derestricted cytokine in cancer so it is involve in differentiation and growth of various malignant tumor cells. Tumorigenesis involve in different tumor models such as lung, ovarian, colon and breast cancer that is due to the signaling of IL-6-JAK-STAT pathways (Varghese *et al.*, 2002).

At the binding line of IL-6-IL-6R-GP130 hexameric complex there are fourteen oncogenic mutations are present that are mostly related to cancer of colon (7), stomach (1), breast (1), lung (1), endometrial (2) and liver (2) (Güven-Maiorov *et al.*, 2014).



**Figure.2: The structure of IL-6, IL-6RA, and IL-6RB complex (PDB Code\_Chains: 1p9m\_ABC). Atoms of interface residues are represented with balls.**

### 3. RECEPTORS AND SIGNALING OF IL-6

Receptors of the IL-6 are including in the family of class I cytokine receptors. In class I receptors greater affinity signal transduction and ligand binding components are presents. IL-6R has two separate constituents. It has ligand binding portion which has 80-kDa molecular weight and it is linked to the IL-6 (Mahira *et al.*, 2012; calabrese & Rose-jhon, 2014).

It can be present in two forms such as soluble and membrane bounded form. On the other hand the signal transduction part of the IL-6R is made up of glycoproteins 130 and can be known as IL-6Rb chain. GP130 has the ability of signal transduction of IL-6 and establishment of binding site. Gp130 is important molecule in the whole family of IL-6 cytokines for signaling (Mahira *et al.*, 2012; calabrese & Rose-jhon, 2014).

Circulating complex is formed when the IL-6Ra that is soluble form bind with the IL-6. Now binding of this soluble form occurs with the cells that will express the gp130 and expression of gene as well as signal transduction occurs. For mediation of proinflammatory response this complex is very important that lead towards gp130 expression and known as trans- signaling (Sheller *et al.*, 2011).

Ligand activation of the gp130 takes place by the variety of ways it includes cytoplasmic tyrosine kinases activation and transcription factor activation. No intrinsic kinase domain is present in the gp130 but various studies reveals that Janus kinase 1 (JAK1), JAK2 and tyrosine kinase 2(TYK2) of the JAK family are related constitutively with gp130. Signal transducer and activators of the transcription (STATs) occurs with the help of the kinase activation that is done by the tyrosine phosphorylation of the latent cytoplasmic transcription factor. STAT3 and Ras protein are activated by the gp130 and IL-6. When activation of Ras protein occur it will lead toward the hypophosphorylation of the mitogen-activated protein kinase (MAPK) and resulted in increased activity of serine/threonine kinase (Ibi & Yamda, 2015). Phosphorylation of NF-IL6 factor (nuclear factor for IL-6) occurs by the MAPK on threonine 235 and serine 231 that is important for binding of DNA. In the different acute phase proteins activation occurs with the help of NF-IL6 (Hong *et al.*, 2007) .

### 4. ACUTE PHASE RESPONSE OF IL-6

The reaction of an organism to the disturbance due to neoplastic growth, immunological disorder, infection and tissue injury is involved in acute phase response. It is considered that it is advantageous for the injured organisms to maintain

the homeostasis after the infection. In acute response IL-1, IL-6, interferons and IL-6 are involved and these are involved in various functions which include accumulation of clots and platelets, activation of monocytes and granulocytes and blood vessel leakage (Heinrich *et al.*, 1990)

Innate immune system is enhanced by the IL-6 that activates the acute phase which leads toward protection against damage of tissue (Kubistova *et al.*, 2012). By the liver cells release of acute phase protein occurs into the plasma of blood, on the other hand release of other proteins is inhibited. These proteins are very specific in action and mimic the antibodies. IL-6 enhances the production of two main proteins that are serum amyloid A and C-reactive protein (CRP). CRP is used to enhance the phagocytic rate of bacteria while SAA is used to alter the gene transcription rate of proteins (Rincon *et al.*, 2012). Fibrinogen that is essential clotting factor increased by IL-6 while transferrin and albumin level are diminished at the same time. This leads toward systemic reaction that includes enhanced production of glucocorticoids, complement activation, fever, erythrocyte sedimentation and enhanced clotting (Gruys *et al.*, 2005).

### 5. ACTION OF IL-6 ON B- AND T-LYMPHOCYTES AND PLASMACYTOMA

IL-6 increases production of immunoglobulin A, G and M by directly activating the B cells and enhances production of IL-5 and IL-4. It plays an important role in terminal differentiation of B cells into secretions of immunoglobulin (Shanley *et al.*, 1996; Wegner *et al.*, 2013). On normal resting B cells IL-6 has no effect because these cells do not show any receptor site for IL-6 while receptors for IL-6 are shown by the activated B cells and respond to IL-6 antibody secretion and production. With Epstein-Barr virus, B cells have been pronounced to react to IL-6 with propagation in a paracrine manner (Wang *et al.*, 2010; Nguyen *et al.*, 2014).

In plasmacytoma (malignant cell tumor within soft tissue or axial exoskeleton) cells function of IL-6 is a powerful factor for growth. IL-3 and IL-6 enhance the differentiation and propagation of precursors of malignant plasma cells in various myelomas. IL-6 is also important for the proliferation and activation of antigen receptor dependent T cells. For the activation of T cells the action of IL-6 is coupled with IL-1. IL-6 initiates the humoral as well as cellular defense mechanism and monocyte and neutrophil oxidative burst response (Smith *et al.*, 2007).

### 6. PATHOLOGICAL ROLE OF IL-6 IN DEVELOPMENT OF DISEASES

When synthesis of IL-6 occurs momentarily then it involves in organism defense from environmental stress such as injury and infection collectively (Dalrymple *et al.*, 1996). It also provides signals for biological events. When stress is diminished then the production of IL-6 also vanishes with the help of negatively regulated systems that contain CRP and serum IL-6 levels (Lopes *et al.*, 2013).

If dysregulation of IL-6 remains continuous it will lead toward cancer, different chronic inflammatory and autoimmune diseases. It was known as all HIV positive patients also contain the Kaposi sarcoma associated herpes virus that persists the production of IL-6 that is virus derived which activates the gp130 that leads toward disease (Rose-John *et al.*, 2006).

### 7. ROLE OF IL-6 IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects the 1% worldwide population of women (Maeda, 2006). It includes the inflammation of small joints and synovium that causes the juxta-articular and articular cartilage destruction that leads toward the osteoporosis, fatigue and anemia (Srirangan & Choy, 2010; Ogata *et al.*, 2012).

IL-6 is a pleiotropic cytokine which takes part in production of auto-antibodies and B-cell maturation which causes the activation of CRP that plays an important role in the pathogenesis of RA (Turiano *et al.*, 2012). IL-6 is involved in the production of pro-inflammatory lymphocytes that is Th17. It enhances the adaptive immune response, moves from acute to chronic inflammation, development of articular symptoms, enhances joint erosion and enhanced extracellular turnover (Srirangan & Choy, 2010).

### 8. INTERLEUKIN-6 IN PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

This disease is divided into two groups such as ulcerative colitis and Crohn's disease. Both of the diseases contain the relapsing bowel inflammation that reacts to immunosuppressives and glucocorticoids (Saxena *et al.*, 2014). Persistent inflammation occurs in the submucosa and mucosa. Environmental factors as well as various predisposing genes interact and cause the disease (Turiano *et al.*, 2012).

IL-6 is function for immune and non-immune system and adaptive and innate immunity. Its production is enhanced by the activation of cell and it remains normal under control of catecholamines, secondary sex steroids and glucocorticoids. It is considered that the interaction of complexes and activation of pathways lead toward the Bowl disease (Taka *et al.*, 2012).

### **9. INTERLEUKIN-6 PROMOTER POLYMORPHISMS (-174 G/C) IN SYSTEMIC LUPUS ERYTHEMATOSUS**

This disease is chronic autoimmune disorder in which inflammation of different organs occurs as well as gathering of different complexes occur due to B cell hypersensitivity. Mostly the lungs, joints, brain, skin and blood vessels are affected by this disease (Elnerae *et al.*, 1992). Deposition of immune complexes occurs that destroyed by own body immune system. Major symptoms are swollen joints, extreme fatigue, rashes and fever and this disease is mostly occurring in females as compare to males (Maggio *et al.*, 2006).

Both the genetic and environmental factors are involved in initiation of disease. IL-4 preactive B cells are transformed by the IL-6. It is also involve in the various biological process such as platelet production and metabolism of bone. High level of mRNA and IL-6 is seen in the patients of SLE (Chua *et al.*, 2009).

### **10. ROLE OF IL-6 IN SCHIZOPHRENIC PATIENTS**

Schizophrenia occurs due to activation of inflammatory system. Involvement of central nervous system occur and IL-6 level in cerebrospinal fluid is important. To know the cause of disease it's necessary to measure the level of IL-6 and CSF.IL-6 that is present in the serum is remain high in patients of schizophrenia (Danel & Kaman, 1999; Lopes *et al.*, 2013)

### **11. IL-6 AND HYPOPROLIFERATIVE ANEMIA**

When IL-6 is combined with cytokines that are proinflammatory then the anemia of inflammation occurs. Modern studies showed that IL-6 activates the hepatocytes to release the hepcidin. Hepcidin is a used to inhibit the reticuloendothelial release and intestinal absorption of iron (Kamimura *et al.*, 2014).

### **12. IL-6 AND CANCER**

IL-6 is very important factor for the various types of tumors. There is great relationship between the tumors and the inflammation (Terzic *et al.*, 2010). Enhanced antiapoptotic, activation of androgen gene receptors and cell cycle gene expression occurs due to the activation of IL-6 with STAT3 pathways. It has major role in ovarian and prostate cancer. More production of proinflammatory cytokines important for the cachexia (muscle atrophy, loss of weight and fatigue), and tumor related symptoms (Sallam *et al.*, 2012).

The role of IL-6 in the angiogenesis, migration, cancer progression and in carcinogenesis is very important. Vascular endothelial growth factor (VEGF) is important for the angiogenesis that is also enhanced by the IL-6 (Nagasaki *et al.*, 2014).

The effect of the IL-6 on the cell line of the breast cancer is inhibitory but it has the ability to enhance the metastasis. 2174G/C polymorphism has the ability to promote the phenotype of the breast cancer. When more expression of the IL-6 occurs it will lead towards metastasis and angiogenesis in breast cancer (Hong *et al.*, 2007; Pedersen and Fischer., 2007).

### **13. CONCLUSION**

IL-6 has both pro-inflammatory and anti-inflammatory functions so we can use it for various clinical investigations. It has role in various diseases but majorly in the cancer. When it's over production occur different type of cancer occurs it causes the angiogenesis that lead toward tumor production. So if we control the signaling pathway of the IL-6 we will control the different type of diseases.

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