

# Interleukin-23

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## Abstract

Interleukin-23 (IL-23) is a pro-inflammatory cytokine that was discovered in 2000. It is part of the IL-12 family of cytokines which also has IL-27 as a member. This group broadly, is responsible for aspects of the inflammatory cascade which result in immune mediated disorders or alternatively in immune enhancement. IL-23 is produced by antigen presenting cells and thus is involved with the regulation of T-helper cells. IL-23 induces IL-17 production and has a wide variety of influence, both positive and negative in various disease processes.

## Structure

IL-23 is structurally comprised of two subunits, the p 19 subunit (4-fold helical) and the IL-12 p 40 (kD) subunit. They are linked by di-sulfide bonds. IL-23 was discovered in 2000 and the basic structure was elucidated at that time [1-3]. The p19 subunit is a 19K mw subunit that is linked by disulfide bonds to the p 40 subunit. P19 is produced by T cells and endothelial cells, as well as by other antigen presenting cells. It is composed of four [4] exons and three [3] introns. It is related to structurally to IL-6, even though IL-6 and IL-23 are not in the same family. The production of p 40 is more confined to cells such as antigen presenting cells (macrophages) [2]. It is comprised of 8 exons and 7 introns and has three domains. Biologically active IL-23 requires both subunits to be synthesized in the same cell. There is no cell to cell transfer. The p 40 subunit allows for binding to both natural killer cells and to T lymphocytes [3-5].

IL-23 is stimulated by the activation of toll-like receptors (TRLs) from their ligands such as lipopolysaccharide. As a result, p40 and p19 are more prominently expressed [2].

There are several different factors that regulate IL-23. Lipopolysaccharide from Gram negative bacteria; IL-10; Beta-glucans from fungi and Gamma Interferon all tend to regulate IL-23 production [6,7].

## Function

IL-23 may induce the production of gamma interferon and thus for local early non-specific inflammatory response development. It may also act to enhance Th 17 cells, especially as regards bacterial infections. It will enhance the activation of natural killer (NK) cells and regulate antibody production via interaction with T-helper cell subsets.

As with other cytokines (and other biological molecules) IL-23 interacts with IL-23 receptors on cells to induce its' biological activity. The receptor complex is comprised of IL-23R, which is unique for the IL-23 molecule and IL-12RB1, a shared molecule with IL-12. IL-23R binds selectively to the p19 subunit mentioned above. IL-23RB1 binds to the IL-12 p 40 subunit. IL-23R (human) is a 629 amino acid transmembrane protein. It has homology with gp 130 and IL-12R (Beta) [2].

## Pathology

Like many cytokines IL-23 has both positive and negative attributes from the standpoint of pathology or disease enhancement or inhibition. IL-23 is major influencer on the early production of the immune response including gamma interferon (IFN). IFN in turn may induce Th1 responses and other aspects of cell mediated immunity. IL-23 also is one of the factors responsible for activation of Natural Killer cells, T-cell production, and importantly regulation of the production of antibody. Th17 cells are "matured" by IL-23. All of these actions are important in the non-specific aspects of the immune response especially in the early stages. These help to induce other aspects of the immune response in the fight against infection. IL-23 along with IL-12 and IL-27 are involved in antitumor regulation [8]. IL-23 has been shown to be a major influencer of mucosal immunity at the surfaces of skin, the gut, and the lung. It influences both T-dependent and T-independent immunity. It exerts these effects by the influence of either Th1 or T17 associated cytokines. IL-23 acts as a suppressor of Treg cells which essentially prevents unwanted immune responses. As such IL-23 overcomes the Treg cell effect and this cellular immunity is induced as a result of infection in the gut. There are a variety of gut pathogens that evoke a significant IL-23 response, which encompasses host defence. IL-23 is at least partially responsible for epithelial cells to produce other cytokines which induce anti-microbial factors against various bacteria and fungi infections [9].

However, the most significant aspects of the understanding around IL-23 are related to pathology.

## Psoriasis

This cytokine related disease affects about 2% of the population worldwide. It is caused by an imbalance and overexpression of IL-23. IL-23 activates Th-17 and Th-22 cells which in turn produce IL-17 and IL-22, which activate the inflammatory cascade [10,11]. IL-17 causes

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upregulation of the inflammatory response linked to keratinocytes in psoriatic skin. Leukocytes are also recruited to a disease area by IL-19, often in concert with IL-36 which activates STAT3 which causes hyperplasia and plaque formation. Successful targeting of IL-17A results in reduced pathology and increase in quality of life. Studies in human psoriasis patients (with flow cytometry) have shown that in volunteers with active untreated psoriasis IL-17A, IL-22 and gamma interferon are all increased, which indicate high levels of Th17 cells. Biopsies of psoriasis lesions have shown elevated levels of the same cytokine [12].

## Tumors

IL-23 may be considered either a ying or a yang molecule relative to tumor growth in animals. Exogenously produced and overexpressed IL-23 have a potent anti-tumor effect expressed through memory T cells. In the case of endogenously produced IL-23, tumor growth is promoted. It does so by inducing the classic inflammation pathways. These include macrophage infiltration, angiogenesis and an increase in matrix metalloproteinase development [13].

## Inflammatory bowel disease (IBD)

This group of diseases includes ulcerative colitis (UC) and Crohn's Disease (CD), both of which are chronic intestinal track inflammatory diseases. CD is associated with a Th1 cytokine pattern and UC a Th2 cytokine pattern. The elucidation of the role of IL-23 in these diseases has largely been done by in vivo studies. When IL-23 is blocked host immunity is somewhat limited and these diseases are also modulated. Anti-IL-23p19 given for colitis induced disease in mice eliminated the disease [14]. IL-12p40 antibody has been shown to neutralize CD in the clinic. These two pieces of information show a strong correlation between IL-23 presence and bowel disease.

## Rheumatoid arthritis (RA)

This complex disease which is chronic and systemic is also caused by an imbalance in the cytokine network with a result that there is inflammation of joints and cartilage which over time leads to issues with other organs and tissue. Joints affected by the RA contain monocytes and macrophages, T cells and plasma cells. It is useful to note that tumor necrosis factor (TNF) is the currently targeted cytokine for treatment of this syndrome. The IL-23p19/IL-17 complex is essential in the development of both RA and multiple sclerosis [15]. IL-23 is responsible for the regulation of Th17 cells in terms of stimulation of IL-17. IL-17 then stimulates other cytokines such as interferon and TNF which in turn causes synovial inflammation and joint destruction [16]. Should IL-17 be blocked in some fashion these diseases are modulated.

## Treatments

Ustekinumab and Risankizumab are both monoclonal antibodies directed at IL-23 for the treatment of plaque psoriasis. Ustekinumab's mechanism of action is to prevent human IL-23 (and IL-12) from bonding to the IL-12RB1/23R receptor chain on the natural killer and T-cells [17]. Thus, IL-12 and IL-23 mediated cell activation is prevented. As a result, cytokine production is prevented.

Risankizumab binds to the p 19 subunit of the interleukin [12]. It has shown efficacy in clinical trials for the treatment of plaque-psoriasis. Should the subunit be blocked, the differentiation results of TH-17 and TH-22 which activate the inflammatory cascade are prevented. Thus, risankizumab inhibits the cascade which activates IL-17 and prevents the IL-17 recruitment of leukocytes to psoriatic lesions, with the end result of plaque formation.

## Conclusion

IL-23 is an enigma, and a wonder in terms of biological molecules in terms of its diverse functions. Like many cytokines it has both disease-preventing and disease-causing aspects. The number and variety of other inflammatory mediators that it stimulates is astounding, especially when one considers the variety of diseases that occur as a result of IL-23 stimulation. But conversely, it also has protective effects, sometimes related to the same disease (tumor development). The continual development of new compounds to interact with IL-23 will have broad applications related to the syndromes caused by this molecule.

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