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Mini Review

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Interleukin-6

Clyde Schultz*

Department of Biology University of Calgary, Calgary, Alberta, Canada

Abstract

Interleukin-6 (IL-6) is a cytokine produced by a variety of immune cells in response to non-specific stimuli. IL-6 can be found in every body tissue and its' production is not localized by tissue type or by cell type. This cytokine is important as a signal to other cells, which in response stimulate other cytokines such as Interleukins 1, 2, 17 and Tumor Necrosis Factor (TNF) to be produced. IL-6 is implicated in a variety of disease states from arthritis to ocular inflammation, to implications with certain forms of mental illness.

Introduction

Structure

IL-6 is the best studied member of a group of cytokines that have similar structure but different specific functions [1]. Other members include IL-11, leukemia inhibitory factor, ciliary inhibitory factor, IL-27 and IL-31. IL-6 is approximately 24 kDa and is a glycosylated protein. It is composed of a four-helix bundle (A, B, C, D) which is a characteristic of the IL-6 family and has three receptor binding sites referred to as 1, 2 and 3. Site 1 contacts the IL-6R. Site 2 comprises the central areas of domains A and C, and is a gp130 contact between domains 2 and 3, and site 3 contacts domain 1, which is the Ig domain of gp130. Site 1 is formed by helix D and the c-terminal section of the AB loop. This determines the specificity of the IL-6 binding site. Site 2 is comprised of residues located in the middle of helices A and C. Site 3 consists of residues on the AB loop at the N-terminal area. All members of the IL-6 family of cytokines, except for IL-31 share the membrane glycoprotein gp130 as a common receptor [2,3].

Function

IL-6 has a variety of roles in the body. It induces the maturation of platelets and activates stem cells. It activates osteoclasts leading to bone resorption. It is found in the tear fluid in response to stimuli such as contact lens wear [4]. IL-6 will induce vascular endothelial growth factor (VEGF) in response to inflammation. This increases angiogenesis. Not all occurrences of IL-6 stimulation are positive. In this last case, VEGF stimulation leads to blood vessel encroachment in the retinal segment and thus age related macular degeneration [5]. Further, IL-6 activation can lead to dermal fibroblast collagen production and thus contribute to psoriasis and sclerosis [6].

In inflammation caused by an infectious agent, IL-6 is produced by monocytes and macrophages after stimulation by toll like receptors or TRLs. For non-infectious inflammation, such as occurs by trauma damage, or dying cells produce TRLs to produce IL-6. IL-6 stimulation can induce C-reactive protein (CRP) serum amyloid A, and fibrinogen. CRP stimulation is also used as an inflammation biomarker. IL-6 induces B cell differentiation, and along with transforming growth factor stimulates IL-17 producing T helper cells for the induction of autoimmune tissue injury [5,7,8].

As mentioned, IL-6 stimulates both inflammatory and auto-immune processes in diabetes, depression, arthritis, and systemic lupus erythematosus. Inflammation in the acute stage is characterized by infiltration of neutrophils, followed by monocytes and T-cells hours to a day or so later. IL-6 presence is necessary for T-cell recruitment. It plays a role in T and B-cell differentiation. IL-21 production which occurs at least partially due to IL-6 stimulation will promote B helper capabilities of CD4+ T-cells.

Signaling

IL-6 functions at the cellular level by interacting with the cell receptor for IL-6 (IL-6R). One of two forms of IL-6R may result. In the first case, the transmembrane form, an IL-6/IL-6R complex results which selectively binds to gp130 [8,9]. This first case is the classic signaling as a result of the formation of two molecules each of IL-6, IL-6R and gp130. gp130 is found in all body tissues, including the ocular environment. Since some cells lack IL-6R, signaling can also be accomplished through sIL-6R, which is a soluble form followed by association with the gp 130 pathway. The sIL-6R/IL-6 complex has the ability to interact with cells via membrane bound gp130 which makes it capable of interacting with most cell types, unlike IL-6R, thus increasing the number and types of cells IL-6 may interact with [9]. This is somewhat different than other cytokines [10].

Treatment

In the instances where the presence of IL-6 requires intervention, Tocilizumab a human monoclonal antibody is used as treatment. It blocks both the transmembrane and serum forms of IL-6 receptors, thus blocking signaling and preventing T cell activation as well as antibody secretion. It is proscribed for patients who have active

Correspondence to: Clyde Schultz, Department of Biology University of Calgary, 2500 University Drive, Calgary, Alberta, Canada, E-mail: schultzc@ucalgary.ca

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rheumatoid arthritis. It is given intravenously at 4-week intervals, and is adjusted by body weight, starting at 4 mg/kg. There are some safety concerns associated with tocilizumab use such as infusion reactions and infections. However, some of this is related more to the IV treatment itself and not necessarily to the drug [11].

Treatment of uveitis with tocilizumab was found effective in patients with cystoid macular edema, Birdshot chorioretinopathy and idiopathic granulomatous panuveitis. The patients affected by these last diseases had become refractory to immunosuppressive drugs [12].

Conclusion

Interleukin 6 is an important signaling intermediate in the human immune system. It interacts with complement and other cell receptors. Treatment and prevention of IL-6 stimulation is key to disease treatment in several areas. Among these are arthritis, uveitis and diabetes. Tocilizumab is the currently the only treatment for IL-6 induced disease. There are other molecules under development but none as yet approved for human use. The blockage of IL-6 is important as a treatment for inflammatory disease.

References

1. Gelinas AD, Davies DR, Edwards TE, Rohloff JC, Carter JD, et al. (2014) Crystal structure of interleukin-6 in Complex with a Modified Nucleic Acid Ligand. *J Bio Chem* 289: 8720-8734. [Crossref]
2. Chow D, He X, Snow AL, Rose-John S, Garcia KC (2001) Structure of an extracellular gp130-cytokine receptor signaling complex. *Science* 291: 2150-2155. [Crossref]
3. Yawata H, Yasukawa K, Natsuka S, Murakami M, Yamasaki K, et al. (1993) Structure-funciton analysis of human IL-6 receptor: dissociation of amino acid residues required for IL-6 binding and for IL-6 signal transductions through gp130. *EMBO J* 12: 1705-1712.
4. Schultz C, Kunert KS (2000) Iinterferon-6 Levels in Tears of Contact Lens Wearers. *J Interferon Cytokine Res* 20: 309-312. [Crossref]
5. Taga T, Kishimoto T (1997) Gp130 and the interleukin-6 family of cytokines. *Annu Rev Immunol* 15: 797-819. [Crossref]
6. Grossman R, Krueger J, Granelli-Piperno A, Murphy DP, May LT (1989) Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. *PNAS* 86: 6367-6371.
7. Ishibashi T, Kimura H, Shikama Y, Uchida T, Kariyone S, et al. (1989) Interleukin-6 is a potent thrombopoietic factor in vivo in mice. *Blood* 74: 1241-1244.
8. Kotake S, Sato K, Kim KJ, Takahashi N, Udagawa N, et al. (1996) Interleukin 6 and soluble interleukin 6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like formation. *J Bone Miner Res* 11: 88-95. [Crossref]
9. Boulanger MJ, Chow DC, Brevnova EE, Garcia KC (2003) Hexameric structure and assembly of the interleukin-6/IL-6 alpha receptor gp130 complex. *Science* 300: 2101-2104. [Crossref]
10. Scheller J (2006) Updating IL-6 classic and trans-signaling. *Signal Transduct* 6: 240-259.
11. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, et al. (2008) Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double blind, placebo-controlled, randomized trial. Lancet 371: 987-997. [Crossref]
12. Curnow SJ, Falciani F, Durrani OM, Cheung CM, Ross EJ, et al. (2005) Multiplex bead immunoassay analysis of aqueous humor reveals distinct cytokine profiles in uveitis. *IOVS* 46: 4251-4259.