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Interleukin-17

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Abstract

Interleukin 17 (IL-17) is comprised of a group of 6 known cytokines that have a unique structure relative to other cytokines and are involved in cellular signaling. IL-17 has both positive and negative aspects, and can trigger the immune system in a protective sense in response to infection or cause diseases such as psoriasis.

Structure

IL-17 is a di-sulfide containing a 155 amino acid sequence protein of about 35 kDa. The structure is essentially 2 peptides [1]. The first peptide is comprised of 23 amino acids and the second is comprised of 123 amino acids. As such, it is homo-dimeric. Each dimer is under 20kDa [2]. The IL-17 family of cytokines are comprised of four cysteines that form two disulfide bonds. The related IL-17 cytokines have 6 members labelled A to F [3]. IL-17 E is also known as IL-25. Members of the group are can be produced by a variety of cells including epithelial cells [4,5,6].

IL-17 is not structurally related to any other cytokine. This makes it unique among this group of biological molecules which function largely as chemical messengers.

Function

IL-17 is expressed by a variety of cells in the body including epithelial cells, and has the ability to initiate a significant inflammatory response that includes induction of granulopoiesis factors and neutrophil related chemokines [5,7]. It can initiate acute phase responses in concert with IL-6 [8]. In combination with tumor necrosis factor it can up-regulate a variety of genes which encode for the inflammatory cascade. IL-17 and TNF can induce neutrophil migration to a specific area, often within a matter of minutes. It should be noted that TNF and IL-17 are not always induced at the same time [9]. The induction of IL-17 is dependent on the expression of some other cytokines such as IL-1B and IL-23.

IL-17 is produced by a small subset of Th cells called Th17 cells. T cell development occurs in the thymus and results in either CD-4 positive T cells or CD-8 positive T cells. CD-4 positive T cells are helper T cells and depending on whether IL-12 or IL-4 are the main influencer the cells become either Th1 or Th2 cells (10). Th1 cells develop under the influence of IL-12 and produce interferon-gamma. Thus, Th1 cells support cell mediated immunity. Interferon-gamma activates macrophages and promotes the elimination of pathogens. Th2 cells develop under the influence of IL-4 and support B cells, enabling antibody class switches (IgM to IgG), thus supporting humoral immunity. When Th1 predominates there is a bias toward autoimmune disease such as multiple sclerosis and rheumatoid arthritis (RA) [11].

IL-17 is known to be secreted by Th17 cells, and induced by the presence and activity of macrophages, natural killer (NK) cells, dendritic cells and lymphoid inducer cells [7,9,12].

Pathology associated with IL-17

IL-17 has been shown to be involved with periodontal bacteria and thus the associated infection [4]. The relationship of this disease (with IL-17) is complex in that it has both a protective and destructive aspect to the presence of the cytokine. If IL-17 is induced, it in turn induces an acute inflammatory response that is destructive to disease causing bacteria. Should the acute inflammatory response develop into a chronic response, then this conversion becomes tissue destructive. IL-17 can mediate and induce a response to pathogens and in concert with IL-22, antimicrobial peptides can be produced.

The understanding of the effects of IL-17 mediated pathology has increased since the discovery of the Th17 subset of Th cells [10]. Rheumatoid arthritis as with other autoimmune diseases occurs as the result of the presence of IL-17 or the Th17 pathway [11]. IL-17 acts as a stimulant for TNF-alpha, IL-1 beta, and IL-6 from cartilage, macrophages and bone cells [6]. The presence of IL-17 induced IL-6 serves to maintain the IL-17 T cell population in a positive feedback loop. In addition, other cytokines are produced which serve to recruit macrophages, neutrophils to the areas of inflammation, thus enhancing inflammation at the site. The deformities that result involve cartilage and bone erosion, a key element of RA.

Psoriasis is a chronic skin disorder with key features including vascular proliferation and infiltration of macrophages, T-cells and neutrophils [13]. The mechanism of action of IL-17 in psoriasis may stem from its partial regulation of IL-22. Interleukins 17 and 22 act together to express skin antimicrobial peptides including S100A7 (psoriasin) which when elevated in patients correlate with disease onset.

In contrast to autoimmune diseases IL-17 tends to play a protective role in microbial infection. IL-17 modulates cytokines to promote polymorphonuclear cell expansion as a result of infection [4,8]. It causes the stimulation of chemoattractant for neutrophils and other immune cells causes them to migrate to areas of infection, especially at the mucosal surfaces. Klebsiella pneumoniae and Citrobacter rodentium are both modulated by the presence of IL-17.

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Treatment

Direct treatment for IL-17 induced pathology is a cause of intense study currently. Treatment for pathology caused by excess IL-17 is with inhibitors such as Cosentyx (secukinumab), which is a monoclonal antibody [14]. It has been approved by FDA for the treatment of plaque psoriasis. Other compounds being investigated include the active form of Vitamin D which has been found to hamper the production of IL-17 produced by Th17 cells [15].

Conclusion

The elucidation of IL-17 as a major contributor to disease in both a positive (in the case of microbial infections) and negative in the case of autoimmune disorders is a cause of some amount of wonder in scientific circles [7]. IL-17 can act as a feedback to promote or down regulate the production of other cytokines depending on the degree and type of stimulation. Treatments for 1L-17 induced conditions will become more important and more common as research continues on this interleukin.

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