Interleukin-18

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Abstract

Cytokines are similar to hormones in that they are chemical messenger molecules released by cells. Cells have binding sites for the cytokines on the outside of their plasma membranes. Binding of a cytokine to a receptor can cause various cellular events such as upregulation of the expression of a gene, or a change in cellular processes. Interleukin-18 (shown in Figure 1 on page 1) is one such cytokine [3]. Interleukin-18 (IL-18) has been implicated in processes as diverse as the promotion of inflammation, bone loss, asthma and Alzheimer's disease [10, 8, 2]. This review will discuss the discovery of Interleukin-18 and some of the currently known processes it is involved in.

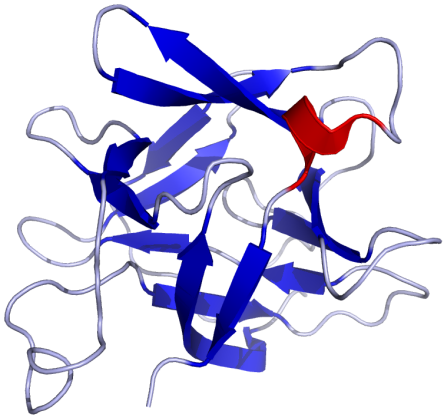

Figure 1: *Structure of Interleukin-18*

I. Background

Interleukin-18 was discovered in 1989 when an unknown mechanism was observed to trigger production of interleukin-γ. Murine cells previously exposed to lipopolysaccharide (LPS) were exposed to *Mycobacterium bovis*. Nakamura, et al. observed an increase in interleukin-γ driven by a then-unknown mechanism. Originally thought to only be a part of triggering interleukin-γ, what is currrently know as IL-18 was first named interleukin-γ-inducing factor [7]. IL-18 is now known to have other important immunological functions including the regulation of innate and acquired immune responses.

In the absence of a promotional signal, IL-18 is expressed constitutively. When upregulated by a promoter binding to a promoter-region upstream of exon 1 of IL-18, production is increased[8]. Typical concentrations for cytokines are in the picomolar (10^{-12}) range whereas activation can raise the concentrations 1 000 fold to the nanomolar (10^{-9}) range [3].

II. Actions

High levels of IL-18 are associated with many disease and autoimmune processes. Leick, et al. conducted experiments on obese and non-

obese subjects and concluded that obese subjects had elevated levels of IL-18 and IL-18R mRNA[5]. These results were confirmed by data from the Dallas Heart Study[11]. The presence of elevated levels of IL-18 is believed to play a role in insulin resistance, which can lead to diabetes. Exercise was found to lower the levels of IL-18 showing that lifestyle changes can lower IL-18 and, it is believed, lower susceptibility to insulin resistance and diabetes [5].

IL-18 is also believed to play a role in atherosclerosis. Atherosclerosis is the accumulation of white blood cells and fatty deposits in the walls of the arteries. The accumulation of deposits is aided by high levels of low-density lipopolysaccharides (LDLs). Clearing of the accumulation is facilitated by high-density lipopolysaccharides. According to data obtained through the Dallas Heart Study, high levels of IL-18 are correlated with atherosclerosis. After adjusting for other factors that lead to atherosclerosis, elevated IL-18 was not found to be viable as a new diagnostic tool for prediction of atherosclerosis [11]. Though it is not useful as a predictor, it does play a role in atherosclerosis. Lectin-like oxidized LDL receptor-1 (LOX-1) is thought to play a role in plaque rupture. Experiments conducted by Mitsuoka, et al. showed that IL-18 increases soluble LOX-1 cleavage by 3-4 times, thus implicating IL-18 in the rupture of atherosclerotic plaques [6].

In addition to atherosclerosis, IL-18 has been associated with inflammation of epithelia in the lungs. Clusters of immune cells form in lung and other tissue creating clumps associated with inflammation. This condition is called sarcoidosis [1]. Sarcoidosis is associated with T_H1 cells. As previously stated, IL-18 is produced constitutively by epithelial cells. Murine lung cells treated with LPS as well as human sarcoidosis patients experienced an up-regulation of expressed IL-18, whereas murine lung cells treated with ovalbumin[1] (OVA) and human asthma patients did not exhibit up-regulation of IL-18. Since lung epithelia are the first line of defense for inhaled pathogens, the expression of IL-18 by these cells demonstrates its participation in early immune defenses [2].

IL-18 has also been shown to work in concert with T_H1 cells to bring about bronchial asthma when naïve mice were presented with both antigen and IL-18, but not with antigen alone. Stimulation of T_H1 cells with antigen and IL-18 caused them to become pathlogical, and stimulated their production of IL-13 and interferon-γ, which induced severe airway inflammation [4].

Interestingly, stimulation of T cells with IL-12 and IL-18 exhibit T_H1 response, whereas stimulation with IL-2 and IL-18 exhibit T_H2 response, even in the absence of antigen. Ishikawa, et al. have proposed that this pathway of T_H1 or T_H2 cytokine production without TCR binding be named "innate type 1 or type 2 activation" [4]. In fact, IL-12 and IL-18 actually inhibit differentiation of T_H2/T cytotoxic 2 cells [9].

While IL-18 can bring about inflammation and stimulate the release of inflammatory cytokines by T_H cells, it can also serve to inhibit the inflammatory response by inhibition of IgE production. Knockout mice that are IL-18$^{-/-}$ have higher levels of IgE and IgG1 production compared to wild-type mice in response to OVA/alum[2]. This demonstrates the regulatory role IL-18 plays in immunity. IL-18 driving the immune system away from the allergic response is shown when CD8 T cells produce IL-18 during interaction with antigen presenting cells in conjunction with IL-12. This suggests that drugs targeting IL-18 might be useful in treating allergic response [9].

III. Conclusion

IL-18 is a prolific cytokine involved in many immune processes. As outlined in this review, it is involved in inflammatory processes, as well as the suppression of allergic responses. It can be found where there is obesity, heart

[1] The primary protein found in egg white.

[2] Aluminum hydroxide - an adjuvant that stimulates the innate immune system and increases potency of antigen.

disease, endotoxin such as LPS, sarcoidosis, asthma, the list goes on.

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