Review

Cytokines in Immune Response and Disorders: Cytokines and Soluble Inhibitors

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Abstract: Over a long period of time, animals have built defense mechanisms to block external intruders through a complex evolutionary process. The structure created at the center is called the immune system. In animals with a vascular system, immune cells circulating in the blood perform most of the role. Cytokines are substances that direct immune function and are not only produced by immune cells but also secreted by non-immune cells, contributing to the proliferation and differentiation of blood cells. Most blood cells are red blood cells that supply oxygen in the body, and a small number of white blood cells (WBC) perform immune functions. Even under normal circumstances, mammalian WBC are produced in the bone marrow, differentiate into various immune cells, and proliferate under the stimulation of cytokines. However, when infected with external pathogens, viruses, bacteria, fungi, and parasites, cytokines are produced exponentially and temporarily induce proliferation and differentiation of immune cells defending the host from pathogens. Once all pathogens are destroyed by immune cells, excessive cytokine activity is downregulated by soluble antagonists, such as cytokine binding proteins and ligands, but which have receptor antagonist properties. In this review, we will discuss the roles of cytokines, which are immune enhancers, and soluble cytokine binding proteins, which are immunosuppressants, and various autoimmune diseases that arf44ise from immune imbalance.

Keywords: cytokine; cytokine binding protein; soluble inhibitor; immune cell proliferation; immune cell differentiation

1. Infection and Immune Response

An infection is the invasion of pathogens such as viruses, bacteria, fungi, and parasites resulting in illness. Hosts defend against infectious pathogens through their immune systems. Mammalian hosts often respond to infectious pathogens with an innate response, including inflammation, followed by an adaptive response [1]. The immune system responds to infectious pathogens in the skin, tissues, and blood. It consists of the innate and adaptive immune systems, which work closely together to perform different tasks to protect host against infectious pathogens. The innate immune system is the first line of defense against infectious pathogens and known as "non-specific" immune system because it responds similarly to all infectious pathogens. When the innate immune system fails to destroy infectious pathogens, the adaptive immune system can still clear the infection by specifically recognizing and targeting the pathogen. Unlike the innate immune response, the adaptive immune system reacts more slowly than the innate immune system but is more accurate when it responds. Moreover, the adaptive immune system can build an immunological memory that enables it to fight germs faster and stronger upon subsequent infections [2,3].

2. Cytokines in Immune Response

Initiating and coordinating an effective immune response requires mechanisms for immune cells to communicate with each other. Cytokines convey immune cell functions and are generally composed of proteins or glycoproteins smaller than 30 kDa, although some are larger than 30 kDa [4]. Cytokines play a role in regulating immune and inflammatory responses, and these effector molecules are produced constitutively at low levels but transiently at exponential levels to locally control the amplitude and duration of the immune response [5]. The two

main producers of cytokines that influence both innate and adaptive immune responses are T helper (Th) cells and macrophages, but cytokines can be transiently induced and secreted by virtually all nucleated cells, including non-immune cells. Most of the cytokines produced by CD4+ T cells, especially at the onset of an immune response, were thought to play a critical role in pathological or physiological outcomes [6–11]. Cytokines such as interleukin (IL), tumor necrosis factor (TNF), and interferon (IFN) family are known to be contributed to infectious and autoimmune diseases [5]. TNF, IL-1, and IL-6 are proinflammatory cytokines produced early after pathogen infection. Unlike acute inflammation, chronic inflammation occurs in the absence of infection due to genetic, environmental, or aging-associated disorders. Chronic inflammation is caused by proinflammatory cytokines such as TNF, IL-1, and IL-6, and chronic inflammation diseases can be treated with anti-TNF, IL-1, and IL-6 antibodies or soluble binding protein inhibitors [12–15].

3. Recovery from Infection

While infection induces the immune response, the increased immune response is returned to normal levels by immunosuppressive proteins such as TNF binding protein and IL-18 binding protein [16–22]. The enhancement of the immune response derives from a variety of cytokines, such as the proinflammatory cytokines TNFα and IL-1β which are induced very early after bacterial infection [23]. Type 1 IFNs are induced after viral infections and Th2 cytokines are induced after multicellular parasites such as helminths. Single-cell parasites and intracellular bacterial infections induce Th1 immune responses like viral infections [24–27]. The induction of these cytokines stimulates immune cell proliferation and promotes differentiation, thereby enhancing immune cell function to destroy and eliminate infectious pathogens.

After the infectious pathogen is eliminated, the increased immune response returns to homeostasis. For this purpose, immunosuppressive soluble binding inhibitors are produced, which function to restore normal immune levels [28–30]. However, if soluble binding inhibitors, which are immunosuppressants, fail to suppress the upregulated immune response after pathogen infection, a life-threatening cytokine storm can occur [31].

4. Immune Disorder

Most acute inflammation is caused by the infectious pathogens mentioned above, whereas chronic inflammation occurs in the absence of infectious pathogens. The cause of chronic inflammation is cytokine dysregulation due to aging, environmental, and genetic factors (Figure 1). Th1 autoimmune disease such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis are well known for their chronic inflammation driven by the proinflammatory cytokines TNFα, IL-1β, and IL-6 [32]. Anti-TNFα monoclonal antibody therapies (e.g., Humira; adalimumab, Remicade; infliximab, Simponi; golimumab, Cimzia; Certolizumab pegol) as well as a soluble TNFα receptor (also known as soluble TNFα binding protein; Enbrel; Etanercept) have been used to treat Th1 autoimmune disease such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis for last four decades [33–35]. Unlike soluble TNFα receptor, neither the soluble IFN nor IL receptors are used to neutralize ligand activity. Reasons why soluble IFN or IL receptors may fail to neutralize ligand activity due to their receptor composition include: That is, TNFα receptors act as homotrimers, whereas IFN or IL receptors act as heterodimers or heterotrimers (Figure 2) [36].

IL-1 receptor 1 (IL-1R1) antagonist (Kineret, also known as Anakinra) inhibits IL-1α and IL-1β activity by binding to the IL-1Rα chain without recruiting the co-receptor IL-1Racpwhich competes with IL-1α and IL-1β (Figure 3A) [37,38]. However, Rilonacept is a dimeric fusion protein consisting of the extracellular portions of IL-1R1 and IL-1R3 (also known as IL-1Rα and IL-1Rβ chain) in series with the Fc region of human IgG1, which binds and neutralizes IL-1α and IL-1β (Figure 3B). Anti-IL-1 therapy is used for familial Mediterranean fever (FMF), a prototypical IL-1 driven disease, rather than Th1 autoimmune disease [39]. Anti-IL-6 monoclonal antibody therapy (Actemra also known as Tocilizumab) is used to treat Th1 autoimmune disease [40,41] but is not popular as an anti-TNFα therapy. The remaining anti-cytokine therapies, such as IL-4, IL-5, IL-12, IL-13, IL-17, and IL-23, are monoclonal antibodies against ligands and receptors that block cytokine activity [42–44].

Anti-IL-5 (Nucala also known as Mepolizumaband) and -IL-4 & -IL-13 (Dupixent also known as Dupilumab) are used for Th2 autoimmune diseases such as atopic dermatitis and asthma like allergic diseases [45], while anti-IL-17 and -IL-23 are used for Th17 and Th23 autoimmune diseases, respectively. Unlike anti-ligand, anti-IL-4 and -IL-13 (Dupixent, also known as Dupilumab) block both IL-4 and IL-13 activity by targeting the IL-4Rα chain, a co-receptor for IL-13. Anti-IL-13 (Adtralza (EU/UK) and Adbry (US), also known as Tralokinumab; Ebglyss, also known as Lebrikizumab) is also used in Th2 autoimmune diseases targeting the IL-13 ligand [46]. Anti-IL-12 (Stelara, also known as Ustekinumab) targets both IL-12 and IL-23 in the p40 heterodimer ligand, targeting Th1 and Th17 downstream of IL-12 and IL-23 in autoimmune diseases [47].

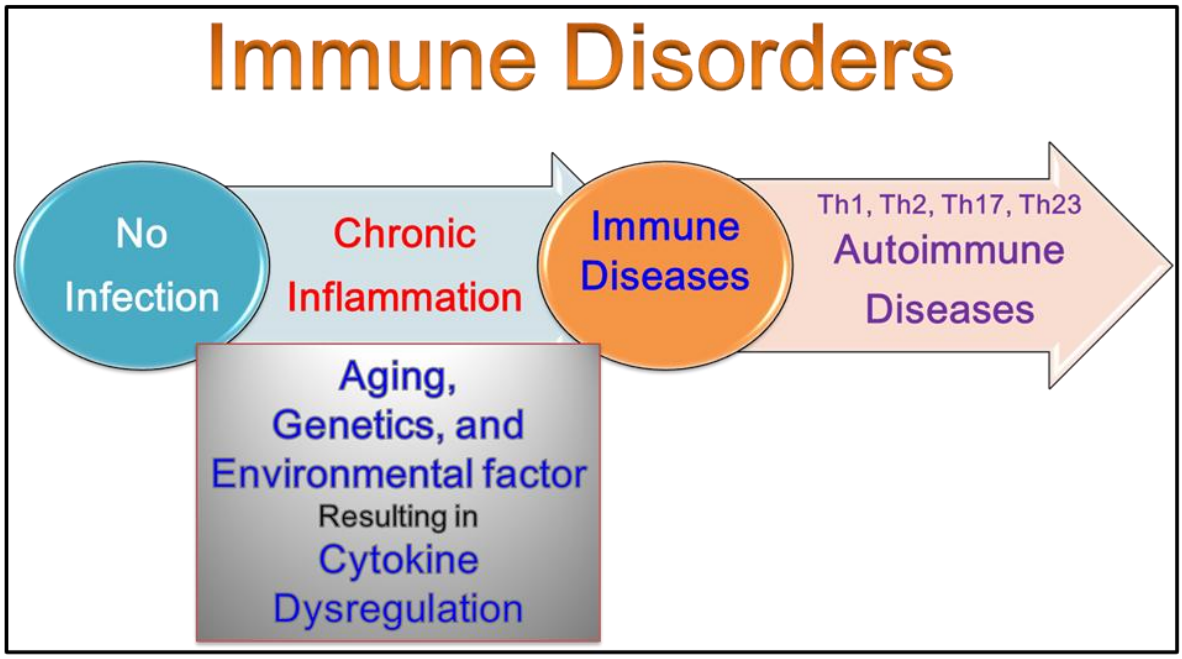

Figure 1. Immune disorder. Autoimmune diseases are caused by cytokine regulation disorders caused by aging, environmental, and genetic factors.

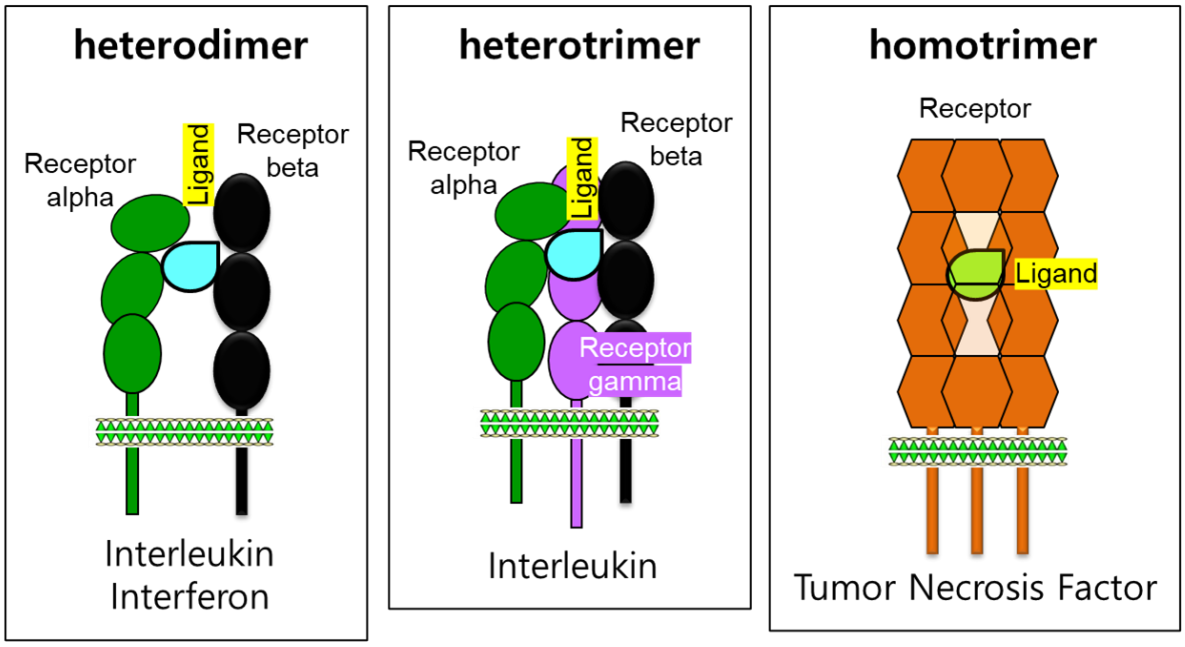

Figure 2. Composition of cytokine receptors**.** Interleukin & Interferon heterodimer (**left**), Interleukin heterotrimer (**middle**), and Tumor Necrosis Factor homotrimer (**right**) are illustrated.

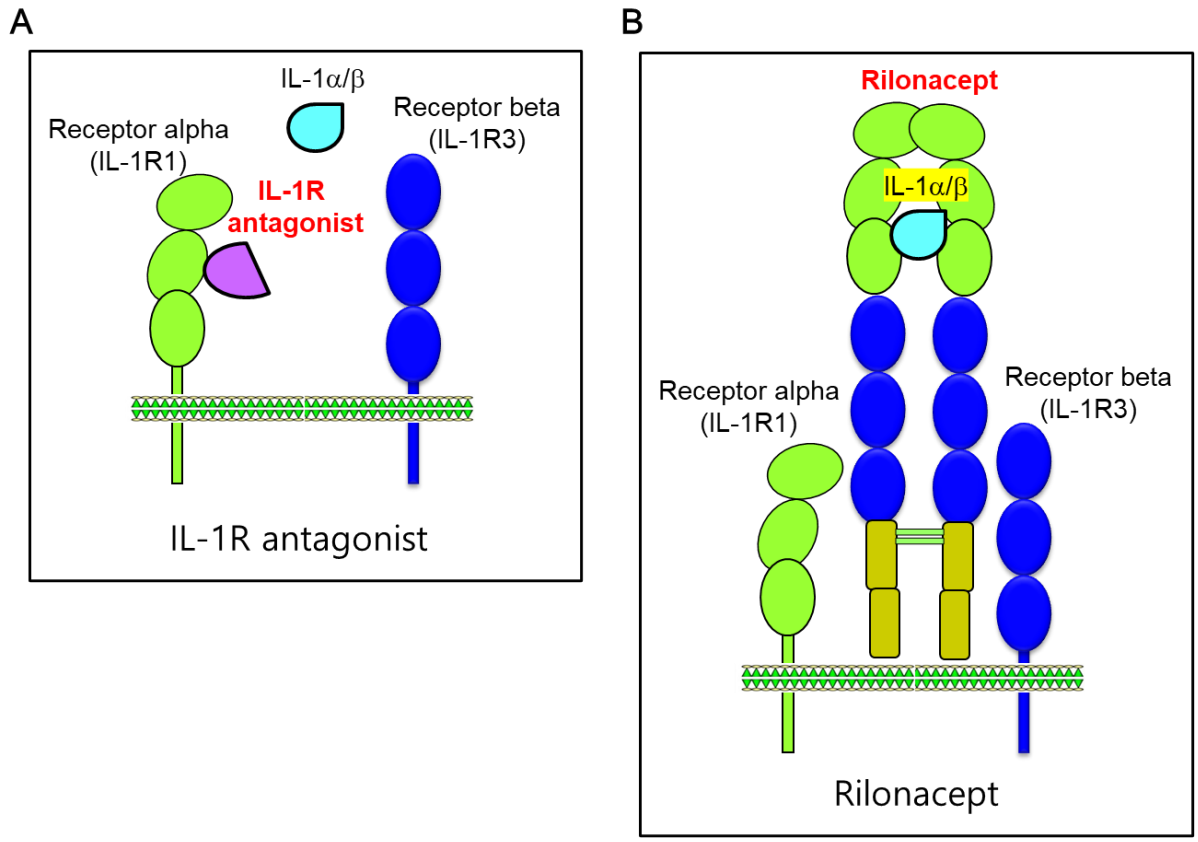

Figure 3. Action of IL-1R antagonists and Rilonacept**.** (**A**) IL-1R antagonist binds to the IL-1Rα (also known as IL-1R1) chain and competes for the binding of IL-1α/β. (**B**) Rilonacept binds to IL-1α/β and blocks IL-1Rα chain binding.

5. Conclusion

Cytokines are essential factors that induce immune responses through proliferation and differentiation of immune cells, but they also cause various autoimmune diseases. Infections with various pathogens induce Th1 and Th2 cytokines depending on the pathogen type. Intracellular pathogens such as viruses, unicellular parasites (falciparum, babesia and leishmania) and intracellular bacteria (M. tuberculosis and leprosy) induce Th1 cytokines, whereas common bacteria and multicellular parasites induce Th2 cytokines, contributing to acute inflammation. However, chronic inflammation caused by the induction of Th1 and Th2 cytokines due to aging, environmental, and genetic factors causes autoimmune diseases, bringing serious health problems to modern human society.

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Abbreviations

IFN, interferon; IL, Interleukin; Th, T helper; TNF, tumor necrosis factor; WBC, white blood cell.

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