Mini Review

Cytokines in Pathogen Infection and Autoimmune Disease

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Abstract: Immune responses have long been classified into T helper (Th)1, Th2, and Th17, with different Th type immune cells classified according to the cells that secrete specific cytokines. However, careful examination of cytokine production allows distinction between Th1 and Th2 depending on the type of infectious pathogen. For instance, Th1 cytokines are produced after intracellular pathogens such as intracellular bacteria, viruses, and protozoa whereas Th2 cytokines are produced after extracellular pathogens such as multicellular parasites. Autoimmune diseases are caused by chronic inflammation due to overproduction of Th1 or Th2 cytokines without a clear cause, but are related to aging, genetic factors, and environmental factors. This brief review explores the regulation of immune responses by cytokines, outlining potential theories for understanding infectious and inflammatory autoimmune diseases.

Keywords: Th (T helper); cytokine; intracellular pathogen; extracellular pathogen; autoimmune disease

1. T helper (Th)1/Th2 T Cell Cytokines

Cytokines are soluble proteins responsible for the biological activities of innate and adaptive immune responses that protect the host from various pathogens [1]. There are many different cytokines, functionally divided into two groups such as pro-inflammatory and anti-inflammatory [2]. Cytokines are mainly produced by T cells that have antigen-specific receptors on their surface (Figure 1A,B). Therefore, T cells can recognize foreign antigens of pathogens, and in the case of autoimmune diseases, they can also recognize their own antigens in normal tissues [3]. Murine helper T cell clones have been described to explore how immune responses to invading pathogens can be mediated. T cells express cell cluster of differentiation (CD) 3 and have been found to express CD4 (Figure 1B) or CD8 (Figure 1A) on their cell surfaces. T cells that express CD4 are also called helper T cells and are known to produce the most cytokines. CD4 T cells are subdivided into Th1 and Th2, and the cytokines they produce are called Th1-type cytokines and Th2-type cytokines (Figure 1B) [4].

MHC I molecules present peptides synthesized by antigen-presenting cells, which are primarily generated by proteasomal degradation of defective ribosomal products (DRiPs) and other self-proteins [5]. These endogenous peptides, which are typically 8–12 amino acids long, are transported from the cytoplasm to the endoplasmic reticulum (ER) by the transporter for antigen processing (TAP) [6]. ERp57 enzyme of the thiol oxidoreductase family is present in the ER [7–9] and this molecule attaches indirectly to its substrate, an endogenous 8–12 amino acid residue, by binding to the molecular chaperone calreticulin of the peptide loading complex [10,11], which are then presented on the cell surface for surveillance by CD8 T cells (Figure 1A).

Antigen presentation by MHC II presents peptides (length of range from 13 to 25 amino acids) derived from other organisms. Peptides presented by MHC II molecules are derived from proteins found outside the cell, such as pathogens, environmental antigens, or self-proteins released from other cells [12,13]. These peptides are produced when specialized antigen-presenting cells, including B cells, dendritic cells (DCs), and macrophages, ingest extracellular proteins through various processes such as phagocytosis, pinocytosis, or receptor-mediated endocytosis [13]. Ingested exogenous proteins are broken down into smaller peptide fragments within endosomes

or lysosomes, and these fragments are loaded onto MHC II molecules present on the cell surface for surveillance by CD4 T cells (Figure 1B).

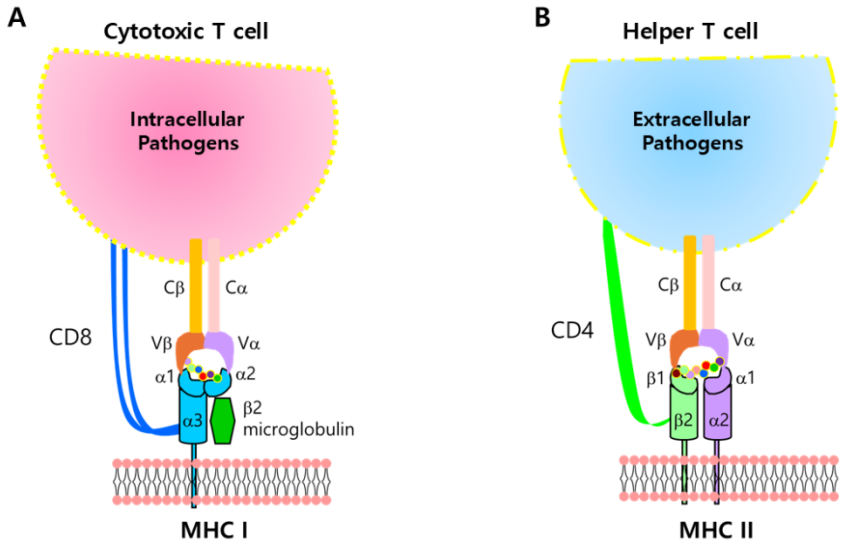

Figure 1. MHC I and II presentation of antigen peptide to T cell. (**A**) MHC I consists of an alpha chain with three domains connected to beta 2 microglobulin. Endogenous 8–12 amino acid residues are presented to the CD8 T cell receptor via the alpha 1 and alpha 2 variable regions of MHC I. (**B**) MHC II consists of an alpha chain and a beta chain, each of which has two domains. Exogenous MHCII-binding peptides are typically 13 to 25 amino acids long and are presented to the CD4 T cell receptor through the alpha and beta variable regions.

2. Th1, Th2, Th17 T Cells, and B Cell Development for Eliminating Different Pathogens

Unlike predetermined T cell phenotypes, Th1 and Th2 T cells represent the final stages of a multistep differentiation process from a common precursor T cell population and have distinct cytokine secretion profiles. A key question is how these differentiation decisions are influenced by the various pathogens the immune system encounters. Infectious pathogens can influence the properties or types of DCs with which naive CD4 T cells interact [14].

CD4 Th1 T cells produce the inflammatory cytokines interleukin (IL)-12, interferon (IFN) α, and tumor necrosis factor (TNF) α, which kill viruses, intracellular bacteria (*M. Tuberculosis* and *M. Lepromatosis*), parasites (Protozoa; *Plasmodium falciparum* and *Leishmania*) as well as perpetuate autoimmune diseases. However, CD4 Th2 T cells produce the anti-inflammatory cytokines IL-4, IL-5, and IL-13, which help clear extracellular parasites helminth intestinal parasites (*Ascariasis, Enterobiasis*) and those Th2 cytokines are also involved in promoting immunoglobulin (Ig) E and mast cell responses in allergies (Figure 2) [14]. The overproduction of Th2 cytokines responds to Th1-mediated intracelluar pathogens. Thus, the optimal situation appears to be one in which humans generate balanced Th1 and Th2 responses appropriate for the immune challenge [15]. Various studies have shown that Th17 T cells that produce IL-17 play a role in eliminating fungi and extracellular bacteria through circulating neutrophils in peripheral blood cells. B cells are activated by Th1, Th2, and Th17 depending on the type of pathogen infection (Figure 2).

3. Pathogen-Induced Th1 and Th2 T Cell Activation by Combination of Various Cytokines

Several cytokines possess interesting properties, for example IL-18 could be a Th1 cytokine or Th2 cytokine depending on pathogen infection (Figure 3). For example, intracellular pathogens such as viruses, intracellular bacteria (*M. Tuberculosis* and *M. Lepromatosis*), and single parasite protozoa (*Leishmania* and *Plasmodium falciparum*) infections stimulate the production of IL-12, IL-2, and IFNα in the presence of IL-18 to derive Th1 T cells. IL-12 is the most dominant stimulant in the presence of IL-18 to derive IFNγ which is a key Th1 molecule against intracellular pathogens (Figure 3, Left). However, extracellular pathogens such as helminths (multicellular parasites), gram-positive and gram-negative bacterial infections stimulate the production of IL-4 and IL-13 in the presence of IL-18 to derive Th2 T cells for elimination of extracellular bacteria and multicellular parasites (Figure 3, Right).

Chronic inflammation in the absence of pathogen infection causes autoimmune diseases such as Th1 autoimmune diseases (RA, Rheumatoid Arthritis; IBD, Inflammatory Bowel Disease; Psoriasis) and Th2 autoimmune diseases (Asthma and Atopy), as illustrated at the bottom of Figure 3. According to various studies, allergic diseases are caused by Th2 weight imbalance. Therefore, recently, methods to reduce the incidence of allergic Th2 autoimmune diseases by switching allergic Th2 responses to Th1 responses have been studied. Some groups have studied the use of high-dose exposure to allergens to enhance Th1 responses in established diseases [16], while others have studied the use of the tuberculosis vaccine in childhood to induce stronger Th1 responses [17,18].

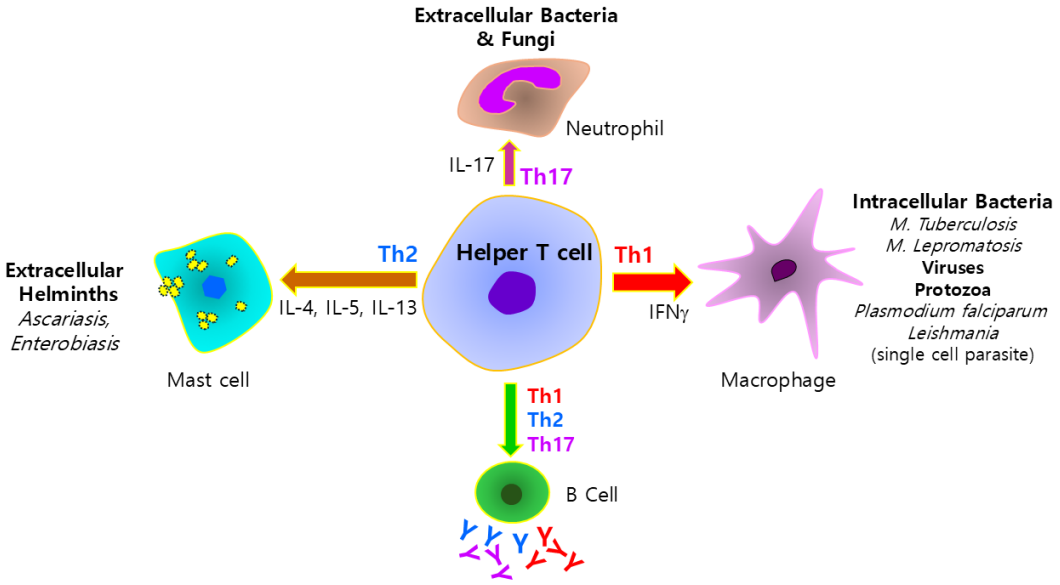

Figure 2. Th1, Th2, Th17 cells produce cytokines to eliminate various pathogens via different immune cells. Intracellular bacteria and protozoa are eliminated by IFNγ-mediated macrophage activation produced by Th1 T cells (**right**), while extracellular nematodes are eliminated by mast cell activation mediated by IL-4, IL-5, and IL-13 produced by Th2 T cells (**left**). Extracellular bacteria and fungi are eliminated by IL-17-mediated neutrophil cell activation (above) produced by Th17 T cells. Th1/2/17 T cells activate B cells that produce pathogen-specific antibodies, which then eliminate a variety of pathogens through complement activation.

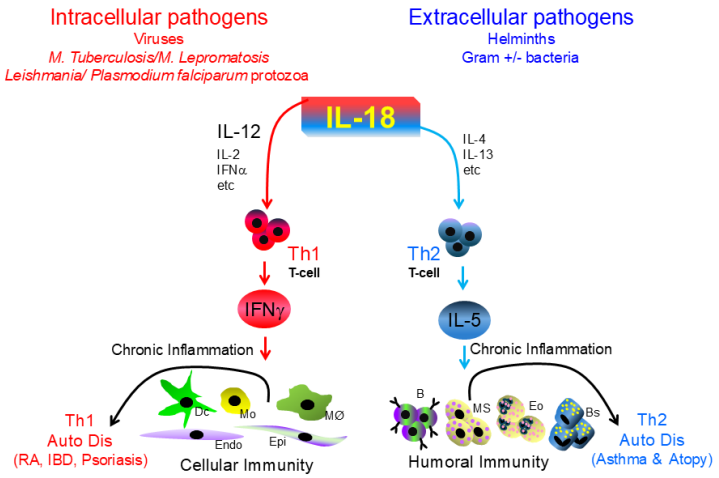

Figure 3. The dual cytokine IL-18 induces immune responses**.** Intracellular and extracellular pathogens induce Th1/Th2 immune cells, remove pathogens, and overproduced substances to induce chronic inflammation leading to Th1 and Th2 autoimmune diseases. Th1 cytokine IFNγ stimulates Dc (dendritic cell), Mo (monocyte), Mθ (macrophage), Endo (endothelial), and Epi (epithelial) cells, while Th2 cytokine IL-5 stimulates B, MS (mast cell), Eo (eosinophil), and Bs (basophil) cells.

4. Summary

Immune responses have long been classified into T helper (Th)1 and Th2, but recently, they have been classified into various Th type immune cells according to the cells that secrete specific cytokines, and are named Th17, Th22, Th23, and Th25. However, a closer look at cytokine production can distinguish between Th1 and Th2 relying on the type of infectious pathogen. For example, Th1 cytokines are produced by intracellular pathogens such as intracellular bacteria, viruses, and protozoa, whereas Th2 cytokines are produced by extracellular pathogens, such as common bacteria and multicellular parasites (Figure 3).

The antigen of intracellular pathogen, which is synthesized within the cell presenting antigen through MHC I (Figure 1A), whereas the antigen of extracellular pathogen synthesized form pathogens and then endocytosis or phagocytosis by cell presenting antigen through MHC II (Figure 1B). The outcome of the CD8 T cell response is critical to clearing intracellular pathogens such as viruses and protozoa to regulate the size of the memory pool after resolution of infection [19–21]. The T cell receptor (TCR) of CD8 T cells is stimulated by mature dendritic cells (DCs) expressing cognate antigen in the MHC I context, initiating the activation of naïve pathogen-specific CD8 T cells. Activated CD8 T cells release granzymes that directly influence antigen-presenting DCs to eliminate pathogens within infected cells.

It is difficult to explain how CD4 T cells produce key Th1 cytokines mainly because intracellular pathogens are typically recognized by CD8 T cells. Activation of Th1 CD4 T cells by IL-12 is as follows: IL-12 is a key molecule that induces the Th1 cytokine IFNγ from CD4 T cells. IL-12 is mainly produced when intracellular pathogens invade dendritic cells (DCs) [22–27]. Intracellular pathogens, such as viruses or protozoan infections, activate antigen-presenting cells (APCs) to contribute to IL-12 expression [28]. IL-12 is involved in promoting inflammatory responses and is essential for eliminating viruses and protozoa by regulating IFNγ and other cytokines (Figure 2). IL-12 in the presence of IL-18 synergistically induces the Th1 cytokine IFNγ, which is important for clearing intracellular pathogen infections (Figure 3).

In general, autoimmune diseases are largely divided into Th1 and Th2 autoimmune diseases. In an aging society, Th1-type autoimmune diseases such as rheumatoid arthritis, chronic colitis, and psoriasis, which are common in the elderly, appear, whereas Th2-type autoimmune diseases such as atopic dermatitis and asthma occur in the younger generation, who are more dependent on genetic factors and the environment [29–34]. In modern societies, younger individuals are more prone to Th2 autoimmune diseases, possibly due to genetic factors and reduced exposure to environmental antigens or parasites [35]. The exact cause of these Th1 and Th2 autoimmune diseases has not yet been identified. According to various studies to date, the first factor is genetic factor; the second is environmental factor.

Autoimmune diseases, such as rheumatoid arthritis or type 1 diabetes, have a genetic component; specific genes can increase an individual's susceptibility. While genetic factors play a role, environmental factors, such as infections, diet, smoking, and stress, can trigger or worsen autoimmune diseases in people who are genetically predisposed [36,37]. Autoimmune diseases tend to run in families, and genetic factors may be involved in diseases such as hemophilia, type 1 diabetes, multiple sclerosis (MS), systemic lupus erythematosus (SLE), myasthenia gravis, Sjogren's syndrome, rheumatoid arthritis, and Graves' disease. While there is no way to prevent autoimmune diseases yet, more in-depth research on various factors such as genetics, family history, and environment, as well as personalized information, may help predict or prevent various autoimmune diseases.

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Abbreviations

APCs, Antigen-presenting cells; CD, cluster of differentiation; DCs, dendritic cells; DRiPs, Defective ribosomal products; ER, endoplasmic reticulum; IBD, Inflammatory bowel disease; IFN, Interferon; Ig, Immunoglobulin; IL, Interleukin; MHC, Major histocompatibility complex; MS, Multiple sclerosis; R, receptor; SLE, Systemic lupus erythematosus; TAP, Transporter for antigen processing; Th, T helper; TNF, tumor necrosis factor.

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