The Role of T- Helper Cells in Immune Response with Specific Discussion on Atopic Allergy

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INTRODUCTION

In the past couple of years, several studies have demonstrated that T- helper cells play an important role in the induction and reaction process of allergy. The T-helper cell (T-h) is a kind of T lymphocyte. At first, in the year 1921 Praustniz and Kustner, as quoted by Romagnani, stated the concept that allergy is an interaction between allergens and the IgE (Immunoglobulin E) specific antibody that is attached to IgE receptors on mast cells or mastocytes, which would then release its mediators. Other factors that also play a role in the development of allergy is lymphokine, produced by T-cells, which regulate IgE antibody production by the B-cell.[1] Lymphokine or cytokine is a hormone-like substance released by T-cells, B-cells, or other cells, that function as intercellular signaling substances in the regulation of immune responses towards outside stimuli.[1]

Allergic reactions occur as a result of the response of a group of T-h cells. The response that occurs is related to the pathophysiological aspect of allergy, which is the production of IgE antibodies, activation and attraction of mast cells, basophils and eosinophils, mucous hypersecretion and subepithelial fibrosis.[1] Since patients with atopic allergy are commonly found, knowledge on the response of the T-h cell in allergic reactions open a great opportunity for the development of immunotherapeutic strategies targeted towards specific allergens in atopic individuals.[1,3] To find out more on the role of the T-h cell in allergic reactions, this paper shall first discuss the T-h cell itself, its proliferation and differentiation, cytokine production, receptor type, stimulation mechanism and its role in immune response in general.

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T-HELPER CELLS (T-H CELLS)

The T cell consists of 65-80% of all lymphocytes in circulation. In the beginning of development in the thymus cortex, the T cell undergoes maturation characterized by the development of specific surface antigens called cluster designations (CD) that differentiate the type, differentiation stage, and function of individual T-cells. During subsequent maturation and differentiation in the medulla, some antigens would reside, while others disappear and others appear, creating sub-groups of T cells. T cells that lose their CD4 antigen but continue to demonstrate CD8 antigen is called the CD8+ T cell antigen or the T cytotoxic, while T cells that lose their CD8 but maintain CD4 molecules are called CD4+ T cells or Th cells. These two kinds of T lymphocytes would later enter the circulation as 2 populations with separate functions. T cells that have never been exposed to antigens are called naïve T cells (pre Th cells/ precursor T cells, Virgin T helpers). Naïve T cells recognize antigens presented by antigen-presenting cells (APC), such as dendritic cells, B cells, and macrophages. After the recognition of specific antigens, the T cells would proliferate and differentiate into CD4+ effector cells that act to assist B cells in antibody production. A proportion of activated T cells would return to resting state and become CD4+ memory cells (Figure 1).[2]

CD4+ effector cells could enter peripheral tissue or locations of recognized antigens during inflammatory or allergic reactions, while CD4+ memory cells, other than migrating to the location of inflammation, also migrate to lymph nodes and are able to undergo further stimulation with recognized antigens. The ability for a cell to migrate during inflammatory reactions is closely related to the function of the Th cell and the molecular mechanism of cell migration to related locations.[1-4]

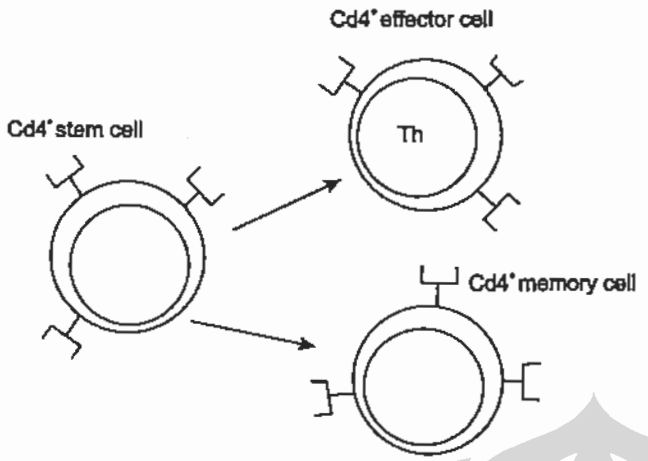

Figure 1. The Formation of Effector Cells and Memory Cells Form Activated Th Cells. Quoted from Stites.[2]

THE ROLE OF TH CELLS IN THE IMMUNE PROCESS

Th cells are classified into two categories. Such classification is based on the difference in cytokine secretion by each category. This classification differentiates the function and differentiation of the two categories of Th cells in the immune system, since in cellular or humoral immune responses, Th cells would differentiate into effector T cells that produce different cytokines according to predetermined function.[5] The first group of Th cells are called T helper-1 cells (Th1 cells), and the second group is called T helper-2 cells. The role of these two groups in the immune response is more dominant towards one group. Th1 cells play a greater role in cellular immunity against intracellular pathogenic microorganisms such as Listeria, Mycobacterium tuberculosis, and viruses through the activation of cytotoxic T cells, and play a more dominant role in delayed type hypersensitivity reactions and autoimmune diseases. In autoimmune diseases, host tissue cells are destroyed, as in the case of diabetes mellitus, multiple sclerosis, etc.

Th2 cells assist B cells in the production of antibodies in humoral immunity and play an important role in the immune process against extracellular pathogenic microorganisms, parasites, and in allergic reactions.[2-4] During humoral immune responses, such as in the case of allergic reactions, T helper cells are more dominant towards Th2. Thus, in allergic disorders such as rhinitis, asthma, and contact dermatitis, Th2 cells play a more dominant role in influencing IgE, mast cells, and eosinophils.

TH CELL STIMULATION MECHANISM IN THE IMMUNE RESPONSE

The success of an immune response depends on the ability of Th cells from the thymus cell to recognize and differentiate antigens. Naïve T cells recognize antigens through peptide fragments presented together by class II Major Histocompatibility Complex (MHC) molecules on APCs that would bind with T cell receptors (TCRs). T cell receptors are heterodymers, consisting of 2 S-S molecule chains. There are two kinds of TCRs, alpha-beta TCRs and gamma-delta TCRs. Interaction with antigens would only express one of these two kinds of TCRs, particularly alpha-beta TCRs.[2] During humoral immune responses, the recognition and contact with antigens via TCRs determine the response of B cells towards stimulation through their receptors to proliferate and differentiate to produce antibodies. APCs works to process the antigens and present them to specific immune system cells through MHC expression on the cell's surface. T cells are activated only if they could recognize the antigens presented by APCs through MHCs. Activation of T helper cells cause the production and release of cytokines and activates Th cells to proliferate and differentiate into effector cells and plays a role in the development of cellular or humoral immune responses.[2,3]

FACTORS THAT INFLUENCE TH CELL STIMULATION AND DIFFERENTIATION

The process of Th cell differentiation in an immune response begins with the ligation of TCR with an antigen, influenced by the presence of cytokine produced at the initial stimulation response of naïve T cells that contain CD4. Antigen binding with alpha-beta or gamma-delta TCRs would activate phosphokinase, causing phosphorilation of intracellular serine or tyrosine that cause changes in gene transcription in the nucleus of T cells, which would in turn transfer signals after the ligation of antigens with TCR. These signals would then stimulate naïve T cells to actively proliferate and differentiate into Th1 or Th2 cells through the intermediary stage called Th0 cells. Th0 cells would quickly differentiate into Th1 or Th2 cells by means of different cytokines in separate immune responses based on antigen stimuli.[2,6]

In the last couple of years, there has been proof of the role of co-stimulatory molecules B7 on APCs, which bind to CD28 receptors on the surface of T cells and selectively influence Th cell stimulation and differentiation.[2,5,6] Attachment of CD28's to B7's create co-stimulatory signals that would enhance stimuli resulting from TCR-antigen ligations during stimulation of Th cell ac-

tivity, to produce cytokines and the direction of differentiation. A study by Gause et al stated that Th1 cell formation depends more on B7-CD28 ligand compared to Th2 cells.[6]

Antigen dose is also an important factor that determines differentiation of T helper cells into Th1 or Th2.[4] An increase in antigen dose could change an immune response from Th1 cells to Th2 cells, and visa versa. Differentiation of T helper cells into Th1 cells is stimulated by moderate antigen doses, while response from Th2 cells require a much higher antigen concentration.[4] During inflammatory reactions, the of the migration and location of the two different kinds of cells inside certain tissues depend on factors such as adhesion molecules and the type of cytokine receptors on individual cells.[7]

THE ROLE OF CYTOKINE IN TH CELL DEVELOPMENT AND REGULATION

As we know, at the initial antigen contact, naïve T cells require 2 signals, attachment between T helper cells antigen receptors and the class II MHC antigen complex on the surface of APCs, and co-stimulatory signals that enhance signals between the ligation between TCRs and antigens.[2,8] These two signals would induce several biochemical reactions within T cells that result in the formation of the cytokines interleukin 2 (IL-2) by T cells. The function of IL-2 is to auto-activate (via autocrine stimulation) T cells through IL-2 receptors. Furthermore, IL-1, a protein or cytokine produced by APCs, is able to stimulate T cell development and autoactivation of the APCs themselves. Autoactivation causes cytokine release that plays a role in cell development and differentiation (see Figure 2).[2]

During antigen stimulation via APCs, naïve T cells produce IL-2 through the intermediary form Th0, which produces IL-2, interferon gamma, and IL-4 (see Figure 3).[2]

Activated macrophage produces IL-12 would influence Th cell activity and differentiation into Th1 and would produces interferon gamma and IL-2. Interleukin produced by these Th1 cells would enhance immune responses by involving macrophages and other phagocytes in killing intracellular pathogenic bacteria. Interferon gamma stimulates B cells into producing antibodies that fix complements and stimulate macrophages and mononuclear phagocytes into phagocytosis. In addition, interferon gamma secretion also attracts other leukocytes to that location, causing an inflammatory reaction and stimulating B cells into producing antibodies that act as potent opsonines. The whole effect of Th1 cells effect signals for the process of killing by phagocytes.[2-4] Stimulation in the IL-4 environment stimulates Th2 differentiation and influences further immune responses by mast cells and eosinophils. Th2 cells secrete IL-4, IL-5, as well as IL-6, IL-10, and IL-13. Cytokines produced by Th2 cells have a chemotactic effect on B cells, mast cells, basophils, and eosinophils, and stimulate these cells to grow and differentiate according to individual roles in the immune response of allergic reaction or inflammation. Interleukin 4 and IL-13 stimulate B cells into producing IgE that binds with mast cells and eosinophils when in contact with antigens or allergens.

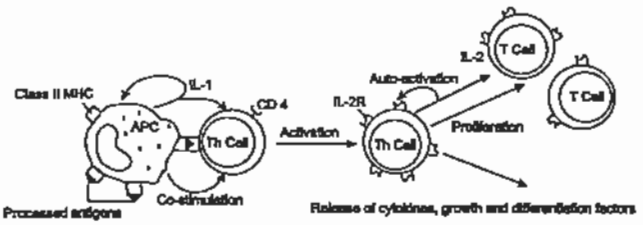

Figure 2. Th Cell Activated. Quoted from Stites.[2]

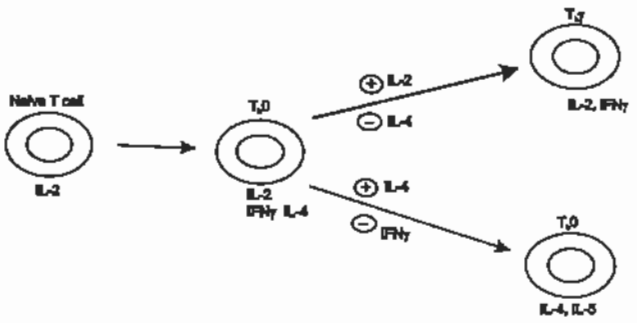

Figure 3. Differentiation of Th Cell into Th1 and Th2. Quoted by Stites.[2]

Th1 and Th2 cells have the ability to inhibit each other's growth. IL-4 produced by Th2 causes inhibition in the development of Th1 cells, while IFN gamma produced by Th1 inhibits Th2 cell development. So, the two cell populations inhibit each other through the interleukins they produce. The result of this regulatory process is an immune response with a dominant effect towards one of the two Th groups.[2,4]

THE ROLE OF CHEMOKINES

Lymphocyte response towards IL-12 or IL-4 depends on a strong bind between cytokines and their receptors. Antigen stimulation through APCs bound to TCRs determine changes in Th cells towards Th1 or Th2. Activation of TCRs affect different chemokine receptors on

Th1 and Th2 cells.[4,5] Chemokines are cytokines with chemotactic function, which attract leukocytes and determine their position within tissue during inflammation.[9] The difference in chemokine receptors produce a change in selective chemotaxis that is believed to play a role in Th cell tissue specific homing during inflammation.[7]

PROFILE OF CHEMOKINE RECEPTORS ON TH1 CELLS

A chemokine receptor expressed by Th1 cell is CXCR3, whose expression is enhanced by IFN gamma. Other chemokine receptors that are often encountered on Th1 cells are CCR5's, that function as chemo-attractant for macrophages and neutrophils.[9,10]

PROFILE OF CHEMOKINE RECEPTORS ON TH2 CELLS

Th2 cells have eotaxin receptors called CCR3. Eotaxin is produced by epithelial cells, endothelial cells, and fibroblasts. Eotaxin production is stimulated by IL-3 and IL-5 and increases during allergy or asthma.[6] CCR3 receptors are located on Th2 cells as well as on eosinophils, basophils, and mast cells. CCR3 activation on eosinophils, basophils and Th2 cells stimulate cells into moving to the location of inflammation,(chemotaxis). Eotaxin receptors or CCR3 plays a great role in Th2 cell response. Other chemotactic receptors on Th2 cells are CCR4 and CCR8.[9,10]

THE ROLE OF TH CELL IMMUNE RESPONSE IN ALLERGY

In general, there are several classifications of allergic diseases, such as atopic allergy, drug allergy, and contact dermatitis. This discussion will focus on atopic allergy.

ATOPIC ALLERGY

Atopic allergy is a type I hypersensitivity reaction in individuals who are have a genetic sensitivity towards certain antigens called allergens, in the form of excessive IgE production. There are various allergens, such as dust, pollen, bed bugs, animal fur, various foods, and other substances. Clinical manifestations of allergy are most often found in 3 target systems, the respiratory tract, gastrointestinal tract, and the skin. Exposure towards such allergens produces symptoms such as asthma, urticaria, rhinitis, diarrhea, and vomiting. The term "atopic" signifies these clinical symptoms, which usually manifest in individuals with family member who suffer from the same symptoms, demonstrating allergic reactions towards allergen exposure.[1,3,11]

PATHOPHYSIOLOGY

If someone who has been exposed to a certain antigen, subsequent exposure to the same antigen produces a secondary immune response to eliminate the antigen. In allergy, the immune response is excessive, causing tissue destruction. Such reaction never occurs on the first exposure, which is a unique characteristic of the person with allergy.[11]

Exposure to allergen in an allergic individual causes an interaction between the allergen presented by APCs and Th cells and B cells, stimulating the production of IgE antibody, which subsequently adheres to mastocytes and basophils. Allergic symptoms occur when the IgE adhering to mastocytes and basophils react with associated allergens. Allergen interaction with IgE causes cross linking between 2 Fce receptors, causing cell degranulation and release of certain substances, such as histamine, vasoactive amines, eosinophil chemotacting factor (ECF), neutrophil chemotacting factor (NCF), leukotrien, prostaglandin, and thromboxane, which produce allergic symptoms. Histamine causes vasodilatation and increases vascular permeability and stimulates smooth muscle contraction, causing tightening of the respiratory tract due to edema and hypersecretion of thick mucous. This causes obstruction of the respiratory tract, as in asthma. In the skin, histamine causes a local allergic reaction in the form of erythema and pruritus. ECF and NCF attract eosinophils and neutrophils to the site of inflammation. Leukotrien, prostaglandin, and thromboxane also play a role in the chemotactic process by attracting and bringing cells together to the site of inflammation and enhancing the allergic response.[1,11]

ETIOLOGY

The etiology of allergy is still unclear, but there is a hypothesis that there are 2 influential factors, genetic and environmental factors. The ability to produce IgE is influenced by genetic factors, since offspring of allergic patients have a tendency towards allergy. It turns out that atopic individuals have more than 1 gene that influence the response of Th2, such as the cytokine gene, cytokine receptor gene, and so forth. The IL-4 gene is a gene that regulates IL-4 expression. Up to now, it is still unclear which gene is most responsible for the development of an allergic response in an atopic individual, but this IL-4 gene is believed to play a significant role in the

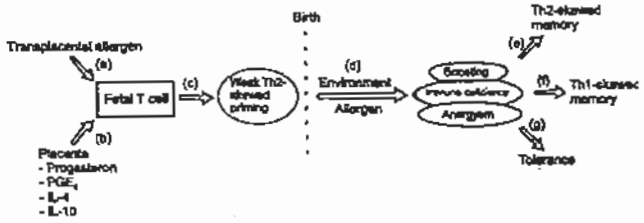

Figure 4. Immune Response Regulation of T Cells Towards Allergens prior to and after Birth. Quoted from Holt.[13]

allergic process and immune response in atopic individuals. There is proof that IL-4 induces B cells into "isotype switching" IgG into IgE.[1,12-14]

Environmental factors are classified into two groups, congenital environment and postnatal environment.[1,12-14] Figure 4 depicts how during pregnancy, maternal environment influences the development of the Th2 response. Initial stimulation of T cells occurs when the allergen enters the fetal body through the placenta, especially in the last trimester (a). The fetal response towards this allergen usually occurs in the placental environment in the form of progesterone, prostaglandin E2 (PGE2), IL-4 and IL-10 (b), which naturally causes the initial formation of Th2 response and inhibits the formation of Th1 cells (c). After birth, the results of exposure to the same allergens in the environment (d) depends on genetic factors, which causes immune response advancement along three different pathways, through Th2 boosting effect (e), immune deviation in the form of a change from Th2 immune response into Th1 (f), or anergysm, which would create a tolerance towards the allergen (g).[13]

Sensitivity towards allergy is determined by a balance between the increase in the effect of Th2 and immune deficiency, in the form of a change in response from Th2 to Th1 at the beginning of life. A reduction in Th1 function is a primary risk factor for atopy.[13,14] An increase in the prevalence of allergy is believed to be related to a decrease in the incidence rate of infection during childhood, such as tuberculosis (TB), which could induce production of cytokine that are antagonistic towards immune response from Th2 to Th1. Positive tuberculin reaction is related to a lower incidence rate of asthma, lower IgE levels, and cytokine profile that demonstrate protective response by Th1. This demonstrates that childhood TB infection modifies the immune response that inhibits development of atopic diseases. Studies in developed nations demonstrate that a reduction of TB infection and perhaps other childhood infections is an important factor in the tendency of increase in atopic diseases in the last decade.[1,12-14]

THE MECHANISM OF TH2 CELL STIMULATION DURING ALLERGY

The Th cell that plays a role in allergy is Th2. It has been known that stimulation of Th2 cells depend on contact between the antigen nd the T cell, and the type of cytokine it produces. Allergens with a specific response by Th2 would stimulate accumulation of inflammatory cells and increase of adhesion molecule activity, which initiates a complex series of allergic reactions. During its interaction with the B lymphocyte, the antigen captured by the B cell through IgM on the surface of the B cell would be presented together with class II MHC to Th2 cells. Th2 cells would then express CD 40 ligand that would bind with its receptor on the B cell, CD40. Such stimulation is enhanced by co-stimulatory signals B7 and CD28, also through IL-4 that is produced by Th2 cells, causing optimal stimulation of B cells to proliferate and produce IgE (Figure 5).[15]

Th2 cells themselves, through the interleukin they produce, plays in most of the pathophysiologic manifestations in allergic patients. Figure 6 depicts how after contact between allergens presented by APCs together with class II MHC and TCR, the TCR is activated on Th0, which quickly differentiates into Th2 cells. Th2 cells would then express IL-3, IL-4, IL-5, and IL-13, which have effects on inflammatory cells such as mast cells, basophils, and eosinophils, as well as increase antibody production by B cells, especially IgE, and the development of an inflammation reaction. IL-4-release by Th0 plays a role in the development and formation of Th2 cells as well as strengthen the formation of Th2 response during an allergic reaction. Interleukins 4 and 13 are required for IgE production during an allergic reaction.[11,14-16] IgE production and mast cell degranulation illustrates the acute

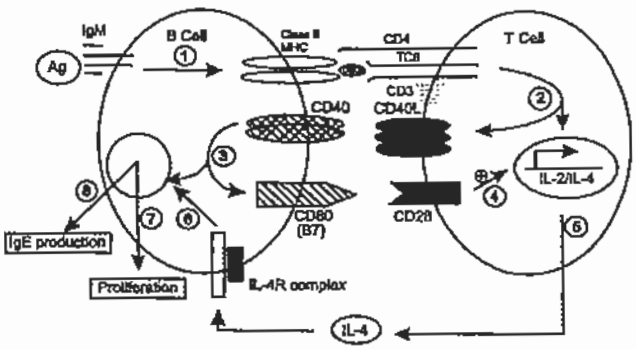

Figure 5. B Cell and T Cell Interaction in the Formation of IgE. Quoted from Bacharier.[15]

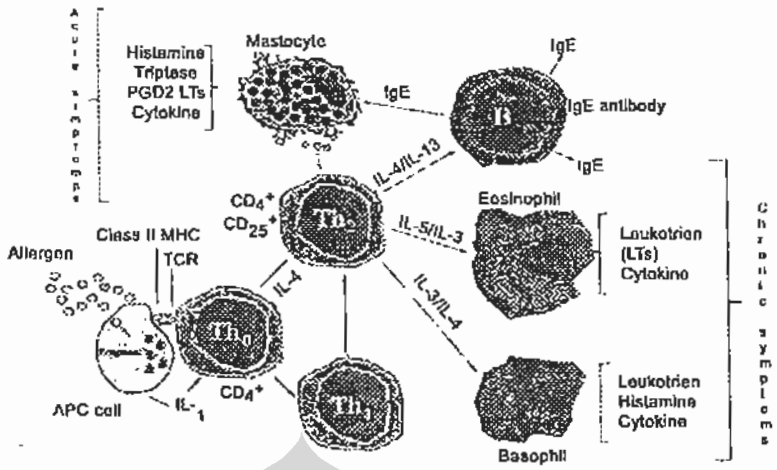

Figure 6. Allergy Process Scheme. Quoted by Creticos.[15]

phase of the inflammation process. The subsequent phase occurs within several hours of the acute reaction, called the late response, in the form of attraction of inflammation cells characterized by the accumulation of eosinophils and basophils, cytokine production by Th2 cells, and development of an inflammation reaction within the tissue.[15]

THE ROLE OF INTERLEUKIN IN AN ALLERGIC REACTION

Interleukin 3 regulates the migration of eosinophils and basophils that are not yet sensitized to the site of inflammation,[17] while IL-4 plays a role in the adhesion and of rolling of eosinophils on endothelial cells. Development of mast cells and basophils is influenced by IL-4, IL-9, and IL-10.[17,18] IL-13 has a similar role and function to IL-4, which is to influence IgE production during an allergic reaction. Interleukin 4, IL-9 and IL-13, stimulates chemotaxis, fibroblast growth, synthesis of extracellular protein matrix, and in asthma plays a role in mucous hypersecretion and increases metaplasia of mucous cells in the bronchi.[1,17-19] Interleukin 5 produced by Th2 cells plays a role in eosinophil chemotaxis, differentiation, and proliferation, as well as stimulates eosinophils in playing its role in the killing process, as in the case of cytotoxicity against worms.[3] Interleukin 5 plays a role in inflammatory effector cells such as eosinophils by stimulating eotaxins produced by epithelial cells, endothelial cells, and fibroblast, which then activates eotaxin receptors (CCR3) on inflammation cells, particularly eosinophils, basophils, and mast cells. Interaction between IL-4, IL-3, IL-5, IL-9 and eotaxin attracts eosinophils, basophils, and mast cells to the target tissue or inflammation site. Eotaxin also attracts Th2 cells via CCR3 receptors on Th2 cells.

An increase in the secretion of IFN gamma and IL-12 inhibits the formation of Th2 cells by reducing IL-4 and IL-13 secretion, causing formation of Th1 cells (response change from Th2 to Th1). A condition that predominates immune response by Th1 cells and suppression of Th2 mechanism causes a change in the allergic response.[1,12,13]

SUMMARY

We have discussed the T helper cell from its differentiation and factors that influence its stimulation, such as the interleukin pattern it produces, receptor type, stimulation mechanism, and its role in the immune process. Th cell response begins as antigen stimulation presented by APCs together with Class II MHCs through TCRs enhanced by co-stimulatory signals produced by cytokines. Cytokines or interleukins that are produced play an important role in the differentiation of Th cells into Th1 cells through IL-12 and IFN gamma or into Th2 cells via the formation of IL-4, which has separate roles and functions in the immune response.

The development of allergy is influenced by 2 factors, the genetic factor and environmental factors prior to and following birth. Interaction between these two factors plays a role in the development of an immune

response towards allergy in an atopic person. Even though the gene that plays a role in allergy consists of several genes (multigenetic), the IL-4 gene is considered as the most important genetic factor in the allergic response of an atopic individual. Expression of the IL-4 gene and its products help induce B cells into going through isotype switching of IgG into IgE. Sensitivity towards allergy is determined by a balance between an increase in Th2 effects and immune deviation in the form of changes in Th2 response to Th1 in the beginning of life. A more dominant effect of the response by Th2 cells compared to Th1 cells enhances the risk of allergic reaction, while a decrease in Th1 function is a primary risk factor in the development of atopy. Environmental factors such as childhood infections can change a dominant Th2 prenatal immune response into a predomination towards Th1 cell response, which provides a more protective effect against allergy. This would explain the increase in the prevalence of atopic disorders in the last decade in developed nations, along with the reduction in the incidence of tuberculosis infection.

Cytokines, particularly IL-4, plays a role in IgE formation and cause allergic reactions as well as ignites the process of attracting inflammatory cells, especially eosinophils, to the target site. During allergy, collaboration between specific cytokines such as IL-4, IL-5, IL-13, and their receptors play a role in the development of reaction. Knowledge and information on the role of Th cells and the two groups could explain the pathophysiology of the reaction that occurs in immune responses against allergens, which could be used as the bases of development of treatment or immunotherapy.

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