

Cow's Milk and Autoimmunity

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The most common food allergy in early childhood is known as cow's milk allergy (CMA).^[1,2] The symptoms can be mild or as serious as to be life-threatening.^[1,3] The majority of the children that suffer from CMA have this allergy just for the first three years of their childhood, although it is a lifelong allergy for a minority. CMA is thought to be associated with the increasing risk of other allergic disorders. Besides that, an allergy to different cow's milk proteins (CMPs) may cause an immunoglobulin E (IgE) response.^[1,4]

When the patients are exposed to CMA repetitively, it results in chronic allergic inflammation which is accompanied by anatomic and also physiological damage. Eosinophilic gastroenteropathy may be one of these results.^[5-9] In some cases where this allergy is permanent, it is found that susceptibility to respiratory diseases, such as asthma, may develop.^[5,10,11] It is also known that lung functions in the later stages of life may be influenced by the seriousness of childhood asthma. CMA can be caused by three forms of inflammatory mechanisms: 'acute onset' IgE-mediated allergies, delayed onset non-IgE-mediated allergies, and mixed type mediated allergies.^[5,12,13] The immunoglobulin-free light chains (Ig-LFCs) that are leading the inflammation and causing a rapid

ABSTRACT

When a mother stops breastfeeding, the baby is given cow's milk-based baby foods. The prominent proteins found in cow's milk are frequently known to be significant allergens. Even though most allergies to such proteins are reversible, a small percentage of children will have them for the rest of their lives. Cow's milk allergy (CMA) develops in a protein-specific manner, resulting in a rapid or gradual immune response. The pathogenesis of cow's milk allergy is influenced by both innate and adaptive immunity. This pathogenesis is linked to the progressive increase in immune response due to T-helper 2 (Th2) cells, as well as the decrease in the functionality and density of regulatory T (Tregs) cells. This situation may contribute to the autoimmunity that is occurring as a result of the activation malfunction of T and B cells which are the principal agents of the immune system. Additionally, the inflammation which becomes chronic because of the CMA may contribute to a group of autoimmune diseases. This review aimed to better understand the relationship between cow's milk and autoimmunity.

Keywords: Allergy, autoimmunity, cow's milk allergy, inflammation

allergic reaction in mice with CMA are associated with numerous autoimmune disorders. Multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) are some of the examples.^[5,14]

COW'S MILK

Cow's milk contains 30 to 35 grams of protein per liter. Whey protein accounts for 20% (6 g/L) of cow's milk proteins, while casein accounts for the remaining 80% (28-30 g/L). These types of protein form as a result when protein breaks into half, which may be either due to the rennin action or the acidification of the milk to the pH of 4.6.^[1,15] Whole casein contains four types of large proteins and these are alpha-S1-casein, alpha-S2-casein, beta-casein, kappa-casein and gamma-casein.^[1,16-18] These four distinct proteins are encoded in the

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different loci of the same chromosome.^[1,19] Multiple sensitizations to various casein proteins are mostly seen in the patients who have sensitivity to whole casein.^[1,20] Whey is essentially made up of globular proteins. These important globular proteins are alpha-lactalbumin (α -Lac) and beta-lactoglobulin (β -Lg) and they are synthesized in the mammary glands. Other whey proteins such as bovine serum albumin (BSA), lactoferrin (Lf), and immunoglobulins come from blood.^[1,15,20-22] More than 50% of the patients with CMA have susceptibility to casein, α -Lac, and β -Lg which are considered as principal allergen proteins.^[1,15,23] Besides that, BSA, Lf, and immunoglobulins are considered as less important allergens. Somehow, in a precise microarray that was recently performed, it is also shown that Lf can be classified as a strong allergen that is seen often (41%) among cow's milk allergens.^[1,24] Lactobacillus, which is responsible for lactic acid fermentation, also induces proteolytic enzyme synthesis.^[1,25] Following that, hydrolyzation of milk proteins affects the digestibility of milk and the production of bioactive peptides. Also, proteolysis can reduce the CMA by breaking the epitopes (the attachment point that provides antigen to be recognized by the immune system).^[1,26-28]

AUTOIMMUNITY

Autoimmunity can be explained as the immune response that is directed against the antigens of the body itself.^[29,30] The critical elements of the adaptive immunity, T, and B cells, provide the development of lymphocytes when they function properly and when they do not, the autoimmunity responses occur.^[31] Examples of such autoimmune responses may be listed as self-reactive T cells that are avoiding self-selection, a shift in T helper type (Th1/2) cytokines, clonal growth, reduced regulatory T (Treg) cell function, and the accumulation of CD28-T cells.^[32] The mission of the Th1 cells is to induce the secretion of immunoglobulin G (IgG) antibodies which are innate immune responses to bacteria and viruses, via activating B cells. The mission of the Th2 cells is to induce the secretion of IgE antibodies which are innate immune responses to parasite worms and allergens including food allergens, via activating B cells.^[33,34] The activation of B cells is related to disease or organ-specific autoantibodies.^[32] Both the atopic (allergic form) and the autoimmunity causes irregular responses against non-infectious substances.^[35, 36]

The injection of purified CD4+CD25+ T cells into nude (athymic) mice resulted in a variety of autoimmune diseases, which could be prevented

by injecting T cells depleted in the CD4+CD25+ population. Additionally, in most cases, the CD4(+) CD25(-) which are in the control of T-cell-mediated diseases, are revealed to be effective as T cells.^[35] In a study that is performed with the autoimmune diabetes transgenic model, it is shown with the T-cell receptor (TCR) that is used in the model, that the CD4(+) CD25(+) and CD4(+)CD25(-) T cells have a similar protective effect.^[35,37] In this transgenic model which TCR is used to recognize the antigen, CD4+CD25+, and CD4+CD25- T cells are shown to be almost equally protective against the proliferation of naive T cells in vivo and in vitro.^[35,38] The focus of most studies related to Tregs are the effects of CD4(+)CD25(+) T cells on naive T cells. Despite that, in vitro study of CD4(+)CD25(+) T cells show they also prevent B lymphocytes from proliferating from lipopolysaccharides (LPS). CD4+CD25+ T cells were also found to downregulate T cell-mediated production of self-reactive antibodies in an adoptive transfer system.^[35,39] Besides that, CD4(+) CD25(+) T cells are shown to prevent DNA antibodies from activation in a transgenic model.^[35,40,41] As a result, Treg cells regulate the development of antibody responses against self and foreign antigens either directly by limiting B lymphocytes or indirectly by inhibiting Th cell differentiation.^[35,36,39]

COW'S MILK ALLERGY AND THE IMMUNE SYSTEM

The effect of the CMA on the immune system can occur in two types: acute onset or delayed onset. In the IgE cell-mediated acute onset reactions; mast cells are activated, intermediaries such as histamine and arachidonic acid metabolites are secreted. There is no structural damage occurring in the gastrointestinal tract. In the non-IgE mediated delayed onset reactions, T cells can be the intermediary. This reaction causes damage to the gastrointestinal tract. With the help of lysosomal enzymes, macrophages are inhibited and cytokinins are secreted to the damaged tissue. The severeness of this tissue damage is related to the Th1/2 ratio. In the more severe damages, Th1 tissue damage can be responsible.^[42]

Innate and adaptive immunity strongly affects the formation of allergy and its characteristics

Dendritic cells (DCs), tissue mast cells, basophils, and eosinophils take place as the components of innate immunity. Dendritic cell processes exemplify, and present most allergens including cow's milk in order. This is an important feature of most of

these important allergens. Besides that, DC allows the formation of allergic inflammation by initiating cellular and secretory immune response starting steps.^[5] Tissue mast cells and basophils take place in IgE mediated allergy axis.^[5,43,44] In research performed with mice, it is revealed that the mast cells become active by Ig-fLC and allow the secretion of pro allergenic agents.^[44,45] The degranulation of mast cells then influences the secretion of agents including histamine, which stimulates epithelial and endothelial cells to secrete eotaxin.^[5,46] That gives rise to the eosinophils infiltrating in the inflamed tissue with basophils.^[5,47] The response mechanism of innate immunity components such as monocytes and neutrophils during CMA is not well understood. Neutrophils, gamma/delta ($\gamma\delta$), and natural killer (NK) T cells are known to aggregate in the inflamed digestive tissue in the CMA patients but its active role is unknown.^[5,48-50] Furthermore, mouse tissue subgroups of $\gamma\delta$ and NK T cells are suggested to be having a regulatory role to suppress the food allergy.^[5,51,52] Accumulation of these cells in the inflamed area causes increased inflammatory chemokines levels and may cause the activation of the cytokines in the circulation indirectly. Therefore $\gamma\delta$ and NK T cells can contribute to chronic inflammatory responses.^[5,6,53] CD(+) T cells have a significant impact on the adaptive immune response. Th1, Th2, Th17, Treg cells, or CD4+ T cells may critically affect the inflammatory response and this way inflammation can be resolved or it can be permanent. It can be said that the physiological importance of Th1 and Th17 cells are eliminating both the cellular and extracellular pathogens. Besides that, Th2 cells are contributing to the pathogenesis of allergy with the interleukin-4 (IL-4), IL-5, IL-13 secretory pathways even though their main function is to eliminate extracellular parasites. It is also found that the IL-4, IL-5, IL-13 levels in the blood are high in patients with CMA. These patients form immune responses specific to the cow's milk proteins (CMPs).^[5,54-60] The suppressive role of Treg cells may partially contribute as a potential regulatory mechanism for allergy.^[5,61] The slight balance between the Treg and the Th2 cells, the balance that includes the density and the functionality of cells, determines the way that allergy follows.^[5,62] As a result of the disruption of Treg cells and their recurrence, many different types of inflammation may occur. Patients with protein-specific CMA who have more Treg cells in their circulatory systems have more minor symptoms and a more positive duration of disease.^[5,63,64]

FOOD ALLERGY

It is a sensible fact that allergy is the most common and the earliest initiation of chronic non-communicable diseases (CNDs). It is important for understanding the immune mechanism of the interactions of food allergy with metabolic diseases, autoimmunity, cancer, and other CNDs including other allergy types. Dietary patterns, microbial patterns, behavior, and environmental pollution are pointed to as common risk factors for CND.^[5,65,66] These factors may disrupt Treg cells. Also may cause similar immune system changes that cause CNDs to occur. Inflammation spirals out of control when Treg cells are disrupted. Uncontrollable inflammation is underlined in most CNDs.^[5,65,67] It is suggested that there is a connection between decreasing number of Treg cells and inflammatory dysregulation that is seen in CNDs such as obesity, insulin resistance.^[5,68] Even though the mechanism that is responsible for it still needs to be confirmed, generally immune dysregulation is thought to occur simultaneously with CNDs, which is therefore arguable. Following that, another interesting fact is newly obtained from the National Health and Nutrition Examination Survey (NHANES). It is said that in the United States, among children and teenagers, the levels of IgE and C-reactive protein (CRP) are higher in individuals who have obesity.^[5,69]

COW'S MILK SENSITIZATION AND DIGESTIVE SYSTEM

The relationship between cow's milk sensitization (CMS) and the esophagus can be explained by a massive eosinophil leak.^[42,70] Nevertheless this situation is not specific to the kids who are sensitive to milk. It responds when the milk is removed from the diet. Besides that, eosinophils are found in large amounts in the lamina propria area in CMS unlike in reflux.^[42,71] When kids with CMS are compared to individuals with primary esophagus reflux, it is found that the expressions of CD25 and HLA-DR, which are indicators of T cell activation, are increased. This proves the T cell activation. However, the higher synthesis of the chemokine eotaxin (chemotaxis subgroup of eosinophils) was more notable. In the babies with esophagus reflux which is caused by CMS, a different epithelial chemokine distribution is found.^[42,72] Enteropathy can be related to cow's milk consumption when the short intestine mucosa is abnormal. Mucosal damage is found related to T cell activation. This situation is reversible when cow's milk is removed from the diet. If the damage is not

reversed, infections that are caused by *Escherichia coli* can occur in a way that contributes to gastrointestinal inflammation.^[42]

Milk is an important food source for growth and development. Breast milk is consumed in the early stages of life. When a mother stops breastfeeding the baby, cow's milk-based baby foods are consumed. Later on, generally, cow's milk is consumed. However, cow's milk allergy is one of the most common food allergies because of the allergen proteins. Therefore CMA is seen in the early stages of life. But this allergy is only permanent for a minority. The process of this allergy occurring is rapid through IgE. The slow process of allergy which is thought to be through the effect of T cells can be permanent. Adaptive and innate immunity affects the CMA development together. Chronic inflammation may cause anatomic and physiological damages. Tissue mast cell degranulation stimulates the release of histamine, eotaxin in endothelial and epithelial cells which then leads to basophils and eosinophils together to move along the inflamed tissues. Other innate immune system components such as neutrophils and components that are found more in mice than humans, $\gamma\delta$ and NK T cells are not clearly understood with their roles in an allergic mechanism. Even so, they are suggested as a regulator for food allergy suppression. On the other hand, CD4(+) T helper cells and Treg cells are playing an important role in adaptive immune response and therefore they affect the reversibility of the inflammation. The imbalance between Th2 and Treg cells causes Th2 response to increase and inhibit Treg cells production. These in general stimulate the development of inflammation. Treg cells negatively affect allergy development while Th2 cells are contributing to the allergy. Thus, among the individuals with CMA, more Treg cells in the blood is a sign of less severe symptoms of this allergy. Considering all of this information, efficient production and proper function of Treg cells is beneficial to the immune system and is critical in dealing with allergic reactions and inflammation-related diseases.

In conclusion, since T and B lymphocyte dysfunction has been linked to autoimmunity, allergy may contribute to autoimmune diseases by disrupting T and B cell functions. The link between cow's milk and autoimmunity was found to be indirectly related to the immune system's response to CMA in this review. The number of detailed studies that will directly address the relationship between cow's milk and autoimmunity should be increased.

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