The role of CD8+ Treg cells in allergic asthma

Rola regulatorowych limfocytów T CD8+ w alergicznej astmie oskrzelowej

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Summary
Asthma is a multifactor respiratory disorder that originates from airways hyper reactivity and chronic inflammation. Advance in the field of asthma research demonstrated that the defects in the function of some special T cells population are responsible for the airway hyper responsiveness in asthma. Cytokines produced by T lymphocytes during a skewing T helper 2 immune response represent the basis of asthma pathogenesis. An overproduction of Interferon-gamma (IFN-γ) and interleukin-4 (IL-4) by T lymphocytes characterizes the allergic immune response. This phenomenon leads to an increase of IL-4/IFN γ ratio and IgE production upon exposure to aeroallergens that would not cause harm to otherwise healthy subjects. The main difference between the immune response to allergens in healthy and allergic subjects is the frequency of interleukin (IL)-10–secreting T cells, which suppress other IL-4–secreting subsets. Known as regulatory T cells, these controllers namely the CD8+ Treg subsets impact the Th2/Th1 balance in different manners. Th2 mediated immune response leads to hyper responsiveness and excessive inflammation in the airways. Alike their CD4+ Treg counterparts, CD8+ Treg cells are mainly divided into the naturally occurring (nTreg) and the induced (iTreg) phenotypes based on their origin and surface markers. Of these two subsets, the former is characterized by the high expression of the transcription factor 3 (FOXP3). Mutations in the gene coding for FOXP3 cause defect in the maintenance of immune homeostasis by Treg cells. A better insight in the role of CD8+ Treg cells in allergic asthma will help improve the management of asthma. This review presents an overview of CD8+ Treg cells and their relevance to allergic asthma.

Streszczenie
Astma jest wieloskładnikową chorobą dróg oddechowych, charakteryzującą się nadwrażliwością dróg oddechowych i obecnością przewlekłego procesu zapalnego. Badania naukowe nad astmą wykazały defekt w funkcjonowaniu subpopulacji limfocytów T odpowiedzialnych za nadwrażliwość oddechową w astmie. W patogenezie astmy najważniejszą rolę odgrywają limfocyty T, o profilu cytokinowym Th2. Immunologiczną odpowiedź w alergiach charakteryzuje nieprawidłowa produkcja interferonu gamma (IFN-γ) i interleukiny 4 (IL-4). To zjawisko prowadzi do wzrostu współczynnika IL-4/IFN-γ i nadmiernej produkcji IgE po ekspozycji na alergeny. Taka reakcja nie występuje u osób zdrowych. Uważa się, że zasadnicza różnica charakteryzująca odpowiedź na alergeny u ludzi zdrowych i alergików, polega na częstości sekcji IL-10 przez limfocyty T regulatorowe, które w taki sposób hamują limfocyty T produkujące IL-4. Wiadomo, że regulatorowe limfocyty T, kontrolują głównie limfocyty efektorowe CD8+ i równowagę pomiędzy subpopulacjami limfocytów T, CD4+ o profilu cytokinowym Th1 i Th2. Indukcja odpowiedzi immunologicznej typu Th2 prowadzi do nadwrażliwości i zaostrzenia procesu zapalnego w astmie. Tak jak regulatorowe limfocytamy T, CD4+, Treg CD8+ dzielą się na subpopulacje obejmujące naturalnie występujące limfocyty regulatorowe (nTreg) CD8+ i indukowane Treg CD8+. Te subpopulacje charakteryzują się wysoką ekspresją czynnika transkrypcyjnego FOXP3. Mutacje genu FOXP3 prowadzą do zaburzenia równowagi pomiędzy limfocytami efektorowymi i regulatorowymi. Uważa się, że lepsze poznание roli regulatorowych limfocytów T, szczególnie CD8+, pozwoli na skuteczniejsze „zarządzanie” astmą. Przedstawiona praca jest przeglądem wiedzy o Reg CD8+ i ich roli w astmie alergicznej.

Key words: Allergies, Asthma, regulatory T cells, Th1/Th2 response
Słowa kluczowe: Alergie, Astma, regulatorowe limfocyty T, odpowiedź Th1/Th2

Introduction
Despite remarkable advances in the understanding of the pathobiology of asthma, its prevalence is still increasing and 100 millions additional cases are expected by the year 2025[24]. Atopy is characterized by T helper 2 (Th2) biased immune response. It predisposes to asthma which is a mul-
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tifactor respiratory disorder that originates from interaction between genetic and environmental factors. Allergic asthma is a multifactor disease characterized by persistent allergen induced chronic airway inflammation, remodeling and airway hyper responsiveness (AHRS). T-helper type 2 (Th2) cells play an important role in orchestrating the disease process through the release of cytokines like IL-4, IL-5 and IL-13 however, genetic baggage and exposure to infectious agents during infancy were though to predispose to allergies. Primary exposure to common antigens during the sensitization phase causes Immunoglobulin class switching from IgG to IgE, increasing the level of IgE. A delayed immune response follows hours later causing an influx of inflammatory cells such as eosinophils into the airway. Antigen specific CD8+ T_{reg} suppress the delayed type hypersensitivity reaction [10] which suggests their implication in asthma. The clinical manifestation of asthma results from the great array of mediators secreted during the allergic cascade namely histamine and leukotrienes. The factors that determine the development of immunity or tolerance in allergic and healthy subjects respectively are still not fully elucidated. The hygiene hypothesis stipulates that exposure to pathogens during infancy stimulates the immune response and protects against the activation of a potent Th2 mediated immune response either during maturation of the immune system. In contrast, the increase in the prevalence of allergic disorders correlates with the decrease in the prevalence of Helicobacter pylori infections. [19]. Th2-skewed parasitic helminthes infections rather protects against the development of allergies disorders which also suggests that, other factors including environmental triggers determine the risk of developing allergic reaction upon exposure to allergens. The modified hygiene hypothesis clarifies some uncertainties surrounding the original version of the hypothesis by explaining genetic correlations between polymorphisms and the predisposition to allergies. Several polymorphisms including those affecting the lipopolysaccharide (LPS) receptor CD14, and TLR2 were shown to influence genetic predisposition to allergies [13]. The parallel increase in the prevalence of Th2-mediated allergic diseases along with the frequency of Th1-mediated autoimmune diseases raises questions about a mutual feedback mechanism between Th1 and Th2 responses. Strong evidence suggests the implication of T cells with regulatory properties in the deregulated immune response leading to allergic and inflammatory disorders. The discovery of regulatory T cells and their suppressive effects on the proliferation of Th2 cells, updated the hygiene hypothesis. Regulatory T cells such as CD8+ T_{reg} cells maintain self-tolerance to allergens, controlling the development of allergies. CD8+ T_{reg} cells secrete cytokines that suppress both the inflammatory and allergic response occurring during asthma exacerbation. The distinction between suppressor T cells and other T cells populations is based on the nature of their received signals in the thymus, the level of their expressed markers and secreted cytokines. Suppressor T cells are mainly divided into the naturally occurring (nT_{reg}) and the induced (iT_{reg}) phenotypes based on their origin and surface markers. Of these two populations, the former is characterized by the high expression of the transcription factor 3 (FOXP3) and the alpha unit of IL-2 (CD25) [36]. Mutation in the gene coding for FOXP3 causes impairment in the maintenance of immune tolerance by T_{reg} cells including the CD8+ T_{reg} subsets. A better understanding of the implication of CD8+ T_{reg} cells in the allergic cascade could be helpful for novel phenotype based asthma therapy.

Regulatory T cells

The aim of our immune system is to recognize and attack foreign agents while maintaining tolerance to self-antigens; minimizing T cell mediated immunopathology such as bronchial asthma. Tolerance to self is a complex process maintained by diverse interrelated mechanisms including immune suppression regulatory cells are the mastermind cells involved in the maintenance of peripheral tolerance and immune homeostasis in the airway. A great array of evidence confirms their implication in TH2-mediated immune responses such as asthma. The concept of T cells mediated immune suppression dates back to the 1970 when Gershon and Kondo first described CD8+ suppressor T cells (CD8+ T_{reg}) and their role in immune tolerance. Interest in CD8+ T suppressor cells was hampered by methodological and technical problems until Sakaguchi introduced CD4+ T_{reg} subsets. Therefore, CD8+ T_{reg} cells were the originally described suppressor cells, but they have received less attention and significant progress in their characterization has been made only recently.

CD8+T Regulatory Cells

Human and animal investigation showed impairment in CD8+ T_{reg} cells function in people affected by allergy and inflammation [31]. CD8+ T regulatory T cells have been isolated in both human and rodents [23]. Due to their poor characterization, distinct subsets and markers of CD8+ T_{reg} cells have not been well identified. Markers such as CTLA-4, GITR, CD103, CD127, CD122, CD134, CD62L, and CD45RB are used to differentiate them from conventional activated T cells. Thymic derived human naturally occurring CD8+ T_{reg} isolated from healthy subjects were shown to express CD4+ T_{reg} cells markers such as CD25, FoxP3, GITR, and CTLA4. They suppress in a direct cell-to-cell contact dependent way, similarly to the naturally occurring CD4+CD25+ Tregs. Human CD8+ T_{reg} subsets exhibit less suppressor effect on the proliferation of Th2 subsets than on Th1 and Th0 clones [25]. Impairment in their function was identified in mice models of experimental autoimmune encephalomyelitis (EAE), inflammatory bowel disease and allergies. Human CD8+ T_{reg} cells were suggested to evolve from the same line as cytotoxic T cells (CTL) based on the frequency and nature of received environmental stimuli [20]. It has been postulated that, at the end of their mission, CTL
may acquire suppressive function by inhibiting some of their surface molecules such as ILT3 [18]. The classification of CD8+ Treg cells is controversial and diverse schemes were proposed. Some assumptions suggest the classification of CD8+ Treg cells into the naturally occurring and the inducible subsets whereas other suggest their classification into auto-reactive subsets and those that target harmful foreign particles. Moreover, a classification of CD8+ Treg cells based on their suppressor mechanism divides them into those that act via cell–cell contact mechanism and those that secrete either IL-10 or the transforming growth factor- beta (TGF-β) [6]. The implication of CD8+ Treg cells in immune modulation was confirmed by data from experimental T cells vaccination and in knockout mouse [39].

Mode of action of CD8+ Treg cells

Although the implication of Treg cells on the activation and expansion of T cells is well documented, their full mechanism of action is still not fully elucidated. Different models were proposed for the mechanism whereby Treg cells maintain proper immune response. Treg cells can suppress naive T cells through direct contact with target cells or APCs and by using various secreted cytokines. Inoculation of naturally occurring Treg cells prevented Treg cell-mediated autoimmune and allergic diseases in animal models. Abnormal levels of these cells and impairment in their function were demonstrated in immune disorders in human and mice. Interestingly, naturally occurring CD8+ Treg cells suppress the activation and proliferation of CD8+ T cells in an unconventional manner [14]. This property would be beneficial for their future clinical applications for the diagnostic, management and prophylaxis of allergic reactions. Naturally occurring regulatory T cells may interfere with any stage of the allergic cascade including: B-cell proliferation, immunoglobulin production and class switching [37]. Moreover, T regulatory cells interfere with the activation and function of natural killer (NK) and memory T cells. The attempt to understand the full mechanism of action of CD8+ Treg cells is ongoing and three main models are currently under review. Molecular evidences based on in vitro assays analysis uncover the mystery surrounding Treg cells. It has been suggested that Treg cells suppress the proliferation of T cells and the production of their cytokines. This function is assumed in vitro in a cell-to-cell contact dependent manner. The inhibition of the suppressor function of Treg cells upon blockade of the interaction between Treg cells and their responder cells by a semi-permeable membrane in vitro confirms this assumption [7]. The interaction between Treg cells surface molecules such as Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) and lymphocyte-activation gene 3 (LAG3), expressed by CD8+ Treg and co stimulatory molecules expressed by APCs including CD80 and CD86 is required for this contact-dependent mechanism [38]. The binding of CTLA-4 to B7 expressed by activated T lymphocytes inhibits co-stimulation signals. Mutations in CTLA-4 molecules prevent its binding to B7 molecules leading to autoimmunity and allergy. Although CTLA-4 is expressed by both Treg and naive T cells, it is constitutively expressed by the former. The activation of Treg cells enhances the expression of CTLA-4; a key surface molecule in Treg activity in vivo and in vitro. Ectopic expression of the transcription factor FOXP3 in naive T cells upregulates CTLA4 expression and promotes immune suppression. In addition to the cell-cell contact mediated mode of action, Treg cells may act in a cytokines mediated fashion. Of the various mediators described in this model, interleukine-10 (IL-10), transforming growth factor beta (TGF-β) and IL-2 are necessary for their in vivo suppression. IL-10 is a potent anti-inflammatory cytokine that may be exploited in asthma therapy. Polymorphisms in the IL10 promoter were shown to influence IL-10 transcription. Further investigation of such polymorphisms may lead to a better understanding of the control of T cell proliferation by Treg. The blockade of IL-10-receptor by injection of antibodies accelerates graft rejection of transplants due to impaired regulatory T cells function. CD8+FOXP3+ Treg control experimental allergic encephalomyelitis (EAE) through local secretion of IL-10. Moreover, defects in CD8+CD28- Treg cells were described in Experimental Inflammatory Bowel Disease. TGF-β represents another important molecule in the function of Treg cells. Its relevance to inflammation and host immunity is well documented. The transformation of naive T cells into Treg cells requires the contribution of TGF-β. Most FOXP3+ Tregs constitutively express high affinity IL-2 alpha receptors (CD25). Naturally occurring Tregs are anergic, do not produce IL-2 and require external sources of this interleukin to activate. This cytokine up regulates FOXP3 expression in human Tregs via both the STAT3 and STAT5 pathways. Treg cells can induce T and B cells apoptosis using cell contact-dependent and granzyme B-dependent tactics [2].

Cross-talk between MCs and CD8+ Treg cells

Regulatory T cells were shown to prevent self-reactive or pathologic T cells response in autoimmune and allergic disorders. CD4+CD25+ Treg cells suppressed airway inflammation in a double-transgenic murine model. However, they could not prevent AHR in response to inhaled OVA which suggests that CD4+CD25+ Treg cells require the collaboration of other cells such as mast cells and dendritic cells to prevent allergic diseases [28]. Indeed, mature dendritic cells can induce the development of IL-10, producing regulatory CD4+ T cells that maintain tolerance upon high-dose intranasal antigen challenge in mice. A cross communication between regulatory T cells and mast cells (MC) determines the extent of mast cells degranulation during the allergic cascade. Moreover, a bidirectional interaction between MCs and T cells has been shown to enhance mast cells degranulation during the allergic cascade. MCs are involved in the inflammation during allergic immune response and in tumor-associated inflammation. MCs exert a major regulatory role in adaptive immune response by communicating directly with T cells and other immune cells [15]. Mast cells interact with other im-
mune cells using their cell surface receptors and ligands. A mutual communication between MCs and Treg cells is associated with various immunological processes namely peripheral tolerance in skin allografting. Specific mast cells population with suppressor ability have been recently described as mast cells regulatory cells (MCR) [3]. These unique mast cells subsets appear to maintain immune tolerance to self and environmental antigens by controlling both effectors and regulatory T cell responses. Nevertheless, the naturally occurring CD4+CD25+Foxp3+ Treg cells secrete IL-9 which is a chemokine and growth factor required for mast cells activation. Cytokines including IL-10 and TGF-β which are secreted by Treg cells are crucial for mast cells suppressor capability. Another evidence evolved from findings that mast cells stimulation in presence of Treg cells results in a increased level of cyclic adenosine monophosphate (cAMP) concentration and reduced Ca2+ influx, independently of intracellular phospholipase Cg (PLCg). Interestingly, MCs activation generates tolerogenic DCs that induce CD8+CD103+ Treg cells. These CD8+regulatory T cells control acquired immune responses. The interaction of OX40-expressing Treg cells with OX40L-expressing MCs altered MC degranulation and the immediate hypersensitivity reaction in vitro and in vivo respectively which confirms the crucial role of MC in the complex immunoregulatory mechanism. The cross talking between Treg cells and mast cells could be an ideal target for novel asthma therapies.

CD8+Treg cells in asthma

Advances in biotechnology and molecular genetic has resurrected the investigation of the contribution of CD8+Treg cells in autoimmune and allergies [34]. Allergen specific CD4+ Treg cells produce inhibitory cytokines, such as IL-10 and transforming growth factor beta (TGF-β) that inhibits inflammation in the airways. CD4 Treg cells rely on the input from CD8+Treg subsets to maintain a balanced immune response. Alike their CD4+ counterparts; CD8+Treg cells secrete IL-10 and TGF-β. IL-10 prevents the class switching from IgG4 to IgE. Th2 cells secrete IL-4 which causes increase in the level of IgE due to the immunoglobulin class switching. Although IL-10 producing Treg cells are not present in the peripheral blood of non allergic subjects, they are frequent in the peripheral blood of nonallergic subjects. Asthma is characterized by the hallmark of airways hyper responsiveness and inflammation. Although there are only few evidences of the direct role of CD8+ Treg cells in asthma, their implication in allergies and inflammation processes is well documented [28]. The cross linking between OX40 ligands on the mast cells and OX40 on the Treg inhibits mast cells degranulation and mucus production [29]. OX40, a co-stimulatory molecule belonging to the TNF receptor family up-regulates the antiapoptotic proteins Bcl-xL and Bcl-2 [12]. It also regulates the memory development of CD4 lymphocytes and the activation of CD8 cells. OX40 can inactive Foxp3+ Treg cell function, activating naive DCs that induce an adaptive immune response during tumor rejection. CD8+ Treg cells can either directly or indirectly inhibit the secretion of pro-inflammatory cytokines using CD28 and CTLA4 [16]. Airway eosinophilia and bronchial hyper responsiveness characterizing asthma are mediated by IL-4, IL-5; two mediators that are involved in allergic response [32]. Both IL-4 and IL-5 induce the expression of endothelial VCAM-1 that binds to VLA-4 receptors displayed on eosinophils. This interaction activates eosinophils and promotes their migration to the site of inflammation. Ig class switching converts most IgG into IgE. The cross linking of IgE on the surface of mast cells leads to their degranulation and secretion of various cytokines. These mediators exert a double effect in asthma in that they favor eosinophils migrations while contributing to B-cell activation and Ig class switching. CD8+Treg cells maintain airway tolerance to allergens in different manners. They may alter the expression of VCAM-1 on endothelial cells preventing their binding to VLA-4 expressed by eosinophils. Consequently, this mechanism alters the migration of eosinophils to the site of inflammation hence, its anti-inflammatory potential. Moreover it prevents the engagement of CD40 displayed on APCs with CD40L expressed by T cells. The binding of CD40 to CD40L is necessary for the regulation of thymus-dependant humoral immune responses [5] that induces B cell proliferation and Ig secretion.

Summary

The mutual rise in the prevalence of Th1-mediated autoimmune diseases in parallel with Th2-mediated allergies refutes the hypothesis of a mutual feedback between Th1 and Th2 immune responses and suggests an immunoregulatory control of the Th1/Th2 balance. Data presented throughout this review are few of the large repertoires of evidence supporting the contribution of CD8+ Treg cells to the maintenance of peripheral tolerance. Most reports regarding the implication of Treg cells in the pathogenesis of asthma evolved from their interaction with CD4+ Treg cells. CD4+regulatory T cells exert their suppressive mechanism partially through their cytokines namely IL-10 and TGF-β. These cytokines are also secreted by CD8+ Treg cells. The suppressor mechanism of CD4+Treg cells depends on their collaboration with CD8+ Treg subsets. Based on the similarities in the cytokine profile of these two regulatory T cells and their mutual cross talking, the implication of CD8+Treg cells in the pathogenesis of bronchial asthma is logical. Sensitization to environmental allergens appears to start sometimes before birth but the risk of developing asthma depends on genetic predisposition and a regulatory mechanism carried out by regulatory T cells. Regulatory T cells induce specific immunological tolerance to fetal antigens during pregnancy. The numbers of Treg cells were shown to increase during normal pregnancy with a low numbers resulting in pregnancy loss and pre-eclampsia. Increased suppression by CD4+CD25+ T cells and increase production of IL-10 contributes to the anti-inflammatory effects of corticosteroids in allergic inflicted inflam-
matory disorders such as asthma. Similarly, IL-10-producing CD8+ T<sub>reg</sub> cells suppress CD4+ T<sub>reg</sub> cells and naive CD8+ T cells. Indeed CD8+ T<sub>reg</sub> cells exert their suppressive function by cells to cells contact or using diverse cytokines including IL-10 and TGF-β that switch the antibody production from immunoglobulin E (IgE) towards the non-inflammatory iso-
types IgG4 and IgA. A great array of evidence confirms the direct contribution of CD8+ T<sub>reg</sub> cells to the maintenance of immune tolerance. CD4+CD25+ cells suppressed airway in-
flammation in a double-transgenic murine model however, they could not prevent AHR in response to inhaled OVA which suggests that CD4+CD25+ T<sub>reg</sub> cells require the col-
laboration of other cells to prevent allergic airway disease.

Specific CD4+ T<sub>reg</sub> subsets namely Tr1 cells were able to prevent IgE and Th2 expansion in a mouse model of allergic airways dis-
ease through the production of IL-5 and interferon gamma (IFN-γ) [11]. Antigen-specific CD8+ Tregs suppress other T cells populations during delayed type hypersens-
sitivity (DTH) using interferon gamma (IFN-γ) and major his-
tocompatibility complex-associated Qa-1b antigens [40]. Exposure to heat-killed Mycobacterium vaccine induced CD4+CD45RBlow T cells that reduced both Th2 mediated airway inflammation and AHR after allergen challenge using both IL-10and TGF-β [1]. Mature dendritic cells can induce development of IL-10– producing regulatory CD4+ T cells that maintain tolerance upon high-dose intranasal antigen challenge in mice. Inhibitors of Th2 and Th1 cells development namely dexamethasone and vitamin D3 respectively were able to induce human and mice IL-10–producing reg-
ulatory T cells in vitro [17]. CD4+CD25+ T<sub>reg</sub> cells isolated from atopic donors suppressed allergen-stimulated T cells with less potency than those from nonatopic donors which shows that defect in their suppressor effect plays a role in atopic disorders. Corticosteroids increase the frequency of naturally occurring T<sub>reg</sub> cells in an IL-10 dependent mecha-
nism. CD3-specific monoclonal antibodies therapy exert its immediate and long-term potential in immunological dis-
orders by inducing naturally occurring CD8+CD25+ regulatory T cells.[27]. Nevertheless other data showed that , anti-Tu-
mor necrosis factor-alpha(TNFα)therapy generates a new subset of T<sub>reg</sub> cells that take over the defective anti inflammatory function of the CD4+CD25hi T<sub>reg</sub> cells isolated from the peripheral blood of patients with active rheumatoid arthritis (RA) [22]. CD8(+)* T cells suppressed naive T-cell prolif-
eration in a cell contact-dependent mechanism under the control of TLR8 ligands[35]. Dermatophagoides pteronyssi-
nus immunotherapy expanded the CD8+CD25+Foxp3+T<sub>reg</sub> cells that directly induced apoptosis of CD4+CD45Rhi+cells. CD4+CD25+ regulatory T cells could reverse the inflammation process in colitis[33]. CTLA4 is one of the characteristic markers of regulatory T cells including the CD8+ T<sub>reg</sub> subsets. Administration of CTLA4-Ig before Antigen (Ag) chal-
lenge or sensitization prevented Ag-induced airway hyper-
responsiveness and pulmonary eosinophilia by decreasing the level of the Th2 derived cytokine namely IL-4. B7/CD28–CTLA4 co stimulation is crucial for Th2-mediated disorders such as bronchial asthma.[8].Airway hyper responsiveness and pulmonary eosinophilia are two main features of bron-
chial asthma. Both T-cell recruitment and differentiation dur-
ing allergic inflammation in the airways are mediated by the CD28 and CTLA4 receptors. CD8+ CD103+T regulatory cells peripheral maintain tolerance and prevent the anterior chamber-associated immune deviation (ACAID) due to their ability to suppress Th1 and Th2 mediated immunity [21]. T<sub>reg</sub> cells were thought to mediate suppression in cytokine de-
pendent and cell contact-dependent manner however, other reports suggests that T<sub>reg</sub> function depends on their contact with Tconv cells suggesting a bidirectional signals between these two cells subsets . Given the importance of CD8 T<sub>reg</sub> in maintaining immune homeostasis, their full characterization will be beneficial for novel asthma therapy.

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