For the Cure of Atopic Dermatitis

Subjects: Allergy

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Patients with atopic dermatitis (AD) are seeking a permanent cure. This entry provides three working hypotheses and perspectives for the cure of AD by restoring immune homeostasis (immune tolerance state) through activation of regulatory T (Treg) cells as follows. (1) A decreased number or function of Treg cells is a critical event leading to the development and maintenance of AD. (2) Activation of Treg cells is an effective therapeutic approach for long-term clinical improvement of AD. (3) Many different immunomodulatory strategies activating Treg cells can provide a long-term treatment-free clinical remission (cure) of AD by induction of immune tolerance state. Currently available Treg cell-targeted immunomodulatory therapies for AD include allergen immunotherapy, microbiota, vitamin D, polyvalent human immunoglobulin G, and monoclonal antibodies to the surface antigens of T cell or antigen-presenting cell.

Keywords: hypersensitivity ; immunomodulation ; allergy and immunology ; immunotherapy ; immune tolerance ; atopic dermatitis ; atopic eczema ; regulatory T cell

1. Introduction

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disorder characterized by itching and eczematous lesions. It is often associated with a personal or familial history of allergic diseases [1][2][3]. Hypersensitivity reaction (allergic reaction) to environmental agents has been suggested as a pathogenetic mechanism responsible for the development and maintenance of chronic skin inflammation in patients with AD [3]. However, the precise pathogenetic mechanism underlying AD remains unclear. The standard therapies for AD, including topical corticosteroids or calcineurin inhibitors, focus on controlling skin inflammation [1][2][3]. A significant number of patients with AD can be further improved by systemic immunomodulatory agents including corticosteroids, cyclosporine, or methotrexate. However, there are toxicity risks associated with prolonged use of these compounds [3]. Monoclonal antibody to interleukin (IL)-4 receptor alpha and Janus kinase inhibitors suppressing T-helper type 2 (Th2) cell-mediated inflammation can provide significant clinical improvement in patients with moderate-to-severe AD [4][5][6][7]. These findings demonstrate that hypersensitivity reactions mediated by Th2 cells play a key role in the pathogenesis of AD [4][5][6][7]. These results also demonstrate that AD is a systemic immune disease, and that systemic immunomodulation is an efficient strategy for the treatment of AD. However, the Th2-targeted therapy could not modulate upstream immune dysfunction causing Th2 cell activation and could not provide a long-term clinical improvement (LTCI) of AD. Thus, further development of novel therapeutic modalities for AD that can improve a long-term clinical outcome and provide a long-term treatment-free clinical remission of AD (disease-modifying therapy) is required. Studies in patients with AD and AD mouse models have shown that immune dysfunction caused by a decreased number and/or function of regulatory T (Treg) cells is critical for Th2 cell activation and immunoglobulin E (IgE)-mediated inflammation [8][9]. Therefore, an immunomodulatory strategy that activates Treg cells is an ideal therapeutic approach to induce immune tolerance and achieve an LTCI of AD.

2. Unmet Needs of Patients with AD

Patients with AD are seeking a permanent cure. This fact is supported by the persistence of various complementary and alternative therapies for AD [10], as well as multiple internet and social media contents created by patients with AD who want to share their personal experiences on successful AD self-management. However, physicians are explaining to patients suffering from AD that there is still no cure for AD and that it should be managed by continuous medical treatments [3]. This significant mismatch between patient's needs and current medical therapies for AD necessitates further development of novel immunomodulatory strategies to achieve an LTCI of AD.

3. Hypothesis on the Pathogenesis of AD

AD is a multifactorial disorder caused by multiple pathogenic elements, including genetic predisposition, environmental triggers, immune dysfunction, hypersensitivity reaction, chronic skin inflammation, and skin barrier defect [2][3].

Unfortunately, the precise interactions among the multiple pathogenic elements involved in the development and maintenance of AD are not fully understood. Epidemiological and experimental evidence suggests that an impairment of immune tolerance state caused by decreased number and/or function of Treg cells resulting from the exposure to various environmental toxicants is responsible for a rapidly increased prevalence of allergic diseases in the industrialized world [3][11][12][13][14]. In this hypothetical pathogenesis model for AD, a human subject with a genetic predisposition for the development of AD is exposed to environmental toxicants (such as air pollution, volatile organic chemicals, phthalates, and bisphenol A) through the respiratory mucosa, gastrointestinal mucosa, or skin. The exposure to environmental toxicants decreases the number and/or function of Treg cells and impairs immune homeostasis (loss of immune tolerance state) in the subject. The toxicant-induced decreased number and/or function of Treg cells induces hypersensitivity in the human subject through the activation of Th2 cells and the development of an IgE response to common environmental agents. Exposure to sensitized allergens and/or chemical irritants induces a hypersensitivity reaction and chronic inflammation of the skin, which induces and maintains the clinical manifestations of AD (pruritus, dryness, and eczema) (**Figure 1**).

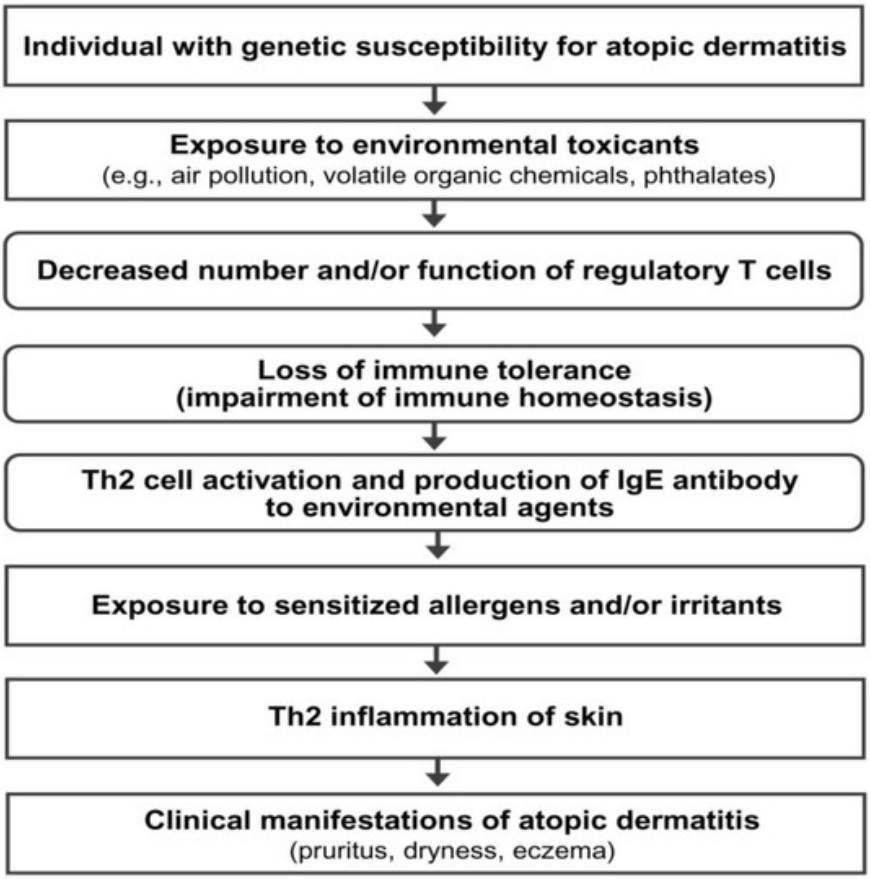

Figure 1. Hypothetical pathogenesis model for atopic dermatitis. Th2 cells, T-helper type 2 cells; IgE, immunoglobulin E.

Based on the above hypothesis on AD pathogenesis, a decreased number and/or function of Treg cells suppressing IgE and Th2 cells plays a critical role in AD pathogenesis. Therefore, immunomodulatory strategies that activate Treg cells may be a useful therapeutic approach for inducing an LTCI or long-term treatment-free clinical remission of AD (disease-modifying therapy) by induction of immune tolerance (recovery of immune homeostasis).

4. Previous Reports on the Long-Term Clinical Improvement of AD

Previous reports have suggested that an LTCI of AD can be achieved through three methods. First, a marked change in the living environment, also known as climatotherapy (relocation of a patient to a different region with a beneficial climate such as a foreign country with favorable weather and clean air), has been reported to induce an LTCI of AD [15][16]. However, the LTCI induced by a marked change in the living environment usually disappears shortly after the patient returns to their previous environment, indicating that change in environmental factors alone cannot normalize the disordered immune system of patients with AD [15][16]. Second, allergen immunotherapy induces an LTCI in some patients with AD [17][18]. Multiple clinical studies have reported an LTCI of AD after allergen immunotherapy [17][18][19][20]. Third, up to 70% of children with AD experience a natural LTCI of AD before puberty [21]. Induction of immune tolerance (recovery of immune homeostasis) is the most probable mechanism of an LTCI observed in children with AD [3], although scientific studies could not directly demonstrate this hypothesis. Mimicking the immunological mechanism responsible for the

natural LTCI of AD in children (induction of immune tolerance) may be an ideal therapeutic approach for achieving an LTCI of AD [3].

5. Five Questions and Three Hypotheses on the Regulatory T Cell-Targeted Immunomodulatory Strategies to Achieve a Long-Term Clinical Improvement of AD

The present author developed five key questions on the immune mechanisms that induce natural LTCI in children with AD and the LTCI observed after allergen immunotherapy in patients with AD (**Table 1**). Additionally, the present author proposes three working hypotheses and perspectives on immunomodulatory strategies to achieve an LTCI of AD (**Table 2**). These hypotheses and perspectives suggest that various immunomodulatory strategies activating Treg cells can induce an immune tolerance and achieve an LTCI in patients with AD.

Table 1. Five questions on the immune mechanism responsible for a long-term clinical improvement observed in patients with atopic dermatitis.

1. What is the mechanism of natural induction of a long-term clinical improvement of atopic dermatitis in children?
2. Is the induction of immune tolerance responsible for a natural long-term clinical improvement of atopic dermatitis in children?
3. Is the activation of type 1 regulatory T cells a key mechanism inducing a natural long-term clinical improvement of atopic dermatitis?
4. Is the activation of type 1 regulatory T cells a common mechanism inducing a long-term clinical improvement of atopic dermatitis by allergen immunotherapy and a natural long-term clinical improvement in children with atopic dermatitis?
5. Can various kinds of immunomodulatory strategies activating regulatory T cells provide a long-term clinical improvement in patients with atopic dermatitis?

Table 2. Three hypotheses and perspectives to achieve a long-term clinical improvement of atopic dermatitis by regulatory T cell activations.

1. A decreased number or function of regulatory T cells is a critical event that causes the activation of Th2 cells, leading to the development and maintenance of atopic dermatitis.
2. Activation of regulatory T cells * is an effective therapeutic approach to achieve a long-term clinical improvement of atopic dermatitis.
3. Many different immunomodulatory strategies activating regulatory T cells can provide a long-term clinical improvement of atopic dermatitis by induction of immune tolerance.

* Activation of regulatory T cells means an increase in the number and/or function of regulatory T cells. Th2 cells, T-helper type 2 cells.

6. Mechanism of Immune Tolerance and Rationale of Regulatory T Cell-Targeted Immunomodulatory Therapy for AD

Immune tolerance has been historically defined as a state of unresponsiveness of the immune system to self-antigens and foreign antigens (e.g., proteins and allergens) [22][23]. Prior exposure to a specific antigen has been suggested to induce immune tolerance to the antigen [22][23]. Immune tolerance is crucial for normal physiology, and defects in immune tolerance can lead to autoimmune and allergic diseases [24][25]. However, the present author prefers the term “immune homeostasis” because it is more scientifically appropriate than “immune tolerance” for several reasons. First, “immune tolerance” can be misinterpreted as having no immune response to self or foreign antigens. A well-controlled immune response (immune homeostasis) can maintain a harmoniously controlled immune response in contrast to an exaggerated immune response that can be harmful to the host. A low-grade, well-controlled autoimmune response to a self-antigen is physiological, and this response helps to remove denatured or altered self-antigens [26]. Well-controlled immune

responses to microbial organisms also protect the body from severe infections (septicemia and viremia) or hyperactivation of the immune system. Hyperactivation of the immune system induced by viral infection causes uncontrolled systemic inflammation, cytokine release (cytokine storm), multi-organ failure, and death in the coronavirus disease 2019 [27]. Treg cells are a functionally defined subpopulation of T cells that modulate the immune system and play a critical role in immune homeostasis (a well-controlled immune response to self-antigens and foreign antigens), thereby preventing the development of autoimmune diseases, allergic diseases, and allograft rejection [28][29]. Animal experiments have suggested that decreased number and/or function (deficiency or dysfunction) of Treg cells serves as a key immune abnormality responsible for the development of autoimmune and allergic diseases [30].

Treg cells are classified as natural Treg cells (nTreg cells) and induced Treg cells (iTreg cells) [31]. nTreg cells express forkhead box P3 (Foxp3), CD4, and CD25 markers [32][33][34]. nTreg cells mediate “central immune tolerance” by deleting autoreactive lymphocyte clones before they develop into fully immunocompetent cells during lymphocyte development in the thymus [35]. Peripheral immune tolerance is mediated by iTreg cells and develops after T cells mature and enter the peripheral tissues and lymph nodes [36]. In peripheral immune tolerance, the immune response to a certain antigen can also be decreased by repeated antigenic exposure or by antigenic exposure in tolerogenic conditions [36]. iTreg cells arise extra-thymically from conventional (or naïve) $CD4^+$ helper T cells in the presence of transforming growth factor-β (TGF-β), retinoic acid, and T cell receptor (TCR)-mediated antigen presentation by antigen-presenting cells (dendritic cells (DCs) or macrophages) in the peripheral tissue or nearby lymphoid tissue [31]. Among the iTreg cells, the IL-10-producing $CD4^+$ Treg cells without Foxp3 expression (type 1 Treg cells: Tr1 cells) play a key role in allergen tolerance and can be induced by allergen immunotherapy in humans [37][38][39][40]. Previous studies have indicated that allergen-specific Tr1 cells are the predominant type of T cell response to allergens in healthy individuals and prevent unwanted hypersensitivity reactions to environmental antigens, such as house dust mites, pollen, and food [41][42]. There are significant differences in the proportions of three different allergen-specific T cell subtypes (T-helper type 1: Th1, Th2, and Tr1 cells) in peripheral blood between healthy non-allergic human subjects and allergic individuals [42]. The imbalance in the ratio of allergen-specific Th1, Th2, and Tr1 cells appears to be critical in the development of allergic diseases, and recovery of balance among allergen-specific Th1, Th2, and Tr1 cells may provide remission of allergic diseases, including AD [42]. Therefore, immunomodulatory approaches activating Tr1 cells with antigen-specific and/or antigen-nonspecific stimulations could induce an LTCI of AD by inducing immune homeostasis (immune tolerance state).

The presence of inborn errors of immunity (IEI) caused by genetic mutations that affect the immune system is important scientific evidence supporting the hypothesis that immune dysfunction resulting from a decreased number and/or function of Treg cells is critical in the pathogenesis of allergic diseases, including AD [30][43]. IEI are clinically expressed as increased susceptibility to infections, autoimmunity, allergy, bone marrow failure, and/or malignancy [44]. In human subjects, mutations of the Foxp3 gene (a master control gene of Treg cells) resulting in absent or dysfunctional Treg cells are responsible for immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, which is clinically characterized by neonatal autoimmune enteropathy, diabetes and thyroiditis, food allergies, and skin eczema [43][45]. AD is a frequent clinical manifestation observed in IPEX syndrome [43][45]. Another example is Wiskott–Aldrich syndrome (WAS) [46][47]. WAS is a rare X-linked recessive disease characterized by eczema, thrombocytopenia, immune deficiency, and bloody diarrhea [43]. WAS is caused by the genetic defects producing defective proteins (WAS proteins) that have a central role in actin polymerization and cytoskeletal rearrangement. Both nTreg cells and iTreg cells are defective in WAS [46]. In the WAS, the eczematous eruption is indistinguishable from AD when diagnostic criteria for AD are used and clears dramatically after a successful transplantation of bone marrow (hematopoietic stem cells) from a healthy donor [47]. This evidence from IEI demonstrates that Treg cell dysfunction is critically involved in the pathogenesis of the AD [30][43].

7. Immunomodulatory Strategies Activating Regulatory T Cells for AD: In Vivo Activation

The Treg cell-targeted immunomodulatory therapies for AD include allergen immunotherapy, microbiota, vitamin D, polyvalent human immunoglobulin G (IgG), monoclonal antibodies to the surface antigens of T cell or antigen-presenting cell, and adoptive transfer of autologous Treg cells or genetically engineered Treg cells expanded in vitro (**Table 3**).

Table 3. Immunomodulatory strategies activating regulatory T cells for the treatment of atopic dermatitis.

Strategies with proven clinical efficacy by at least one randomized clinical trial

(1) Allergen immunotherapy

(2) Microbial therapy (probiotics)

(3) Vitamin D

(4) Subcutaneous or intramuscular injection of polyvalent human IgG from multiple healthy blood donors

(5) Intramuscular injection of autologous total IgG

(6) Monoclonal antibody to antigen on the surface of T cells (anti-OX40 antibody)

Strategies without proven clinical efficacy in patients with atopic dermatitis by a clinical trial

(1) Sirolimus (also called rapamycin)

(2) Metformin

(3) Butyrate

(4) Adoptive cell therapy with ex vivo expanded regulatory T cells

IgG, immunoglobulin G.

8. Combinations of Different Modalities Activating Regulatory T Cells

Theoretically, combinations of currently available methods that can activate Treg cells (allergen immunotherapy, microbiota, vitamin D, polyvalent human IgG, and small molecular chemicals) may maximize the clinical improvement of patients with AD. High dose vitamin D3 enhanced the clinical efficacy and immunomodulatory effects of subcutaneous allergen immunotherapy in a grass pollen-driven mouse model of asthma [48]. In a randomized, controlled clinical trial including children with allergic rhinitis, vitamin D supplementation combined with grass pollen sublingual immunotherapy was more effective in reducing nasal and asthma symptoms than grass pollen sublingual immunotherapy alone [49]. In patients with allergic rhinitis and vitamin D deficiency, vitamin D supplementation in the build-up phase of subcutaneous allergen immunotherapy with house dust mite extract significantly decreased the symptom–medication score of allergic rhinitis compared to subcutaneous allergen immunotherapy alone [50]. In a previous double-blind, placebo-controlled, randomized clinical trial, repeated intradermal injections of immune complexes made of house dust mite antigens and autologous antibodies to house dust mite antigens produced significant clinical improvement in patients with AD [51]. These examples suggest that various combinations of different modalities activating Treg cells can improve a long-term clinical outcome of AD (**Figure 2**).

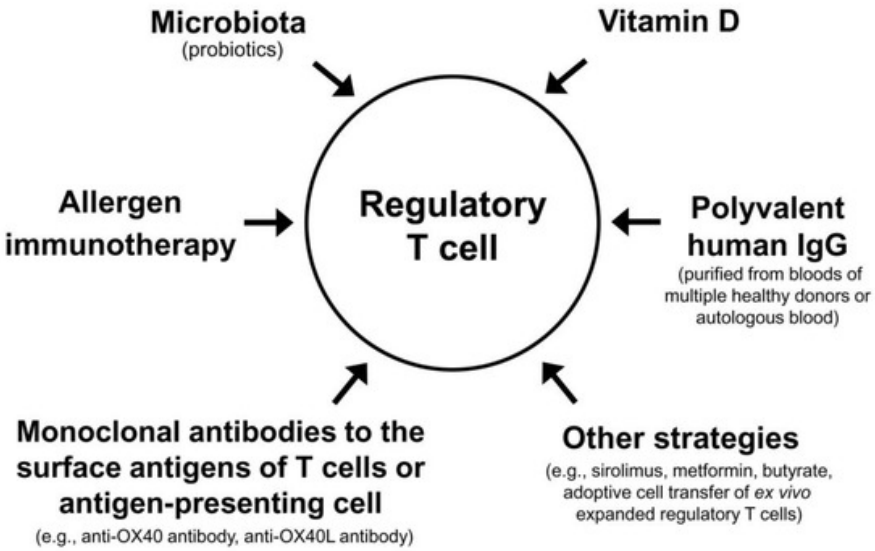

Figure 2. Regulatory T cell-targeted immunomodulatory strategies to achieve a long-term clinical improvement of atopic dermatitis by monotherapy or combination therapy.

9. Conclusions

Immune dysfunction resulting from a decreased number and/or function of Treg cells is critical in the pathogenesis of allergic diseases, including AD. Treg cell activation could be a common immune mechanism responsible for the LTCI observed in patients with AD after allergen immunotherapy and the natural clinical remission observed in children with AD. Therefore, an immunomodulatory strategy that activates Treg cells could be an ideal therapeutic approach to achieve an LTCI of AD. The present author proposes a hypothesis that many different immunomodulatory strategies inducing a sufficient long-term activation of Treg cells can improve the long-term clinical outcome and provide a long-term treatment-free clinical remission of AD by induction of immune tolerance (**Figure 3**). Further studies on the clinical efficacy of various Treg cell-targeted immunomodulatory therapies should be conducted to improve the long-term clinical outcome in patients with AD.

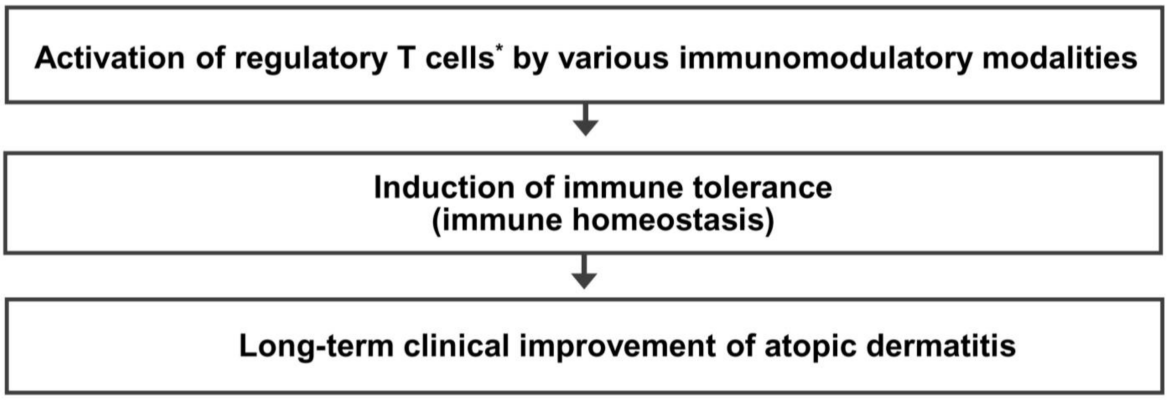

Figure 3. Regulatory T cell-targeted immunomodulatory therapies to achieve long-term clinical improvement of atopic dermatitis by induction of immune tolerance. The present author proposes a hypothesis that many different immunomodulatory strategies inducing a sufficient long-term activation of regulatory T cells can improve long-term clinical outcomes and provide a long-term treatment-free clinical remission of atopic dermatitis by induction of immune tolerance. * Activation of regulatory T cells means an increase in number and/or function of regulatory T cells.

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