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The Role of T Regulatory Cell in Asthma: A Review

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Abstract: The chronic asthma is characterized by the inflammation of the airways brought on by an overabundance of T helper cell type 2 (Th2) responses. All therapy, which included the inhaling synthetic glucocorticoids, is only able to manage the Th2-driven chronic eosinophilic inflammation; it is unable to alter the body's immunological tolerance to the outside antigens. The primary cells which regulates the immune response are the regulatory T cells, or Tregs. The Tregs cells are essential for controlling the autoimmune, allergy, and different immune process. The basic traits of Tregs is known as immunomodulatory processes, this review included the Tregs' advancements in the treatment of asthma. As more as research on Treg regulation mechanisms will lead to improved asthma medications and management techniques.

Key points: Asthma, Regulatory T-cells, Treg cells, autoimmune.

I. Introduction

The development, progression, and duration of allergic disorders, such as asthma, are influenced by T-helper cell type (Th)2 lymphocytes. The general public's understanding of how T-regulatory (Treg) cells regulate the autoimmune illnesses, infectious diseases, asthma, and allergen has grown significantly in recent years [1]. The natural killer (NK) cells, CD8+ Treg cells, and other CD4+ Treg cell subsets are among the several Treg subsets that have been identified. The immune response's negative regulatory cells are involved in controlling a variety of immunological responses, including the autoimmune responce, allergy, and graft-versus-host reactions [2]. Tregs are responsible for "maintaining" the Th2 cell immune response within a typical range. Asthma and other allergy disorders can arise when Tregs are not functioning properly, which prevents them from successfully suppressing the Th2 response. Tregs are therefore the primary regulatory mechanism that keeps the organism immunely tolerant to the external antigens and inhibits the overreactions by Th2 [3].

II. T-regulatory cells in nature

The CD4+CD25+ Treg cells, which make up 10% of all cells are produced in the thymus and found in the blood. In animals, the transfer of the Treg cells demonstrated to reduce the transplant rejection as an autoimmune disease [4]. Anti-CD3 can activate the Treg cells, which exhibit a normal a/b TCR repertoire. The expression of the activator marker CD25 may be explained by the demonstrated strong TCR affinity of nTreg cells for peptides that may be estimated in the peripheral [5]. However, it is currently uncertain which target auto antigens the Treg cells recognize. Some

evidence suggests that conventional CD4+ T-cells can also produce the Treg cells in the periphery when exposed to pathogen-derived antigens [6] .

III. Tregs classification

According to where they come from, Tregs can be classified as either induced Tregs (iTregs) or natural Tregs (nTregs). The transcription factor forkhead box P3 (Foxp3) is expressed by nTregs, also referred to as thymus-derived Tregs (tTregs), which are derived from thymocytes [7]. During thymus development and selection, the nTregs acquire stable genetic and phenotypic traits and primarily produce immunological tolerance to autoantigens. The nTregs exhibit a low expression of CD127 and high expression of CD4, CD25, and Foxp3 [8] .

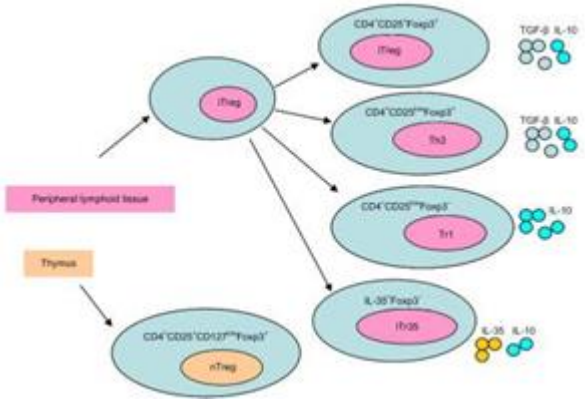

Figure 1. The key features of CD4+ regulatory T cell (Treg) subgroups based on immunosuppressive cytokine production and cell-surface markers [9] .

IV. The Tregs Markers

There are currently no unique surface markers for Tregs; nevertheless, Foxp3, is a specific marker for Tregs identification. Although these markers are not exclusive to Tregs, the Tregs exhibit a low levels of CD127 and high levels of CD25.Certain chemicals on the surface have been identified as possible Tregs identification markers [10]. The CD73 is a multifunctional glycoprotein with 5'-nucleotidase activity that is immobilized outside of the cell membrane [11]. The CD73 hydrolyzes AMP to adenosine, which can then attach to effector T cells' A2A receptor and inhibit the immune system. Large amounts of extracellular adenosine production could be one of the key mechanisms by which Tregs carry out their immunosuppressive function [12].

V. The release of cytokines.

Tregs had the ability to release the cell-lysing substances including granzymes A and B as well as active cytokines like TGF-β, IL-10, and IL-35[13]. The IL-12 family's including the IL-12α and IL-27β chains combine to form the heterodimer known as IL-35. The Tregs secrete the recently identified cytokine IL-35, whereas other effector T cells do not [14]. In 2007, the researchers examined the differences in Treg and Th17 cell proliferation and discovered that the IL-35 that can suppress the Th17 cell expression and increase the Tregs proliferation [15]. Later, research revealed that "iTr35," are a novel subset of Tregs that suppresses the immune system. Consequently, it is hypothesized that iTr35 is a crucial for the development of tolerance infection [16].

VI. Tregs' biological impacts and processes

The immune energy and suppression are the two main traits of Tregs, the immune energy manifests as the Tregs had the ability to inhibit the CD4+CD25− T cell and CD8+ T cell activation and proliferation is known as the suppression effect of Tregs [17]. The intercellular interaction and the release of suppressive cytokines are the primary mechanisms by which Tregs produce their suppression effect [18].

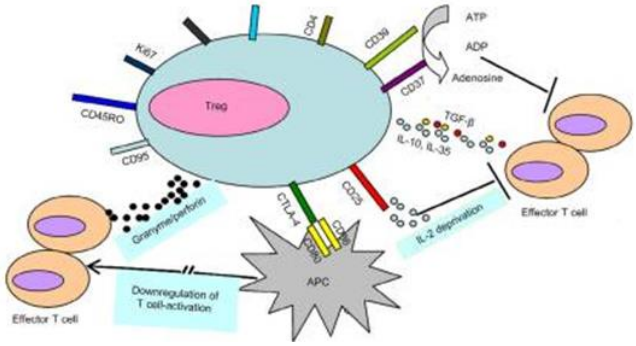

Figure 2. The process of suppression [19]

VII. The Treg suppression methods

The Tregs use a variety of methods to inhibit the effector T cells as it produce the immunosuppressive cytokines (IL-10, IL-35, and TGF-β), also it used granzyme and perforin to induce the cell death, it also used CTLA-4 to down regulate the stimulatory molecules in APCs to prevent T cell-activation [20].

VIII. Cell contact

The Tregs can block the other effector T cells activation by APCs by producing CTLA-4, which allows them to combine with B7 molecules on the APCs surface. Furthermore, the granzyme-perforin-dependent pathway allows Tregs to eliminate CD4+ or CD8+ T cells [21]

IX. Indirect effect of Tregs

By secreting the IL-10, IL-35, and TGF-β, Tregs can reduce the local immune response without major histocompatibility complex restriction. Additionally, Tregs can restrict the T cell proliferation by expressing CD25, also known as IL-2R, which allows them to damage the cytokine IL-2, which is necessary for T cell differentiation [22].

X. Induced iTreg differentiation

The peripheral naive CD4+ T cells that create iTregs need to be stimulated with the right antigen and have IL-2 and TGF-β present [23]. "iTregs" are generated in vitro, while "pTregs" are cells generated in vivo. Although they make up a small percentage of CD4+ T cells, iTregs are comparatively abundant in the local tissues and are crucial for local immunological tolerance [24].The Potential cause of Treg differentiation instability can developed into harmful T cells in certain medical circumstances. The mouse IL-4Rα gene mutation at site 790 activates the IL-4 and IL-13, increasing the susceptibility of mice to allergy disorders [25]. The mouse IL-4Rα gene mutation at site 576 enhances the production of both IL-4 and IL-6. In asthma, the IL-6 stimulates the Treg differentiation toward Th17 cells, which in turn results in a mixed Th2-Th17 immune response [26].

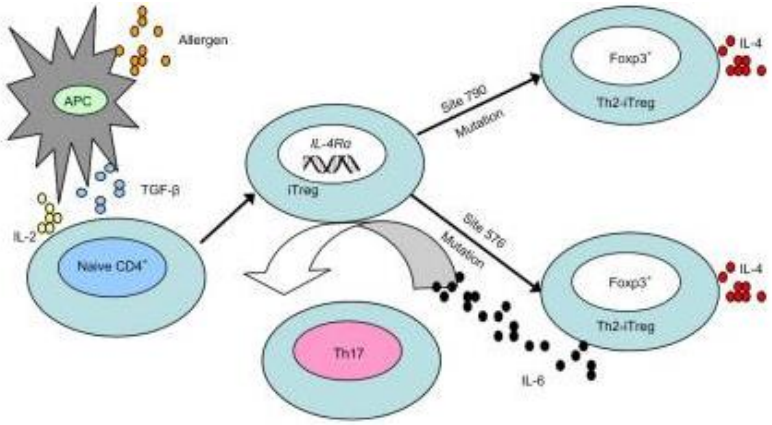

Figure 3. The mechanism of Tregs differentiation [26].

XI. Asthma and Tregs

Numerous studies have demonstrated that the pathophysiology of asthma and the amplification of the Th2 response are mostly caused by the functional abnormalities and inadequate differentiation of Tregs [27]. According to some study, the peripheral blood included the T helper cells IL-2 and the Tregs cells were lower in moderate asthma patients compared to healthy people. The polyendocrinopathy, enteropathy, and X-linked syndrome (IPEX) can result from mutations in the human Foxp3 gene [28].

XII. Treg induction both in vitro and in vivo

Treg differentiation can be enhanced by sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT). Through the Toll-like receptor 2 (TLR2) pathways, intestinal probiotics stimulate Tregs [29] . Certain medications, including as methimazole, rapamycin, and vitamin D3 (VitD3), can enhance the Treg suppression and the transplanting antigen-modified iTregs that have been grown in vitro could be a promising asthma treatment [30].

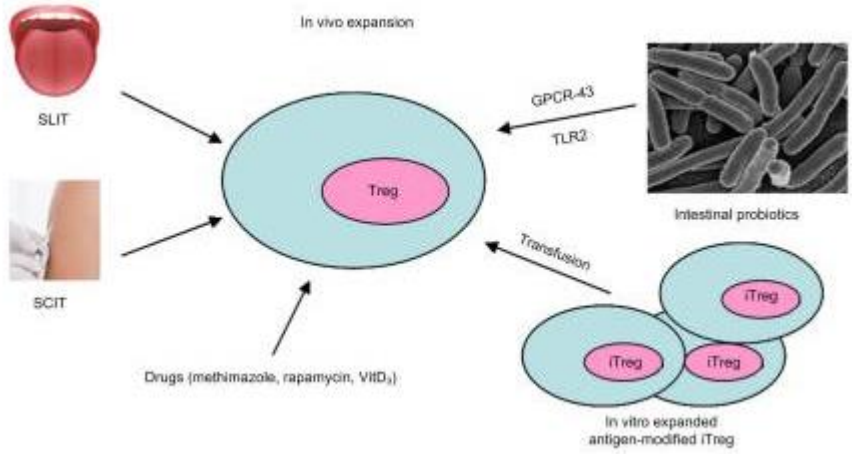

Figure 4. Treg induction both in vitro and in vivo [31]

XIII. Enhancement of Tregs' suppressive function

Numerous medications, including rapamycin, methimazole, and vitamin D3 (VitD3), have also been inadvertently shown to impact the Treg activity [32]. The reduction of thyroid autoantibodies is the mechanism by which methimazole treats the Graves' disease, but according to an in vivo investigation, methimazole can restore Tregs' aberrant suppressive function [33]. In vitro research has shown that rapamycin, an immunosuppressive medication used to stop graft rejection, encourages Treg proliferation. The vitamin D3 has the ability to impact Tregs and both the innate and acquired immune responses [34].

IX. Conclusion:

In essence, asthma is a chronic condition characterized by inflammation from the airways and the body's aberrant immunological tolerance to antigens is the main cause of an overactive T helper response. The primary mechanism via which the body sustains the immune responses to allergens from the outside is Tregs. Currently, a treatment that involves inhaling synthetic glucocorticoids can only manage persistent eosinophilic inflammation caused by the Th2 response; it is unable to alter the body's immunological tolerance to exogenous allergens. Therefore, research on Treg regulation mechanisms will be helpful in developing more effective asthma medications and management techniques.

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