Review:

Regulatory T cells and asthma

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Abstract: Asthma is a chronic disease of airway inflammation due to excessive T helper cell type 2 (Th2) response. Present treatment based on inhalation of synthetic glucocorticoids can only control Th2-driven chronic eosinophilic inflammation, but cannot change the immune tolerance of the body to external allergens. Regulatory T cells (Tregs) are the main negative regulatory cells of the immune response. Tregs play a great role in regulating allergic, auto-immune, graft-versus-host responses, and other immune responses. In this review, we will discuss the classification and biological characteristics, the established immunomodulatory mechanisms, and the characteristics of induced differentiation of Tregs. We will also discuss the progress of Tregs in the field of asthma. We believe that further studies on the regulatory mechanisms of Tregs will provide better treatments and control strategies for asthma.

Key words: Regulatory T cell; Asthma; Transforming growth factor β (TGF- β); Interleukin 10 (IL-10); IL-35
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1 Introduction

Previous extensive studies have shown that asthma is a disease of chronic airway inflammation mainly driven by the T helper cell type 2 (Th2) response. The over-enhancement of the Th2 response is reflected by significantly elevated expression levels of interleukin 4 (IL-4), IL-5, and IL-13, among various cytokines in vivo, leading to pathophysiological manifestations, such as airway eosinophilic inflammation, high serum immunoglobulin E (IgE) level, and airway hyperresponsiveness (AHR) (Reddel and Levy, 2015). The theory of Th2/Th1 cell imbalance has been used to explain the pathogenesis of airway inflammation in asthma (Berker et al., 2017), and insufficient differentiation of Th1 cells is thought to be a major cause leading to the over-differentiation of

Th2 cells. However, later studies showed that the theory of Th2/Th1 cell imbalance has obvious limitations, as the over-differentiation and activation of Th2 cells in asthma are not due merely to insufficient differentiation of Th1 cells.

In recent years, regulatory T cells (Tregs) have been found to play very important roles in regulating the immune responses of the body. Tregs, the negative regulatory cells of the immune response, take part in the regulation of multiple immune responses, including allergic, autoimmune, and graft-versus-host responses. When an antigen stimulates the differentiation of naive CD4⁺ T cells into Th2 cells, it also promotes cell differentiation into Tregs. The roles of Tregs involve “maintaining” the immune response of Th2 cells within a normal range. When Tregs are dysfunctional and fail to effectively suppress an excessive Th2 response, asthma and other allergic diseases can develop. Therefore, Tregs are the key regulatory mechanism by which the body maintains immune tolerance to external harmless antigens and prevents excessive Th2 responses.

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2 Classification and biological characteristics of Tregs

2.1 Classification of Tregs

Tregs can be divided based on their origin into natural Tregs (nTregs) and induced Tregs (iTregs) (Komatsu et al., 2009). The nTregs are derived from thymocytes and are also known as thymus-derived Tregs (tTregs) and express the transcription factor forkhead box P3 (Foxp3). The nTregs obtain stable phenotypic and genetic characteristics during thymus selection and maturation and mainly induce immune tolerance to autoantigens. The nTregs express CD4, CD25, and Foxp3, with low CD127 expression (Abbas et al., 2013). $CD4^+CD25^+$ Tregs account for 5%–10% of mature human or mouse $CD4^+$ T cells.

The iTregs, also known as peripherally induced Tregs (pTregs), are derived from the peripheral lymphoid tissue outside the thymus, in which naive $CD4^+Foxp3^-$ conventional T cells are transformed after contacting with an antigen and in the presence of immature transforming growth factor-dendritic cells

(TGF-DCs), IL-10, and interferon (IFN)- γ (Jordan et al., 2001). The iTregs mainly regulate immune responses caused by non-self infections and external harmless antigens. Thus far, no specific cell surface markers for identifying iTregs have been identified. There are three main types of iTregs (Komatsu et al., 2009): $CD4^+CD25^+Foxp3^+$ iTregs, expressing the specific transcription factor Foxp3; $CD4^+CD25^{low}Foxp3^+$ Th3 cells, mainly secreting TGF- β ; and $CD4^+CD25^{low}Foxp3^-$ type 1 regulatory T (Tr1) cells, secreting high level of IL-10. The iTregs can suppress the immune response induced by autoantigens and regulate the immune response induced by external antigens at a certain level (Komatsu et al., 2009). Tr1 cells secrete IL-10 to suppress T cell proliferation, while Th3 cells secrete TGF- β and IL-10 to mediate the suppression function. Thus, iTregs play a critical role in maintaining the peripheral immune tolerance (Fig. 1).

2.2 Markers of Tregs

Foxp3 is a specific marker for identifying Tregs, but it is expressed in the nucleus; no specific surface

Fig. 1 Classification of regulatory T cells

Major characteristics of subsets of $CD4^+$ regulatory T cells (Tregs) based on cell-surface markers and immunosuppressive cytokine secretion. nTreg: natural Treg; iTreg: induced Treg; Th: T helper cell; Tr1: T-regulatory cell type 1; TGF- β : transforming growth factor β ; IL: interleukin

markers are currently available. Tregs express high levels of CD25, cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), human leukocyte antigen-antigen D related (HLA-DR), CD45RO, CD95, and Ki67, with low levels of CD127; however, these markers are not specific to Tregs (Miyara et al., 2009). Some surface molecules have been found as potential markers for the identification of Tregs.

High expression of CD39 has been observed in more than 80% of mouse CD4⁺Foxp3⁺ Tregs (Deaglio et al., 2007). Moreover, CD39 is highly expressed on the surfaces of human CD4⁺CD25^{high} T lymphocytes, while CD4⁺CD25⁻ cells hardly express CD39. CD39 is rarely expressed on the surface of Foxp3⁻ cells. However, not all Foxp3⁺ cells express CD39, and only about 40% of CD39 is expressed on the surfaces of human Foxp3⁺ cells in contrast to murine cells. It is worth noting that CD39 expression is positively correlated with Foxp3 expression. CD39 mainly decomposes extracellular adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and adenosine monophosphate (AMP) through hydrolysis. The immunosuppressive effect of CD39⁺Foxp3⁺ Tregs is significantly higher than that of CD39⁻Foxp3⁺ Tregs (Deaglio and Robson, 2011).

CD73 is a multi-functional glycoprotein immobilized outside the cell membrane and has 5'-nucleotidase function. CD73 can be co-expressed with CD39 outside the membranes of various cells and hydrolyses AMP into adenosine, whereas adenosine can bind to the A2A receptor of effector T cells and plays an immunosuppressive role (Wang et al., 2013). Extracellular generation of adenosine in large quantities may be one of the important pathways for Tregs to play their immunosuppressive role (Sitkovsky et al., 2008).

2.3 Secretion of cytokines

iTregs can secrete suppressive cytokines, such as TGF- β , IL-10, and IL-35, and cell-lysing molecules, such as granzymes A and B (Sakaguchi et al., 2009).

IL-35 is a heterodimer consisting of an IL-12 α chain and an IL-27 β chain that belong to the IL-12 family. IL-35 is a newly discovered cytokine secreted by Tregs but not by other effector T cells (Bardel et al., 2008). When researchers studied the changes of proliferation in Tregs and Th17 cells in 2007, they found that the heterodimer consisting of the IL-27 β chain

Epstein-Barr virus induced gene 3 (Ebi3) and the IL-12 α chain p35 can promote Treg proliferation and suppress Th17 cell expression (Niedbala et al., 2007); the heterodimer was designated IL-35. Subsequently, a study reported that IL-35 can directly shut down the immune function of T cells through the Neuropilin-1/Semaphorin A pathway (Delgoffe et al., 2013). IL-35-induced Tregs, referred to as "iTr35", are a new type of Treg, which perform their immunosuppressive function by secreting IL-35 and IL-10. In contrast to TGF- β -induced iTregs, iTr35 does not express Foxp3, and the maintenance of its function is not related to Foxp3. More importantly, iTr35 is highly stable in vivo compared with TGF- β -induced iTregs. Therefore, it is speculated that iTr35 plays an important role in the formation of infection tolerance (Olson et al., 2013).

3 Biological effects and mechanisms of Tregs

The two major characteristics of Tregs are immune anergy and suppression (Komatsu et al., 2009). Immune anergy is reflected by a lack of response to stimulation with a high concentration of IL-2 alone or low-level proliferation in a low-response status after activation by T cell receptor (TCR)-mediated antigen-presenting cells. The suppression effect of Tregs refers to the fact that the activated Tregs can suppress the activation and proliferation of CD4⁺CD25⁻ T cells and CD8⁺ T cells. The suppression effect of Tregs is achieved mainly through intercellular contact and secretion of suppressive cytokines (Fig. 2).

3.1 Cell contact

Tregs can competitively bind to B7 molecules on the surfaces of antigen-presenting cells (APCs) through expressing CTLA-4, thereby suppressing the activation of other effector T cells by APCs (Read et al., 2000; Liang et al., 2008). Additionally, Tregs can kill CD4⁺ or CD8⁺ T cells via the granzyme-perforin-dependent pathway (Grossman et al., 2004; Gondek et al., 2005).

3.2 Indirect effect

Tregs can suppress the local immune response through secreting IL-10, IL-35, and TGF- β (Kitani

Fig. 2 Suppression mechanisms of Tregs

Tregs suppress effector T cells by multiple mechanisms: (1) Tregs produce immunosuppressive cytokines (IL-10, IL-35, and TGF- β); (2) Tregs induce cell death via granzyme and perforin; (3) Tregs transfer cAMP to effector T cells which generate immunosuppressive adenosine; (4) Tregs inhibit T cell-activation by APCs through downregulating costimulatory molecules in APCs via CTLA-4; (5) Tregs consume cytokine IL-2 through IL-2R (CD25) which is required for T cell differentiation. TGF- β : transforming growth factor- β ; cAMP: cyclic adenosine monophosphate; APC: antigen-presenting cell; Treg: regulatory T cells; CTLA-4: cytotoxic T lymphocyte-associated antigen-4; IL: interleukin

et al., 2003; Nakamura et al., 2004; Collison et al., 2007; Stanilov et al., 2016), an immunosuppression mechanism that has no major histocompatibility complex restriction. Moreover, Tregs can consume the cytokine IL-2, which is required for T cell differentiation, through expressing CD25, i.e. IL-2R, thereby suppressing T cell proliferation (Thornton and Shevach, 1998).

4 Induced differentiation and stabilization of iTregs

4.1 Induced differentiation of iTregs

iTregs are produced from peripheral naive CD4⁺ T cells, which require appropriate antigen stimulation and the presence of IL-2 and TGF- β . Cells produced under in vitro conditions are “iTregs”, and cells produced in vivo are “pTregs”. Despite their low proportion in CD4⁺ T cells, there are relatively large numbers of iTregs in local tissues, and they play an important role in the local immune tolerance of the organs.

TGF- β , one of the most important cytokines, induces Foxp3 expression and iTreg differentiation.

A lack of the *TGF- β 1* gene in mice can lead to an iTreg differentiation disorder. The signalling pathway of TGF- β -induced Foxp3 expression has been elucidated and requires the phosphorylation and activation of the transcription factor Smad. The Smad3 molecule downstream of TGF- β and nuclear factor of activated T cells is involved in the acetylation of the H4 histone in the promoter region of the *foxp3* gene, making it easier to express Foxp3 (Won and Hwang, 2016). Smad2 is responsible for maintaining Treg differentiation when Smad3 is absent; the differentiation of TGF- β -induced Tregs is completely suppressed only if both factors are absent (Melnik et al., 2016). Additionally, TGF- β facilitates *foxp3* gene expression by promoting the demethylation of the methylated site in the *foxp3* gene. This is also an important mechanism of TGF- β -mediated stabilization of iTregs (Kanamori et al., 2016).

4.2 Differentiation and stability of iTregs

The mechanism of stable Treg differentiation lies in the fact that the transcription factor Foxp3 can maintain stable expression of CD25 and CTLA-4 on the surfaces of Tregs (Rudensky, 2011). However, in recent years, studies have found that in some disease conditions, iTregs are no longer immunosuppressive,

instead showing the phenotypic and immune characteristics of effector T cells (Zhou et al., 2009; Krishnamoorthy et al., 2012). This instability is currently the greatest obstacle encountered in the clinical application of Tregs, and its underlying mechanism has not been fully elucidated.

Tregs can use the transcriptional programme of target Th cells to express the major transcription factors of the target cells, such as the transcription factor T-bet of Th1 cells and the interferon regulatory factor 4 of Th2 cells, which determine the respective cells' functions (Zheng et al., 2009; Koch et al., 2012). This process is controllable under physiological conditions; however, it is out of control in chronic inflammation, leading to the "betrayal" transition of Tregs into pathogenic effector T cells (Komatsu et al., 2014; Charbonnier et al., 2015a). Two mutations have been associated with this phenomenon. The first mutation from tyrosine to phenylalanine at site 790 in the mouse *IL-4R α* gene results in a loss of the immunosuppressive effect of tyrosine in this receptor and activates the downstream signal transducer and activator of transcription 6 (STAT6) through IL-4 and IL-13. Such a mutation, similar to the polymorphism of the human *IL-4R α* gene, facilitates STAT6 activation, making mice more susceptible to allergic diseases

(Tachdjian et al., 2010; Mathias et al., 2011). The behaviour of the re-edited "Treg" is similar to that of Th2 cells, which can secrete IL-4 and always express Foxp3 (Noval Rivas et al., 2015). The second mutation is located at site 576 of the *IL-4R α* gene and results in glutamate being substituted by arginine (Hershey et al., 1997). This site mutation can cause increases in IL-4 and IL-6; IL-6 promotes the differentiation of antigen-specific iTregs towards Th17 cells and ultimately leads to a mixed Th2-Th17 immune response in asthma (Massoud et al., 2016). Replication of this site mutation into sensitized and stimulated mice aggravates allergic airway inflammation (Rosa-Rosa et al., 1999; Tachdjian et al., 2009; Xia et al., 2015), suggesting that this site mutation can aggravate the condition of asthma and increase the difficulty of treatment (Fig. 3).

5 Tregs and asthma

A growing number of studies have shown that the insufficient differentiation and functional defects of Tregs are key reasons for the enhancement of the Th2 response and the pathogenesis of asthma. One study (Baatjes et al., 2015) reported that patients with

Fig. 3 Possible mechanism of instability of Treg differentiation

In some disease conditions, iTregs differentiate into pathogenic T cells. Site 790 mutation in the mouse *IL-4R α* gene activates STAT6 through IL-4 and IL-13, which makes mice more susceptible to allergic diseases. Site 576 mutation in the mouse *IL-4R α* gene increases both IL-4 and IL-6 secretion. IL-6 promotes the differentiation of iTregs towards Th17 cells and ultimately leads to a mixed Th2-Th17 immune response in asthma. APC: antigen-presenting cell; TGF- β : transforming growth factor- β ; iTreg: induced regulatory T cell; Th: T helper cell; IL: interleukin

mild asthma had fewer $CD4^+CD25^{\text{high}}Foxp3^+$ Tregs in the peripheral blood than non-asthma normal individuals. Another study found that children with asthma had fewer $Foxp3^+$ Tregs in the lungs than normal children (Hartl et al., 2007). Animal studies also showed that removal of Tregs in mice before sensitization aggravated airway inflammation and AHR (Lewkowich et al., 2005); the retransfusion of nTregs or iTregs from normal mice into ovalbumin (OVA)-sensitized and challenged mice with asthma significantly suppressed AHR, while it reduced the number of eosinophils as well as the IL-5 and IL-13 levels in the bronchoalveolar lavage fluid (BALF) (Joetham et al., 2017). Human *Foxp3* gene mutation can lead to rare immune dysregulations, polyendocrinopathy, enteropathy, and X-linked syndrome (IPEX). The patients may have severe eczema, high IgE, eosinophilia and food allergies, and other clinical manifestations (Gambineri et al., 2003). Researchers investigated the function of Tregs in children with X-linked syndrome and found that their capacity for suppressing effector T cells was impaired (Charbonnier et al., 2015b). Animal studies found that TGF- β and IL-10 secreted by Tregs markedly suppressed airway inflammation and AHR in asthma (John et al., 1998; Fu et al., 2006), whereas the blocking of TGF- β

or IL-10 aggravated airway inflammation and AHR (Stämpfli et al., 1999; Hansen et al., 2000; Nakao et al., 2000; Oh et al., 2002).

The study of Tregs will bring new methods and directions to the treatment of asthma. Presently, Treg treatments are mainly divided into two types: increasing the number of Tregs and improving the suppression function of Tregs. By the different origins of Tregs, the former method can be further divided, i.e. in vivo induced generation of Tregs and transfusion of in vitro expanded iTregs (Fig. 4).

5.1 Induction of in vivo Tregs

Antigen-specific immunotherapy (ASIT) and intestinal probiotic immunity are the main methods of in vivo induction of Tregs. ASIT involves giving a specific allergic antigen to a patient to induce their desensitization to the antigen and to maintain their tolerance long term. According to the method of administration, ASIT is mainly divided into sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT). ASIT is presently considered the only method that may cure allergic asthma (Burks et al., 2013). The exact mechanism of ASIT treatment for allergies or asthma has not been fully elucidated; nonetheless, there is evidence that Tregs participate in

Fig. 4 Induction of Tregs in vivo and in vitro

Both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) can increase differentiation of Tregs. Intestinal probiotics induce Tregs through Toll-like receptor 2 (TLR2) pathway or G protein-coupled receptor 43 (GPCR43) pathway. Some drugs, methimazole, rapamycin, and vitamin D₃ (VitD₃), can improve the suppression function of Tregs. Transplantation of antigen-modified iTregs expanded in vitro may be a promising treatment to asthma

this process. Clinical studies observed increased differentiation of Tregs, with increased expression of IL-10 and low Foxp3 methylation levels in patients receiving effective ASIT treatment (Swamy et al., 2012; Suárez-Fueyo et al., 2014). The effects of Tregs induced by ASIT could last for more than three years (Nieminen et al., 2009). However, ASIT is not universal and is currently limited by technical problems in the detection and preparation of high-precision allergens since there are only a few clinically detectable antigens available. Additionally, although SCIT shows better efficacy than SLIT, the former increases the risk of fatal allergic response, and SLIT is unavailable for patients in the acute phase. Moreover, there is a lack of standard, normalized treatment regimens, and the course of ASIT treatment remains controversial (Stelmach et al., 2012). Despite many difficulties, we still believe that in the future, improved ASIT will become an effective means to control asthma.

A human's early living environment after birth has a strong correlation with the development of allergic responses and asthma (Heederik and von Mutius, 2012). The hygiene hypothesis suggests that the reduction of exposure to microbes in early life is associated with the onset of late-stage asthma (Wills-Karp et al., 2001). It is currently thought that this phenomenon may be associated with Tregs. Studies have shown that the lipopolysaccharide (LPS) A secreted by *Bacteroides fragilis* can induce the differentiation of CD4⁺ T cells to iTregs via the TLR2 pathway, resulting in stronger suppression and IL-10 secretion capacities (Round and Mazmanian, 2010; Round et al., 2011). In the intestinal tract, the short-chain fatty acids produced from fermentation of food fibres by some bacteria can act on T cells through G protein-coupled receptor 43 and can protect mice from intestinal inflammation by inducing Treg expansion (Smith et al., 2013). Recently, it was reported that oral antigens and microbes jointly induced retinoic acid receptor-related orphan receptor γ t (ROR γ t) expression of iTregs in the intestinal mucosa. Specific resection of ROR γ t in Treg cells resulted in increased differentiation of GATA-3⁺Foxp3⁺ Tregs and increased cell-mediated IL-4 and IL-13 secretion. Thus, it was concluded that intestinal probiotics regulated Th2 responses and DC activation using the expanded ROR γ t⁺Foxp3⁺ Tregs (Ohnmacht et al., 2015). It

remains unclear whether those allergy- or tolerance-promoting bacteria are associated with GATA-3⁺ and ROR γ t⁺Foxp3⁺ Tregs, and further studies will be helpful in identifying therapeutic targets for promoting immune tolerance.

5.2 Retransfusion of in vitro expanded Tregs

Studies have shown that the transfusion of antigen-specific Tregs has more efficacious advantages than the transfusion of polyclonal Tregs and can accurately act on the lesion site (Albert et al., 2005; Sagoo et al., 2011). Animal studies have also shown that transplantation of antigen-modified Tregs can suppress or control certain diseases (Prinz and Koenecke, 2012; Lapierre et al., 2013). Several clinical studies of graft-versus-host disease (GVHD) prophylaxis, haematologic disease, type I diabetes, and organ transplantation are currently in progress. Most of these studies have used in vitro expanded antigen-modified iTregs, and only one has used transfusion of gene-edited Tregs (Jethwa et al., 2014). The results in some of these studies have shown good efficacy and safety. To date, we have not seen any studies of transfusion of Tregs in asthma. Nevertheless, in a clinical trial, the researchers transfused in vitro expanded specific OVA-iTregs into 20 patients with refractory Crohn's disease. These patients generated good tolerance, which had a dose-dependent relationship with the transfusion of OVA-iTregs (Desreumaux et al., 2012). The above findings indicate that the transfusion of antigen-specific Tregs may also play important roles in the prevention and control of asthma. It should be emphasized that the clinical transformation of antigen-modified Tregs transfusion technique still faces many difficulties, such as the small number of Tregs that can be collected in the peripheral blood and the lack of reference standards for in vitro expansion and transfusion techniques. The course of treatment and the transfusion amount of Tregs are pending further research.

5.3 Improvement of the suppression function of Tregs

A number of drugs, such as methimazole, rapamycin, and vitamin D₃ (VitD₃), have also been accidentally found to affect the function of Tregs. The mechanism of methimazole treatment for Graves' disease is to reduce thyroid autoantibodies (Sato et al.,

2012). However, an in vivo study found that methimazole can repair the abnormal suppression function of Tregs (Klatka et al., 2014). Rapamycin is an immunosuppressive drug used to prevent graft rejection, and in vitro studies have found that rapamycin promotes Treg expansion (Scottà et al., 2013; Lu et al., 2014). VitD₃ can affect both the innate and acquired immune responses and can influence Tregs. Our previous in vitro experiments showed that VitD₃ regulated the LPS-induced Th17/Treg imbalance in mice with asthma (Jiang et al., 2015). VitD₃ can directly promote Foxp3⁺ Treg and IL-10⁺ Treg; meanwhile, it can act on effector T cells by secreting the suppressive factors IL-10 and TGF-β and by upregulating cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression. Among the four clinical trials of VitD₃ treatment for asthma that had been completed, three trials demonstrated improvements in asthma. The only failed study might be due to its dependence on only oral administration of VitD₃, whereas the administration in the other three was combined with the basic medication for asthma (Yawn et al., 2015). Although the abovementioned drugs may become potential methods for the treatment of asthma, their roles in asthma are not yet completely understood, and further study is needed especially on the regulation of Tregs.

In summary, asthma is essentially a chronic disease of airway inflammation due to excessive immune responses of the body to external harmless allergens. The key reason for generating an excessive Th2 response lies in the abnormal immune tolerance in the body to antigens. Tregs are the main mechanism by which the body maintains immune responses to external harmless allergens. Presently, a treatment based on inhalation of synthetic glucocorticoids can only control Th2 response-driven chronic eosinophilic inflammation, while it cannot change the immune tolerance of the body to external allergens. Therefore, studies of the regulatory mechanisms of Tregs will be useful to find better treatments and control strategies for asthma.

Compliance with ethics guidelines

Sheng-tao ZHAO and Chang-zheng WANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题目：调节性 T 细胞与哮喘

概要：哮喘是一种由于 II 型 T 辅助细胞 (Th2) 反应过度而引起的慢性气道炎症疾病。目前以吸入糖皮质激素为基础的治疗仅能控制 Th2 驱动的慢性嗜酸性炎症，但是不能改变机体对外界过敏原的免疫耐受状态。调节性 T 细胞 (Tregs) 是免疫应答的主要负调节细胞，Tregs 在调节变态反应、自身免疫反应、移植物抗宿主反应和其他免疫反应中发挥着重要作用。在本文中，我们综述了 Tregs 的分类和生物学特性、免疫调节机制及诱导分化特性。我们也探讨了 Tregs 在哮喘领域的研究进展。我们相信，进一步对 Tregs 调控免疫反应机制的研究会为哮喘防控提供更好的治疗方案和策略。

关键词：调节性T细胞；哮喘；转变成生长因子 β (TGF- β)；白介素10 (IL-10)；IL-35