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Crosstalk between Dendritic Cells and Regulatory T Cells: Inducing Immune Tolerance in Allergen-Specific Immunotherapy

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Abstract

Background: Allergen-specific immunotherapy (AIT) is a major therapeutic approach in allergy management to induce long-term immune tolerance to allergens. The success of AIT relies on immunological mechanisms, particularly the interaction between dendritic cells (DCs) and regulatory T cells (Tregs).
Method: This narrative review uses a literature search method on Google Scholar, PubMed, Scopus, and Web of Science databases with appropriate keywords.
Result: Treg cells play a critical role in regulating and suppressing DC activity, thereby promoting the formation of a tolerogenic phenotype in DCs through multiple molecular mechanisms. These mechanisms include the production of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), and inhibition of the expression of costimulatory molecules essential for activating effector T cells. In addition, Tregs can remove antigen-pMHCII complexes from the DC surface, thereby reducing the ability of DCs to present antigen to effector T cells and directly induce apoptosis in certain DCs through Fas/Fas Ligand interactions.
Conclusion: This interaction promotes allergen-specific tolerance by establishing an immune environment that inhibits allergic effector cells. Understanding the molecular pathways of Treg-mediated DC suppression is critical for developing more effective and safe therapies.

Keywords: Allergen-Specific Immunotherapy (AIT), Regulatory T cells, Dendritic cells, Immune Tolerance, Allergy

INTRODUCTION

Allergy is an excessive or abnormal immune response caused by exposure to substances that are harmless to most people. Allergies are characterised by an inflammatory response mediated by IgE antibodies that recognise and bind to specific allergens (1,2). When IgE binds to an allergen, it triggers the release of inflammatory mediators from mast cells and basophils, causing symptoms such as itching, swelling, and even anaphylaxis (3,4). The prevalence of allergies in recent decades has tended to increase, with an estimated 30% of the global population experiencing some form of allergy. Allergies have an impact that is not limited to physical discomfort. However, they can also significantly reduce an individual's quality of life, affect productivity, and increase the burden on the public health system (5,6).

In general, allergy management still focuses on a symptomatic approach to relieve symptoms arising from allergic reactions (7,8). This therapy includes the use of antihistamines, decongestants, and corticosteroids. These drug classes aim to inhibit the effects of inflammatory mediators such as histamine and leukotrienes, which provide short-term therapeutic assistance. These drugs cannot yet address the underlying cause of allergies and do not provide a long-term solution or change the immune response to allergens (9,10). In addition, long-term use of these drugs also causes unwanted side effects such as sedation, sleep disturbances, decreased

concentration, and a higher risk of infection due to the use of corticosteroids (11,12).

Allergen-specific immunotherapy (AIT) is needed as an innovative therapeutic approach to induce immune tolerance and provide a permanent solution for allergy sufferers (13,14). AIT aims to alter the immune response to an allergen by introducing a controlled dose into the patient's immune system (15). AIT works by inducing immune tolerance through repeated exposure to a specific allergen to shift the response from initially being dominated by type 2 helper T cells (Th2) to regulatory T cells (Tregs) (1,15). This shift is associated with decreased production of IgE and increased production of IgG4, which are markers of immune tolerance (16–18).

Regulatory T Cells (Tregs) are a subpopulation of T cells that maintain immune homeostasis and prevent allergic reactions (19). Tregs work by inhibiting the activity of other immune cells, including dendritic cells. In the context of allergies, Tregs have a role in suppressing the activation of dendritic cells (DCs) that can trigger allergic reactions (20,21). DCs act as antigen-presenting cells that initiate and direct the immune response (21,22). The interaction between Tregs and DCs is critical in determining whether the immune response will be tolerogenic or reactive (21,23). In the context of AIT, understanding how Tregs can modulate DC function to create tolerogenic conditions becomes particularly relevant.

Although studies have examined the role of Tregs and DCs in immune tolerance, there is still a lack of understanding of the specific mechanisms underlying this interaction, especially in the context of AIT. This article aims to review the literature to better understand the molecular mechanisms underlying the interaction between Tregs and DCs in the context of AIT. Hopefully, this understanding will pave the way for designing more effective therapeutic strategies that improve tolerance to allergens and minimise the risk of adverse allergic reactions. In addition, it is hoped that through an increased understanding of DC suppression by Treg cells, opportunities for the development of targeted allergen formulations, as well as the use of biomarkers to predict the success and response of therapy, will be created.

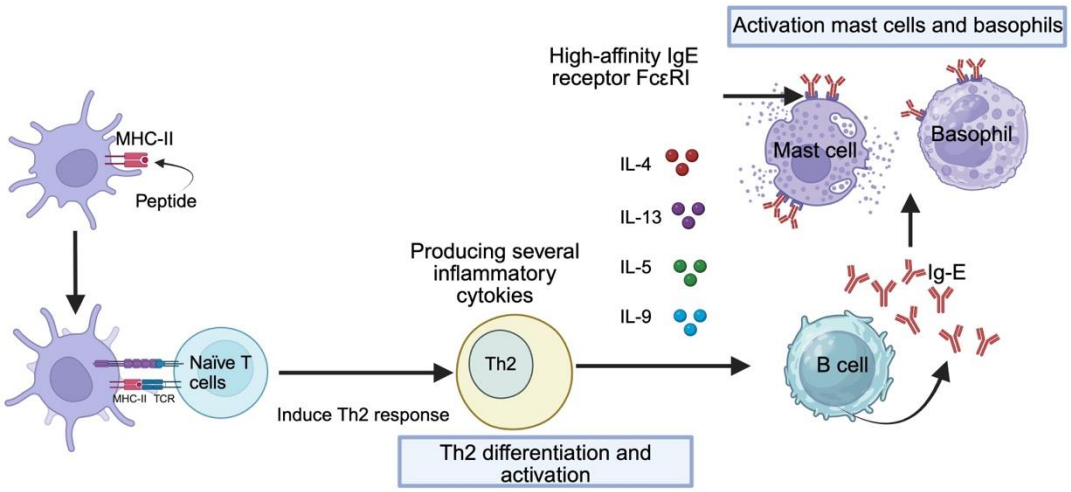

Figure 1. Pathogenesis of Allergic Response, *illustration created with BioRender.com*.

METHOD

This study uses the Literature Review method by searching and collecting information from various relevant and scientific primary sources. Data searches were conducted using the keywords "Dendritic Cell and Regulatory T Cell Interaction," "Allergen Specific Immunotherapy," "Immune Tolerance," and related molecular mediators (such as IL-10,

TGF-beta, IDO, CTLA-4) in the Google Scholar, PubMed, Scopus, and Web of Science databases. The data used must meet the inclusion and exclusion criteria. Inclusion criteria are: articles that specifically discuss DC-Treg interactions in the context of AIT and immune tolerance induction; publications in the form of original research (experimental and clinical) or reflecting high impact; publication range of the last 5-100 years (with a focus on the previous five years and seminal literature); English language articles; and full text availability. Exclusion criteria are articles that are not relevant to the focus of the study, cannot be fully accessed, or do not meet the scientific quality standards required for this narrative observation.

RESULTS

Allergy Pathogenesis

Allergy is an exaggerated immune response to exposure to substances that are harmless to most people, known as allergens. This reaction occurs due to the introduction of allergens, which causes T cell activation and the production of IgE antibodies, which contribute to allergy symptoms ranging from mild to severe, such as severe anaphylaxis (1,20). The pathogenesis of allergy begins with sensitisation, where an individual is exposed to an allergen for the first time. Dendritic cells (DCs) function as antigen-presenting cells (APCs) that capture and process allergens and then present them to CD4+ T cells in the lymph nodes (Figure 1) (24). This T cell activation leads to differentiation into type 2 helper T cells (Th2), which produce pro-inflammatory cytokines such as IL-4, IL-5, IL-7, and IL-13 (25). This cytokine triggers the production of immunoglobulin E (IgE) by B cells, which bind to allergens and high-affinity receptors, namely FcεRI on mast cells and basophils (26,27). Re-exposure to the allergen causes degranulation of mast cells and basophils, which release pro-inflammatory mediators such as histamine, leukotrienes, and prostaglandins (26,28). These mediators are responsible for allergy symptoms such as increased blood vessel permeability, vasodilation of blood vessels, and bronchoconstriction, resulting in clinical symptoms of itching, swelling, and difficulty breathing. This process shows how complex interactions between immune cells and allergens can lead to adverse allergic reactions (29,30).

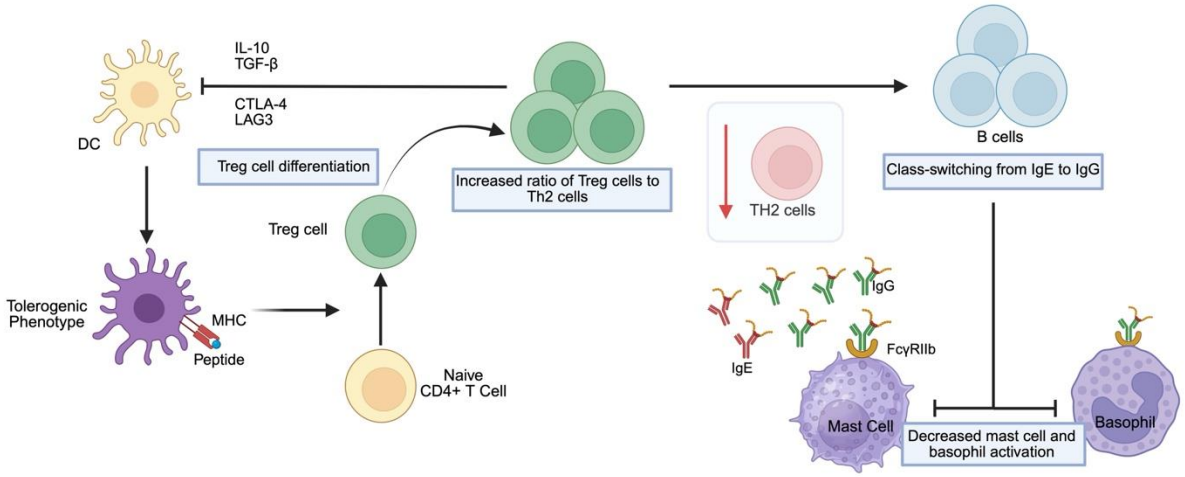

Figure 2. Mechanisms Driving Immune Tolerance in Allergen-Specific Immunotherapy, illustration created with *BioRender.com*.

Allergen-specific immunotherapy (AIT)

Allergen-specific immunotherapy (AIT) is a promising therapeutic approach to treating allergies. It hopes to induce immune tolerance to exposure to specific allergens (31). The AIT method introduces controlled

doses of relevant allergens, aiming to modulate the patient's immune response and reduce the severity of allergic symptoms in the long term (32). AIT effectively treats IgE-mediated allergies such as allergic rhinitis, conjunctivitis, asthma, and insect venom allergies (31).

AIT is a treatment designed to treat the cause of allergic disease by inducing tolerance to specific allergens (26,27). By achieving immune tolerance, the immune system can recognise an allergen as harmless, reducing or eliminating the excessive immune response. This process involves presenting the allergen to the immune system in gradually increasing doses, hoping to shift the immune response from a harmful allergic reaction to a safer tolerance (32).

This process begins with introducing allergens into the body, where dendritic cells (DCs) function as antigen-presenting cells (APCs) (Figure 2). Dendritic cells capture allergens through endocytosis or phagocytosis mechanisms and then process the allergens into smaller peptides. These peptides are bound to MHC class II molecules and presented to CD4+ T cells by interacting with the T cell receptor (TCR) (33). Upon activation, CD4+ T cells can differentiate into different subtypes, depending on the cytokine environment present. In the context of AIT, increased production of anti-inflammatory cytokines such as IL-10 and TGF-β, often produced by regulatory T cells (Tregs), plays a significant role in directing T cell differentiation toward a tolerogenic phenotype. Tregs, induced by allergen exposure, suppress the activation of effector T cells and reduce the production of pro-inflammatory cytokines such as IL-4 and IL-5, contributing to allergic reactions (34,35).

This Treg activation contributes to increased immunoglobulin G (IgG) production, particularly the IgG4 subtype, which functions as a barrier antibody, inhibiting the interaction between allergens and IgE-producing immune cells. By reducing IgE levels through inhibition of the Th2 response, which plays a role in allergic reactions, AIT effectively reduces allergy symptoms, such as rhinitis, asthma, and anaphylactic reactions, and increases tolerance to allergens (34,35). Through this mechanism, AIT changes the antibody profile and creates a more tolerogenic immune environment, contributing to the long-term reduction of allergic symptoms. In addition, AIT also affects dendritic cells by promoting their transition into tolerogenic dendritic cells. These dendritic cells can produce cytokines that support tolerance and express different costimulatory molecules, leading to the induction of Tregs and inhibition of effector T cells. Thus, AIT changes the T cell response and modulates the interaction between dendritic cells and T cells, ultimately leading to immune tolerance to allergens.

Regulatory T cells (Treg)

Regulatory T cells (Treg) are a subpopulation of T cells that play a crucial role in maintaining immune homeostasis and preventing autoimmune and allergic reactions. Treg cells can be identified by expressing surface markers such as CD4, CD25, and the transcription factor FoxP3, key markers for their differentiation and function (34,36). Tregs suppress the activation of effector T cells and regulate the immune response in a particular manner, thereby preventing overreaction to harmless antigens, such as allergens (37).

The mechanism of T regulatory cell (Treg) suppression in the context of allergen-specific immunotherapy (AIT) is critical to achieving immune tolerance to allergens. Tregs play a role in suppressing the activity of effector T cells, which can lead to excessive allergic reactions. One of the main ways Tregs do this is by producing anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which inhibit the proliferation and activation of effector T cells. In addition, Tregs can interact directly with dendritic cells, altering their function so that dendritic cells no longer produce signals that stimulate effector T cell activation (37,38). Tregs can also induce apoptosis in effector T cells through the Fas/FasL interaction mechanism and the secretion of cytotoxic molecules such as

perforin and granzymes (39). In this way, Tregs help maintain balance in the immune system, prevent overreaction to allergens, and support desirable tolerance formation in AIT.

Dendritic Cells (DCs)

Dendritic cells (DCs) are antigen-presenting cells (APCs) that play an essential role in the immune system. DCs can capture, process, and present antigens to T cells, including Tregs and effector T cells (21,40). In the context of allergies, DCs are essential in determining the type of immune response that will be produced, whether pro-inflammatory (reactive) or tolerogenic (41). The following is an explanation of the role of DC in the context of allergies:

1. Introduction and Presentation of Allergens

DCs can capture environmental allergens, such as pollen, dust, or food, through phagocytosis or endocytosis. DCs recognise allergens through Pattern Recognition Receptors (PRR) on their surfaces, which bind specific molecular patterns on the allergen. After the allergen is captured, DCs will mature by increasing the expression of Major Histocompatibility (MHC) molecules and co-stimulatory molecules such as CD80/CD86. DC maturation allows them to present allergens to T cells effectively (42,43)

2. T cell activation

Mature DCs present allergens to naive T cells through interactions between MHC and T cell receptor (TCR) and co-stimulatory signals so that T cells can be activated. DCs can influence T cells to differentiate into specific subtypes, such as T helper type 2 (Th2) cells that play a role in allergic reactions. Th2 can produce pro-inflammatory cytokines such as IL-4, IL-5, and IL-13, contributing to B cell activation and IgE production (42,44).

3. Role in the formation of tolerance

DCs can function in two ways: promoting tolerance or triggering allergic reactions. DCs can acquire a tolerogenic phenotype under certain conditions that induce T-cell tolerance. This can be achieved through the activation of $CD4^+CD25^+FoxP3^+$ Tregs, the production of tolerogenic cytokines such as TGF-β and IL-10, and microimmune conditions that are rich in tolerogenic cytokines and low in pro-inflammatory cytokines (40).

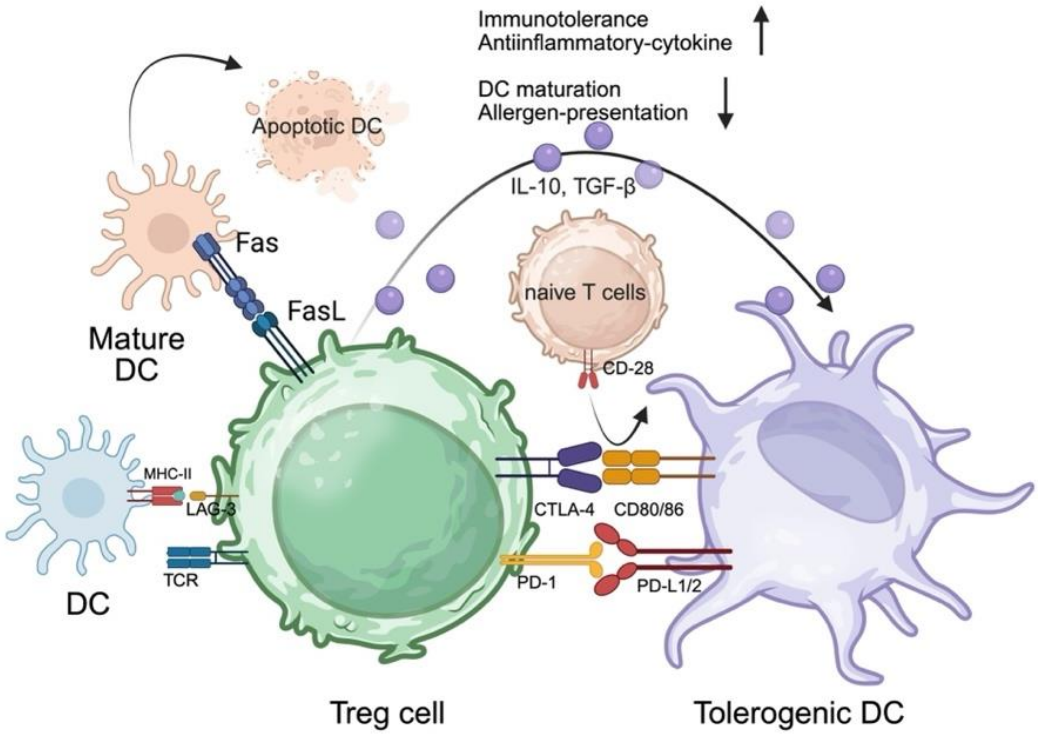

Figure 3. Interaction between Regulatory T Cells and Dendritic Cells in Immune Tolerance Formation, illustration created with *BioRender.com.*

Interaction of Tregs with Dendritic Cells (DC) in the Formation of Immune Tolerance

The interaction between dendritic cells (DCs) and T regulatory cells (Tregs) is a key component in allergen-specific immunotherapy (AIT) that contributes to the establishment of immune tolerance to allergens. This process begins when dendritic cells recognise an allergen and then present allergen fragments on major histocompatibility complex (MHC) molecules on their surface. When dendritic cells present allergens in the context of tolerogenic signals, they can promote the differentiation of T cells into Tregs, which function to suppress excessive immune responses (40,42). Tregs, in turn, can modulate dendritic cell function by secreting anti-inflammatory cytokines such as IL-10 and TGF-β, which inhibit effector T cell activation and reduce pro-inflammatory cytokine production. This interaction creates a positive feedback loop that supports immune tolerance, where Tregs suppress effector T cells and influence dendritic cells to function in a more tolerogenic capacity (37,38). By understanding the mechanisms of these interactions, researchers can design more effective AIT strategies that reduce allergy symptoms and improve patients' quality of life by inducing long-term tolerance to allergens.

The mechanism by which T regulatory cells (Treg) suppress dendritic cells (DC) to produce tolerogenic conditions involves a complex molecular process in which various surface molecules, cytokines, and transcription factors play an essential role in regulating the immune response.

1. Surface Molecules

Tregs express several surface molecules that contribute to their interaction with dendritic cells. One key molecule is CTLA-4 (Cytotoxic T-lymphocyte Antigen 4), which inhibits costimulatory signals. CTLA-4 competes with CD28 on T cells for binding to CD80/CD86 on dendritic cells. When CTLA-4 binds to CD80/CD86, it reduces costimulatory signals, leading to reduced activation of T-cell proliferation (45,46). During AIT, there is an increase in CTLA-4 expression on Tregs, contributing to the formation of tolerance to the allergen. This helps shift the immune response from reactive to tolerogenic. Studies have shown that increased CTLA-4 expression on Tregs is associated with a better response to AIT. This suggests that CTLA-4 plays a vital role in regulating immune tolerance and may be a biomarker for therapeutic efficacy (47).

In addition, Tregs also express surface molecules, namely PD-1 (Programmed Cell Death Protein 1), which interact with the PD-L1 ligand on dendritic cells (48). This interaction plays a vital role in inducing suppressive signals that contribute to the formation of immune tolerance (49). The signals resulting from these interactions inhibit the proliferation and differentiation of effector T cells, including Th2 cells that play a role in allergic reactions. PD-1/PD-L1 interactions can also inhibit the maturation of dendritic cells, which reduces their ability to present antigens to T cells (48,50). This helps prevent excessive T-cell activation against allergens. By changing the functional profile of DCs, Tregs help create a tolerogenic state, where T cells are more likely to become Tregs or nonreactive T cells. PD-1/PD-L1 interactions also form tolerogenic memory T cells, which may provide long-term protection against allergic reactions (51).

LAG-3 (Lymphocyte Activation Gene 3) is a surface molecule expressed by T cells, including T regulatory cells (Treg), which have a suppressive function, one of which is on DC cells (52,53). LAG-3 binds to MHC class II molecules expressed on the surface of DCs. This interaction is similar to CD4 and MHC class II, but LAG-3 functions as an inhibitor. When LAG-3 binds to MHC class II, it induces suppressive signals that reduce T cell activation. This leads to decreased proliferation and cytokine production by effector T cells. The interaction of LAG-3 with DCs affects T cells and modulates the function of DCs. When LAG-3 binds to MHC class II on DCs, it can alter the cytokine profile produced by DCs (53,54). For example, DCs interacting with LAG-3-expressing T cells tend to produce more anti-inflammatory

cytokines, such as IL-10 and TGF-β, supporting a tolerogenic state (55,56).

2. Cytokine Production

Tregs produce various cytokines that play a role in DC suppression by producing IL-10 and TGF-β, which can inhibit DC maturation and activation. When DCs are immature, they have a lower ability to activate T cells, reducing the immune response (57,58). IL-10 is one of the central cytokines produced by Tregs (59). IL-10 binds to the IL-10 receptor (IL-10R) expressed on the surface of DCs. This binding activates the JAK1/STAT3 signalling pathway involving the transcription factor STAT3 (Signal Transducer and Activator of Transcription 3). STAT3 activation leads to changes in gene expression that favour a tolerogenic state in DCs (60,61). STAT3 activation inhibits the expression of co-stimulatory molecules, such as CD80 and CD86. These molecules are required for T-cell activation. By decreasing the expression of CD80 and CD86, IL-10 reduces the ability of DCs to activate effector T cells, reducing the excessive immune response to allergens (62,63). STAT3 activation can also increase the expression of tolerance-promoting ligands, such as PD-L1 (Programmed Death-Ligand 1). Increased PD-L1 on DCs contributes to the induction of anergy in effector T cells that interact with DCs. IL-10 also changes the cytokine profile produced by DCs. Under normal circumstances, DCs can produce pro-inflammatory cytokines such as IL-12 and TNF-α, which promote T cell differentiation into effector T cells (Th1 or Th2). However, in the presence of IL-10, these pro-inflammatory cytokines are reduced, and DCs are more likely to produce tolerance-promoting cytokines, such as TGF-β (64,65). Overall, the effects of IL-10 on DCs lead to a shift in the functional profile from pro-inflammatory DCs to tolerogenic DCs. Tolerogenic DCs are less able to activate effector T cells and are more likely to promote immune tolerance (66).

In addition, TGF-β (Transforming Growth Factor-beta) also plays a vital role in DC suppression, promoting DC differentiation into a tolerogenic form that is more capable of promoting tolerance than activation (67,68). TGF-β secreted by Tregs binds to TGF-β receptors expressed on the surface of DCs. These receptors consist of two types, namely TGF-βRI and TGF-βRII (67). The binding of TGF-β to these receptors induces dimerisation and activation of signalling pathways involving SMAD (Sma and Mad homolog) proteins. Upon binding, TGF-βRI activates SMAD2 and SMAD3 through phosphorylation. The activated SMAD proteins then form a complex with SMAD4, which functions as a transcription factor. This complex then translocates to the nucleus, binding to specific response elements on DNA to regulate gene expression (69,70). Activation of the SMAD pathway by TGF-β leads to the transcription of genes that support a tolerogenic state in DCs. TGF-β reduces the expression of co-stimulatory molecules such as CD80 and CD86 on the DC surface (55,71). This molecule is typically required to activate effector T cells. By decreasing the expression of this molecule, DCs become less able to induce T-cell activation, which contributes to the reduction of excessive immune responses. TGF-β can also increase the expression of the ligand PD-L1 (Programmed Death-Ligand 1), which supports tolerance (72). This process is crucial in changing the functional profile of DCs from pro-inflammatory to tolerogenic. DCs in a tolerogenic state tend to produce anti-inflammatory cytokines, such as IL-10, and reduce the production of pro-inflammatory cytokines, such as IL-12 and TNF-α. This contributes to a more balanced regulation of the immune response and reduces the risk of allergic reactions (64,67).

3. Induction of Apoptosis in Dendritic Cells

Tregs can express surface molecules, namely Fas Ligand (FasL), as part of their mechanism to induce apoptosis in target cells (23). When Tregs interact with DCs, FasL binds to the Fas receptor (CD95) expressed on the DC surface, triggering conformational changes in the Fas receptor, leading to the recruitment of adaptor proteins such as FADD (Fas-Associated protein with Death Domain) (73,74). FADD recruitment triggers the activation of caspase-8, a key protease in the

cell death pathway. Caspase-8 activation further leads to other caspases, including caspase-3, a key executor in the apoptosis process (75,76). Caspase-3 activation causes degradation of cellular components, including DNA, proteins, and other cellular structures, leading to DC cell death. This process is known as apoptosis, a programmed cell death that does not trigger an excessive inflammatory response (77,78). As the number of activated DCs decreases, their ability to present antigens to T cells also decreases. This leads to reduced activation of effector T cells, which are essential in controlling excessive immune reactions.

DISCUSSION

A complex molecular interaction fundamentally mediates the induction of allergen-specific immune tolerance through Allergen Specific Immunotherapy (AIT) between dendritic cells (DCs) and regulatory T cells (Tregs). Tregs play a central role in modulating DCs toward a tolerogenic phenotype (tolDC), a prerequisite for dampening allergic responses (20,21). The primary mechanism involves the interaction of CTLA-4 on Tregs with CD80/CD86 ligands on DCs, which not only inhibits effector T cell co-stimulation via CD28 but also actively induces the expression of the immunosuppressive enzyme Indoleamine 2,3-dioxygenase (IDO) in DCs. This IDO activity creates a tryptophan-depleted and kynurenine-rich microenvironment, further suppressing effector T cells and promoting anergy. This process is reinforced by other Treg surface molecules such as PD-L1 and LAG-3, which transmit additional inhibitory signals to DCs and effector T cells. In addition, Treg-derived cytokines, especially IL-10 and TGF-β, directly maintain the immature or semi-mature state of DCs, suppress the production of pro-inflammatory mediators by DCs, and inhibit effector T cell responses, thereby creating a positive feedback cycle that is essential for successful AIT (37,38).

A deeper understanding of these molecular mechanisms, where Tregs actively shape DC function through CTLA-4, PD-L1, LAG-3, IL-10, and TGF-β, has significant clinical implications (47,49,57,58). In addition to direct modulation of DCs, Tregs contribute to the tolerogenic environment by inducing apoptosis of effector T cells, for example, through Fas-FasL interactions or the release of granzymes, which clear pro-inflammatory cells (73,74). The clinical relevance of this pathway is evident from the success of therapies such as CTLA-4-Ig fusion proteins (e.g., abatacept) in autoimmune diseases, which mimic the CD80/CD86 inhibition mechanism by Tregs. Furthermore, key molecules such as CTLA-4, PD-L1, IDO, IL-10, and TGF-β are potential biomarkers to predict patient responsiveness to AIT, monitor tolerance induction, and personalise treatment strategies. This knowledge also drives the development of novel AIT adjuvants and cellular therapies, such as using ex vivo-generated tolDCs or engineered Tregs that optimally express these tolerogenic factors. Thus, leveraging this understanding of the DC-Treg axis leads the AIT field toward a precision immunology approach for restoring robust and sustained immune tolerance.

CONCLUSIONS

Suppression of dendritic cells (DCs) by regulatory T cells (Tregs) plays a crucial role in the success of allergen-specific immunotherapy (AIT) in establishing a tolerogenic state that suppresses the excessive immune response to allergens. Tregs regulate and suppress DC activity, leading to a tolerogenic state through several mechanisms, including the production of anti-inflammatory cytokines and the inhibition of costimulatory molecules. In addition, Tregs can remove antigen-pMHCII complexes from the DC surface, thereby reducing the ability of DCs to present antigen and activate effector T cells and induce apoptosis. By changing the functional profile of DCs from pro-inflammatory to tolerogenic, Tregs help create an environment that supports tolerance to allergens, thereby reducing allergic symptoms and enhancing the effectiveness of AIT. Understanding the mechanisms of DC suppression by Tregs is essential for developing AIT in the future, opening

opportunities to design more effective and specific therapies by optimally enhancing the induction of tolerogenic DCs. This strategy seeks to increase therapeutic efficacy and minimise side effects by strengthening the molecular signalling pathways.

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