Review Article

Role of regulatory T cells in the development of skin diseases*

*Papel das células T reguladoras no desenvolvimento de dermatoses**

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Abstract: T cells, particularly CD4+ T cells, have been associated with many aspects of skin disease. Current evidence suggests, however, that the role of CD4+ T lymphocytes in the development of cutaneous inflammation surpasses that of pro-inflammatory activation of effector T cells that direct the immune response. T cell subtypes with regulatory capacity, such as CD4+CD25+^{high} Tregs, have been identified. Recent observations suggest that in some skin diseases the function of these cells is modified. Therefore, the development and function of Treg cells in Dermatology are currently attractive topics because of their importance in controlling the immune system response against tumors and infectious diseases, as well as in inhibiting auto-immunity and allergy development. Therefore, defective regulatory mechanisms may allow a breach in peripheral immune tolerance followed by chronic inflammation and disease. Functional abnormalities and contributions of different subtypes of regulatory T cells in the development of dermatological illnesses are detailed in this review. Possible targets for therapy and modifications of regulatory T cells caused by immunomodulators used in Dermatology are highlighted.
Keywords: Dermatology; Skin diseases; T-Lymphocytes; T-Lymphocytes, suppressor-inducer; Therapeutics

Resumo: *Células T, em particular as células T CD4+, têm sido associadas a muitos aspectos das doenças de pele. A evidência atual sugere, porém, que o papel dos linfócitos T CD4+ no desenvolvimento de inflamação cutânea excede o de ativador pró-inflamatório das células T de ação que dirigem a resposta imune. Subtipos de células T com capacidade reguladora, tais como Tregs CD4+CD25+^{bigb}, têm sido identificadas. Observações recentes sugerem que em algumas doenças da pele a função dessas células está modificada. Portanto, o desenvolvimento e a função de Tregs na dermatologia são atualmente um tópico atraente devido a sua importância no controle da resposta do sistema imune contra tumores e doenças infecciosas, bem como inibindo o desenvolvimento de auto-imunidade e alergia. Assim, mecanismos reguladores defeituosos podem permitir a quebra da tolerância imune periférica seguida por inflamação crônica e doença. Detalham-se as anormalidades funcionais e a contribuição de diferentes subtipos de células T reguladoras no desenvolvimento de doenças dermatológicas nesta revisão. Acentuam-se os possíveis alvos terapêuticos e as modificações dos T reguladores causados por imunomoduladores usados no campo da dermatologia.*
Palavras-chave: Dermatologia; Dermatopatias; Linfócitos T; Linfócitos T supressores-indutores; Terapêutica

INTRODUCTION

In no other part of the body are inflammatory reactions more apparent than the skin.[1] Inflammation may be beneficial, as in defense against tumors or infections, or deleterious, as in dermatitis and psoriasis. Some of these diseases have seen their prevalence double over the last 10 or 15 years since they affect many people worldwide.[2,3]

The skin is an immunological organ that has

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antigens for T cells and produces many types of cytokines and inflammatory mediators.[4,5] The complex relationships between cells and inflammatory mediators in skin diseases are starting to be unveiled. Several diseases are defined by the production of antibodies and lymphocytes against infectious and environmental antigens.[6,7] Additionally, some may result from the triggering of an immune response against auto-antigens of the epidermis or dermis.[8]

Today, any dermatologist opening a scientific journal on Immunology or Dermatology will observe that suppressor T cells, renamed regulatory T cells – Tregs, have become a central concept in immunological vocabulary.[9] Regulatory T cells participate in the prevention of autoimmune diseases and other dermatoses.

Hundreds of publications on Tregs have validated the existence of this single line of T cells. The CD4+CD25+^{high}Foxp3+ Treg subpopulation is developed in the thymus and may be peripherally induced during the course of a normal immune response. A repertoire of T cells predisposed against autoantigens is used,[10] yet controversy remains over the mechanism of action. *In vivo* analyses support the model in which Tregs directly or indirectly modify activation and differentiation of pathogenic T cells by means of an effect on antigen-presenting cells.[11]

The biology and suppression mechanism of these cells are discussed in this review, as well as the manner by which Tregs prevent sensitization and how this regulation process becomes defective or is overcome in individuals with skin disease. Other aspects are mentioned, including immunomodulating therapy that induces inhibitory signals using Tregs. Additionally, we will address the potential for manipulation of Tregs for therapeutical purposes as an attractive form of treatment for many skin diseases. The comprehension of the beneficial mechanisms of these treatments may contain important lessons for immunoregulation of skin diseases.

METHODS

Objective

To conduct a literature review on the role of regulatory T cells associated with the development of skin disease.

Criteria for consideration of studies for this review

All studies, including reviews, clinical trials, editorials, letters, meta-analyses, practical guides, randomized clinical trials and controlled clinical trials published up to January 2006. There was no restriction as to study language.

Research strategy for study identification

Relevant studies were identified in the following electronic databases:

a) MEDLINE (since 1966)

b) Ovid OLDMEDLINE(R) 1950 to 1965

c) EMBASE (as of 1980) and CINAHL (since 1982)

d) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

e) LILACS (Latin American and Caribbean Health Science Information)

f) CancerLit

g) Science Citation Index Expanded (SCI-EXPANDED) – 1945-present

h) Social Sciences Citation Index (SSCI) – 1956-present

i) Arts & Humanities Citation Index (A&HCI) – 1975-present

j) Books@Ovid January 11, 2006

The references of the selected studies were analyzed. Non-published or ongoing studies were researched via correspondence with specialists in the field, authors of relevant projects, and pharmaceutical companies. Summaries of congresses were researched manually.

The search strategy

1. Regulatory T cell OR T-Lymphocytes, Regulatory OR Suppressor Cells OR CD4+CD25+ OR CD25+ Treg Cells OR Th3 Cells OR Tr1 Cells;
2. Skin OR derm* OR cutan* OR Skin disease OR Dermatosis OR Dermatoses;
3. Immunosuppressants OR Immunosuppressive Agents OR Immunomodulators OR Biological Response Modifiers;

These were combined with the search strategy in order to locate articles.

Study selection method

Titles and summaries identified in the investigation were analyzed by the author. Possibly relevant texts were obtained for evaluation. The author decided which publications satisfied the inclusion criteria and quality methodology.

Potential conflict of interest

The author involved in this review performed this appraisal without any known conflict of interest.

REGULATORY T CELLS

Development of an immunological concept

Regulatory T cells

Biological systems are subject to complex regulatory controls and the immune system is no exception. We know that the immune system has the poten-

tial to generate lymphocytes against auto-antigens. Experiments, however, suggest that individuals cannot easily be immunized against their own tissues.[12] Therefore, a suppression mechanism is necessary to control potentially pathogenic immune cells. Owen suggested that this tolerance against one's own tissues is acquired during the development of the immune system,[13] and Burnet proposed that the clonal selective destruction of lymphocytes for auto-antigens occurs primarily in the thymus.[14]

The destruction of auto-reactive lymphocytes is the primary mechanism that leads to tolerance, but we know that this system is not perfect. B and T lymphocytes can be isolated from normal individuals.[15,16] Nishizuka and Sakakura proposed another mechanism for controlling auto-reactive cells. They observed that mice thymectomized between the second and fourth days of life developed an organ-specific autoimmune disease.[17] This aggression can be prevented by restoring T cells from the adult thymus or spleen of genetically identical individuals.[18] The generation of regulator T cells was proposed in order to explain this mechanism of auto-tolerance attributed to the thymus.[19]

Other studies observed that the prevention of autoimmune diseases was diminished by the reduction of CD4+ T cells, but not of CD8+ T cells, indicating that regulatory cells belonged to the CD4+ T cell class of lymphocytes.[20] Sakaguchi subsequently characterized these regulatory cells as natural CD4+CD25+ Tregs that express Foxp3.[21,22]

Suppressor T cells

Another control point of the immune response is established when the normal immune response is initiated. A different mechanism must be set off in order to control the magnitude of the response and its termination?. This regulation should contribute to limiting clonal expansion and effector cell activity. Soon after the discovery that T lymphocytes function as helper cells for B-lymphocytes, RK Gershon proposed that they could also act as cells capable of suppressing the immune response.[23] This subpopulation of suppressor T cells was considered a controller of both auto-reactive and effector cells. A suppressor cell was functionally defined as a lymphocyte that inhibits the immune response by influencing the activity of another type of cell involved in a cascade of suppression factors, a network of anti-idiotypic T cells, and counter-suppressive cells.[24]

Many of the experiments carried out contain data that support the existence of suppressor T cells. However, the mechanism responsible for these suppressive phenomena was never clearly characterized, and consequently interest in the field of suppressor T cells has gradually dwindled.[25] The discovery of Th1/Th2 cells led researchers to abandon the concept of suppressor T cells. Therefore, suppression was the result of counter-regulatory cytokines.[26] As pointed out by Green and Webb, the letter ''S'' started to resemble a foul word in cellular immunology, and its use was considered synonymous of scarce data with excessive interpretation or a mystic phenomenon.[27]

Regulatory T cells are suppressor T cells

Suppressor T cells reappeared as regulatory T cells (Tregs) in the late 1990s when several subpopulations of T cells were identified as having the capacity to inhibit the proliferation of other cells.[28] Shevach et al. were the first to call attention to the fact that regulatory T cells and suppressor T cells are the same.[29]

Therefore, the term 'regulatory' gradually replaced the term 'suppressor'. The main problem, however, is not that cells are called regulatory when they should be called suppressors, but that they are considered suppressors. We should understand that regulatory T cells are, in fact, immune response directors instead of its suppressors.[30]

Phenotype of the regulatory T cell

Tregs are produced in the thymus and are found in peripheral blood and in secondary lymphoid organs.[31] Natural regulatory T cells express CD25 constitutionally. The ? chain of the IL-2 receptor, CD25, is a marker of T cell activation. However, most activated T cells express CD25 with low to moderate intensity ($CD25+^{int}$; int = intermediate). Only 1% to 3% of them express CD25 with a high intensity ($CD25+^{high}$).[32] The $CD25+^{high}$ population functions as a regulator.[33]

In the blood, $CD25+^{high}$ Tregs express the intracellular cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). Additionally, they present a phenotype of memory cells since they are CD45RO+, CD45RBlow , besides CD62L and CD38 with a low intensity.[34-36] Other markers have been identified as well, such as PD1 or members of the super family of tumor necrosis factor receptors – TNFR, such as the glucocorticoid-induced TNFR-related protein - GITR.[37]

Further studies have revealed that the Foxp3 gene (forkhead box p3) seems to be vital in the development and function of $CD25+^{high}$ Tregs.[38] FOXP3, the human analogue of murine Foxp3, was found as a mutation in patients affected by immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (Ipex). In contrast to the other markers of $CD25+^{high}$ Treg, Foxp3 is not induced in the T cells after stimulation.[39] Foxp3 is necessary for the development of $CD25+^{high}$ Tregs.[40] Foxp3 plays a vital role

in the generation of CD25+^{high} Tregs and is the most specific marker available (Figure 1).

Regulation mechanisms of the immune system

The regulation mechanism of the immune system by CD25+^{high} Tregs is not well understood. Studies have not yet arrived at a simple mode of action. Most studies concluded that CD25+^{high} Treg cells suppress by means of a mechanism dependent on cell-to-cell contact,[41] The involvement of a molecule tied to the surface was proposed. Such a molecule has not yet been identified, although CTLA-4 is a candidate.[43] Suppression requires activation of regulatory T cells by their receptor (TCR) or CD3. However, the presence of antigen-presenting cells (APC) is not required for suppression to occur *in vitro*.

The *in vivo* involvement of cytokines was proposed. CD25+^{high} Treg cells are capable of producing IL-10.[44] Production of IL-10 by regulatory T cells is necessary for the suppression of certain forms of autoimmune intestinal inflammation.[45] Another mechanism that depends on cell-to-cell contact is suppression by the transforming growth factor-β (TGF-β).[46] As to the involvement of TGF-β in suppression by these cells, it has become evident that the suppression of CD8+ T cells that induce auto-immunity of tumor rejection requires a TGF-β receptor in the CD8+ T cell.[47,48] Therefore, inhibition of CD8+ T lymphocytes needs TGF-β.

A third mechanism of action was proposed by the combination of the other mechanisms. Two independent papers showed that human regulatory cells are capable of inducing, by contact, suppressive properties in CD4+CD25- T cells when they are cultivated *in vitro*.[42] This infectious tolerance was initiated after CD4+CD25+^{high} Tregs began to produce TGF-β[49] or IL-10.[50]

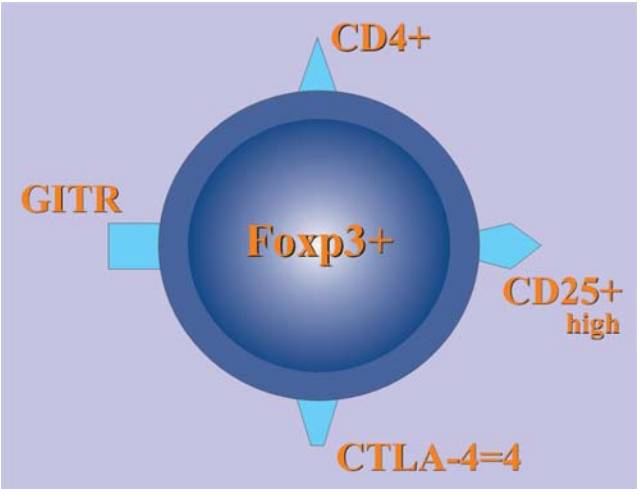

FIGURE 1: Phenotypical expression of natural regulatory T cell. Natural Treg cells express CD4, CD25^{high}, GITR (glucocorticoid-induced TNFR-related protein) and CTLA-4 (intracellular cytotoxic T-lymphocyte-associated antigen-4) in the membrane and Foxp3 in the nucleus

Outras células reguladoras

Several other types of regulatory T cells, such as the γδ, T cell, the NKT cell, and CD8+ T cells were described.[51] Regulatory CD4+ T cells can be divided into the induced type that secret interleukin-10 (IL-10) and TGF-β, such as TR1 cells,[46] and auxiliary T cells (T-helper 3, Th3).[52] Naturally occurring cells known as CD4+CD25+^{high} Tregs are the focus of this review (Chart 1).

REGULATORY T CELLS AND SKIN DISEASES

Regulatory homeostatic balance

The homeostatic balance of the immune system is obtained by healthy cellular and humoral responses. Some inflammatory agents, whether physical, chemical, or infectious, induce an intense immune response. This immune response against them frequently results in tissue damage that could be more intense if it were not for the interference of regulatory mechanisms (Figure 2). As has already been specified, Treg cells help limit the damage caused by a vigorous immune response. Natural Treg cells may respond to an ample variety of auto-antigens, although there is evidence that they may also respond to antigens expressed by microbes.[53] Induced regulatory T cells, such as TR1 or Th3, may develop from CD4+ T cells when exposed to specific conditions.[54,55]

Similarly, excessive activity of Treg cells may limit the magnitude of the immune response, which may result in failure to control an infection. On the other hand, the absence of the T regulator may result in intense inflammation and autoimmune dermatitis. Tissue damage may also result from the development of effector cells against their own auto-antigens (Figure 3).

This review discusses the action exerted by regulatory T cells, especially CD4+CD25+^{high} Tregs on skin diseases. In most cases, these diseases are chronic. The various types of influence of these cells suggest that they may act by suppressing or augmenting immunity. The control of Treg cells may affect the results favorably or may be deleterious. However, other factors, such as the immune status and genotype, and the presence of concomitant diseases or other infections may also have an influence. This part of the review also discusses how the manipulation of this balance can be therapeutically explored.

Chart 1: Main subpopulations of natural and induced regulatory cells

Treg Subpopulation	Regulatory mechanism	Expressed transcription factor	Function
CD4+CD25+ Tregs	Cell contact, cytokines (IL-10?)	Foxp3	Auto-immunity suppression; inhibiting rejection of alo-antigens and the response induced by bacterial infection; UV-mediated suppression
TR1 cells	IL-10	Foxp3 (?)	Auto-immunity suppression
Th3 cells	TGF-β		Auto-immunity suppression
NKTregs	IL-4, IL-10, TGF-β, cytotoxicity		Eliminating tumors and viral pathogens; auto-immunity suppression; modulation of immunity protecting against UV-induced tumors

Skin diseases

Contact dermatitis

Contact dermatitis is one of the first human diseases in which the role of the T regulator was demonstrated. Results indicate that CD8+ T cells specific for nickel (Ni) are directly related to the expression of contact dermatitis by nickel, while CD4+ T cells specific for Ni may have a regulatory function, possibly via release of IL-10.[56] It seems that clones of nickel-specific CD4+ T cells in non-allergic individuals exhibit a low production of IFN-γ and an increased production of IL-10 in comparison to clones of allergic patients. These Ni-reactive IL-10^{high} CD4+ T cell clones remind us of a TR1 subpopulation.[57] New studies show that other haptens that are inducers of delayed-type hypersensitivity also induce a migration of regulatory T cells to inflamed skin.[58] In this case, the CD8+ T cells are also effector cells, and CD4+CD25+^{high} cells are regulators.[59]

CD4+ effector cells in the presence of Ni, and

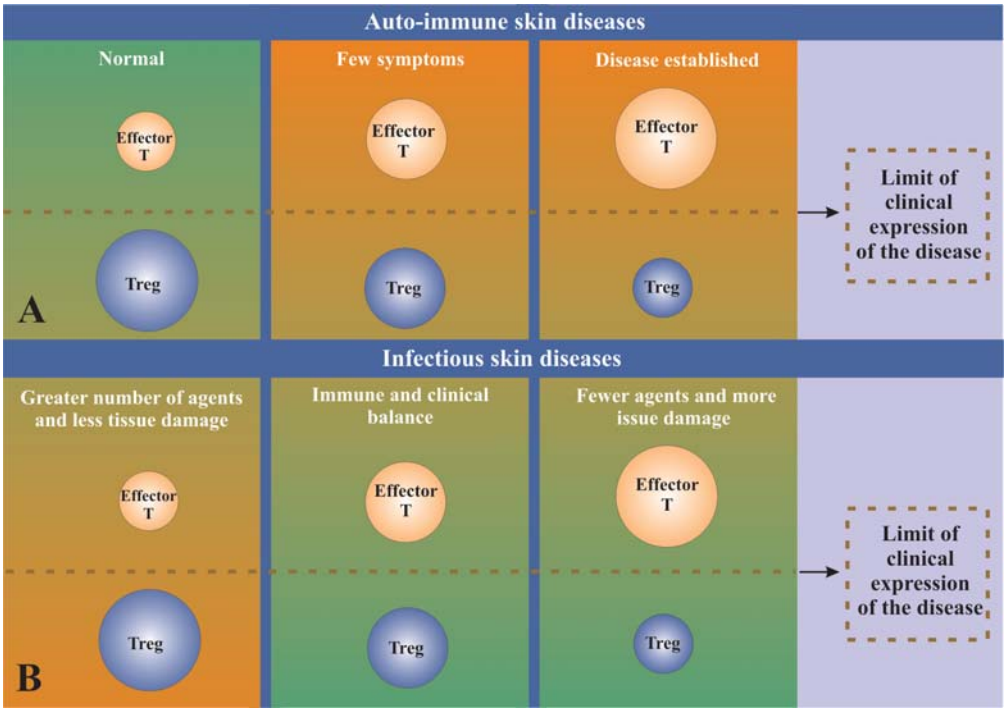

Figure 2: Immune response regulation mechanisms. The force balance between Tregs and the effector T CD4+ cells may present in a different manner depending on being an auto-antigen or a pathogen. In Figure 2A, the clinical expression of autoimmune skin diseases is shown. In this case, there is clinical manifestation only when the number and function of Tregs are significantly reduced. Figure 2B displays clinical manifestations that may occur in extreme cases. In case of excessive Treg function, the result shows reduction of effector lymphocytes against the pathogen, an increase in its number and less tissue damage. The contrary applies to effector cells against the pathogen that surpass the number and function of Treg. The ideal immune and clinical response occurs when there is a balance between functions

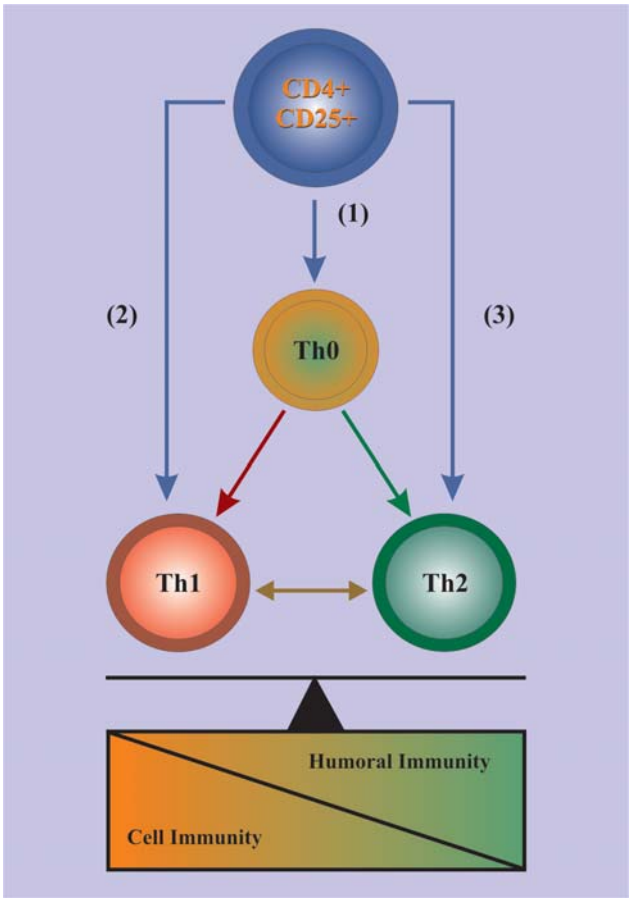

FIGURE 3: Regulatory homeostasis balance. The Tregs cells may interfere in the immune response by modulating primarily the Th1 and Th2 responses. Tregs cells may hinder the development of Th0 cells.[1] Or facilitate the Th1 response by diminishing its number or function, which results in a response that is predominantly cellular.[2] Moreover, it may stimulate primarily Th2 response and humoral production by IL-10 production.[3]

TR1 cells reactive to Ni or treated with extracts of TR1 cell cultures exhibited a lowered capacity to stimulate a specific Th1 response to nickel. Therefore, TR1 can regulate the expression of allergic diseases mediated by the Th1 response via the release of IL-10.[60] TR1 cells may limit excessive reactions against haptens by blocking the specific Th1 response. The high incidence of TR1 in non-allergic individuals also suggests that these cells can determine if the immune response will be silent or develop further. CD4+CD25+^{high} Treg cells suppress contact hypersensitivity reactions by blocking the influx of effector cells into the inflamed tissue *in vivo*.[61] These aspects identify immunotherapy targets for allergic contact dermatitis.

Atopic dermatitis

Th2 cells play a critical role in the pathogenesis of atopic dermatitis. Nonetheless, the immune mechanisms that reduce and protect against the development of this disorder are poorly understood.[62] A spectrum of CD4+ T cells, including Th3, TR1 and Treg CD4+CD25+^{high}, and NKT cells seem to participate in the regulation of atopic diseases.63 This may be related to the fact that patients with Ipex develop serious dermatitis, high levels of IgE, and sometimes, eosinophilia.[64] Atopic dermatitis can result from an inappropriate balance between CD4+CD25+^{high} Treg cells activated by the allergen and Th2 effector cells. This imbalance may result from a deficiency in suppression by the regulatory T cells or by strong activation signals that supersede the regulatory mechanism.[65] As to the first possibility, the increase of regulatory cells confers protection against atopic inflammation.[66] However, other authors documented that patients with atopic dermatitis have a CD4+CD25+^{high} Treg population that is not numerically or functionally different from that of normal individuals.[67]

Psoriasis

Psoriasis is sustained by the activation of pathogenic T cells. In psoriasis, the subpopulation of CD4+ T lymphocytes in peripheral blood, phenotypically CD25+^{high}, CTLA-4(+), Foxp3^{high}, is deficient in its suppressor functions.[68] This is associated with an accelerated proliferation of the CD4+ T cell response.[69] The presence of non-functional CD4+CD25+^{high} Treg cells in peripheral blood and in tissues may lead to a reduced capacity to contain pathogenic T cells and to a hyperproliferation of the psoriatic plaque *in vivo*.[70] These findings represent a critical component of this autoimmune disease and may have implications for potential therapy by manipulation of CD4+CD25+^{high} Tregs *in vivo*.

Alopecia areata

CD4+CD25+^{high} Treg cells have inhibitory properties against the development of autoimmune diseases.[71] Alopecia areata, a disease that affects the anagen phase of hair follicles, has the participation of CD4+CD25+^{high} Treg cells in the mechanism of the disease. It was noted, for example, that in the draining lymph node and spleen of experimental models affected by the disease, only a few CD4+CD25+^{high} Treg cells were detected even though the number of CD25+ cells was unchanged.[72] These data suggest that the status of the disease is maintained by the expression of elevated cytokine levels, an increased number of CD4+ e CD8+, but reduced levels of CD4+CD25+^{high} Treg cells.

Similar observations were encountered in humans; mononucleate cells from peripheral blood of patients with alopecia areata contain an increase of

recently activated CD4+CD25+CD154+ T cells resistant to apoptosis, characterized by CD95-. These data indicate a progressive loss of Tregs in patients with alopecia areata.[73] However, delayed-type hypersensitivity reactions as a means of treatment for alopecia areata have no impact on T regulators.[74] In summary, CD8+ T cells may be the principal inducers of hair loss.[75] Nevertheless, the expression of the disease is determined by CD4+CD25+^{int} T cells, while CD4+CD25+^{high} Treg cells have a regulatory role.[76]

Candidiasis

During the experimental infection of mice with *Candida albicans*, the reduction in CD4+CD25+^{high} Treg cells induces a better control of infection, but it is associated with an increase of the intestinal inflammatory lesion.[77] PTherefore, the reduction of natural Treg cells leads to a better primary control of infections by *C. albicans*. Nevertheless, there is an increase in tissue lesions as well as a loss of immunity against reinfection unless the regulator cells are reconstituted.[78] This model shows that a balance dependent on natural Treg cells can be established between the host and the pathogen that benefits both.

Leishmaniais

The experimental infection model with *Leishmania major* provided a good example of the fact that natural Treg cells are necessary for pathogen survival. In the *L. major* infection model without cure, the infection results in progressive lesions caused by the Th2 response.[79] It is important to consider the role of IL-10 produced by natural CD4+CD25+^{high} Treg cells in the susceptibility to L. major, since these cells seem to suppress the capacity of the CD4+ T lymphocytes specific for L. major to produce a sterile cure.[80] Hence, the amplitude of the response and the subsequent tissue lesion are controlled by natural Treg cells.[81] IL-10 produced by CD4+ T cells is as important as IL-4 in the progression of susceptibility to infections by L. major. This observation raises the issue as to whether these cytokines are secreted by the same Th2 cells or produced by a discrete subpopulation of CD4+ T cells that arises from different cell clones activated by other antigens.[82]

Ultraviolet radiation (UV)

A reduction in immune response induced by UV was observed in several models. For example, it was demonstrated that the application of an allergen to skin exposed to UV does not result in sensitization, but in tolerance to the hapten.[83] This tolerance can be transferred to animals not previously sensitized.[84] The T regulator responsible for this type of tolerance belongs to the CD4+CD25+^{high} subtype.[85]

DNA damage is considered the greatest molecular inducer of UV-induced immunosuppression. Migration of dendritic cells containing damaged DNA seems to set off the production of Tregs in the lymph node.[86] Based on these data, it is possible to consider that these cells perform a role in photocarcinogenesis. Participation of the T suppressor in tumors induced by UV has been described since 1982.[87] However, it was only recently that these cells were characterized as natural killer T suppressor cells (NKT).[88]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease. As is true in other related entities, its etiology is unknown. Multiple defects in the immune systems of patients with this condition have been described. The involvement of regulator T cells in this disease is under study. Patients with active SLE exhibit a quantitative defect of natural CD4+CD25+^{high} Treg cells. A decrease in natural CD4+CD25+^{high} Treg cells correlates with the clinical seriousness of the skin lesions.[89] This defect is absent during the remission of the disease. Relapses of SLE are therefore associated with the global decline of these cells and do not represent some phenomenon of tissue redistribution.[90]

Herpes

Another example of the connection between the T regulator and a pathogen has been observed in infections with the herpes simplex virus (HSV). Treg cells protect the tissue of the lesion mediated by CD4+ T lymphocytes when it is submitted to a low intensity viral infection, a situation compatible with the establishment of immunity against reinfection. Natural CD4+CD25+^{high} Treg cells suppress virus-specific CD8+ T cells and retard viral elimination. Actually, non-pathogenic doses of the virus may induce tissue damage in the absence of natural Treg cells.[91] A greater resistance to the viral challenge determined by CD4+ e CD8+ T cells was also demonstrated in these animals.[92] Regulator T cells isolated from lesions *in vitro* exhibit an inhibitory effect involving IL-10.[93] Natural CD4+CD25+^{high} Treg cells were also encountered among inflammatory cells of sensory ganglions infected by HSV. It is possible that these serve to prevent the destruction of infected neurons in the site by the effector T cells.[94] These results suggest that the manipulation of regulatory cell function may be a useful approach for the control of immunoinflammatory diseases induced by the virus.

Epstein-Barr virus

Regulator T cells seem to also modify the immune response to infection by the Epstein-Barr virus (EBV) in human beings. The EBV infection induces IL-10-secreting Treg cells that are specific for the latent membrane protein 1 (LMP1) of the EBV. These cells inhibit the Th1 response against EBV proteins, which should facilitate viral persistence and promote the induction of tumors associated to the EBV.[95]

AIDS

AIDS is associated with the loss of CD4+ T cells and progressive immune dysfunction. Evidence suggests that immunity against infection by the human immunodeficiency virus (HIV) may be controlled by natural Treg cells.[96,97] Removal of Treg cells from peripheral blood results in an increase of the anti-HIV CD4+ T response. Paradoxically, depletion of regulator T cells in the HIV infection is associated with immune activation and worsening of the patient's clinical status,[98,99] since the response of CD4+ and CD8+ T cells specific against the HIV is diminished by the Treg cells.[100] This suppression depends on cell-to-cell contact and does not depend on cytokines, supporting the idea of natural Treg cell involvement.[101]

At the Universidade Federal do Paraná it was recently demonstrated that Tregs in children infected with HIV might regulate the expression of inflammatory and infectious dermatoses, altering their prevalence in this population according to the immune status of the individual.[102] Additionally, in another study of the same population, it was noted that Treg cells can also interfere in the expression of the response to environmental allergens evaluated by the prick test.[103]

Pemphigus vulgaris

TR1 cells were preferentially isolated from peripheral blood of healthy individuals who carry the genetic tendency for developing *pemphigus vulgaris* (PV) and from only a minority of patients with PV. The TR1 cells exhibited their inhibitory effect on the proliferation of auto-reactive Th clones responsive to desmoglein 3 (Dsg3). This capacity was not dependent on cell-to-cell contact and was mediated by cytokines IL-10 and TGF-β. These findings suggest that these cells may be involved in the maintenance of auto-tolerance to Dsg3.[104] In another study, blocking of the interaction between CD40 and CD154 and the monoclonal antiCD154 (antiCD154 mAb) antibody reduced the production of IgG antiDsg3 and prevented the formation of lesions in the experimental model of PV. The resulting tolerance to Dsg3 was transferred by the splenic cells of animals treated with anti-CD154 mAb. These data suggest that anti-CD154 mAb induced tolerance to Dsg3 by the induction of immunoregulator cells.[105] Hence, TR1 cells responsive to Dsg3 or immunoregulator cells induced by treatment with anti-CD154 may represent an ideal tool for therapeutically restoring Dsg3-specific immune tolerance.

CLINICAL AND THERAPEUTICAL CONSEQUENCES OF T REGULATORS

Today, regulator T cells are now better known.[106] They were isolated from human beings and animals.[25] An improved understanding of the role of T regulators in skin diseases may lead to the identification of new targets for treatment. More specifically, the goal is to manipulate natural regulator cells or those induced by means of an increase or decrease of their function, depending on the circumstances.

Tolerance depends on natural CD4+CD25+^{high} Treg cells that arise in young CD25- cells and regulate their effect by means of IL-10 and CTLA-4. The induction of a dominant tolerance in an allograft depends on regulatory T cells and does not necessarily result in an attenuation of the response against pathogens. Thus, there is an interest in the development of tolerance protocols in clinical aspects of transplants.[107] Proliferative and cytotoxic events involving T cells, Tregs, and NK have been implicated in the therapeutical effect of bone marrow transplants in treatments for autoimmune diseases.[108]

In the specific field of dermatology, the stimulation of Treg cells may be important in autoimmune diseases. For example, blockage of T lymphocyte stimulation, as in the use of the antibody associated to CTLA-4 (cytotoxic T lymphocyte-associated antigen 4-immunoglobulin, CTLA4Ig), reverts the development of psoriatic plaques.[109]

Auto-injections of regulator T cells are a promising approach to modulation of inflammation and autoimmune diseases.[110,111] Nevertheless, there is a significant decline in the function of natural CD4+CD25+^{high} Treg cells of peripheral blood in patients with autoimmune diseases when compared to that of healthy individuals.[112,113] In order to overcome this difficulty, cytokines were used to stimulate the growth of regulator T cells. IL-15 allows a significant *in vitro* expansion of regulator cells.[114] Natural CD4+CD25+^{high} Treg cells obtained by ex vivo expansion through stimulation with allogeneic antigen-presenting cells and IL-2 were capable of modulating the graft-versus-host disease (GVHD).[115]

On the other hand, induction of natural CD4+CD25+^{high} Treg cells may facilitate the establishment and maintenance of immunological tolerance. Depletion of natural CD4+CD25+^{high} Treg cells may be an effective way of reversing the tolerance induced by malignant tumors and increasing the activity of the

immune system against cancer epitopes.[116,117]

For now, we should be attentive to the effect of immunomodulator drugs on these cells. For example, tacrolimus, an inhibitor of calcineurin, increases the inhibition of Treg cells in atopic dermatitis.[67] Fludarabine reduces the frequency and suppressive function of natural CD4+CD25+^{high} Treg cells.[118] Low doses of cyclophosphamide induce the inhibition of natural CD4+CD25+^{high} Treg cells and consequently increase the immune response in an apparently paradoxical effect.[119] Along the same line, cyclophosphamide decreases the function, proportion, and number of natural CD4+CD25+^{high} Treg cells that suppress the induction of contact hypersensitivity.[120]

Currently, corticosteroids constitute the most effective treatment for inflammatory skin diseases. These drugs are effective in inhibiting the function of Th2 cells, eosinophiles, and epithelial cells. However, treatment with these drugs during the presentation of the epitope may result in an increased tolerance by suppressing the development of dendrite cells that secrete IL-10, which are necessary for the induction of T regulators. Therefore, treatment with corticosteroids may increase the subsequent effect of the T response and aggravate, on the long run, the course of inflammatory diseases.[121] This aspect may also be related to the rebound effect of inflammatory diseases once these drugs are removed

CONCLUSION

Currently, regulatory or suppressor T cells have their existence recognized despite skepticism on the part of most immunologists. They may be isolated from peripheral blood in humans. Other regulatory cells may be induced by the natural progression of the immune response.

Natural CD4+CD25+^{high} Treg cells and other cells seem to play a vital role in maintaining tolerance to endogenous antigens and in regulating the immune response induced by exogenous antigens. In recent years, more research has been done on their involvement in several skin diseases. Treg cells may be altered, qualitatively or quantitatively, in skin diseases in humans, suggesting their role in the pathophysiology of these illnesses. A detailed comprehension of the associations among the various regulator cells may help in understanding the events that lead to the appearance of skin diseases. In due course, a specific way to manipulate the function of regulator T cells according to the desired effect will be the goal. ❑

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