Summary
Shimon Sakaguchi and Noriko Sakaguchi
History of $CD25^+CD4^+$ regulatory T cells

Naturally arising $CD4^+$ regulatory T cells, the majority of which express CD25, were discovered as a T-cell subpopulation that engages in dominant control of self-reactive T cells and thereby inhibits the development of autoimmune disease. Their reduction or functional alteration leads to the development of autoimmune disease in otherwise normal animals including humans. A key feature of $CD25^+CD4^+$ regulatory T cells is that they are produced by the normal thymus as a functionally distinct and mature subpopulation of T cells, contrasting with other types of regulatory or suppressor T cells that are induced in the periphery by specific ways of antigenic stimulation. There is now accumulating evidence that $CD25^+CD4^+$ regulatory T cells play key roles not only in the establishment and maintenance of immunologic self-tolerance but also negative control of various types of physiological and pathological immune responses.

Key Words: HSP60 regulatory T cells, suppressor T cells, immunologic self-tolerance, imunoregulation, CD25, Foxp3, IPEX.

Summary
Dirk Homann and Matthias G. von Herrath
'Natural' and 'induced' regulatory T cells – purpose and problems associated with an emerging distinction

It is by now well established that there is a multitude of phenotypical and functional varieties of T cells with regulatory function (T_rs). One issue that remains mostly unclear is the type of antigens such cells recognize in vivo in the context of both physiological and pathophysiological situations. The purpose of this chapter is a discussion of more recent findings in regards to Treg antigen-specificity and function. We will describe some common denominators that we believe can help to identify and characterize T_rs, a critical precondition for their use in immunomodulatory therapies. Overall, "natural" as well as "induced" Tregs display a pronounced diversity that appears commensurate to "normal" effector and/or memory T cells. Thus, T_rs are probably best characterized by their precise antigen specificities and effector functionalities.

Key Words: T_r, adaptive, homeostasis, thymus, regulation, antigen specificity, therapeutic potential, induction, regulatory T cells.

Summary
Robert N. Barker and Frank J. Ward
The role of interleukin-10 in regulatory-T-cell suppression: reconciling the discrepancies

The importance of $CD4^+$ regulatory T (T_r) cells in the control of immune responses and immune-mediated pathology is now recognized, but their means of action are not fully understood. There is evidence for two major forms of suppression, the secretion of inhibitory cytokines such as interleukin (IL)-10 and transforming growth factor (TGF)-β, and ill-defined mechanisms dependent on direct physical contact between T_r cells and their targets. Secreted cytokines are predominant mediators of suppression by Tr cells of the induced form, which are generated under certain conditions of antigen exposure, and include IL-10-producing T_r1 cells. However,

controversy surrounds the means of suppression by natural $CD25^+$ T_r cells that are thought to arise in the thymus. $CD25^+$ T_r-cell suppression appears entirely dependent on cell-cell contact *in vitro*, but in some models of experimental pathology inhibition *in vivo* is mediated by cytokines such as IL-10. The importance of cytokine-dependent $CD25^+$ Tr cell suppression may be greater *in vivo* than *in vitro*, but varies between models due to the nature of immune stimulus, the activity of other cell types capable of secreting T_r cytokines and inter-relationships between T_r populations. Understanding what form of suppression is relevant to different pathologies will be crucial in harnessing the therapeutic potential of T_r cells.

Key Words: Interleukin-10, suppression; regulatory T-cell, immune pathology, $CD4^+$ T-cell.

Summary

Esther N. M. Nolte-'t Hoen and Marca H. M. Wauben

Activation and distribution of regulatory T cells in naive and antigen-stimulated immune systems

Several T cell subsets capable of inhibiting the activation of other T cells have now been characterized, and are referred to as regulatory T cells. The best-described regulatory-T-cell population consists of a subpopulation of $CD4^+$ T cells expressing the interleukin-2 receptor α-chain (CD25). These $CD4^+CD25^+$ T cells could both control autoreactive T cells *in vivo* and inhibit proliferation of $CD4^+CD25^-$ T cells *in vitro*. Mouse, rat and human studies indicate that regulatory T cells can be found in lymph nodes, spleen and blood. However, limitations in cell numbers and availability often hamper the simultaneous analysis of regulatory T cells in the various compartments of the immune system. Although their presence in blood indicates that regulatory T cells migrate, it is not known whether these cells, just like naïve $CD4^+$ and $CD8^+$ T cells, continuously re-circulate through the different lymphoid compartments. Furthermore, questions about where regulatory T cells are being activated, and where they exert their regulatory function in naïve and antigen-stimulated immune systems, largely remain to be answered. In this chapter, we will discuss the activation and distribution of regulatory T cells by using recent data on regulatory T cells in naïve and arthritic rats as a guideline.

Key Words: Regulatory T cells, $CD4^+CD25^+$, immunoregulation, immunosuppression, cellular activation, CD134, lymphoid organs, homing, arthritis.

Summary

Kevin J. Maloy and Fiona Powrie

Regulatory T cells and the innate immune system

In historical terms, the innate and adaptive immune systems were considered as separate entities, primarily due to the differences in how they recognize pathogenic organisms. Whereas innate cells utilize a limited set of invariant, germline-encoded receptors, the enormous repertoire of antigen receptors expressed by different B and T cells tended to focus attention on the adaptive immune system as the decisive factor in immune responses. However, over the last decade, there has been a growing realisation that cells of the innate immune system perform a vital 'instructive' role in determining which types of adaptive immune response will be generated. Similarly, adaptive immune responses generate potent feedback signals that influence the activation state of the innate immune system. The object of this review is to discuss how $CD25^+CD4^+$ regulatory T cells participate in the crosstalk between the innate and adaptive immune systems, in order to allow effective immune responses against pathogens while avoiding harmful immune pathology.

Key Words: Innate immunity, regulatory T cells, dendritic cells, toll-like receptors, immune pathology, IL-10.

Summary

Nadia Giarratana, Giuseppe Penna, Silvia Gregori, Kenn C. Daniel, and Luciano Adorini
Exploiting the potential of regulatory T cells in the control of type 1 diabetes

Compelling evidence shows that regulatory/suppressor T cells control immune responses and that this capacity could be used to treat autoimmune diseases. These cells are heterogeneous, and several T-cell subsets have been shown to exert suppressive activity. Among them, naturally occurring T cells expressing CD25 and Foxp3 ($CD25^+$Ts) have been best characterized. The potential of $CD25^+$Ts as immunotherapeutic agents has been carefully analyzed in type 1 diabetes (T1D) models, a Th1-cell-mediated autoimmune disease in which the role of $CD25^+$Ts is well documented. One approach has been to generate *ex vivo* large amounts of $CD25^+$Ts and transfer them to pre-diabetic or diabetic recipients. This has been accomplished using either a cocktail of inducing agents and growth factors, or dendritic cells pulsed with an autoantigenic peptide, and in both cases a significant inhibition of T1D development, and even a reversal of overt disease, has been achieved. An alternative strategy exploiting the potential of $CD25^+$Ts makes use of immunomodulatory agents, such as anti-CD3 monoclonal antibodies (mAbs) or vitamin D analogs, to induce or enhance $CD25^+$Ts cells in T1D models. While these approaches appear, in experimental models, to arrest and even revert T1D development, associated with up-regulation of $CD25^+$Ts cells, it remains to be seen if they can as successfully interfere with disease development in T1D patients.

Key Words: Type 1 diabetes, NOD mice, immunointervention, suppressor T cells.

Summary

Sophie Candon and Lucienne Chatenoud
Regulatory T cells in type I diabetes

Type 1 diabetes is caused by a progressive activation of autoreactive $CD4^+$ and $CD8^+$ T cells, leading to the destruction of insulin-producing pancreatic β cells. In the non-obese diabetic (NOD) mouse, an animal model for type 1 diabetes, the existence of a delay between histological signs of islet infiltration (insulitis) and the onset of disease suggests that during this time window, immunoregulatory mechanisms are at work to counter anti-islet immune responses. Two major $CD4^+$ T-cell subsets capable of suppressing pathogenic autoreactive T cells have been identified. Quantitative and/or functional defects in these regulatory T-cell subsets seem to be involved in the establishment of the disease. Different therapeutic approaches based on the *in vivo* induction or *ex vivo* expansion of regulatory T cells have been tested in the NOD model and have in some cases led to clinical trials.

Summary
Clare Baecher-Allan, Vissia Viglietta, and David A. Hafler
The potential for targeting $CD4^+CD25^+$ regulatory T cell in the treatment of multiple sclerosis in humans

Multiple sclerosis (MS) is an inflammatory, autoimmune-mediated disease of the central nervous system that involves lymphocyte activation and results in intermittent episodes of neurologic dysfunction. The correlation between MS and HLA direct receptor 2 (DR2) and the results of twin studies that demonstrated a higher concordance for MS in monozygotic twins as compared to the general population indicate a strong genetic basis for the disease. The central role for T cells in the etiology of MS has been inferred from data derived from studies of animal models including experimental autoimmune encephalomyelitis (EAE), the most widely used animal model for MS, and the analysis of human clinical samples. Data have long indicated that MS may result from a loss of proper regulation of self-reactive T cells in individuals who develop the disease. We will present recent data that demonstrate directly that a specific subset of T cells known as $CD4^+CD25^+$ T regulatory cells is deficient in its activity when isolated from patients with MS as compared to healthy individuals, and how increasing the function of these specific regulatory T cells may alter a number of immune-deviations associated with MS.

Key Words: Autoimmunity, regulation, suppression, multiple sclerosis, CD25, regulatory T cells.

Summary
Jocea M. van Amelsfort, Johannes W. J. Bijlsma and Leonie S. Taams
Immunotherapy of rheumatoid arthritis using CD4+CD25+ regulatory T cells

Rheumatoid arthritis (RA) is a disease characterized by a chronic inflammation of the joints, which eventually leads to irreversible joint damage. Several cell types are important in the pathogenesis of RA, such as T cells, B cells and macrophages. The most important goal in the treatment of RA is to halt the chronic inflammation and restore the imbalance between immunity and tolerance in the immune system. $CD4^+CD25^+$ regulatory T cells (T_R) have been shown to be able to suppress T-cell proliferation and cytokine production, in both mice and humans. Several recent studies have focused on the presence and function of these cells in RA. In the synovial fluid of RA patients both the percentage and the suppressive activity of T_R are increased compared to the peripheral blood. This suggests a negative-feedback system at the site of inflammation, in which the inflammation is inhibited, insufficiently, by $CD4^+CD25^+$ T_R cells. Expansion or further enhancement of the function of $CD4^+CD25^+$ T_R cells would be an attractive therapeutic goal in RA, since it might restore the balance between aggressor and regulatory cells. In this review we will discuss the involvement of $CD4^+CD25^+$ T_R cells in the pathogenesis of RA, and consider their therapeutic potential.

Key Words: Anergy, suppression, tolerance, immunoregulation, T-lymphocytes, rheumatoid arthritis, patients, synovial fluid.

Summary
Douglas S. Robinson and Eleanor M. Ling
Potential for manipulation of regulatory T cells in treatment or prevention of allergic disease

Allergic diseases are associated with Th2-type T-cell responses to common allergens such as house-dust-mite and pollen antigens. As the importance of active immune suppression by regulatory T cells in prevention of autoimmune disease has been appreciated, the role of these cells in prevention and development of allergic sensitization has been addressed. Recent data suggest that human peripheral blood $CD4^{+}CD25^{+}$ T cells can suppress allergen-driven Th2 responses *in vitro*. Furthermore this suppression seems less effective in atopic and allergic individuals. Additional regulatory subsets have been implicated in control of allergic sensitization, including interleukin (IL)-10-producing T cells. Allergen immunotherapy has been used for many years to control symptoms of allergic disease and recent evidence suggests that this treatment may induce regulatory T cells that reduce Th2 responses and prime for IgG4 switching. Greater understanding of the role of regulatory T cells in allergic disease, mechanisms of suppression, and reasons for failure of suppression should allow modification of immunomodulatory therapy for treatment and prevention of allergic disease.

Key Words: Atopy, allergy, T-cell, regulation, suppression, immunotherapy.

Summary
Katie E. Birch, Milica Vukmanovic-Stejic, John R. Reed, Malcolm H. A. Rustin, and Arne N. Akbar
The role of regulatory T cells in cutaneous disorders

There is increasing evidence to suggest that regulatory T cells have a critical role in maintaining a balance between immunity and pathology through their suppression of T-cell responses. Although the extent to which regulatory T cells are able to modify immune responses in inflamed and normal skin remains unclear, regulatory T cells have been found within the skin and express molecules that enable skin-specific migration. They have been implicated in several inflammatory skin disorders including eczema, psoriasis, contact dermatitis reactions and infections such as cutaneous leishmaniasis. Depletion of the regulatory-T-cell subset in animal models has resulted in enhanced B16 melanoma rejection and improved responses to tumour vaccines. It has already been shown that regulatory T cells are influenced by various therapeutic regimes currently used to treat skin disorders. In the future, regimes designed to enhance regulatory T-cell function may allow for the integration of intrinsic immunoregulation with therapeutically used immunosuppressants in order to maximize therapeutic efficacy.

Key Words: Skin, regulatory T cell, CD4+CD25+, atopic dermatitis, psoriasis, delayed type hypersensitivity reaction, infection, immunosuppression.

Summary
Kathryn J. Wood and Ahmed Akl
The potential role of CD25+CD4+ regulatory T cells in the induction and maintenance of transplantation tolerance in humans

The achievement of long-term graft survival without the need for immunosuppressive drugs is a major goal in transplantation. A balance between deletion and active regulation/suppression of

donor alloantigen reactive T cells is likely to be an effective way of achieving both short-and long-term control of immune responsiveness after organ or cell transplantation.
Strategies for generating T cells with suppressor/regulatory activity (T_R) both *in situ* in a transplant recipient as well as *ex vivo* by manipulating and expanding recipient T cells to develop regulatory activity offer great potential for the development of new and complementary therapeutic strategies for promoting specific unresponsiveness in clinical transplantation in the future. T_R cells that can prevent or control graft rejection are enriched among subpopulations of $CD4^+$ T cells that express high levels of the α-subunit of the interleukin (IL)-2 receptor CD25. While this may not be the only population of immunoregulatory T cells functional in the setting of transplantation, T_R cells within the $CD25^+CD4^+$ population have attracted much attention recently and will therefore be the focus of this chapter. At present, the origin, allo-recognition properties, molecular basis for the suppressive activity as well as the most effective strategy for generating alloantigen-responsive T_R cells either *in vivo* or *ex vivo* remain unclear and therefore much work needs to be done before T_R cells can safely and effectively be used in clinical transplantation.

Key Words: Transplantation, tolerance, rejection, alloantigens, immunoregulation, suppression.

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