

Regulatory T cells: back to the future

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ABSTRACT

Regulatory T cells seem to represent the resurrection of the old suppressor T cells. Although of a different phenotype, regulatory T cells are able to suppress many T cell-mediated immune responses. While most basic knowledge about these cells is derived from animal studies, the recent identification of these cells in humans has further attributed to their characterisation by *in vitro* analysis. Results obtained have led to broad speculations about therapeutic potential by interference with these regulatory T cells. This review is an introduction to the world of regulatory T cells and contains an historical overview with respect to the identification and characterisation of these T cells. A distinction is made between naturally occurring regulatory T cells (nT_{reg}), which require cell-cell contact for suppression, and inducible regulatory T cells (iT_{reg}), which predominantly mediate suppression via cytokine-dependent pathways. Although only limited studies on regulatory T cells in human disease are available today, the possible clinical applications are discussed in light of the other side of the coin, i.e. the danger of interfering with homeostatic mechanisms in the immune system.

KEYWORDS

Immune regulation, homeostasis, therapy, regulatory T cells

INTRODUCTION

Regulatory T cells (T_{reg}) are currently in the spotlight of immunological research. In the last decennium of the previous century the immunopathogenesis of immune-mediated diseases was explained by the T helper (T_h)₁/T_h₂ balance. Nowadays, aberrant numbers and/or functions of T_{reg} are incorporated in our view of the disturbance in the immune system of these diseases. Consequently, manipulation of T_{reg} is considered very promising as

a therapeutic option. What are these T_{reg} exactly? As a matter in fact, regulation by T_{reg} is limited to suppression, and not activation, of immune responses. However, since suppressor T cells were banned during the 1980s,¹ this term could not easily be revived. At that time, research on suppressor T cells focussed on finding an antigen-specific soluble factor. When it appeared that this factor could not exist at all, suppressor T cells left the stage. Nevertheless, a couple of tenacious scientists demonstrated unequivocally that in animal models T cells are able to suppress several experimental autoimmune diseases.²⁻⁴ These suppressor T cells, which are different from the originally defined suppressor T cells, are now referred to as T_{reg}. The identification of these cells in the human has resulted in a publication boom on T_{reg} during the last four to five years.⁵ The most attention is being paid to the natural occurring CD25⁺CD4⁺ T_{reg} (nT_{reg}) and the inducible T_{reg} (iT_{reg}), including the T_{RI} and T_{h3} cells. This introduction to the exciting world of T_{reg} will first highlight the relevant animal models that enabled the discovery of T_{reg}. Next, the main characteristics of human T_{reg} will be described in relation to health and disease. Finally, the therapeutic potential of these cells will be discussed in light of possible consequences of T_{reg} based therapies.

ANIMAL MODELS

Basically, there are three animal models that have significantly contributed to the current interest in T_{reg}. First, the Penhale model for autoimmune thyroiditis is induced in rats by thymectomy and subsequent repeated low-dose total body irradiation (4x 250 rad).² Autoimmune disease can be prevented by the adoptive transfer of T cells derived from healthy, syngeneic rats. In particular T_h cells with a low-level expression of CD45RC (CD45RC^{low}) appear responsible for this effect, which is mediated by the cytokines interleukin (IL)-4 and transforming growth factor (TGF)-β.⁶ Typically, depending on the

major histocompatibility complex (MHC) haplotype, rats develop thyroiditis or diabetes.⁷

Second, the colitis model, as explored by Powrie, also originated in the rat.⁴ The adoptive transfer of T_h cells with highly expressed CD45RC (CD45RC^{high}) to T cell deficient rats results in severe wasting disease. Just as in the Penhale model, the CD45RC^{low} T_h cells of healthy rats are able to counteract the pathogenicity of the CD45RC^{high} T_h cells. In mice the adoptive transfer of CD45RB^{high} T_h cells (CD45RB is the mouse equivalent of rat CD45RC) to T cell deficient recipients results in colitis, an experimental model for inflammatory bowel disease (IBD).⁸ The CD45RB^{low} T_h cells protect against colitis via the cytokines IL-10 and TGF- β , but not IL-4.⁹

Third, neonatal thymectomy of mice on day 3 (d3Tx), but not day 7, will result in autoimmune gastritis (AIG), thyroiditis and/or diabetes.³ This effect is attributed to insufficient thymic output of T_{reg} during the first week of neonatal life. Indeed, reconstitution of d3Tx mice with T cells of healthy mice prevents the development of autoimmune disease. The responsible T_{reg} have been characterised as being CD25⁺CD4⁺ T cells (nT_{reg}) by adoptive transfer studies.¹⁰ The cytokines IL-4, IL-10, and TGF- β could not be attributed any significant role in this model.¹¹

PHENOTYPIC MARKERS

As can be concluded from information obtained in the animal models, CD45RC and CD25 (IL-2R α) are two cell-surface receptors that are associated with T_{reg} . CD45RC is a splice variant of the leucocyte common antigen CD45. In the rat CD45RC expression divides T_h cells in two subsets: CD45RC^{high} and CD45RC^{low} T_h cells. The suppressor activity is confined to the CD45RC^{low} subset as demonstrated in several *in vivo* situations.^{4,6,7} Upon *in vitro* stimulation these cells, but not the CD45RC^{high} T_h cells, produce the anti-inflammatory cytokines IL-4, IL-10 and IL-13.¹² Also in humans, CD45RC expression enables the distinction of two CD4 T cell subsets with opposite cytokine profiles (Saoudi and Damoiseaux, to be published).

While the suppressor activity of CD45RC^{low} T_h cells has never been demonstrated *in vitro*, this is definitely the case for the CD25⁺CD4⁺ nT_{reg} . These nT_{reg} , which are typically confined within the CD45RC^{low} T_h cell subset, are pre-eminently able to inhibit the proliferation of CD25⁻ T_h cells in *in vitro* settings.¹³ In mice and men, cell-cell contact is indispensable for the suppressor effect observed *in vitro*, while soluble factors, such as cytokines, play no crucial role in their mode of action. It should be stressed that this mode of action holds only for nT_{reg} , but not for iT_{reg} (vide infra). The identification of a surface marker, in particular CD25, and the establishment of *in vitro* methods for functional analysis have greatly attributed to

the identification of T_{reg} in humans. In humans, the level of CD25 expression may even discriminate between true nT_{reg} and activated T cells that also express CD25. Indeed, the nT_{reg} appear to be confined within the cells with high CD25 expression.¹⁴

Recently two more specific markers for nT_{reg} have been identified: Neuropilin-1 (Nrpl) and Foxp3.^{15,16} Nrpl is a cell-surface receptor that is involved in axon conductance, angiogenesis, and cellular activation. In mice this receptor is constitutively expressed by nT_{reg} and clearly discriminates between nT_{reg} and activated T cells since the latter do not express Nrpl. The expression of this marker has not yet been examined on human nT_{reg} . Foxp3 is the second new marker associated with nT_{reg} and receives a lot of attention these days. The name Foxp3 actually refers to the gene (*FOXP3*) encoding a transcription factor of the forkhead/winged-helix family (scurfin). The relation between this gene and nT_{reg} originates from the human disease IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) as well as the Scurfy mouse. Mutations in *FOXP3* result in the complete absence of nT_{reg} and the spontaneous development of autoimmune diseases of the endocrine organs, but also IBD, atopic dermatitis, and fatal infections. Foxp3 not only controls development, but also function of nT_{reg} . The expression of Foxp3 is almost specific for nT_{reg} in mice; however, expression in the human population is less restricted. Expression is not observed on activation of conventional T cells or differentiation in Th_1 , Th_2 , or NK-T cells. Initially, expression of Foxp3 was only detected by reverse transcription polymerase chain reaction (RT-PCR) and this largely precluded single cell analysis. However, recently monoclonal antibodies have become available that enable detection of the transcription factor by intracellular staining in mice and men.

The discovery of multiple markers for nT_{reg} has raised the question whether nT_{reg} are a homogeneous population. Selective depletion studies in mice have revealed that this is not the case.¹⁷ Reconstitution of nonobese diabetic (NOD) T cell deficient mice with CD25⁺ T cells results predominantly in AIG, comparable with the 3dTx model. Besides, these animals develop late-onset diabetes, but no colitis. Reconstitution with CD62L⁺ T cells, on the other hand, induces full-blown diabetes in the same type of recipients, but neither colitis nor gastritis. Finally, reconstitution with CD45RB^{high} T cells results only in severe colitis. These results underline the diversity and organ specificity of nT_{reg} in the control of distinct autoimmune diseases.

INNATE nT_{REG} VS ADAPTIVE iT_{REG}

The CD25⁺CD4⁺ nT_{reg} is a naturally occurring T cell subset that constitutes about 1 to 5% of the overall

lymphocyte population in peripheral blood. As concluded from murine studies, the nT_{reg} are generated as a separate T cell subset in the thymus.^{13,18} The important role of the thymus was already apparent in the Penhale thyroiditis model as well as the 3dT_x model. Intrathymic development of nT_{reg} requires a relatively high avidity interaction between the T cell receptor of the nT_{reg} and the MHC expressed by thymic stroma, in particular the cortical epithelium. Additionally, also IL-2 and coligation by B7-CD28 and CD40-CD40L interactions have appeared to be important in the development of nT_{reg} . Since selected thymocyte subsets are able to suppress the pathogenicity of autoreactive T cells, it can be concluded that nT_{reg} already acquire their function in the thymus.¹⁹ The latter observation has been confirmed with human CD4⁺CD25⁺ thymocytes.²⁰ Finally, as observed in the Penhale thyroiditis model, the generation of nT_{reg} is dependent on the presence of the autoantigen. Indeed, peripheral T cells of rats that have undergone thyroid destruction *in utero* are unable to prevent thyroiditis, but retain the ability to prevent diabetes.²¹

In contrast to nT_{reg} , which are considered innate, T_{reg} may also develop from conventional, naive T cells during an immune response.²² The best characterised, inducible T_{reg} (iT_{reg}) are known as the T_{RI} cells. These T_{RI} cells were initially described in mice upon long-term *in vitro* stimulation in the presence of IL-10.²³ Next, T_{RI} cells were also identified in humans and it appeared that besides IL-10, also IFN- α is important for the development of these cells. Although it is evident that not all iT_{reg} are identical to the originally described T_{RI} cells, in this review we will further use iT_{reg} as the general term. The mode of action of iT_{reg} is definitely different from the one described for nT_{reg} (vide supra). Suppression by iT_{reg} is contact independent and mediated by cytokines, in particular IL-10 and to a lesser extent TGF- β . The coexistence of nT_{reg} and iT_{reg} , with each a different mode of action, may explain the observed discrepancy between *in vivo* (cytokine dependent) and *in vitro* (cytokine independent) data, since *in vivo* the respective mechanisms will be intermingled. Besides the cytokine profile there are no characteristic markers for iT_{reg} . The iT_{reg} can be induced in several different ways. First of all, human nT_{reg} are able to transfer suppressor activity to conventional T cells.²⁴ In transplantation biology this process is referred to as infectious tolerance. While the induction is cell-contact dependent, the newly developed iT_{reg} mediate their suppression via cytokines.²² Second, also dendritic cells are able to generate iT_{reg} . Based on murine studies, it has been speculated that in particular semimature dendritic cells induce tolerance instead of effector responses due to a reduced expression of costimulatory molecules and high production of IL-10.²⁵ Finally, as observed in both human and animal research, also infections are able to stimulate

development of iT_{reg} . This may seem a contradiction because the host should benefit from an effective immune response to destroy the invading pathogen. However, keeping the immune response in control is relevant to limit infection-induced immunopathology.²⁶

REGULATORY T CELLS IN HUMAN DISEASES

While most studies on human T_{reg} were performed with cells from healthy individuals, several studies in human diseases have been published during the last two years. These studies have mainly concentrated on autoimmune diseases and infections and deal with frequency and/or function of T_{reg} .^{27,28}

In multiple sclerosis (MS), a T cell-mediated autoimmune disease, it was hypothesised that the control of peripheral autoreactive T cells, which are known to have similar frequencies in patients and healthy individuals, is hampered by a defect in the T_{reg} compartment. While no differences in the frequencies of CD4⁺CD25^{high} nT_{reg} were observed, there is a marked decrease in the effector function of nT_{reg} in MS patients as compared with healthy controls. This includes a defective inhibition of both conventional T cell proliferation as well as T_H cytokine production.²⁹ Human autoimmune polyglandular syndrome (APGS) is characterised by involvement of multiple endocrine organs and thereby somewhat resembles the d3T_x model in mice. While APGS type I is caused by loss of central tolerance, APGS type II might be the result of defective peripheral tolerance, i.e. nT_{reg} . CD4⁺CD25⁺ nT_{reg} are found at a normal frequency in patients with APGS type II, but the suppressor function, as demonstrated in proliferation experiments, is significantly reduced.³⁰ In myasthenia gravis, a prototypical antibody-mediated autoimmune disease, possible disturbances in the regulatory CD4⁺CD25⁺ thymocytes were examined. Results indicate that also frequencies of regulatory thymocytes are normal, while the suppressive function is clearly impaired.³¹ Finally, also in rheumatoid arthritis, characterised by uncontrolled production of inflammatory cytokines, a compromised function of nT_{reg} has been described.³² However, functional deficits involve the inhibition of cytokine production (TNF- α) in conventional T cells as well as the capacity of nT_{reg} to convey a suppressive phenotype (iT_{reg}) to conventional T cells, but not the suppression of T cell proliferation. Both deficits are typically restored to normal by anti-TNF- α therapy. Altogether, these data are indicative of a central role of functional nT_{reg} defects in the aetiology of the wide spectrum of autoimmune diseases.

While autoimmune diseases are associated with a defective T_{reg} compartment, it can be anticipated that chronic

infections may be due to increased numbers and/or function of T_{reg} . In particular CMV and HIV are proposed to induce T_{reg} that inhibit the virus-specific immune response.³³ However, in the case of HIV infection, this seems to be a double-edged sword. While in the majority of healthy HIV-infected individuals $CD4^+CD25^+$ T cells suppress HIV-specific T cell responses *in vitro*, and thereby may be responsible for *in vivo* tolerance induction to HIV, these $CD4^+CD25^+$ T cells also prevent $CD4^+$ T cell activation and thereby reduce the availability of target cells for HIV replication.³⁴

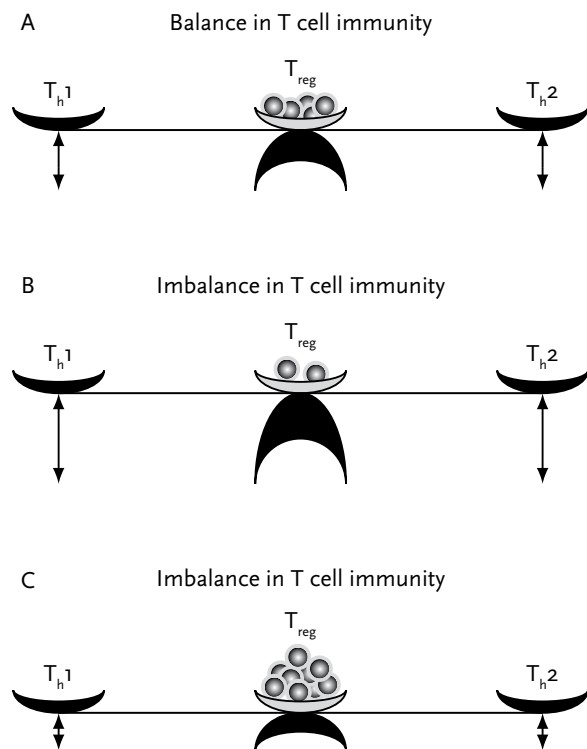
THERAPEUTIC POTENTIAL

Nearly all scientific publications about nT_{reg} and iT_{reg} speculate about the possible clinical applications. If there is excessive immunity, as in autoimmune diseases, asthma and allergy, transplant rejection, and certain cases of early pregnancy loss, increasing the amount and/or function of T_{reg} is supposed to be beneficial. Since iT_{reg} are inducible these cells are the best candidate for manipulation in the diseases mentioned above, but also expansion of nT_{reg} may be achieved by retroviral transduction of T cells with *FOXP3*.¹⁶ Shortage of immunity, as in malignancy or chronic infections, may be due to an excess of T_{reg} . These situations, and also vaccination against infectious diseases, are considered to benefit from a reduction in T_{reg} . Elimination of T_{reg} can be achieved by depleting antibodies reactive with surface receptors of these cells. Since the phenotype of nT_{reg} is better characterised, this subset is the best candidate for depletion. Noteworthy is the fact that anti-CD25 therapy is clinically successful. However, this therapy is aimed at the elimination of activated T cells and to suppress the immune response, in particular in case of transplant rejection.³⁵ This therapy does not result in the generation of autoimmune disease. Also in mice, anti-CD25 therapy does not result in autoimmune disease.³⁶ Apparently, autoreactive T cells present in the periphery need prior activation, for instance by immunisation with the autoantigen or in a lymphopenic situation, before they are able to induce autoimmune pathology in the absence of nT_{reg} .³⁶ Alternatively, the T_{reg} system may be redundant due to the presence of several other T_{reg} subpopulations, such as NK-T cells and $CD8^+$ T cell subsets. For details about these T_{reg} subpopulations see references 37 and 38, and the tables therein.^{37,38}

Interference with the homeostatic mechanisms of the immune system, however, will remain a risky business. The rediscovery of the suppressor T cell has changed the concept of this homeostasis. While the pathology of most immune-mediated diseases can still be explained by the T_{h1}/T_{h2} paradigm, the reciprocal regulation of

both subsets is apparently outdated.³⁷ It appears that the combination of nT_{reg} and iT_{reg} keeps both the T_{h1} as well as the T_{h2} responses in control (figure 1A). Shortage of T_{reg} may result in an excessive T_{h1} or T_{h2} response with the associated immunopathology (figure 1B), while excess of T_{reg} may suppress the respective immune responses (figure 1C). The latter will eventually prevent the generation of effector mechanisms that are required to inhibit tumour outgrowth and to clear the body of infectious agents. Moreover, the induction of iT_{reg} by infections gives further support to broadening the hygiene hypothesis: not only the prevalence of T_{h2} -mediated diseases, such as asthma and allergy, is increasing due to

Figure 1. A simplified scheme on the balance and imbalance in T cell immunity



Regulatory T cells suppress both T_{h1} - and T_{h2} -mediated immune responses in such a way that sufficient immunity remains for clearing infectious agents while unwanted immunopathology is prevented (A). In case of shortage of regulatory T cells the potential amplitude of T_{h1} and T_{h2} responses is increased resulting in excessive T cell immunity as associated with autoimmune disease, asthma and allergy, allograft rejection, and some cases of early pregnancy loss (B). Abundance of regulatory T cells, on the other hand, will reduce the potential amplitude of T_{h1} and T_{h2} responses and therefore may prevent adequate immunity to tumours and infectious diseases, but also effective vaccination against infections (C).

a reduced challenge of the immune system by infections, but also the T_H1 -mediated autoimmune diseases.^{39,40}

CONCLUSION

Altogether it is evident that since the beginning of this century T cells with suppressor functions are again being recognised as new players in the field. Data originally obtained in animal research have recently been confirmed in humans. These include that there are at least two distinct types of T_{reg} : the naturally occurring nT_{reg} , which require cell-cell contact for suppression, and the inducible iT_{reg} , which predominantly mediate suppression via cytokine-dependent pathways. The nT_{reg} are recognisable by the simultaneous expression of CD25 and Foxp3, while iT_{reg} are characterised by their cytokine profile. The analysis of nT_{reg} frequencies and function in several distinct types of autoimmune diseases has revealed that in particular the suppressive function of nT_{reg} is affected in patients with autoimmune disease. The role of T_{reg} in infectious disease seems to behold a paradox since T_{reg} may control severe immunopathology, but at the same time facilitate transition to chronic infections. Although there is extensive speculation about the therapeutic options involving T_{reg} , caution with this therapy is warranted because T_{reg} take part in the homeostatic regulation of the immune system by enabling protective $Th1$ and/or $Th2$ responses but preventing excessive $Th1$ and/or $Th2$ responses.

NOTE

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