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Regulatory T-Cells: Mechanisms of Immune Response Inhibition and Involvement in the Control of Tuberculosis Infection

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Abstract

Studying physiological activity of regulatory T cells (Treg) and the mechanisms of immune suppression utilized by these cells to abrogate excessive inflammation and support immune homeostasis is the hot spot of modern immunology. Treg's physiological activity is released by both distant and contact mechanisms. In this short review, we briefly describe the main mechanisms of immune suppression used by Treg and the role of these cells in immune homeostasis and pathogenesis of tuberculosis (TB) infection.

Keywords: Regulatory T-cells (Treg); Immunological tolerance; Autoimmune reaction; Immune homeostasis; Effector T-cells (TEF); Inhibitory cytokines; Dendritic cells (DC); Antigen-presenting cells (APC); indoleamine-2, 3-dioxygenase (IDO); *Mycobacterium tuberculosis* (Mtb)

Introduction

Studying regulatory T-cells (Treg) is the hot spot of immunology during last 15-20 years. Discovery of the Foxp3 transcriptional factor [1-3], the key element of Treg differentiation, allowed starting a detailed analysis of these cells *in vivo*. The role of Treg cells in maintaining immunological tolerance and controlling autoimmune reactions was discovered in early works [4,5]. In parallel, it was demonstrated that, although depletion of Treg cells results in autoimmune responses predominantly in lungs, skin and liver, these cells actively support immune homeostasis not only in the periphery, but also in lymphoid organs, where they prevent activation of effector T cells (Teff) [1,6,7]. For immune response suppression, Treg cells use both inhibitory cytokines, (e. g., TGF-β, IL-10 and IL-35) and a set of surface molecules (CTLA-4, LAG-3, TIGIT, PD-1, CD25, CD39/73 and others) which interact with target cells, most often Teff and dendritic cells (DC).Thus,Treg's physiological activity is released by both distant and contact mechanisms [8].

In this short review, we will describe the main mechanisms of immune suppression used by Treg and the role of these cells in immune homeostasis and pathogenesis of tuberculosis (TB) infection. The dynamics of activation and inhibition of inflammatory and immune responses during TB course is an important issue. It is likely that early in infection the host benefits from the low level of Treg activity, allowing establishment of specific immunity against the pathogen; however, during the chronic phase of infection it is important that Treg restrict Teff activation thus limiting inflammation and tissue destruction. Along with this required balance, we will also shortly discuss the perspectives of therapeutic application of Treg cells for TB treatment.

Inhibitory mechanisms used by Treg cells

To prevent activation of antigen-presenting cells (APC) Treg utilize a range of different mechanisms schematically displayed in Figure 1. Binding of the CTLA-4 molecule expressed on Treg surface with its B7 (CD80/CD86) ligand on APC surface diminishes the expression of the latter, which, in turn, inhibits co-stimulatory signal provided by CD28 to Teff cells [9]. In addition, CTLA-4 induces production of indoleamine-2, 3-dioxygenase (IDO) in DC. In the local microenvironment, IDO catabolizes tryptophan. Not only tryptophan is important for T-cell proliferation, its catabolism results in accumulation of toxic substances, such as kynurenin, which induces apoptosis in Teff cells [10,11]. Another suggested mechanism of immune response inhibition is suppression of DC maturation via LAG-3 molecule expressed on the Treg surface. LAG-3 structure is similar to that of CD4, providing capacity to interact with the MHC class II. However, contrary to CD4 binding, this interaction results in ITAM-dependent inhibitory signals preventing DC maturation and activation [12,13]. Another cellular target for Treg suppressor activity are Teff cells themselves. Treg cells express on their surface the CD39 exoenzyme, which catalyzes ATP → AMP transformation. Due to enzymatic activity of another Treg surface molecule, CD73, AMP transforms in adenosine, and extracellular adenosine inhibits activation and proliferation of Teff cells [14]. Yet another Treg membrane

molecule involved in inhibition of Teff proliferation is the Galectin-1 lectin, which binds GM1-gangliosides on the surface of the latter [15].

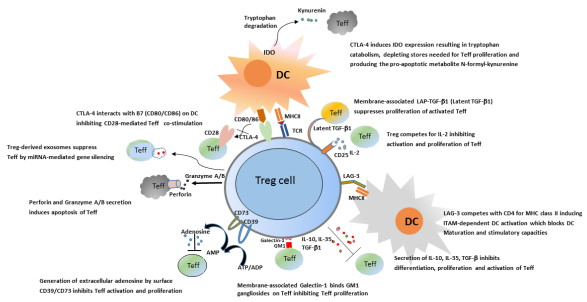

Figure 1: Inhibitory mechanisms used by Treg cells. See the text for details.

An important mechanism of immune response suppression by Treg cells is secretion of inhibitory cytokines TGF-β, IL-10 and IL-35, which interact with many cell types and are powerful anti-inflammatory mediators [8]. Interestingly, Treg cells not only secrete TGF-β, but also express on their surface the so-called latent TGF-β1 (LAP-TGF-b1) which is capable to inhibit proliferation of activated Teff cells after cell-to-cell contact [16]. It was demonstrated very recently that Treg are able to suppress Teff functions by secreting exosomes containing a set of miRNA capable to penetrate into Teff cells and inhibit the expression of several genes, which abrogates cell proliferation resulting in apoptotic death [17]. Another mechanism of immune response inhibition used by Treg is killing of Teff cells by secreting perforin and A/B granzymes, which closely resembles the action of cytotoxic lymphocytes: perforin causes formation of pores in target cell membrane and subsequent injection of granzymes, which belong to the family of serine proteases, induces apoptosis in Teff cells [18].

The data obtained in *in vitro* systems suggested that Treg use an inhibitory mechanism based upon competition for the access to IL-2. IL-2 is the key factor of Treg growth, and Treg cells constitutively express on their surface CD25, the α-chain of high-affinity IL-2 receptor. CD25 – IL-2 binding results in the local IL-2 exhaustion, which limits proliferation and induces apoptosis in Teff cells; quite often, technical assessment of Treg activity is based upon this mechanism [19-21]. However, very recent studies demonstrated that *in vivo* this inhibitory mechanism is relevant exclusively for CD8+ Teff cells [22].

The list of immune response inhibitory mechanisms presented above is certainly not exhaustive, and we expect many clarifications and additions in the near future. Besides numerous effector mechanisms of immune suppression, an important field of research is the elucidation of the pathways of Treg activation, including the classical question of immunology: is the antigen-specific recognition involved in Treg cells activation?

Treg cells and T-cell receptor (TCR)

For a long time, there was a consensus that inhibition of immune response and inflammation by Treg cells has exclusively (or, at least, predominantly) antigen non-specific nature (see Ref. [20,23] for the review). However, many studies convincingly demonstrated that the TCR of Treg cells plays an important role not only at the stage of inter-thymus differentiation and selection, but also determines many aspects of their subsequent activity [24].

Treg cells undergo selection in thymus, as other conventional CD4+ T-lymphocytes do, but the repertoire of their TCR has a clear bias towards high-affinity auto-antigens, thus differing from that of other CD4+ cells; remarkably, repertoire overlapping with Teff concerns exactly auto-reactive clones in the latter population [25-28]. In the periphery, shifts in Treg TCR repertoire depend upon cell localization. Auto-antigen recognition, apparently, plays an important role in survival and homeostatic proliferation of Treg clones, i. e., auto-antigens located in different tissues may select and expand different protective "organ-adapted" Treg clones. This tissue specificity of Treg TCR repertoire was demonstrated in experimental settings: adoptive transfer of Treg cells from the donor lacking a certain organ did not protect recipients from autoimmune disease affecting this organ [29-31]. Treg TCR appeared to be involved in suppression of Teff activation in lymph nodes, since inductive elimination of TCR from the surface of Treg caused destruction of Treg-Teff clusters, decreased Treg suppressor activity and resulted in uncontrolled Teff expansion [32]. Gene engineering studies based upon modifications of adaptor molecules transferring signals from TCR inside the cell also indicated the importance of TCR for Treg inhibitory functioning *in vivo* [33,34].

In the absence of specific inflammatory signals, the main mission of Treg is preventing activation of auto-reactive Teff cells [7,8]. To successfully accomplish this function, Treg should have advantages in TCR binding with MHC class II molecules on the surface of DC presenting auto-antigens compared to Teff. Indeed, due to specific mode of selection in thymus, TCR of Treg cells recognize self-antigens with high affinity. In addition, Treg cells express on their surface high amounts of adhesive and co-stimulatory molecules, which stabilizes their interactions with DC [35]. After pathogen invasion and trafficking of infected DC from barrier to draining lymphoid organs, the background of ongoing antigen recognition/presentation reactions biases toward infectious agent's antigens. Here, Teff cells should have advantages in competition with Treg cells due to enormous diversity of their TCR repertoire, which, by definition, provides more potentially reactive clones compared to a more restricted Treg's repertoire. This results in induction of adaptive immunity and inflammation, which is beneficial for the host until an illusive time point is reached when reactions of immune system become overwhelming.

Immune responses in tuberculous lung and its down-regulation

TB is caused by facultative intracellular pathogen *Mycobacterium tuberculosis (Mtb*) and predominantly affects

the lung. Several important topics concerning TB pathogenesis, including early phase of infection, lung granuloma formation, dissemination and general aspects of immune response were the subject of excellent reviews [36-38], and will not be discussed here. For a long time, TB has been considered as the classical prototype condition of chronic inflammation, which presumes an important role of regulatory mechanisms of both its maintenance and restriction. We intend to concentrate exclusively on a relatively understudied issue of the role of Treg cells in TB infection.

The lung is a barrier organ directly contacting several potentially pathogenic microorganisms and prone to develop inflammatory reactions in response to these contacts. These reactions are meant to restrict multiplication and dissemination of pathogens, but quite often the overwhelming inflammation jeopardizes lung breathing function, thus threatening the host's health. Thus, the balance between inflammatory and anti-inflammatory mechanisms is critical for protection against the *Mycobacterium tuberculosis*-triggered disease, which is not a synonym of protection against infection.

Penetration of Mtb into the lung tissue almost instantly induces innate immune response of the host followed by development of acquired immunity. Enormous innate immune system, which consists of several cell types (neutrophils (NΦ) macrophages (MΦ), dendritic cells (DC) and natural killers (NK) [39]); surface and intracellular receptors, eg., TLR, NOD and others [40,41]; complement system [42], provides the first line of host defense. Orchestrated innate immune response includes the expression and secretion of pro-inflammatory cytokines, chemokines and surface adhesion receptors (often termed "the cytokine storm" [36]) leading to both local and systemic activation of immune system. Nevertheless, this cascade of reactions quite often fails to eliminate mycobacteria from the lungs, and the outcome of infection largely relies on the development and optimal quantitative control of acquired immune response.

For many years, activation of type 1 T cell immune response in the lungs, with CD4+ T-cells, producing IFN-γ for activation of *Mtb*-infected macrophages for intracellular mycobacterial killing, was considered as the most prominent protective mechanism against TB [37,43]. Recently, the direct protective role of IFN-γ produced by lung CD4+ T-cells has been seriously questioned, which arises additional concerns about its possible deleterious role as a very toxic, tissue-damaging substance [44]. Similarly, whereas another major pro-inflammatory cytokine, TNF-α, is essential for maintenance of lung granuloma integrity [45], its excessive secretion is harmful for the lung tissue [46].Several other inflammatory cytokines, such as IL-1, IL-6 and IL-11 are produced in high amounts in response to *Mtb* infection, and for each deleterious, rather than protective, effect has been reported [47,48]. Taken together, this evidence from the literature underlines the importance of anti-inflammatory mechanisms operating in the lung.

Down-regulation of overwhelming inflammation in tuberculous lung is mediated by different cell types, e. g., epithelial cells and CD103+ dendritic cells [49], Gr1+cells from the innate immunity pool [50], and a few T-cell populations, clear boarders between some of which remain not precisely defined. The latter include TR1 cells secreting IL-10 and TGF- β [51] and TH3 cells secreting TGF-β [52]. However, the most prominent regulatory T-cell population is represented by classical regulatory T-cells (Treg) with the CD4+CD25+Foxp3+ phenotype. As in other types of immune responses, during infection Treg cells are essential for inhibition of proliferation and activation of other cell types, as well as for down regulation of pro-inflammatory molecules secretion. In turn, their activity should be strictly controlled, since the lack of a balance in immune system homeostasis may well lead to chronic inflammation, tissue damage and prolonged mycobacterial persistence [53-55].

Treg cells and TB pathogenesis

In the absence of TB infection, small amounts of pulmonary Foxp3-positive cells can be found in perivascular and peribroncheial locations but not in parenchyma [56]. Early after infection, *Mtb*-infected phagocytes start to produce pro-inflammatory cytokines and chemokines, which recruit to the site of infection not only fresh NΦ, MΦ and DC, but also lymphocytes, including Treg cells [57-59]. At this early stage of infection, restriction of mycobacterial growth depends exclusively on innate immune response provided by macrophages and neutrophils. Importantly, neutrophils are much less effective killers of mycobacteria compared to macrophages [60], and this is the first opportunity for Treg cells to influence the level of host protection: recruiting of neutrophils was reported to depend upon CXCL8 signaling pathway provided by Treg [61]. Induction of adaptive immune response occurs after migration of infected phagocytes from the lungs to draining lymph nodes where they prime antigen-specific T-cells. For unknown reasons, DC migration from the lung starts not earlier than 8-11 days post primary infection, and it was hypothesized that Treg cells somehow delay this process, which may have important consequences for the whole infectious course [62].

Backwards migration of primed CD4+ and CD8+ Teff cells from lymph nodes to the lung tissue, along with continuing influx of phagocytes to the primary infection focus, initiate characteristic TB inflammation with granuloma formation. The involvement of Treg cells in granulomatous response is very likely, since these cells are present within inflammatory foci and occupy the same layers of granuloma as CD4+ and CD8+ cells [56-59]. Accumulation of Foxp3+ Treg cells in granuloma supports the hypothesis that during TB infection immune response is suppressed locally, in pulmonary inflammatory sites. It was also speculated that Treg participate in transformation of integral granulomata into necrotic (and later – in cavernous) foci, which leads to Mtb dissemination. At any rate, the content of Foxp3+ Treg cells in patients with miliary TB (a severe form of disseminated infection), both in plasma and BAL, was found to be much higher than in TB patients with other forms of the disease [63].

Quite naturally, possible involvement of Treg cells in maintaining more or less stable, chronic type of TB infection, underlined by mycobacterial persistence and relatively low level

of immune response, was intensively studied and discussed. Thus, it was demonstrated that Mtb-infected DC produce CCL17 and CCL22 chemokines, which attract Treg cells to the sites of infection. In addition, infected DC express the PD-L1 molecule interacting with PD-1 molecule on the surface of Treg resulting in their proliferation and local increase of the Treg pool [64-66]. Furthermore, it was reported that simultaneous activity of Mtb and Treg cells may inhibit DC maturation, and that immature DC provide "immune suppressive environment" in the lung tissue and draining lymph nodes by secreting IL-10, TGF-β and IL-35, thus inhibiting Teff activation and proliferation [67-69]. In addition, switches in the expression of chemokine receptors determining migration behavior is more rapid in Treg cells compared to conventional CD4+ cells. This may accelerate migration and accumulation of Treg in infectious foci [70].

Overall, information provided by the growing amount of publications concerning involvement of Treg in TB pathogenesis clearly shows that Treg play an important role at different stages of infectious process. Those include down-regulation of initial innate response in the lung, inhibition of priming and differentiation of Teff cells in draining lymph nodes, their migration to affected sites of the lung, and local suppression of Teff response within granuloma. The most likely consequence of these inhibitory activities would be better survival of Mtb in the lung and disease progression.

Specificity and diversity of Treg working during TB course

It was discussed above that the repertoire of Treg TCR is biased towards recognition of auto- (or self) antigens. TB progression is accompanied by strong inflammatory reactions resulting in lung tissue destruction and possible release of novel or modified self-antigens (neo-antigens), which may be presented by the MHC class II products and recognized by previously passive Treg clones. This phenomenon may explain an increased Treg: Teff ratio in patients with miliary TB compared to patients with localized TB forms [57]. On the other hand, there is compelling evidence that during TB course activation of pathogen-specific Treg cells occurs in regional lymph nodes, alongside with specific Teff activaion [56,62].

Thus, in the mouse model system, using MHC class II-peptide tetramer approach, Treg cells specific to immune-dominant Mtb class II epitope ESAT6-4-17 were found in the regional lymph nodes [71]. Recognition of the same mycobacterial antigen was used as a tool to study Treg cells isolated from mice expressing transgenic ESAT-6-specific TCR. It was demonstrated that these cells readily proliferate in Mtb-infected mice, while Treg cells of different specificity do not. Moreover, antigen-specific Treg showed a very high capacity to inhibit activation of Teff cells in regional lymph node and their migration to the lung: the presence of 50-75 ESAT-6-specific Treg cells in the lymph node was sufficient for suppression [71].

The conditions required for mycobacteria-specific Treg cells origination remain poorly understood. It is possible that the diversity of the total Treg pool is sufficient to provide the clones that are capable to recognize some antigens of mycobacterial origin in the context of MHC class II molecules. On the other hand, the data from non-tuberculous experimental settings indicate that the common CD4+ Teff cells from gastrointestinal tract under certain inflammatory conditions start to express Foxp3+ and reprogram physiological activity, thus transforming into so-called peripheral Treg cells (pTreg) [72,73]. However, for TB infection this pathway was not proved yet [62]. It also remains unknown whether or not specific Treg activation via TCR is requisite for their suppressive activity at inflammatory sites. *In vitro* studies of the specificity of Treg cells obtained during TB infection are controversial and provide evidence for both non-specific [55] and Mtb-specific [74] mode of Teff inhibition. It is fairly possible that inflammatory sites are infiltrated with Treg cells of different specificity, including self-antigen-, neo-antigen- and pathogen-specific subsets, and characterization of Treg surface markers indicates relatively high diversity of the total Treg population [75-79]. However, it remains unknown what is the functional difference between these cells and how their differentiation and activation depends upon their TCR specificity.

Yet another important issue concerning Treg functioning is plasticity of these cells. Depending on the context of inflammatory and immunological microenvironment, Treg cells markedly change their migration, suppression and homeostatic functions [23]. TB infection is characterized by the type 1 inflammation, with induction of the T-bet transcriptional factor in naïve CD4+ cells and activation of immune response along the IL-12 → IFN-γ axis. It appeared that under conditions of chronic TB inflammation Treg cells acquire the Teff-like phenotype: start to express T-bet, IFN-γ, IL-12R and chemokine receptor CXCR3, which allows migration of these cells towards the sites of type 1 inflammation [71]. What happens with the suppressor function of such cells remains unclear.

Intuitively, understanding Treg differentiation, activation and effector functioning may help to develop TB therapeutic approaches using these cells to control excessive inflammatory and immune reactions in the lung. However, experimental studies in mice provided controversial results, at least concerning a protective effect of Treg depletion *in vivo*. There were reports on an increase in IFN-γ-producing CD4+ cells pool and a decrease of mycobacterial multiplication and the level of lung pathology after Treg depletion [56,62,80], but the results were not confirmed in independent studies [81,82]. This discrepancy may be explained by an imperfection of the Treg depletion method: anti-CD25 antibodies used in the studies cited above eliminate not only Treg cells, but also activated Teff cells. In addition, overlapping autoimmune inflammation, developing on the background of Treg depletion, makes interpretation of the results ambiguous [4,7].

Overall, although we face much more questions than provide answers concerning Treg functioning in TB, there is no doubt that these cells are an important regulatory element of the disease pathogenesis.

Concluding Remarks

Treg cells play critical role in the control of autoimmunity, and many aspects of their physiological activity in **maintenance** of immune homeostasis were clarified in considerable details during last decades. However, in prolonged inflammatory conditions, including chronic infections, Treg biology is much less well defined. What is the balance point in immune homeostasis on the background of TB infection? On the one hand, the host tries to develop adaptive pathogen-specific immune response, and it is desirable to prevent Treg cells from suppressing corresponding Teff cells. On the other hand, an overwhelming immune response should be prevented in order to limit lung tissue destruction and mycobacterial dissemination. How often we observe the clinical picture reflecting the situation when Treg activity, meant to inhibit excessive response, results in "over-inhibition" of protective immunity? These and many other aspects of Treg biology in health and disease require specific attention and further experimental studying.

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