The Yin and Yang of regulatory T cell and therapy progress in autoimmune disease

Yong-chao Qiao a,b, Yan-hong Pan a,c, Wei Ling a, Fang Tian b, Yin-ling Chen a, Xiao-xi Zhang a, Hai-lu Zhao a,b,c,⁎

a Diabetic Systems Medicine, Guangxi Key Laboratory of Excellence, Guilin Medical University, Guilin 541004, China
b Department of Immunology, Xiangya School of Medicine, Central South University, Changsha, Hunan 410078, China
c Department of Immunology, Faculty of Basic Medicine, Guilin Medical University, Guilin 541004, China

A B S T R A C T

Autoimmune diseases (ADs) are primarily mediated by the failure of immunological self-tolerance. Regulatory T cells (Tregs) play a critical role in the maintenance of induced tolerance to peripheral self-antigens, suppressing immoderate immune responses deleterious to the host and preventing the AD development. Tregs and suppressive cytokines are homeostatic with effective cells plus pro-inflammatory cytokines in healthy hosts which is defined as “Yang”, and ADs are usually induced in case of disturbed homeostasis, which is defined as “Yin”. Indeed, the Yin-Yang balance could explain the pathogenic mechanism of ADs. Tregs not only suppress CD4+ and CD8+ T cells but also can suppress other immune cells such as B cell, natural killer cell, DC and other antigen-presenting cell through cell-cell contact or secreting suppressive cytokines. In Tregs, Foxp3 as an intracellular protein displays a more specific marker than currently used other cell-surface markers (such as CD25, CD40L, CTLA-4, ICOS and GITR) in defining the naturally occurring CD4+ Tregs. Though the precise mechanism for the opposite effects of Tregs has not been fully elucidated, the importance of Tregs in ADs has been proved to be associated with kinds of immunocytes. At present, the surface marker, frequency and function of Tregs existed conflicts and hence the Tregs therapy in ADs faces challenges. Though some success has been achieved with Tregs therapy in few ADs both in murine models and humans, more effort should paid to meet the future challenges. This review summarizes the progress and discusses the phenotypic, numeric and functional abnormalities of Tregs and is the first time to systematically review the progress of Tregs therapy in kinds of ADs.

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Keywords: Yin and Yang Autoimmune disease Regulatory T cell Therapy

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⁎ Corresponding author at: Center for Diabetic Systems Medicine, Guangxi Key Laboratory of Excellence, Guilin Medical University, Huan Cheng North 2nd Road 109, Guilin 541004, China.
E-mail address: zhaohailu@glmc.edu.cn (H. Zhao).

http://dx.doi.org/10.1016/j.autrev.2017.08.001
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1. Introduction

Autoimmune diseases (ADs) affect almost 20% of the population [1] and are primarily mediated by an abnormal immune response. When the multiple functions were impaired in the immune system in case of defending against invasion by pathogens, removing aging or dead cells, identifying and removing aberrant cells due to gene mutation, and preventing the development or growth of tumors [2], an autoimmune disease usually occurs. To our knowledge, genetic and environmental factors are mainly facilitated to this disease and it is difficult to heal completely.

Regulatory T cells (Tregs), a subset of CD4+ T cells, characterized with the expression of the transcription factor Foxp3, cytotoxic T lymphocyte antigen 4 (CTLA-4) and high surface expression of CD25, have an important role in controlling immune responses, preventing excessive inflammation, enforcing tolerance against self-antigens and exerting a key homeostatic effect in the immune system [3]. And the breakdown of the immune homeostasis may result in inducing auto-antibodies, inflammatory response and tissue infiltration, which can facilitate the AD development [4]. The suppressing responses mediated by the functions of Tregs include cell to cell contact and the synthesis of immunosuppressive cytokines (TGF-β and IL-10) [3]. Studies indicated that Tregs are important in the pathogenesis of many ADs such as autoimmune hemolytic anemia (AHA) [5], autoimmune thyroid disease (AHD) [3,6,7], rheumatoid arthritis (RA) [8–11], systemic lupus erythematosus (SLE) [10–13], Sjogren syndrome (SS) [14], and systemic sclerosis (SSc) [15–17]. Compromised number and function of Tregs could lead to the defects of autoimmune tolerance and abnormal immune responses [18,19].

The homeostasis of immune response is maintained between Tregs plus suppressive cytokines and effective cells plus pro-inflammatory cytokines in healthy hosts, here we define as “Yang”, and when the homeostasis is broken, ADs are usually induced, here we define as “Yin” (Fig. 1). The Yin-Yang balance theory may be an excellent way to explain the pathogenesis of ADs.

Tregs, displayed the powerful immune suppressive capacity which could restrict the activation and proliferation of effector T cells and restore immune tolerance, could be used as a potent means of treating ADs [2]. Otherwise, in the development of Treg-based therapies for ADs, the defects in immune tolerance and imbalance between Treg and other immune cell were characteristic in the pathology of ADs, so restoring suppressing function through adoptive transfer therapy of Tregs is a major direction in the treatment of ADs.

More and more researchers focus on the Tregs role in ADs, such as the surface markers, frequency number, suppressing function and treatment strategy of Treg, however, their studies still displayed discrepant outcomes [20]. Therefore, the exploration about the role of Tregs in ADs and the correlation about Tregs and other immune cells, such as effector T cells, B cell, natural killer (NK) cell and mononuclear macrophage, possibly give us some insight about the pathogenesis of ADs. In this study, we focus on the correlation about Tregs with cytokines and other immune cells which result in the development of ADs according to Yin-Yang balance theory, and discuss the strategy of Tregs therapies used to treat autoimmune and other immunological disorders.

2. The phenotype and function of different Tregs subsets in ADs

2.1. The phenotype of different Tregs subsets

Some important surface markers and function in Tregs which displayed in Table 1. Tregs characterized with the co-expression of surface markers CD3, CD4 and the interleukin-2 (IL-2) α-chain receptor (CD25) (Fig. 2), own immunoregulatory function. And in consideration of the phenotype and function, Tregs displayed a heterogeneous population [21]. According to the origin of the induction and differentiation, Tregs can be classified into natural Tregs (iTregs) and induced Tregs (iTregs), which generated in the thymus and diffuse to peripheral lymphoid organs respectively [22]. Otherwise, in the CD4+ T cell population, suppressive T cells mainly divided into three subtypes, such as IL-10-producing T regulatory 1 cells (T1, CD4+CD25highFoxp3+), TGF-β-
The known important surface markers and function in Tregs.

<table>
<thead>
<tr>
<th>Surface marker</th>
<th>Receptor</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>CD2</td>
<td>LFA-3</td>
<td>Playing a role in pre-TCR function in double-negative thymocytes, TCR selection events during thymocyte development, TCR-stimulated cytokine production in mature T cells [47,48] and mediating cell adhesion in both T-lymphocytes and in signal transduction [49].</td>
</tr>
<tr>
<td>TCR-CD3</td>
<td>MHC-II</td>
<td>Driving T-cell development, activation, effector functions, and relaying key information from their ligand-binding modules (TCRs) to their signaling modules (CD3ε + CD3ζ and CD3ξα) and on to the intracellular signaling apparatus [50,51].</td>
</tr>
<tr>
<td>CD4</td>
<td>MHC-II</td>
<td>CD4 as a receptor for a constant part of MHC class II molecules interact with the TCR/CD3 complex and participate in T-cell activation possibly through the p56lck tyrosine kinase, which is associated with CD4 at the intracytoplasmic side of the plasma membrane [52].</td>
</tr>
<tr>
<td>CD25</td>
<td>IL-2</td>
<td>Three subunits co-consists the IL-2R and the interaction of IL-2/IL-2R play a key role in T-cell-dependent immune responses by activating a series of signal pathways [53].</td>
</tr>
<tr>
<td>CD122 (IL-2Rα)</td>
<td>IL-2R</td>
<td>CD45 splice variants RA and RO distinguish naive (CD45RA+) from central memory and recently activated (CD45RO+) T cells in peripheral blood [54]. CD45RO expression relates to functional memory within the resting CD4 + population, identifying cells that are capable of proliferating in response to soluble antigen and rapidly produce mRNA encoding IL-4 and IFN-γ [55].</td>
</tr>
<tr>
<td>CD127 (IL-7R)</td>
<td>IL-7</td>
<td>CD28 serves as the surface component of a novel signal transduction pathway that modulates T-cell lymphokine production and increases the resistance of T-cell responses to various immunosuppressive agents [56].</td>
</tr>
<tr>
<td>CD154 (CD40L)</td>
<td>CD40</td>
<td>The formation and perpetuation of the germinal center reaction [57] and mediating B cell responses [58].</td>
</tr>
<tr>
<td>CD62L (L-selectin)</td>
<td>Carbohydrate</td>
<td>Mediating CD4 + T cell entry into lymph nodes [59] and enhancing CD4 + T cell activation [60].</td>
</tr>
<tr>
<td>CD134 (OX40)</td>
<td>TNF</td>
<td>As a primary costimulator of T cells, promote T-cell expansion and restore normal responsiveness to antigen [61]. A key co-stimulatory molecule involved in the regulation of CD4 memory T cells [62]. Enhance survival of T cells and increase memory T-cell generation [63].</td>
</tr>
<tr>
<td>CD152 (CTLA-4)</td>
<td>B7-1 (CD80)</td>
<td>The negative regulatory role in the control of self-reactivity [32,64] and mediating signals via the activation of the ubiquitin ligase Itch probably leading to the enhanced ubiquitination of Itch target molecules resulting in inhibition of T cell activity [65]. Signals were induced by CTLA-4 act directly on activated T lymphocytes [66].</td>
</tr>
<tr>
<td>CD279 (PD-1)</td>
<td>PD-L1 (CD274) and PD-L2 (CD273)</td>
<td>PD-1 and its ligands are involved in the induction of T lymphocyte apoptosis and in regulating the production of nitric oxide, TNF-α, and IL-10. Inducing the deactivation of T lymphocytes or even other responses that are important for maintaining the balance [67].</td>
</tr>
<tr>
<td>LTR</td>
<td>PAMP</td>
<td>As co-stimulatory receptors to enhance TCR-induced Teff cell proliferation, survival and cytokine production [69], block Treg suppressive function and control immune responses [70,71].</td>
</tr>
</tbody>
</table>

Table 1 (continued)

<table>
<thead>
<tr>
<th>Surface marker</th>
<th>Receptor</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITR</td>
<td>TNF</td>
<td>Regulating the CD4 + CD25 + T cell subset, enhancing immune responses [72] inhibiting the suppressive function of Tregs, and triggering Treg differentiation and expansion [73].</td>
</tr>
<tr>
<td>CCR4</td>
<td>CC</td>
<td>Tissue-specific lymphocyte homing [74].</td>
</tr>
<tr>
<td>LFA-1</td>
<td>ICAM-1</td>
<td>Playing a critical role in regulatory T cell homeostasis and as a central receptor in cell-to-cell contact mechanisms utilized by Tregs to suppress effector cells [77].</td>
</tr>
<tr>
<td>ICOS</td>
<td>ICOSL</td>
<td>Regulating CD4 T cell activation and effector function [79] and the adaptive immune system.</td>
</tr>
</tbody>
</table>

Fig. 2. Interaction of surface markers of Tregs with ligands of APC. CD, cluster of differentiation; TCR-CD3, cytotoxic T lymphocyte antigen; ICAM-1, intercellular adhesion molecule-1; ICOS, inducible costimulator; ICOSL, inducible costimulator ligand; LFA-3, lymphocyte function associated antigen-1; MHC-II, major histocompatibility complex-II; PD-1, programmed death 1; TCR, T cell receptor.
suppressor assays [30]. The work of Liu, W. et al. displayed the combination of CD4, CD25, and CD127 could form highly purified population of Tregs based on other cell surface markers, which support that surface molecule of CD127 could be used as a biomarker for Tregs [30].

Cytotoxic T lymphocyte antigen-4 (CTLA-4) (Fig. 2) is constitutively expressed on CD4+CD25+ Tregs and is suggested to play a role in Treg mediated suppression [31]. The work of Kataoka, H. et al. indicated that Treg exert in vitro suppressive activity independent of CTLA-4 expression [31]. CTLA-4 played the negative regulatory role in the control of self-reactivity and was most apparent about the CD4+CD25+ CTLA-4+ immunoregulatory T cells in controlling multiple ADs [32].

Glucocorticoid-induced tumor necrosis factor receptor (GITR) (Fig. 2) expression had increased in CD4+CD25+ cells, a member of the TNF receptor super family, which plays a functional role about regulating the CD4+CD25+ T cell subset [33]. GITR plays a key role in dominant immunological self-tolerance maintained by CD4+CD25+ regulatory T cells and could be a suitable molecular target for preventing or treating ADs [34]. For markers such as CTLA-4 and GITR, not only expressed on Tregs, but also expressed on effector T cells, which is problematic for their functional role about the immunophenotyping [30]. Other surface markers such as CD103, CD223, CD134, CD122, GITR and toll-like receptor (TLR) are not specific in CD4+CD25+ cells and could not represent the suppressing function of Tregs.

Other Tregs subsets, such as CD4+ and CD8+ Tregs: γδ Tregs play an important role in tissue-associated immunoregulation [35]; CD8+ Tregs suppressor lymphocytes identified in humans could inhibit the proliferation of antigen-specific T cells [36]. Natural killer Tregs as a conserved subpopulation of lymphocytes could recognize glycolipid antigens in a CD1d context, and exert a key role in regulation of autoimmunity [37]. The above Tregs secreted regulatory cytokines such as TGF-β and IL-10 and regulated the immune response. Regulatory B cells, characterized with their ability to produce autoantibody, possess additional immune functions, such as the production of cytokines and the ability to function as a secondary APC [38].

2.2. The surface marker function of Tregs in ADs

The key functions of Tregs are to keep the balance of immune response and tolerance with self-antigen. nTregs (CD4+CD25+FoxP3++CD127−CD45RA−) [39], activated by IL-2, play the suppressive effects according to cell direct interactions or cytokine secretion mechanisms. Cell direct interactions presumably involve the Tregs with antigen presenting cells (APCs) or responding T cells. In the cytokine-independent mechanism, such as the immunosuppressive cytokines, IL-10 and TGF-β inhibited the proliferation of effector T cells and the production of cytokines which dependent on FoxP3 [21]. The FoxP3, which encodes a transcription factor, plays a major role in governing the functions of Tregs in autoimmune and inflammatory syndrome in humans and mice. FoxP3–infected CD4+CD25− T cells could significantly reduce the proliferation of CD4+CD25− responder T cells when stimulated with CD3 mAb, and the suppression effect based on the relationship about the inhibition of IL-2 production [26]. In addition, the expression of FoxP3 in Tregs could inhibit the production of cytokines such as IL-2, IFN-γ, IL-4, and IL-10 [26].

iTregs (CD4+CD25+FoxP3+++CD127−CD45RA−) [39] have no function without these antigen stimulated such as during infection, organ transplantation or ectopic expression of non-self antigens and it promotes the suppression by the synthesis of the suppressive cytokines (IL-10 and TGF-β) in an inflammatory environment [40]. Otherwise, iTregs are also activated and expanded through TGF-β, IL-10 or IL-2 [22]. IL-10 has an intimate connection with a series of immune suppressive effects, such as the inhibition of APC function, induction of anergy, differentiation of Tregs, and control of the expansion of other T cell populations [41]. TGF-β, as a multifunctional cytokine circulated in plasma with a biologically inactive form, owned multiple functions, such as regulation of cell proliferation and extracellular matrix production. Otherwise, TGF-β could enhance immunosuppressive function through maintaining the expression of Foxp3 of CD4+CD25+ Tregs.

The surface marker of Tregs, CD122 (IL-2Rβ chain) (Fig. 2), is responsible for IL-2 signal transduction [42] and is used by the receptors of both IL-2 and IL-15 [43]. The high expression about CD122 in Tregs could induce higher binding of IL-2, IL-15, or both. Preferential binding of IL-2 may reduce the availability of this cytokine to effector cells, thus reducing their expansion. IL-15 has been shown to reduce the susceptibility of T cells to activate induced cell death [44]. Therefore, increased expression of CD122 may provide regulatory cells with a survival advantage, allowing immune regulation to persist. Tregs, preferentially bind with IL-2, could reduce the availability of this cytokine to effector T cells, and then reduce their expansion. Some results have proved that IL-15 could reduce the T cells susceptibility and induced cell death [44]. Therefore, CD122 highly existed in Tregs, could provide a survival advantage and allow immune regulation to persist (Table 1).

The main mechanism of suppression response of Tregs was to inhibit the production of IL-2 by responder T cells and interestingly, Tregs have been manifested constitutive expression of CTLA4 (CD152) both in mice and in humans. Fallarino et al. proved that CD4+CD25+ cells, over expressing CTLA-4 by treatment with antibody to CD3, initiated tryptophan catabolism in dendritic cells (DCs) through a CTLA-4–dependent mechanism in mouse [45]. So CD4+CD25+ Tregs could implement their suppressive response either by directly suppressing T cells or indirectly through modulation of APC function [45]. Otherwise, the work of Chen, W. et al. found that the cross–linking of CTLA-4 induces TGF-β production, which may in part contribute to the down regulation of T cell activation. CTLA-4, through TGF-β, may serve as a counterbalance for CD28 costimulation of IL-2 and CD4+ T cell activation [46]. Otherwise, Kingsley, C. I. et al. speculated that there may be a common mechanism of action linking CTLA-4 and IL-10 [41].

3. The interactions between Tregs and other immunocytes

The net correlation existed in series of immunocytes including Tregs, Th1, Th2, Th17, B cell, mononuclear macrophage, NK cell, CD8+ T cell and DC that exert their role by the synthesis of immunosuppressive cytokines or pro-inflammatory cytokines, which displayed in Fig. 3.

3.1. Tregs and Th cells

Th1 cells are necessary to clear intracellular pathogens and Th2 cells are important for clearing extracellular organisms. The Th1 driven responses, mediated by Th1 cell [secretting IL-2, interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α)] and macrophages (secretting IL-1, IL-6, IL-12 and TNF-α) which was defined as cellular immunity, while Th2-driven responses (secretting IL-4, IL-5, IL-6, IL-10 and IL-13), which antibodies and/or immune complexes served as the main mediators that was defined as humoral immunity [81]. The balance of Th1 and Th2 was aimed to keep the cytokines homeostatic in ADs. Just as the homeostasis between Th1 and Th2, the Tregs and Th17 (secreting IL-17, IL-23) were also cross regulated and a variety of molecular switches or mediators can influence the reciprocal differentiation between Tregs and Th17 cells.

TGF-β not only could facilitate the development of Tregs, but also contribute to the induction of Th17 based on the presence of a pro-inflammatory cytokine (IL-6 or IL-1) [81]. Other researchers, Veldhoen, M. et al., have proved that Treg can be substituted by TGF-β1 together with the pro-inflammatory cytokine IL-6 which promotes Th17-cell differentiation; otherwise, the process is amplified by IL-1β and TNF-α. IL-6 plays an important role in driving the transcription of Th17 lineage-specific genes through activating signal transducer and STAT3 which inhibits the Foxp3 expression and the generation of Tregs [82]. Though they could not detect a role for IL-23 in the Th17 cells differentiation, they confirmed its important role in their survival and expansion [82]. More than that, their data indicated that TGF-β1 subverted Th1 and
Th2 differentiation for the generation of Th17 cells in the presence of IL-6 [82]. Mangan, P. R. et al. confirmed that, Th17 cells which tailored to specific classes of pathogens almost evolved to provide adaptive immunity and TGF-β contributed to the development as an important cytokine [83]. The development of Th17 cells has also been linked to IL-23, an IL-12 cytokine family member which shares with IL-12 a common subunit, otherwise, the receptors of IL-23 and IL-12 share a subunit (IL-12Rβ1, IL-23R and IL-12Rβ2) to confer receptor responsiveness and TGF-β can up-regulate the expression of IL-23R which conferred responsiveness to IL-23 [83].

Bettelli, E. et al. proved that IL-6 completely inhibited the expression and generation of TGF-β-induced Foxp3+ Tregs in mice and IL-23 is not the differentiation factor for the generation of Th17 cells [84]. On the contrary, IL-6 plus to TGF-β could induce the differentiation of pathogenic Th17 cells from naive T cells (Fig. 3), which indicated that effector T cell and Tregs may differentiate from the same precursor T cells that depend on the balance of cytokines present in the environment [84]. Otherwise, their results demonstrated a dichotomy which the generation of Th17 could induce autoimmunity and Tregs may prevent the injury of autoimmune tissue [84].

3.2. Tregs and NK cells

NK cells play an important role in the innate immune system which not merely exert cell to cell contact-mediated cytotoxicity against infected cells or tumor cells, but also play regulatory role through promoting or suppressing the functions of other immune cells by the synthesis of chemokines and cytokines [85]. Several studies have proved that Tregs could suppress NK cell effector functions in vitro [86,87], and Smyth, M. J. et al. have indicated that the mechanism could directly suppress NK cell function via the natural-killer group 2, member D (NKG2D) pathways through the activated Tregs in vivo. Otherwise, the relief of the suppression of Tregs could significantly enhance the functional activity of NK cells in the environment of activating IL-12 cytokine, which has the role for enhancing the NKG2D pathway of NK cell activation [88]. The suppressive effect of Tregs exerting on NK cells cytolysis is dependent on the secreting cytokine TGF-β and Smyth, M. J. et al. has proved that the ability of soluble TGF-β could reduce NK cell cytotoxicity and perforin gene transcription [89]. Trzonkowski, P. et al. examined the cytotoxic activity in the cultures of peripheral blood mononuclear cells (PBMC) and separate CD8+ T cell or NK cells mixed with Treg respectively and found that the production of IFN-γ, perforin and the cytotoxic activity of CD8+ T cell or NK cells were decreased in the presence of Tregs. Tregs-producing IL-10 in the cultures may mix the results, and when add the anti-IL10 mAb into the cultures, the outcomes did not change, which indicated that Treg exert the suppressing effect by inhibiting both CD8+ T cell and NK lymphocyte cytolytic activities in a direct cell-to-cell interaction [86].

3.3. Tregs and antigen-presenting cells (APCs)

APC includes monocytes/macrophages, B cells and DCs. Monocytes/macrophages have an important role in the chronic inflammatory process and the destruction of some tissues through the production of pro-inflammatory cytokines (TNF-α and IL-6), and some studies have reported that Tregs could inhibit the proinflammatory properties of monocytes/macrophages [90]. The suppressive effects on monocytes/macrophages were exerted directly by CD4+ CD25+ Tregs and then significantly affect innate or adaptive immune responses. CD4+ CD25+ Tregs own the ability of modulating the monocytes through changing the activation of the cells, and leading to the lowered production of pro-inflammatory cytokine and the hampered function. Low cytokines were produced in monocytes co-culture with CD4+ CD25+ Tregs, but

Fig. 3. The interactions among series of immune cells. CD4+ Tregs could suppress Th1, Th2 and B cells by the synthesis of immunosuppressive cytokines (TGF-β and IL-10), and suppress mononuclear macrophage, NK, CD8+ and dendritic cells by cell-cell contact. IL-6 secreting from dendritic cells and Th2, in combination with Treg-secreting TGF-β promotes the development of Th17 cells. IL-17 secreting from Th17 could facilitate the differentiation of APC and B cells. IFN-γ from Th1 cells may cause the proliferation and cytokine production of mononuclear macrophages and suppress the Th2 and Th17 cells. IL-4 from Th2 cells suppresses the proliferation of Th1 and Th17 cells. IL-12 from APC could promote the proliferation of CD8+ T cells. The red arrows display inhibition and the black arrows indicate promotion, respectively.
large amounts of pro-inflammatory (TNF-α, IFN-γ and IL-6) and suppressive (IL-10) cytokines were produced when monocytes co-cultured with CD4+ CD25+ T cells [90]. Monocytes after CD4+ CD25+ Treg treated, then re-purified after co-culture, and stimulated with LPS, could significantly suppress their capacity about producing TNF-α and IL-6 [90]. Otherwise, the phenotype of monocytes displayed limited up-regulation of HLA class II, CD40 and CD80, and down-regulation of CD86 after pre-culture with CD4+ CD25+ Tregs, which the change of phenotype had functional consequences.

DCs played an important role in the initiation and regulation of immune responses as the professional bone marrow-derived APCs, and the diversity of phenotype and function is related with their stage of maturation and/or to their myeloid or lymphoid origin [91]. TGF-β and IL-10, secreted from Tregs, could influence the differentiation and function of DC [92]. DC may control a series of T cell mediated immune responses by presenting antigens and producing co-stimulatory signals and pro-inflammatory cytokines to T cells, moreover, T cells could increase the function of the DC through cell-cell contact and co-stimulatory receptor-ligand pairs [93]. The work of Cederbom, L. et al. found that CD4+ CD25+ Tregs could down regulated the expression of the costimulatory molecules CD80 and CD86 of DC, which suggested that Tregs could exert their suppressive function through the down-regulation of co-stimulatory molecules [93].

Tregs could inhibit the production of autoantibody [94] with a contact- or death-independent manner by direct inhibition of B cell-mediated IgM production or indirect of CD4+ T cell. Tregs co-cultured with IL-2 could sustain the B cell and secret the detectable levels of IgM [95]. The work of Weingartner, E. et al. observed that some secreted factors may influence the suppression of IgM secretion, and suggested that the Tregs suppression of B cells appeared to be contact-dependent [95]. They supposed that TGF-β secreted by Tregs exert the potential suppressing function of B cell. Previous work indicated that CD4+ CD25+ Tregs could act directly on B cells, and through co-cultured B cells with activated CD4+ CD25+ Tregs, the proliferation of B cells was significantly suppressed. The reason was due to the increased cell death which was caused by a cell to cell contact manner and up-regulated the perforin and granzymes of Tregs, but not mediated by Fas-Fas ligand pathway [96]. The work of Ikizumi, N. et al. proved that natural Tregs could inhibit the activity of B cells in vitro and in vivo by cell contact-mediated mechanisms which directly suppress the autoantibody of B cells [97].

3.4. Tregs and CD8+ T cells

CD8+ cytotoxic T lymphocytes (CTLs) normally have the function about the protection against viruses and elimination of tumor cells, and result in the damage of abnormal or infected cells by TCR/CD8 recognition of MHC-I presented by target cells. Then damage them through the ability to produce the cytotoxic proteins (granzymes and perforin) and pro-inflammatory cytokines (IFN-γ and TNF), and induce the Fas signaling triggering apoptosis pathways. CTLs also play a key point in the development of diabetes and are the most abundant pancreas-infiltrating cells during insulin to mediate beta cell death in early onset of type 1 diabetes [102]. Autoreactive clones of CTLs found in the peripheral blood infiltrated into pancreas and cause disease [103]. It was found that the incidence of diabetes was reduced from 77% to 16% in the perforin-deficient mice, backcrossed with the nonobese diabetic mouse strain, and the disease onset was markedly delayed (median onset of 39.5 versus 19 weeks) in the latter which indicated that CD8+ T cells recall through the presence of CD30 on Tregs and the CD30/CD30L interaction [105]. Programmed death-1 (PD-1) as one of the prototypic inhibitory receptors negatively regulate the proliferation and activation of T cell and exert the suppressive functions through the binding with the ligands (PD-L1 or PD-L2) [106,107]. Treg suppress the activity of CD8+ T cells depend on the expression and interaction of PD-1 expressed on Tregs and PD-1 ligand expressed on CD8+ T cells. Park, H. J. et al. found that the binding of PD-1 and PD-L1 inhibited TCR signaling and caused the deterioration of T cell immune response against chronic viruses [108]. Otherwise, T cell immunoglobulin and mucin domain 3 (Tim-3) expressed in Tregs play the suppressed function by recognizing the ligand galectin-9 [109]. CD4+ CD25+ T cells, through inhibiting IL-2 production and up-regulation of CD25 expression, could suppress the proliferation and producing-IFN-γ of CD8+ T cells, which was mediated by a cell-cell interaction (Fig. 3) and in the absence of APC [110]. CD4+ Tregs from persistently infected mice could suppress IFN-γ production of CTLs and treatment mice with anti-GITR antibody significantly increase the production of IFN-γ, which indicated GITR played an important suppressive response in immune system [111]. Another signal pathways about Tregs suppressing the CTLs are the binding of OX40/OX40L [112] or B7-1/CTLA-4 [113] expressed on CTLs and Tregs respectively.

4. Tregs for AD therapy

4.1. Type 1 diabetes mellitus (T1DM)

T1DM as a chronic inflammatory disease characterized with the T cell-mediated destruction of insulin-producing β-cells and could lead to the development of kinds’ complications. The abnormalities of T cell phenotype and function are potential targets of immune interventions to preserve insulin-producing β-cells [114]. The therapy of Tregs provides many potential advantages such as specific and lasting dampening of inflammation [115]. More effort focused on the role of Tregs as a promising therapeutic tool for the treatment of ADs, and distinguishes the phenotype and function of the different subsets of Tregs.

Due to the adoption of the different phenotypes of Tregs in the research of T1DM, many conflicts about the frequency and function exist in current studies (Table 2). In general, it is widely believed that in the concept of defining the phenotypes of the naturally occurring CD4+ Tregs used as preventing ADs, Foxp3 displays a more accurate marker than currently used cell-surface molecules including CTLA-4, CD45RB, CD25 and GITR, which could not completely discriminate between Tregs and activated, effector, or memory T cells [26].

The therapy with Tregs has been succeeding in both animal models and humans. Stumpf, M. et al. displayed that adoptively transferred with Treg cells from wild type mice could significantly reduce the incidence of mice diabetes [116], Marek-Trzonkowska, N. et al. proved that Tregs infusion in 12 T1DM children treated with autologous expanded ex vivo Tregs with one year follow-up, bring about the increase of Tregs number and C-peptide levels in peripheral blood, and the results indicated that the repetitive administration of Tregs could prolong survival of β-cells in T1DM [117]. Bluestone, J. A. et al. expanded Tregs from patients with T1D and retained their T-cell receptor diversity and demonstrated enhanced functional activity, then the T1DM patients received ex vivo-expanded autologous polyclonal Tregs. The results showed that the Tregs was significantly increased in recipients and retained a broad Treg phenotype long-term which support the development of the Treg therapy [118].

At present, several attempts has been exerted with the aim of re-establishing immune tolerance through the induction or direct infusion of Tregs, which include glutamic acid decarboxylase (GAD) injection [119, 120], autologous umbilical cord blood transfusion [121,122], stem cell educator therapy [123], anti-CD3 therapy [124,125], and hematopoietic stem cell transplantation (HSCT) [126,127]. Some of above therapies has displayed efficacious which significantly increase the suppressive
Table 2
The frequency and function of CD4+ Tregs in human autoimmune diseases.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Surface marker</th>
<th>Changed frequency/function</th>
</tr>
</thead>
<tbody>
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<td>Kim, J. R. et al. [131]</td>
<td>CD4+CD25hiFoxp3+</td>
<td>Increased frequency</td>
</tr>
<tr>
<td>Fathy, A. et al. [181]</td>
<td>CD4+CD25hi</td>
<td>Decreased frequency</td>
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<td>Kim, J. R. et al. [131]</td>
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<tr>
<td>Crispin, J. C. et al. [180]</td>
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<td>Decreased frequency</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu, M. F. et al. [179]</td>
<td>CD4+CD25hi</td>
<td>Decreased frequency</td>
</tr>
<tr>
<td>Crispin, J. C. et al. [180]</td>
<td>CD4+CD25hi</td>
<td>Decreased frequency</td>
</tr>
<tr>
<td></td>
<td>CD4+CD25hiFoxp3+</td>
<td>Normal frequency</td>
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Table 2 (continued)

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<td>Paggi, A. et al. [201]</td>
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<td>Lawton, J. M. et al.</td>
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<td>Gottenberg, J. E. et al.</td>
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<td>Mao, C. et al. [200]</td>
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<td>Gottenberg, J. E. et al. [196]</td>
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<td>Increased frequency</td>
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Table 2 (continued)

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<td>Decreased frequency</td>
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<td>Iwase, O. et al. [210]</td>
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<td>Systemic sclerosis (SSc)</td>
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<td>CD25highFoxp3+CD127−</td>
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<td>Slobodin, G. et al. [212]</td>
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<td>Normal frequency</td>
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<td>Antiga, E. et al. [213]</td>
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<td>Decreased frequency</td>
</tr>
<tr>
<td>Giovannetti, A. et al. [214]</td>
<td>CD4+ CD25 + Foxp3+</td>
<td>Increased frequency</td>
</tr>
<tr>
<td>Broen, J. C. et al. [215]</td>
<td>CD4+ CD25highCD127−</td>
<td>Decreased frequency</td>
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<td>Klein, S. et al. [151]</td>
<td>CD4+ Foxp3+</td>
<td>Normal frequency</td>
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<td>Mathian, A. et al. [150]</td>
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<tr>
<td>Rodríguez-Reyna, T. S. et al. [178]</td>
<td>CD4+CD45RA− Foxp3bright rTregs</td>
<td>Normal suppressive function</td>
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<td>Fenoglio, D. et al. [149]</td>
<td>CD4+ CD25 highCD127+</td>
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<td>Papp, G. et al. [148]</td>
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<td>Fiocco, U. et al. [216]</td>
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<td>Cordiali-Fei, F. et al. [217]</td>
<td>CD4+ CD25 + Foxp3+</td>
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<td>Kataoka, H. et al. [16]</td>
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<td>Increased frequency</td>
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<tr>
<td>Kumar, M. et al. [218]</td>
<td>CD4+ CD25 + Foxp3+</td>
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<tr>
<td>Viggliotta, V. et al. [219]</td>
<td>CD4+ CD25 high</td>
<td>Decreased frequency</td>
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<tr>
<td>Khan, S [17].</td>
<td>CD4+ CD25highFoxp3+</td>
<td>Decreased frequency</td>
</tr>
</tbody>
</table>

function of Tregs and decreased daily dose of insulin requirement, but the others did not achieve the objectives. Though some potential concerns regarding the safety of Tregs immunotherapy existed such as possibly bring about undesired adverse events [115], it is an encouraging treatment for the TIDM patients.  

4.2. Rheumatoid arthritis (RA)

RA, as a chronic inflammatory autoimmune disease, is characterized with unclear etiology including progressive and destructive polyarthritis associated with serological evidence of auto-reactivity which lead to persistent and progressive synovitis [8]. The infiltration of T cell, B cell and monocyte and the proliferation of synoviocyte and endothelial cell contribute to the hyperplasia of the synovium [21] and the abnormality about the frequency and function of Tregs play a key role in initiation and progression of this disease. Though the frequency and function of Tregs are controversial in present (Table 2). The possible reasons of these conflicts may be explained by differences in disease stage and therapy and in the different phenotypic definition of naturally occurring Tregs in the above mentioned studies [128]. However, the suppressive function of Tregs universally got more approved and many studies have been proved that Tregs have an important regulatory mechanism in RA [8,129–131].

Tregs therapy has also implemented in controlling this disease and achieved encouraging results. Morgan, M. E. et al. transferred Tregs into mice which exhibited arthritis symptoms and found disease progression markedly slowed. The results indicated that Tregs could be used for the treatment of systemic, antibody-mediated ADs, such as RA [132]. Autologous stem cell transplantation (ASCT) as a treatment for severe refractory autoimmune disease could restore the normal frequency and function of Tregs in juvenile idiopathic arthritis (JIA) patients [133]. Several promising new approaches inducing immune tolerance has been studied in humans, such as mucosal peptide-specific immunotherapy, immunomodulatory neuromepetides, androgenedulin, urocortin, tolerogenic DCs and genetic manipulation of T cells [134].

Several treatment strategies with the aim of Treg modulation are guessed that may be available therapeutics in RA such as anti-TNF-α blockade, anti-IL-6 therapy, CTLA-4-Ig and anti-CD3 therapy [135]. Otherwise, IL-27 may be a novel and promising therapeutic agent for RA patients [136]. For RA, more effort needs to focus on whether the Tregs could be used as a therapeutic method in humans, not only decrease the severity and progression of this disease but also to cure established disease.

4.3. Systemic lupus erythematosus (SLE)

SLE as a heterogeneous inflammatory chronic autoimmune disorder characterized with multiple organ damages and abnormal immune response, and was breakdown of tolerance to self-nuclear, cytoplasmic and cell surface molecules [137–139]. The etiology of SLE is controversial and some predisposing factors have been found, such as genetic, environmental, infections, and hormonal factors [137], otherwise, Tregs play an important role to suppress autoreactive effector T cells in the immune system and got more focus in recent years. Though the data about the frequency and surface markers of Tregs in SLE were inconsistent (Table 2), the suppressive function existed in SLE was decreased and was got general consent. The discrepancy existed in these studies, one side, because the difference in detection surface markers, gating strategies in flow cytometry, methodology and the Tregs of healthy controls which displayed a large range in previous studies (0.5%–12%). Otherwise, the unstable disease activity status contributes to the change of Tregs, because the increase of Tregs in active disease state was more significant than remission state [131].

Therapy with Tregs in SLE has also made great success both in mice and human. In the clinical translation of Tregs-based immunotherapy of SLE, the amounts of purified CD4+ CD25+ Foxp3+ Tregs were adaptively transferred into lupus-prone (NZBxNZW) F1 mice and the maintaining disease remission were explored. The results indicated that Tregs could prolong the interval of remission induced by conventional cytostatic drugs and this study offered important information and a first proof-of-concept for the feasibility of a Treg-based immunotherapy in the maintenance of disease remission in SLE [140]. In the clinical trials with Treg-based immunotherapy of SLE patients, low-dose IL-2 therapy with the aim of expanding and activating Tregs population could control ADs and inflammation. More importantly, the above study provided that low-dose IL-2 therapy could expand Tregs in human SLE patients [141,142].

4.4. Sjogren syndrome (SS)

SS as one of the most common ADs, characterized with lymphocytic infiltration of all exocrine glands (especially salivary glands), disrupting the glandular epithelium and inducing dry mouth and eye symptoms (xerostomia and xerophthalmia) [143]. Nearly 1–3% in general populations were affected and more significant in women. Though the pathology of SS in not clear, generally the genetic disposition and environmental factors were thought to play an important role [143,144].

The frequency and function of Tregs in SS are also conflicting and only a few researches focus on the role about Tregs in SS patients (Table 2). To our knowledge, therapy with Tregs got achievement **
successively in mice but not put into use in humans. In mouse with thyrocytoma, lacrimal gland-draining cervical LN Tregs were purified and used to prevent dacryoanitis, and the results indicated that the lacrimal gland-protective Tregs exert a key role in preventing lacrimal gland autoimmunity [145]. Otherwise, the difficult about therapy is that the role of Tregs is still unclear in SS. The change of Tregs was variable depend on the activity of the autoimmune process, and the self- or exogenous antigens in target organs in SS may escape from immunological surveillance and clearance. More effort should be paid about Tregs in the pathogenesis of SS which need deserve further investigation.

4.5. Autoimmune thyroid disease (ATD)

ATD characterized with reactivity to self-thyroid antigens that were considered as damaged inflammatory or anti-receptor, and was subdivided into Hashimoto’s thyroiditis (HT) and Graves’ disease (GD) [3, 7]. In ATD patients, peripheral tolerance to self-antigens and the activation of T cell were controlled by Tregs. The pathogenesis of ATD was elusive which has a significant relationship with a series of genetic and environment factors.

Among the published studies, the number and function of Tregs were discrepant (Table 2). The conflicting results may be explained that lacking of the differentiation between GD and HT patients, the isolation method of the Tregs, the inconsistent surface markers of Tregs, the discrepant FCM analysis, the cell-culture durations and the methods of measuring proliferation which result in the diversity. Otherwise, this discrepancy may influence the future therapeutic strategy. If the defect existed in Tregs frequency, the increased Tregs number methods are reasonable against the patient’s own red blood cells [5, 146]. Tregs may play a significant role in the pathogenesis of ATD which was elusive which has a significant relationship with a series of genetic and environment factors.

4.6. Autoimmune hemolytic anemia (AHA)

In humans, AHA is the first recognized organ-specific and antibody-mediated autoimmune disease in which the red blood cells are destroyed prematurely by tissue macrophages because of the inducing of antibodies against the patient’s own red blood cells [5, 146]. Tregs may play an important role in AHA and more effort about Tregs has been paid in the pathogenic mechanism and therapeutic schemes in human patients.

Though some conflicts existed about the frequency and function of Tregs (Table 2), the defects of Tregs has been got unanimous recognition and the alternative strategy about restoring Tregs defects or imbalances has been put into practice. The Tregs therapy was successfully used in murine model. Mqadmi, A. et al. treated with anti-CD25 antibody to control the immunization of RBCs of C57/B16 mice, which significantly increased the incidence of AHA from 30% to 90%. And purify the Tregs from spleens and adoptive transfer into naive recipients which could prevent the induction of autoantibody production [147]. At present, the therapies in AHA patients include taking immunosuppressive drugs along with transfusion or splenectomy, which mainly control but not cure this disease [147].

Tregs exert the key role in controlling the ADs and the immunotherapeutic potential of Tregs could be an efficient therapeutic strategy for treatment of AHA in humans.

4.7. Systemic sclerosis (SSc)

SSc as a systemic autoimmune disease characterized with excessive extracellular matrix deposition and damage of small blood vessels, in which widespread vasculopathy and immunological abnormalities were induced by the fibrosis of the skin and organs and the damage of endothelial cells [148–150]. SSc is usually divided into two clinical subsets: one is diffuse cutaneous SSc characterized with the rapidly progressive fibrosis of the skin and visceral organs, and the other is limited cutaneous SSc characterized with the limited skin fibrosis and the low prevalence of internal organ involvement [148].

The pathogenesis of SSc is still not clear, but the circulating autoantibodies mediated inflammatory processes play a key role in the skin and visceral organs (heart, lungs, or kidneys), otherwise, Tregs immune homeostasis has been proved to have a big role in the fate of SSc through the inducing the peripheral tolerance of potentially pathogenic autoimmune response [149]. Contradictions still existed about the frequency and function of Tregs (Table 2) though some efforts have been made in exploring the importance in autoimmune system which attribute to the different active-degree of the disease, different analysis strategies, samples from different inflamed tissue and inconsistent surface markers in Tregs and so on.

At present the therapeutic options are still limited, and prostanoids and calcium antagonists are recommended for SSc-related digital vasculopathy attacks in patients, otherwise, immune suppressive therapies with corticosteroids, methotrexate, azathioprine, cyclosporine or cyclophosphamide possibly slow the progression of SSc [151]. Extracorporeal photochemotherapy is another good choice for the SSc patients [152]. To our knowledge, the Tregs therapy has not been put into practice. The Tregs-directed therapy with the aim of T cell immune homeostasis is attempting and the treatment could modify both number and activity of Tregs in SSc patients. Persistent research focused on the role of Tregs about proportional and functional change in SSc patients and Tregs mediated therapy could be a new therapeutic option in the future.

5. Conclusions

The homeostasis is kept between Tregs plus suppressive cytokines and effective cells plus pro-inflammatory cytokines in hosts, and when the balance is broken the ADs are possibly induced. Tregs exert the ability of suppressing the immune response and play an important role in ADs. Foxp3 as an intracellular protein displays a more specific marker than currently used other cell-surface markers (such as CD25, CD40L, CTLA-4, ICOS and GITR) in defining the naturally occurring CD4+ Tregs which can prevent autoimmune disease. Tregs not only suppress CD4+ and CD8+ T cells but also can suppress other immune cells such as B cell, natural killer cell, DC and other antigen-presenting cell through cell–cell contact (such as CTLA-4, ICOS, GITR and LAG-3) or secreting suppressive cytokines (such as IL-10 and TGF-β). Though some success has been achieved with Tregs therapy in few ADs both in murine models and humans, more effort should paid to meet the future challenges.

Take-home messages

- The homeostasis is kept between Tregs plus suppressive cytokines and effective cells plus pro-inflammatory cytokines in hosts, and when the balance is broken the ADs are possibly induced.
- Foxp3 as an intracellular protein displays a more specific marker than currently used other cell-surface markers in defining the naturally occurring CD4+ Tregs which can prevent autoimmune disease.
- Tregs not only suppress CD4+ and CD8+ T cells but also can suppress other immune cells such as B cell, natural killer cell, DC and other antigen-presenting cell through cell–cell contact or secreting suppressive cytokines.
- Though some success has been achieved with Tregs therapy in few ADs both in murine models and humans, more effort should paid to meet the future challenges.

Funding

This study was supported by the National Natural Science Foundation of China (81471054).
Conflicts of interest
None.

References


