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Review Article

GENERATION AND FUNCTIONAL ACTIVITY OF REGULATORY T CELL IN CONTROLLING IMMUNE SYSTEM

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ABSTRACT

The regulatory T cells are a subpopulation of T cells which modulate the immune system, maintain tolerance to self-antigens, and abrogate autoimmune disease. T-regs are immunosuppressive in nature and generally suppress induction and proliferation of effector T cells. Several subsets of regulatory T cells includes naturally occurring CD4+ CD25+ T-Reg Cells, antigen-induced TR-1 and TH3 cells, antigen-specific CD4+ T-Reg cells, CD8+ T-Reg cells, TCR γδ+ T-Reg cells etc. Regulatory T cell show some surface molecule or marker like CD4, CD25, CTLA4, GITR and FOXP3. It can also suppress a variety of immune cells including B cells, NK cells, NKT cells, as well as monocytes and dendritic cells. It works gently through some immunosuppressive cytokines such as TGF-β, IL-10, IL-35 etc. This review is thus based on the generation and several functional aspects of regulatory T cell in immune system regulation.

INTRODUCTION

Regulatory T cells are a subpopulation of T cell, that modulate immune system, maintain tolerance to self antigen and abrogate autoimmune disease. Regulatory T cells (Treg) also suppress immune response of other cells. So, formerly it was known as "suppressor T cell". This is an important self check, built into the immune system to prevent excessive reaction. Regulatory T Cells come in many forms, but well understood form express mainly CD4, CD25, FOXP3, and hence is called CD4+ CD25+regulatory T cell. There is another regulatory T cell subset, called induced regulatory T cell, which is also needed for tolerance and suppression. Dendritic cells (DCs) play a key role in initiating immune responses and maintaining immune tolerance. In addition to playing a role in thymic selection, DCs play an active role in tolerance under steady state conditions through several mechanisms which are dependent on IL-10, TGF-B, retinoic acid, indoleamine-2,3,-dioxygenase along with vitamin D. Several of these mechanisms are employed by DCs in induction of regulatory T cells which are comprised of Tr1 regulatory T cells, natural and inducible foxp3+ regulatory T cells, Th3 regulatory T cells. These T regulatory cells develop due to transcription of FOXP3 factor in the thymus and periphery. TCR stimulation, various cytokine such as, IL2, IL7 etc. signal, presence of TGFβ are important in the generation of regulatory T cells. But there are various mechanism of T regulatory cell mediated other cell suppression. Tregs can suppress a variety of immune cells including B cells, NK cells, NKT cells, $CD4^+$, and $CD8^+$ T cells, as well as monocytes and dendritic cells (DCs) (Belkaid and Tarbell, 2009).

Development of Regulatory T Cell

All T cells come from progenitor cells from the bone marrow, which become committed to their lineage in the thymus. All T cells begin as CD4-CD8-TCR- cells at the DN (double-negative) stage, where an individual cell will rearrange its T cell receptor genes to form a unique, useful molecule, which they, in turn, test against cells in the thymic cortex for a minimal level of interaction with self-MHC. If they obtain these signals, they proliferate and express both CD4 and CD8, becoming double-positive cells. The assortment of T reg cell occurs on radio-resistant haemopoietically-derived MHC class II-expressing cells in the medulla or Hassal's corpuscles in the thymus. At the DP (double-positive) stage, they are selected by their interaction with the cells within the thymus and they begin the transcription of Foxp3, and become T reg cells. T reg cell have a larger TCR diversity than effector T cells, biased towards the self-peptides. The process of T reg cell selection is determined by the affinity of interaction with the self-peptide MHC complex. T cell that receives very strong signals undergoes apoptotic death; a cell that receives a weak signal

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will survive and be selected to become an effector cell. If a T cell receives an intermediate signal, it will then become a regulatory T cell (Josefowicz *et al*., 2012).

Subset of Regulatory T cell

Naturally occurring CD4+ CD25+ Treg cells have been extensively studied in mice and humans, and several other subsets of Treg cells have been identified and characterized.

Naturally occurring CD4+ CD25+ t reg cells

This subset represents a small fraction (5–6%) of the total CD4+ T cell population and is derived from thymus without specific antigen stimulation. These cells express a high level of GITR and Foxp3 molecule and mediate immune suppression through a cell–cell contact mechanism (Wang, 2006).

Antigen-induced TR-1 and th3 cells

These Treg cells are induced in peripheral tissues by MHC-peptide stimulation and secrete a huge amount of IL-10 and/or TGFβ, and suppress immune responses through a cytokine-dependent mechanism (Shevach *et al*., 2002). Th3 cells were first isolated as a novel population of T Cells induced upon induction of peripheral tolerance upon oral delivery of myelin basic protein, which is known to suppress experimental autoimmune encephalitis (EAE) in mice. These Th3 cells are class II-restricted T cells with similar αβ TCR as Th1 and Th2 cells. Moreover, they are characterized by production of high amounts of TGF-β along with low amounts of IL-4 and IL-10 with no production of IFN-γ or IL-2. The ability of these cells to suppress EAE is mainly TGF-β dependent. Secretion of TGF-β by Th3 cells drives initiation of Foxp3 in activated T cells, thus driving them towards iTreg (induced T reg) phenotype (Wang, 2006).

Antigen-specific CD4+ TREG cells

CD4+ Treg cells are activated after the exposure to a specific antigen. Although the origin of CD4+ Treg cells remains largely obscure, they may arise from antigen experienced CD4+ CD25− T cells in the suppressive cytokine environment or after interaction with naturally occurring CD4+ CD25+ T cells. Several different subsets of dendritic cell (DCs) can induce both Th1 and Th2 effector cells depending on the dose of antigen. High antigen doses induce Th1 cell development, whereas low antigen doses induce Th2 cell development. Chronic stimulation with low doses of antigen favors the production of naturally occurring CD4+ CD25+ Treg cells (Josefowicz *et al*., 2012).

CD8+ TREG cells

Not all Treg cells are CD4+ T cells. Indeed, CD8+ Treg cells have been identified that mediate immune suppression in an antigen-dependent manner. Such cells usually suppress antigen activated CD4+ T cells in a TCR-specific manner. CD8+ Treg cells can be generated by tumor cells or tumor-infiltrating DCs, and suppress immune cells (CD4+, CD8+ effector cells and DCs) at tumor sites (Wang *et al.*, 2006).

TCR γδ+ TREG cells

TCR γδ+ T cells signify a small population of T cells, consisting of γ and δ TCR chains with limited TCR usage. They are distinct from αβ T cells, and may function as professional antigen-presenting cells (APC) and regulatory cells. (Wang *et al*., 2006).

The T-regulatory cell phenotype

Regulatory T cell show some surface molecule or marker like CD4, CD25, CTLA4, GITR and FOXP3 (Rudensky and Josefowicz, 2009).

1. **CD4**: Acts as a co-receptor for TCR recognition of MHC II/Ag.
2. **CD25**: acts as key T_{Reg} growth factor.
3. **CTLA-4(**cytotoxic T lymphocyte Ag-4): It binds to B7s (CD80/86)on APC and acts as co-stimulatory molecule for the T_{reg} cell (blocking CTLA-4 inhibits T_R).
4. **GITR (**glucocorticoid induced TNF related protein): GITRL level is transiently up-regulated on these APCs upon stimulation via the transcription factor NF-1, and it most likely exerts its main function during inflammatory responses. Indeed, agonistic Abs and (cells expressing) recombinant GITRL enhance T cell proliferation in vitro upon TCR triggering, which suggests that GITR acts as a costimulatory factor for T cells. GITR stimulation on regulatory T cells in co culture with effector T cells was suggested to neutralize the suppressive capacity of regulatory T cells.
5. **FoxP3:** Forkhead box protein3 is also very critical for T_{reg} cell activity and development.

Regulatory t cell differentiation in the thymus:

During thymic differentiation, variations in TCR signaling, i.e, characteristics such as functional avidity and duration are central determinants of T cell lineage fate determination (Josefowicz *et al.*, 2012).

Role of TCR

Particular requirements for TCR signaling is pivotal for Treg cell lineage commitment and for foxp3 induction. The 1st indication that Treg cell are exposed to TCR signal of increased strength came from early findings of increased relative expression of CD4, CD25, CTLA4 by Treg cell, which are all induced upon TCR stimulation. CD4 expression in thymocyte is proportional to the strength of TCR signal they are exposed. CD5 acts as a rheostat that attenuate TCR signaling in a tunable manner through recruitment of tyrosine phosphatase SHP1 to CD5 cytoplasmic tail.

Treg cell selection is likely instructed by TCR with affinities or avidities for self peptide MHC ligand in the range between those that mediate positive selection of conventional CD4+ T cell and stronger signal in self reactive T cell that mediate their negative selection under normal condition. Increased negative selection in the absence of TGFβ receptor on double/single positive (DP/SP) thymocyte led to reduced production of FOXP3+ cells in neonates. FOXP3 gene expression didn't affect the sensivity of negative selection in thymocytes by high affinity TCR ligand (Engel *et al*., 2013).

Role of cytokines

Cytokine signals are required for Treg cell differentiation in thymus. These essential additional signals are IL-2, IL-7, IL-15

etc. High functional avidity TCR signal result in the upregulation of CD25 and a subsequent increase in responsiveness of Treg precursor cells to IL-2 signal that facilitate Foxp3 induction. A transcription factor STAT5 binds to FOXP3 promoter and upregulate Foxp3 induction (Goldstein *et al*., 2013).

Role of FOXP3

FOXP3 (forkhead boxP3) is a protein involved in immune responses, FOXP3 appears to function as a master regulator or transcription factor in the development and function of regulatory T cells (Josefowicz *et al*., 2012). FOXP3 are presumed to exert control via similar DNA binding interactions during transcription. In regulatory T cell model systems, the FOXP3 transcription factor occupies the promoters for genes involved in regulatory T-cell function, and may repress transcription of key genes following stimulation of T cell receptors **(**Lehtimaki and Lahesmaa, 2013).

Tuned TCR signaling and its appropriate coordination with other cell extrinsic and intrinsic cues instruct Treg cell differentiation. But beyond TCR stimulation, numerous experimental condition favour induction of FOXP3, including NFkB signaling, loss of maintainence of DNA methyl transferase activity, deficiency in mTOR and reduction of PI3K signaling (Zhang and Zhao, 2007).

Molecular mechanisms of T-Reg mediated T cell suppression

Despite the rapidly gathering knowledge of Treg cell involvement in immune regulation, our understanding of molecular mechanism of suppression is still limited. Transcriptional profiling of Treg cells versus naive or activated T cells shows a substantial number of genes, including cell-surface molecules and secreted proteins, that potentially function as suppression molecules in Treg cell–mediated immune regulation. Tregs can suppress a variety of immune cells including B cells, NK cells, NKT cells, $CD4^+$, and $CD8^+$ T cells, as well as monocytes and dendritic cells (DCs) (Schmidt *et al*., 2012). There are several different mechanisms of Treg-mediated suppression, mostly on the basis of in vitro suppression assays. These different mechanisms may also operate in vivo depending on the target cell type and activation status as well as the location and cytokine and microorganism milieu of the immune reaction. Thus, the contribution of suppressive mechanisms might be interpreted separately depending on the cell types and their activation state used in in vitro suppression assays. In addition to this, differences may occur depending on the readout, as suppressing the production of certain effector cytokines or the release of cytotoxic granules in vivo and in vitro can occur without concomitant suppression of proliferation. It was also suggested that activation and/or expansion of antigen-specific Tregs may be a prerequisite for Tcons suppression in vivo, as it might result in sufficient Treg numbers to enable contact with target Tcons at the site of the immune response (Sojka and Fowell, 2011).

Tregs have also been described to suppress Tcons by different mechanisms, depending on the experimental setup, site and type of immune response. Tregs can produce immunosuppressive adenosine or transfer of cAMP to Tcons. Tregs can rapidly suppress TCR-induced Ca^{2+}, NFAT, and NF-κB signaling pathway. Tregs can also produce immunosuppressive cytokines (IL-10, TGF-β, IL-35), and they can suppress by IL-2 consumption or can induce effector cell death via granzyme and perforin pathway. Furthermore, Tregs can suppress Tcons indirectly by downregulating costimulatory molecules on APCs (DCs) via CTLA-4 (Klein *et al*., 2003)

Suppression via the immunosuppressive Cytokines (TGF-B), IL-10, AND IL-35

The role of immunosuppressive cytokines in Treg-mediated suppression is still incompletely understood. Despite the importance of TGF-β and IL-10 in several in vivo models, these cytokines seem to be dispensable for other disease models such as autoimmune gastritis as well as for most in vitro systems. Treg-mediated suppression via cytokines is described in more detail below (Suri-Payer and Fritzsching, 2006)

TGFβ

High amounts of membrane-bound and soluble TGF-β are produced by regulatory T cell, and TGF-β blocking partially abrogated the suppression of T cell proliferation in vitro using murine or human T cells, suggesting that Treg-produced TGF-β controls autoimmunity (Fahlen *et al*., 2005). Although TGF-β deficient Tregs can suppress Tcon proliferation in vitro. TGF-β1 production by Tregs is necessary to prevent colitis in several studies. Interestingly, human Tregs could present suppressive activity to target Tcons in a cellular contact-dependent manner (so-called infectious tolerance). Suppressive cells produced by infectious tolerance use a TGF-β mechanism. Thus, TGF-β function in vivo do not only involve direct suppression of effector T cell signaling but also induces Tregs, consistent with lethal autoimmune disease (Wing *et al*., 2008).

IL-10

IL-10 plays an important role in Treg-mediated suppression of intestinal inflammation. Blocking IL-10 or using IL-10 deficient Tregs abrogates the protective effect of Tregs on T cell transfer-induced colitis. While the control of memory/antigen-experienced T cells during prevention or cure of colitis required IL-10, Treg-dependent prevention of naive cell-mediated colitis does not usually require IL-10, showing the involvement of different suppression mechanisms depending on the activation status of the target cell. The importance of IL-10 in Treg function in vivo has extended to infection and EAE models (Schmidt *et al*., 2012). Further, another study revealed that Treg-derived IL-10 is very important for control of inflammation at environmental interfaces but seems to be dispensable for control of systemic autoimmunity. IL-10 or IL-10 receptorless mice do not develop autoimmunity, but are susceptible to colitis in the presence of triggering flora. Although IL-10 can suppress many immune cells including DCs, direct effects of IL-10 on effector/memory T cells are very important in prevention of T cell-mediated colitis. Several recent studies further delineate that IL-10R signaling is needed in Tregs as well as in Th17 cells in order to suppress colonic Th17 responses. IL-10 is dispensable for regulation of IFN-γ and T cell expansion in the lymph node. (Sojka and Fowell, 2011)

Anti-inflammatory IL-10 is produced only by T cells including Tregs and $Foxp3^-$T regulatory 1 (Tr1) cells, but also by other

cells such as regulatory B cells and macrophages. **(**Schmidt *et al*., 2012)

IL-35

The recently discovered cytokine namely IL-35, implicated in Treg-mediated suppression and was shown to directly inhibit Tcon proliferation. Tregs deficient in one of the IL-35 chains had reduced suppressive ability in vitro and in vivo in an IBD model. In contrast to murine Tregs, human Tregs do not constitutively express the IL-35 (Collison *et al*., 2008). Nevertheless, IL-35 may play a key role also in human immunosuppression, as treatment of naive human or mouse T cells with IL-35 induced a so-called iT_R35 regulatory population that mediated suppression via IL-35 but did not need IL-10, TGF-β, or Foxp3. These iT_R35 were found to be strongly suppressive in several *in vivo* mouse models. Although naive human Tregs did not express huge amounts of IL-35, long-term activation of human Tregs led to upregulation of the IL-35 subunits starting at 3 days of activation. These long-term activated Tregs exerted contact independent in vitro suppression in an IL-35-dependent manner. Thus, IL-35 may contribute to infectious tolerance (Chaturvedi *et al*., 2012).

CONCLUDING REMARKS

Regulatory T cells are capable of controlling self reacting lymphocytes. Foxp3 is essential for T cells becoming regulatory T cells. Treg cells were performed various important immunoregulatory activities including induction of transplant tolerance, as well as in autoimmunity and cancer. In mice, due to Foxp3 mutation, scurfy disease occur. Here Treg are lacking in those mouse. Due to Foxp3 mutation, immunodysregulation polyendrocrinopathy enteropathy X linked syndrome (IPEX) occurs in human. The clinical potential of Treg as therapy for transplant recipients as well as patients suffering from autoimmunity has led to extensive studies aimed at understanding the molecular cues that govern Treg development, maintainence, and Treg differentiation. Use of rapamycin enhances Treg differentiation, survival and expansion but suppressing the proliferation of effector T cells. All the subsets of Treg cells are able to prevent immune mediated disease and also autoimmune disease like rheumatoid arthritis, multiple sclerosis, myasthenia gravis etc. (Josefowicz *et al*., 2012). Treg cells have been proposed for use in cell based therapy for autoimmune disease and organ or tissue transplantation (Huynh *et al*., 2014). A growing body of evidence indicates that Tregs do not use only one universal mechanism of suppression, but rather an arsenal of different ones. So far, it is unclear how a Treg "decides" which mechanism to apply, and whether it can switch from one to the other and/or apply several modes of suppression simultaneously. Mechanisms of suppression as well as target T cell susceptibility to suppression likely differ depending on tissue site, cell types involved and activation status of target cell and Treg. Furthermore, different Treg subsets exist and further research should reveal whether these are specialized on a particular suppressive mechanism. Further research is required to elucidate which mechanisms of Treg-mediated suppression or of target T cell resistance to suppression are most important in a particular disease, and possible therapeutic interventions have to be performed extremely carefully (Schmidt *et al*., 2012).

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