# Regulatory immune cells and functions in autoimmunity and transplantation immunology

review article

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**Abstract**

In physiological circumstances, various tolerogenic mechanisms support the protection of self-structures during immune responses. However, quantitative and/or qualitative changes in regulatory immune cells and mediators can evoke auto-reactive immune responses, and upon susceptible genetic background, along with the presence of other concomitant etiological factors, autoimmune disease may develop. In transplant immunology, tolerogenic mechanisms are also critical, since the balance between of alloantigen-reactive effector cells and the regulatory immune cells will ultimately determine whether a graft is accepted or rejected. Better understanding of the immunological tolerance and the potential modulations of immune regulatory processes are crucial for developing effective therapies in autoimmune diseases as well as in organ transplantation.

In this review, we focus on the novel insights regarding the impaired immune regulation and other relevant factors contributing to the development of auto-reactive and graft-reactive immune responses in autoimmune diseases and transplant rejection, respectively. We also address some promising approaches for modification of immune-regulatory processes and tolerogenic mechanisms in autoimmunity and solid organ transplantation, which may be beneficial in future therapeutic strategies.

**Keywords:** autoimmunity, regulatory cells, systemic autoimmune diseases, tolerance induction, transplant rejection

## 1. Introduction

The key role of the immune system is to effectively eliminate pathogens, at the same time leave self-structures unharmed. The protection of self-antigens encompasses several types of controlling mechanisms. In healthy immune system, various central and peripheral tolerance mechanisms exist, such as activation-induced cell death, anergy, clonal ignorance and network of peripheral regulatory cells, which play a protective role to prevent the activation of self-reactive lymphocytes. Immune suppression can be achieved by either cell-cell contact, or via soluble mediators, e.g. anti-inflammatory cytokines. More and more cell types have been shown to have regulatory capacity; besides regulatory B-cells, or regulatory dendritic cells, a key member of the family of immunoregulatory cells are regulatory T cells (Tregs). In autoimmune conditions, the alteration or even breakdown of the aforementioned immune tolerance mechanisms potentially leads to the survival and activation of autoreactive lymphocytes upon encountering the appropriate autoantigen, which may results in consequential tissue and organ damages [1]. In the pathogenesis of autoimmune diseases, various cellular and humoral immune processes have been described both in the innate and adaptive immune systems, including disturbed apoptotic processes, altered cytokine milieu and disproportional T and B cell activation, which result in exaggerated immune responses [2].

Undesirable immune activation is a crucial factor in transplant immunology, as well. Transplantation of solid organs between genetically distinct individuals, in the absence of immunosuppression, will lead to graft-reactive T cell activation upon encountering transplant-derived antigens, which results in transplant rejection [3].

Better understanding of the alterations in immunological tolerance and the potential modulations of the immune regulation are crucial for the effective therapy of autoimmune

diseases. Additionally, despite the potent immunosuppressive medications, induction of tolerance remains a major goal in transplantation, as well.

## 2. Regulatory functions of innate and adaptive immune cells

By recognizing and discriminating self and non-self structures, innate immune system is regarded as the first critical line against infections. Innate immune cells, such as macrophages or dendritic cells (DCs), present pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and nucleotide-binding domain and leucine-rich repeat containing molecules (NLRs), which recognize molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as pathogen-associated molecular patterns (PAMPs) [4]. This recognition triggers a series of signaling cascades that culminate in the activation of transcriptional factors nuclear factor-κB (NF-κB), interferon regulatory factor (IRF) and activator protein-1 (AP-1), which induce a number of downstream genes encoding a broad range of inflammatory cytokines, chemokines, antimicrobial peptides, complement factors and interferons in the activated cells [5].

Dendritic cells play important roles in the initiation and modulation of adaptive immune responses. DCs, which constitute highly heterogeneous cell populations with distinct developmental origins, are generally divided into three main types in human blood. The $CD123^{+}$ BDCA-2 $(CD303)^{+}$ plasmacytoid DCs (pDCs) react to viral infections by secreting type I interferons (IFN), while the two types of $CD11c^{+}$ myeloid DCs (mDCs) consist of CD1c+ and CD141+ mDCs exert phagocytic activity and are important in antigen presentation to antigen-specific T-cells [6,7]. Activated DCs play essential roles in

determining the activation and differentiation of T-cell subsets, by expressing a numerous inflammatory cytokines, chemokines, co-stimulatory molecules and MHC molecules allowing presentation of antigens to T cells [8,9]. The maturation state of DCs is also linked to specific function. Immature DCs are highly immunogenic and promote T cell polarization toward pro-inflammatory T-helper (Th)1, Th2 and Th17 subtypes, on the contrary, immature DCs are rather tolerogenic by expressing low levels of costimulatory molecules and producing anti-inflammatory mediators [e.g. interleukin (IL)-10, transforming growth factor (TGF)-beta] [10]. DCs are seems to be also important for inducing immune tolerance toward harmless components. It is supposed that in the absence of activation, DCs promote tolerance, through either induction of Treg cells or T cell unresponsiveness [11].

Recent studies shed light on the importance of the myeloid-derived suppressor cells (MDSCs) in tolerogenic mechanisms. MDSCs are a heterogeneous group of immature myeloid cells with immunoregulatory function, characterized by an ‘‘immature” phenotype, on the basis of expression of the common myeloid marker CD11b, the expression of CD33 and the absence/low levels of HLA-DR. In steady state conditions, MDSC precursors reside primarily in the bone marrow; however, in certain pathological conditions such as infections, transplantation or malignant tumor, MDSC populations expand and can be detected in the blood and the inflammatory sites. After migrating from the bone marrow, MDSC suppress T cell functions via a number of different mechanisms involving both soluble mediators and cell-cell contact and thereby, generally prevent immune responses [12].

At the level of adaptive immune system, the network of Treg cells is primarily responsible for the maintenance of self-tolerance. Among others, the two major representatives of this system are denoted as induced Treg cells (iTreg) and $CD4^{+}CD25^{bright}FoxP3^{+}$ natural Treg cells [13,14]. The iTreg $CD4^{+}$ T cells gain their suppressor function following activation. In the regulation of peripheral T cell immune responses, several types of iTreg cells participate,

where the most widely investigated subsets are the IL-10-producing T regulatory type 1 (Tr1) cells and TGF-beta-producing Th3 cells [15,16]. Accumulating evidence suggests that the induction by commensal microbes in the gut is the major source of peripheral Treg cells, which raises the relevance of probiotic and prebiotic approaches as potential treatments for autoimmune diseases [17].

Another, recently discovered $CD4^+$ T cell type, the follicular T helper ($T_{FH}$) cells plays an important role in immune responses by mediating antigen specific naive or memory B cell activation in the B-cell follicles of secondary lymphoid organs. The interplay of $T_{FH}$ and activated B-cells is essential for the generation of extrafollicular short-lived plasma cells producing low-affinity antibodies and for germinal centre (GC) responses as well. Within GC, $T_{FH}$ cells promote the development of high-affinity memory B-cells and long-lived plasma cells by providing survival signals to centrocytes, which have undergone somatic hypermutation. Based on the critical role of $T_{FH}$ cells in B-cell activation and antibody production, their failure to maintain self-tolerance potentially leads to the development of autoreactive immune processes [18]. Factors responsible for limiting the availability and function of $T_{FH}$ cells are still not elucidated yet. However, a recently identified new subset of Treg cells, the follicular regulatory T cells ($T_{FR}$) seem to have an important role in regulating $T_{FH}$ cells and preventing the development of autoreactive B cells [19]. Regarding B cell contribution to the function of immune system, besides the well established pro-inflammatory, such as antigen-presenting and antibody-producing role of B cells, certain B cell subsets, so-called regulatory B (Breg) cells have a negative regulatory effect by producing regulatory cytokines such as interleukin (IL)-10, and interacting directly with activated T cells via cell-to-cell contact [20]. Based on the expression of various surface molecules, several populations of Bregs have been reported including B10 cells, $CD1d^{hi}CD5^+CD19^+$ B cells, $CD19^+CD24^+CD38^+$ B cells or $CD19^+CD24^+CD27^+$ B cells etc.;

however, interleukin (IL)-10-production was recognized as one of the most important characters of functional Bregs. By producing IL-10, Bregs suppress the differentiation and proliferation of IL-17-producing Th17 cells, inhibits the secretion of IFN-γ, and reduces the accumulation of natural killer (NK) cells, as well [21].

## 3. Imbalance of effector/regulatory functions and cytokine profiles in autoimmunity and systemic autoimmune diseases

When quantitative and/or qualitative changes occur in regulatory immune cells, pro-inflammatory immune responses can be evoked, and upon susceptible genetic background, along with the presence of other concomitant etiological factors, autoimmune processes can occur, and eventually various autoimmune diseases may develop. In systemic autoimmune diseases, a selective decrease in the number and/or reduced suppressor function of Tregs have been described [22-27]. In a forerunner medical condition for systemic autoimmune diseases, denoted as undifferentiated connective tissue disease (UCTD), the percentage and absolute number of $CD4^{+}CD25^{bright}FoxP3^{+}$ Treg cells were reduced, while the number of inducible Tregs ($CD4^{+}IL\text{-}10^{+}$) was increased in UCTD patients compared with healthy subjects [28]. This progressive divergent shift in natural and induced Tregs clearly predicted the transition from the UCTD, introductory phase to a well-established systemic autoimmune disease [28]. These findings underline the possibility that years before the development of a full-blown autoimmune disease, derailed immune-regulatory processes take place and drive the pathology forward. In line with this notion, in the active phase of systemic autoimmune diseases, the ratios of natural Tregs was found to be decreased compared to patients with

inactive disease [22,24,29]. In autoimmune conditions, the other major regulatory T cell subset, the IL-10 producing Tr1 has been found to differ quantitatively and qualitatively from that of healthy individuals and therefore have an important role in the development of various autoimmune diseases [30]. The IL-10 cytokine besides other functions can suppress the IFN-γ production of Th1 cells as well as having other important regulatory roles in differentiation of various lymphocyte subsets [31,32]. A significant increase in the number of IL-10 producing Tr1 cells has been described in UCTD and further increase was depicted in patients who progressed into definitive systemic autoimmune diseases. We assume that this phenomenon represents a compensatory mechanism in order to counter-regulate the effects of the observed IFN-γ overproduction [28].

In certain, pro-inflammatory conditions, T-cells have the ability to differentiate into Th17 cells, and this process is independent of Th1 or Th2 cell development [33]. Th17 polarization requires the presence of IL-1β, IL-6, IL-21, and IL-23, which cytokines induce the activation of the transcription factor signal transducer and activator of transcription 3 (STAT3). Generally, Th17 cells have a major function in combat against pathogens, they recruit neutrophils and macrophages to the site of inflammation, they are crucial in the initiation of inflammation, mostly against extracellular pathogens [34]. However, the persistent secretion of IL-17 promotes chronic inflammation and can contribute to the pathogenesis of inflammatory and autoimmune diseases. Increased proportion of Th17 cells and level of secreted IL-17 have been associated with numerous inflammatory conditions, and autoimmune diseases, such as SLE [35], Sjögren's syndrome [36] and systemic sclerosis [37]. As we pinpointed previously, the imbalance of pro- and anti-inflammatory mechanisms, indicated by amongst others, Th17 and Treg numbers, or biased cellular functions may initiate and perpetuate autoimmune diseases. Circulating and local skewed cytokine milieu alters the suppressive function of Treg cells. In affected organs of patients with autoimmune diseases

increased IL-6 and transforming growth factor (TGF)-β expression has been described which favor the development of Th17 cells. Moreover, increased concentrations of tumor necrosis factor (TNF)-α, which is characteristic to numerous autoimmune diseases, down-modulates the function of Tregs, further contributing to the disequilibrium between the pro- and anti-inflammatory processes [38].

*3.1. Primary Sjögren's syndrome (SS)*

Primary Sjögren's syndrome (pSS) is a common, chronic, slowly progressive systemic autoimmune disease that predominantly affects the middle-aged women. Histologically, pSS is characterized by mononuclear infiltration and destruction of the exocrine glands, clinically resulting in dry mouth, keratoconjunctivitis sicca and the presence of various exocrinopathic symptoms [39]. In the pathogenesis, different subsets of immune-competent cells, e.g. lymphocyte subsets, dendritic cells and monocytes play a pivotal role. Similarly to other systemic autoimmune diseases, increased cell activation, disproportional programmed cell death, in parallel with faulty autoantigen scavenging are important in the pathogenesis, which processes are partly driven by a skewed cytokine milieu [40,41]. A group of circulating pro-inflammatory cytokines, chemokines and growth factors has been implicated in the pathogenesis of pSS, contributing to the initiation and perpetuation of the cellular and humoral autoimmune processes. In patients with pSS, the following circulating mediators were reported to be increased compared to healthy subjects: IL-1β, IL-2, IL-6, IL-15, IFN-γ and chemokine (C-C motif) ligand 4 (CCL4 or MIP-1β) [42]. The skewed T-cell subsets and circulating cytokine imbalance seem to play important roles in an orchestrated proinflammatory cascade in pSS. Diminished suppressor activity of $CD4^{+}CD25^{bright}$ Treg cells, along with elevated circulating TNF-alpha and IL-6, and reduced IL-10 has also been demonstrated in pSS giving raise to the development of autoimmune processes [25].

Moreover, circulating cytokines have the ability to distinguish/drive pSS patients with ectopic salivary gland germinal centers, a possible forerunner of lymphoma development in the disease [43,44]. Our study on pSS patients with ectopic germinal center formation identified a group of biomarkers which could distinguish from healthy individuals, namely IL-4, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-α, CCL3 (MIP-1α), CCL11 (Eotaxin) and B-cell activating factor (BAFF/BLyS), while germinal center positive and negative pSS patients differed in CCL2 (MCP-1) expression. Interestingly, based on multivariate statistical analyses, the biomarker with the strongest discriminatory power amongst SS patients with, or without ectopic salivary gland germinal centers were CCL11 (Eotaxin), IFN-γ, as well as BAFF/BLyS [42]. Taken these findings together, a group of mediators (e.g. cytokines and chemokines) has the ability to create a pro-inflammatory milieu in pSS patients, presumably contributing to a derailed Th17/Treg balance, as well.

Humoral autoimmune responses, B cell activation and autoantibody production are also important immune abnormalities in pSS. Recent investigations shed light on altered $T_{FH}$ profiles in pSS, suggesting the important role of $T_{FH}$ cells and IL-21 cytokine secretion in autoreactive B cell activation and autoantibody production [45]. Additionally, in labial salivary gland biopsies of pSS patients, $T_{FH}$ cell markers, such as CD84, programmed cell death protein 1 (PD-1) and Bcl-6 were detected in the lymphocytic infiltrations, especially, in more organized lymphoid structures [46]. A recent study suggest that enhanced IL-21 receptor expression of $CD19^{+}CD5^{+}$ B cells and enhanced production of IL-21 by $T_{FH}$ and iNKT cells may play an important role in the pathogenesis of pSS by regulating $C19^{+}CD5^{+}$ B cell functions and increasing granzyme B production, presumably leading to a counter-regulatory effect in the disease [47].

### *3.2. Systemic Lupus Erythematosus (SLE)*

SLE is one of the most well-known systemic autoimmune diseases, mostly affecting younger females, characterized by various organ involvements, encompassing mild to moderate forms, and also severe, progressive variants [48]. A number of cytokines have been implicated in the pathogenesis of the disease, including BAFF/BLyS, TNF-α, IFN- α, IFN-γ, IL-12, IL-23, IL-18, IL-6, IL-10 and IL-17 [49,50].

The backbone of inflammation in SLE is denoted as interferon-signature. The assessment of the key role of this in lupus, led to the discovery of interferon regulatory factor-5 (*IRF5),* which has been shown to be linked to the increased production of IFN-α, and *STAT4*. This unique gene expression profile seemed to be responsible for increased sensitivity to IFN- α [51-53]. The disease course of SLE is characterized relapses and remissions in many cases. Patients with disease flare had significant alterations in a wide variety of soluble mediators at baseline with significantly higher levels of pro-inflammatory mediators, -similarly to other systemic autoimmune diseases- including Th1, Th2, and Th17-type cytokines, several weeks before clinical flare compared to clinically stable patients [54]. On the other hand, regulatory cytokines, including IL-10 and TGF-β were higher in non-flare SLE patients [54]. Furthermore, peripheral Treg cell number and function have been shown impaired in SLE [55,56], along with increased peripheral Th17 cells ratios and serum IL-17 concentrations, especially in patients with active disease [57,58]. The Th17 and Treg ratio indicates that SLE is associated with a reduction in the levels and function of immunosuppressive Treg cells together with an increase in the pro-inflammatory Th17 cells [59].

It is well established in lupus that the imbalance of different subsets of B cells is also crucial for the initiation and perpetuation of the disease. Elevated percentages of circulating $CD4^+CXCR5^+ICOS^+PD\text{-}1^+$ $T_{FH}$ cells were reported in SLE patients. Notably, these cell proportions showed associations with autoantibody titres and the altered ratios of B cell subpopulations [60].

*3.3. Systemic sclerosis*

Systemic sclerosis (SSc) is a systemic autoimmune disease with excessive extracellular matrix deposition and damage of small blood vessels. The autoinflammatory processes lead to the damage of the skin, as well as various visceral organs, such as the heart, lungs, or kidneys [61]. The three main processes can be distinguished in disease development: endothelial damage and dysfunction, pathological immune activation and fibrosis of the affected tissues. The immuno-regulatory abnormalities are in the focus of intense research in SSc. Disorders of the immune system lead to chronic inflammatory processes, abnormal T cell activation, B cell abnormalities, pathogenic autoantibody production and the release of pro-inflammatory cytokines, as well as pro-fibrotic mediator.

Altered balance of Th1 and Th2 cytokines may contribute to the development of fibrosis. In Th2 predominance, plasma level of IL-4 increases, which induces the TGF-β production leading to fibroblast proliferation and accelerated collagen synthesis [62].

The Th17 cells are major contributors to autoimmune processes, and former studies have demonstrated that SSc patients have increased peripheral Th17 cell percentages along with elevated circulating IL-17 levels. Th17 cells also induce TGF-β synthesis and fibroblast proliferation, which underline the potential involvement of Th17 cells in the pathogenesis of SSc [63,64].

Additionally, Tregs with impaired function have been shown to play a role in the initiation and perpetuation of the disease. We have previously described increased Th17/Treg ratio and the altered regulatory function of Treg cells which play a pivotal role in the development and progression of SSc [37,65,66]. Taken together, SSc patients are characterized by higher percentages of activated T cells, and a shift has been shown between the effector and

regulatory T cells. Increased Th17 cell percentages, together with decreased levels of Th1, and altered regulatory T cell subsets are also characteristic to SSc [37].

### *3.4. Mixed Connective Tissue Disease*

Clinically, mixed connective tissue disease (MCTD) is diagnosed based on a group of symptoms, such as arthritis, Raynaud's phenomenon, myositis, esophageal dysmotility, and acrosclerosis along with the presence of autoantibodies reactive with U1 small nuclear RNP (U1RNP) autoantigens [67]. Serum concentrations of both Th1 and Th2 cytokines were significantly elevated in MCTD. Furthermore, the percentage of IL-10-producing $CD4^+$ and $CD8^+$ T cells was higher in patients than in controls, and $CD4^+$ and $CD8^+$ T cells from patients with active MCTD produced significantly more IL-10 than cells in patients with inactive disease or in healthy individuals [68]. MCTD is characterized by various T cell abnormalities, which becomes explicit in the active phase of the disease. Formerly, it was demonstrated that the ratios of peripheral natural Treg cells in patients with MCTD were decreased, especially in patients with active disease. On the other hand, an increase in inducible, IL-10-secreting CD4+IL-10+ Tr1 cells was reported in the disease. The Tr1 cells ratio further increased in patients with active disease. Tr1 cell percentages could represent a compensatory mechanism between type 1 and type 2 cytokine-level harmonization in MCTD [22]. Serum levels of IFN-$\gamma$ and TNF-$\alpha$ were increased along with reduced number of Tregs. The decreased levels of regulatory T cells, along with the increased expression of pro-inflammatory cytokines may tip the fine balance towards autoimmunity in a subset of MCTD patients [69]. Serum and intracellular cytokine assessment, cellular immune-regulatory functional tests are valuable to estimate disease activity in MCTD, as well as may help in sub-categorizing these patients [70].

Taken these findings together, in all these various patient groups with autoimmune conditions, we could identify a circulating cytokine imbalance, a pro-inflammatory milieu, and the development of Th17 cells along with the reduction in numbers/function of various regulatory cell types. The simultaneous, opposing effect of Th17 cells and Tregs has a strong impact on immune homeostasis, deciding and controlling the development of autoimmunity in these patients.

## 4. Regulatory cells in transplant immunology

One of the major goals in organ transplantation is to achieve indefinite allograft survival without the need for life-long immunosuppression. Over last 10-12 years, it has become clear that the balance between of alloantigen-reactive effector cells and the regulatory immune cells will ultimately determine whether a graft is accepted or rejected [71]. The potential use of different regulatory cells as cellular therapies to support long-term graft function is also emerging. Thus, understanding the characteristics of these regulatory populations is paramount.

Following transplantation, both innate and adoptive arms of the immune response are triggered. Surgical stress and ischemia/reperfusion injury (IRI) create an inflammatory environment in the graft which affects cells of both donor and recipient origin. Recipient cells migrate into the graft, and are activated by the locally produced pro-inflammatory cytokines. Donor-derived, resident DCs and macrophages are also attracted to the site of inflammation which leads to the development regulatory properties in these cells. These cells migrate to the draining lymphoid tissue, where they initiate T cell activation [72]. Activated T cells return to the allograft, and donor alloantigens presented by donor-derived or recipient antigen presenting cells (APCs) could promote the expansion and generation of Treg and/or

regulatory B cell populations. The number and power of regulatory immune cells, including those that pre-existed in the recipient or were generated during the course of the response, are not sufficient in the early stage of the allo-response to counteract the effect of various of leukocytes attacking the graft in the absence of immunosuppressive therapy.

Long-term allograft survival without continuous drug-based immunosuppression called operational transplantation tolerance has been evidenced by both experimental and clinical data [73,74]. Various leukocyte sets have been associated with regulatory functions including macrophages, MDSCs, DCs and mesenchymal stromal cells (MSCs), as well as different subsets of T and B cells. They origin, development, phenotype and function has been studied extensively.

*4.1. Regulatory macrophages*

Macrophages are essential component of innate immunity and migrate into inflamed tissues in response to injury. Depending on the microenvironment, macrophages can mount specific functional activities. Classical proinflammatory M1 macrophages are characterized by high levels of proinflammatory cytokines and by promotion of a Th1 response. In contrast, alternatively activated M2 macrophages are thought to be involved in the resolution of tissue inflammation apart from having immunoregulatory functions. Regulatory macrophages (Mreg) are an additional, uniquely characterized group of cells expressing a profile of distinct group of cellular markers, and are able to decrease pro-inflammatory immune responses [75]. Regulatory macrophages produce IL-10 but do not express arginase 1. Mouse Mreg have been shown to inhibit T cell activity in vitro via inducible nitric oxide synthase (iNOS) and delete co-cultured allogeneic T cells via phagocytosis [76]. Human Mreg are suppressive of T cell proliferation via IFN-γ induced indoleamine 2,3-dioxygenase (IDO) activity and contact-dependent deletion of activated T cells [77].

*4.2. Dendritic cells*

DCs are essential for priming antigen-specific T cell responses to alloantigens, but they may also promote tolerogenic responses. It appears that both myeloid (mDCs) and plasmocytoid DCs are able to promote tolerance to alloantigens but DCs' main function is to prime the immune system. Injection of immature DCs harvested from the donor-extends the survival of various allografts when given prior to transplantation [78-80]. In a different model, pDCs were shown to acquire alloantigens while in the allograft, and induced the generation of Treg cells after migrating to the draining lymphoid tissue [81].

pDCs may contribute to immune regulation in liver transplant recipients suggested by higher ratios of pDCs to mDCs found in those with no or decreased immunosuppression. Phenotypic changes, including increased expression of PD-1 ligand and CD86, on pDCs correlated with elevated numbers of $CD4^{+}CD25^{hi}FOXP3^{+}$ Treg cells in liver transplant free from immunosuppressive treatment [82,83].

*4.3. Myeloid-derived suppressor cells*

Myeloid-derived suppressor cells are a heterogeneous population of bone marrow-derived myeloid progenitors. In different pathological conditions such as malignant tumors, infections, transplanted organs and autoimmune diseases, MDSC populations expand and can be detected in the blood, peripheral lymphoid tissues, the spleen, cancerous tissues and inflammatory sites including different grafted organs.

In transplantation, MDSCs have been shown to promote tolerance to alloantigens, as there is direct evidence of a tolerogenic role for MDSCs in heart and islet allografts in mice [84,85], and for inducible nitric oxide synthase (iNOS)-expressing MDSCs in a rat kidney allograft model. Injection of Lacto-N-fucopentaose III activated m-MDSCs results in prolonged graft

survival [86]. The mechanisms used by MDSCs to promote tolerance to alloantigens require further clarification. Some evidence suggests that they may act partly through the induction or sparing of Treg cells. Recent studies in human kidney transplant recipients demonstrated that $CD11b^{+}CD33^{+}HLA\text{-}DR^{-}$ MDSCs were capable of expanding Treg in vitro and their accumulation after transplantation correlated with an increase in Treg in vivo [87]. MDSCs-dependent expansion of Treg was suggested to be mediated by the production of soluble factors such as TGF-β and IL-10.

*4.4. Mesenchymal stromal cells*

Bone marrow-derived MSCs have the ability to move to sites of inflammation, and can also migrate to transplanted organ. The effects of MSCs on the adaptive immune response are closely connected to the effects on the innate arm as myeloid cells are probably the first cells to be affected. MSCs exert their effects on a large spectrum of, including T cells, B cells, natural killer cells, monocytes/macrophages, dendritic cells and neutrophils [88,89]. They hinder the differentiation of dendritic cells, and inhibit their maturation into fully functional antigen-presenting cells [90]. They arrest activated T cells in the G0/G1 phase and decrease their production of IFN-γ and IL-2. MSDs downregulate cytotoxic T lymphocyte-mediated cytotoxicity, and can press $CD4^{+}$ T cells into regulatory phenotype and function. Additionally, MSCs alter the proliferation, cytotoxicity, and IFN-γ production of natural killer cells, and γδ T cells [91,92].

When MSCs are exposed to the graft's inflammatory microenvironment, they display unique immunomodulatory features. On one hand, MSCs inhibit effector T-cell responses but promote the emergence and expansion of regulatory T cells. MSC infusion in experimental models of solid organ transplantation results in Treg-mediated tolerance. MSC synergistic effect with low-dose or transient pharmacological immunosuppression in inducing long-term

graft survival has also been observed. MSCs have been shown to promote the generation of Treg cells both in vitro and in vivo through mechanisms involving prostaglandin E2, TGFβ and cell–cell contact [93,84]. In addition, MSCs may promote the acceptance of allogeneic islets by secreting matrix metalloproteinases, and suppression of graft rejection by inhibiting alloantibody production has also been reported [85,94].

### *4.5. $CD4^+$ regulatory T cells*

The naturally arising, thymus-derived Treg cells primarily suppress responses to selfantigens, but are also able to react to donor alloantigens via cross-reactivity. These cells initially inhibit T cell activation and the development of the effector-type adaptive immune response in the draining lymphoid tissue [95]. Induced Treg cells are generated in response to donor-derived alloantigen. As the allograft provides Treg cells with continuous exposure to graft-derived antigens, induced Treg cells may be more important promoting graft acceptance [96,97].

### *4.6. $CD8^+$ regulatory T cells*

$CD8^+$ regulatory T cells have various phenotypes, including $CD8^+CD28^-$, $CD8^+CD103^+$, $CD8^+FoxP3^+$ and $CD8^+CD122^+$ subsets. Through the secretion several immunosuppressive cytokines including IL-4, IL-10 and TGF-β, and by direct killing of target cells via Fas L/Fas and the perforin/granzyme B pathways, they exhibit suppressive function in both allo- and autoimmune animal models. $CD8^+CD28^-$ $FoxP3^+$ Treg suppress alloimmune responses by inducing immunoglobulin-like transcript (ILT) $3^+$/$ILT4^+$ tolerogenic endothelial cells, and by down-regulating the expression of costimulatory and adhesion molecules [98-101]. Transfer of $CD8^+CD28^-$ Treg from tolerized liver transplant recipients improved acute allograft rejection in rats [102].

The presence of circulating $CD8^+CD28^-$ Treg was associated with good graft in patients receiving liver-intestine grafts even with reduced or absent immunosuppression [103]. In adult liver transplant patients, expansion of $CD8^+CD28^-$ Treg population correlated with lower occurrence of acute or chronic rejection [104]. $CD8^+CD28^-$ cells have been identified in renal transplant recipients treated with the anti-CD52 monoclonal antibody alemtuzumab [105]. These observations demonstrate that $CD8^+CD28^-$ cells are primary effectors of transplant tolerance, and they target the endothelium and APC to induce a tolerogenic phenotype and inhibit $CD4^+$ T helper cell alloreactivity.

New observations imply that another $CD8^+$ subset, the $CD8^+CD122^+$ Treg, may also have a role in suppressing alloimmunity. $CD8^+CD122^+$ cells suppressed murine allograft rejection even more effectively than their $CD4^+CD25^+$ counterparts [106,107].

### *4.7. γδ T cells*

The γδ T cells are innate-type T cells which may also have a regulatory role in transplant patients as an altered distribution of Vδ1- and Vδ2-expressing γδ T cell subsets has been reported in operationally tolerant liver transplant recipients compared with non-transplant control [108,109]. Additional extended studies in large populations of allograft recipients suggest that alterations in the γδ T cell compartment are not limited to tolerant liver recipients. An increased γδ T cell pool was detected in the peripheral blood of most immunosuppressed liver and kidney recipients. The increase was mainly a result of the expansion of Vδ1 T cells. The specific functional role of γδ T has yet to be described, as persistent viral infections are also likely to contribute to these alterations [110].

### *4.8. $T_{FH}$ cells*

In the last ten years, several article indicated the activated B cell involvement in allograft rejection, therefore antibody-mediated rejection (AMR) has increasingly been recognized as a cause of graft damage, dysfunction and loss. The definition of AMR continues to evolve with the latest Banff classification adding criteria to include AMR without immunohistochemical evidence of C4d deposition [111]. The requirements include evidence of tissue injury, antibody interaction with vascular endothelium and the presence of donor-specific antibody. The significance of $T_{FH}$ cells in transplantation has not been fully elucidated yet. B-cell production of high-affinity alloantibody requires T cell help via the indirect pathway of allorecognition. T-cell help must be provided by the interaction between T-cell receptors and class II MHC-peptide complexes on recipient B cells (indirect allorecognition), as opposed to the direct pathway involving direct recognition of donor MHC on donor-derived antigen presenting cells by recipient T cells [112]. Number of studies on circulating $T_{FH}$ in human transplantation is limited. Graav et al [113] demonstrated that circulating $T_{FH}$ cells in human transplantation are reduced immediately post transplant and at 3 months. Patients with preexisting donor-specific antibodies had higher numbers of circulating $T_{FH}$ cells at 3 months compared with those without. These circulating $T_{FH}$ cells in transplant patients was able to induce B cell proliferation and immunoglobulin production in an IL-21-dependent manner. Although $T_{FH}$ cells presumably play a central role in the generation of high affinity alloantibody, and the consequential develpoment of AMR, the relative contributions of the various populations of $T_{FH}$ cells in lymph nodes, circulation and allograft require further investigation.

*4.9. Regulatory B cells*

The role of B cells in transplantation is beginning to emerge in both animal models and humans. Allogenic donor B cells administrated in combination with anti-CD40L permit the

survival of islet as well as murine cardiac allografts [114,115]. Targeting CD45 via anti-CD45-RB after transplantation prevents cardiac allograft rejection. This requires host B cells and interaction of co-stimulatory molecules on B cells and T cells as tolerance could not be induced in transgenic mice lacking B cells and antibodies but and can be achieved with B-cell transfer [116-118]. Neutralization of IL-10 enhances tolerance induction and improves the long-term outcomes of cardiac allograft, and Il-10 expression by B-lymphocytes inhibits B-cell-mediated tolerance induction. Murine studies established a role for T cell immunoglobulin and mucin domain-containing protein 1 (TIMD1) on B cells as its ligation promotes population B cells expansion and regulatory activity [119]. Combined effects of anti-CD45-RB and anti-TIM-1 antibodies have also been investigated in a mouse islet allograft model. This model is dependent on the production of IL-10 by B cells since transfer of IL-10 deficient B cells does not prolong allograft survival. The importance of interactions between TIM-1+ regulatory B-cell/Treg was demonstrated by the observation that depletion of Treg prior transplantation results in rejection [120]. Other studies have shown that IgM+ B cells, but not IgG+ B cells, form clusters within kidney allografts in tolerant rats, and this finding has been interpreted as indicating the presence of B cells with regulatory activity [121].

In humans, most results are from patients with operational tolerance. A specific B cell gene signature in blood of patients that spontaneously developed operational tolerance to kidney transplant after immuno-suppressive treatment withdrawal has been identified by several groups: higher mRNA expression of immunoglobulin light chains, CD20 as well as proliferation and cell cycle genes [122,123]. The mechanism of this suppression mediated by B cells is not fully understood but TGF could play a function as some of modulated genes are target of TGF [124]. Consistent with a regulatory function for B cells in human transplantation, a clinical trial has shown increased risk for acute cellular rejection following

depletion of B cells prior to transplantation. This could be due to a loss of regulatory B cells [125].

## 5. New therapeutic approaches to modulation regulatory cells in autoimmune diseases and transplantation

Cell-based therapies have been studied extensively for their capacity to induce tolerance. Mesenchymal stem cells, regulatory myeloid cells, T regulatory cells, and other cell types are being tested for tolerance induction. Early results with these cell types have been promising, regimens resulting in consistent tolerance, however, have yet to be established.

Regarding Treg cell-based therapies, one of the major challenges in developing is to consistently obtain sufficient numbers of cells for adoptive transfer, since only approximately 1% of peripheral blood mononuclear cells are Treg cells. Various kinds of Treg cell expansion methods have been explored. It was recently revealed that 3500-fold is achievable after 14 days culture in the presence of high amounts of IL-2, T cell expander beads at a ratio of four beads per cell and 100 nm rapamycin. These expanded human Treg cells expressed higher level of Foxp3 than fresh Treg, and had enhanced regulatory ability [126]. However, one of the major hurdles to be overcome is to expand antigen-specific Treg cells, in order to avoid a generalised immunosuppression. The current technology does not easily permit the identification of disease-associated self-antigen specific Treg cells [127]. Additionally, the studies on the effectiveness of $CD4^{+}CD25^{+}$ Treg transplant in the treatment of autoimmune diseases have been mainly evaluated in animal trials only. Nevertheless, the in vitro expansion of Treg cells from autoimmune patients reversed the Treg cell functional defect

[127]. Thus, Treg cell therapy might be a rational approach for the treatment, and investigators are currently attempting to expand its use in autoimmune diseases [128].

Regrading solid organ transplantation, Tregs have been shown to have therapeutic effects, albeit, may not have sufficient potency as a stand-alone therapy [129-132]. They can be expanded *ex vivo* and administered exogenously, or transplanted as part of a tolerated graft. There are several clinical trials utilizing the infusion of *ex vivo* generated Treg, including renal and liver transplant patients. Factors critical to the efficacy of Treg therapy in transplantation are dose, specificity, and adjunct immunosuppression. The future of Treg therapy depends on effective clinical trial designs, advancement in Treg manufacture, and further understanding of Treg biology as well as transplantation tolerance in clinical setting.

Current experimental data place $T_{FH}$ cells in a central role in the formation of high affinity alloantibody resulting in the development of AMR. Further study should clarify attributes of the $T_{FH}$ cell subsets and also identify increasingly precise targets for therapy that may interrupt their function.

Therapeutic approaches targeting DCs for treatment of autoimmune diseases are aimed at either diminishing their immunogenic potential or enhancing their tolerogeneic features. DCs with tolerogenic properties (tolDCs) and loaded with autoantigens may potentially restore self-tolerance by modulating not only Treg subsets but by inducing antigen-specific anergy and hyporesponsiveness of T cells and promoting the generation of Breg cell, as well. [133,134]. In humans, plasmacytoid DCs seem to play a role in the differentation of immature B cells into Bregs [135]. Furthermore, it was reported that tolDCs induce a significant increase in Breg number by the expansion of the already existing Breg population and the conversion of $CD19^+$ B cells into IL-10-producing Bregs [136]. Numerous procedures have been described to obtain tolDCs from monocytes ex vivo, and accumulating evidence from the experimental use of tolDCs in autoimmune diseases such as rheumatoid arthritis (RA),

type 1 diabetes (T1D), atherosclerosis and multiple sclerosis supports the therapeutic potential of tolerogeneic DCs. However, the use of ex vivo-generated tolerogeneic DCs in the treatment of SLE has not yet been reported [10,137]. Currently, there are only a limited number of clinical trials using tolDCs in autoimmune diseases. Intradermally administration of autologous monocyte-derived tolDCs led to increased Breg cell proportions in T1D patients and increased Treg/T effector ratios in RA patients, without any side effects [138,139].

Treatment with MSCs has been tested in many autoimmune diseases, including refractory SLE, systemic sclerosis, Crohn's disease, type I diabetes and collagen-induced arthritis [140]. Recently, Sun et al. reported over 30 patients with refractory SLE who received culture-expanded MScs grafts. These patients demonstrated a rapid amelioration of fatigue, proteinuria, ascites and arthralgias. Clinical data showed that the Disease Activity Index (SLEDAI) was significantly improved after treatment with umbilical cord (UC)–derived mesenchymal stem cells (MSCs) [141].

MSCs_are a promising candidate for cell-based therapies in kidney transplantation, as well. [142,143]. Their efficacy depends on the relative amounts of proinflammatory and anti-inflammatory cytokines. Relevant biomarkers are needed to monitor the inflammatory status of patient to optimize treatment. This may include proportion of regulatory T cells, T-cell polarization balance as well as plasma levels of inflammatory cytokines and chemokines. Quantification of indoleamine 2,3 dioxygenase activity in plasma can also be helpful.

MDSCs were shown, in a rat kidney transplant model, to induce tolerance via anti-CD28 and to accumulate within the allograft [144]. Prolonged survival of islet cell allograft, co-transplanted with MDSC, has also been demonstrated [145]. In humans, MDSCs have been found upregulated after transplantation [146]. Nonetheless, utilization of MDSC as cellular therapy in human transplantation remains hampered do to our still incomplete understanding

of their phenotype, differentiation, functions, and interactions with the inflammatory microenvironment.

Regulatory macrophages (Mreg) offer are an appealing possibility for cellular therapy to obtain tolerance induction in human recipients. In an early trial, the cells were generated by culturing donor splenic mononuclear cells in macrophage colony-stimulating factor with stimulation with IFN-γ. No acute or late adverse reactions were reported when cells were infused (M-CSF) into kidney recipients receiving grafts from deceased donors [147]. Several trials have shown that living-related kidney transplant recipients can be treated preoperatively with Mreg, generated by culturing donor peripheral blood mononuclear cells (PBMCs) in M-CSF with IFN-γ, followed by co-culturing with recipient PBMC. Outcomes were different, but some patients were stable for extended periods of time with minimal immunosuppression [148,149]. Ongoing trials are further evaluating the safety and efficacy of cellular therapies, including Mreg, in achieving tolerance in transplant recipients [150].

## 6. Conclusions

The immune system is normally well balanced to cope with invading pathogens and to tolerate non-dangerous stimuli. The intricate interplay of various proinflammatory cytokines and chemokines, orchestrated by key regulators of the immune system, can lead to the imbalance between regulatory and proinflammatory cells. The breakdown in immune tolerance results in the activation of auto-reactive T and B cells, and with a susceptible genetic background, this can lead to the development of a fullblown autoimmune disease. The concept of utilizing cells that regulate the development of autoimmunity has led to the identification of cell-based therapies for the treatment of autoimmune diseases. Investigations

on transplant immunlogy revealed that these approaches to modulate tolerogenic immune cells could be also beneficial to avoid transplant rejection. Since data are still limited, more trials are needed to establish the proper drug dosages, the number of administered cells and the treatment intervals. We believe that this approach will aid in the diagnosis and therapy design in autoimmune diseases and organ transplantation and will provide an advanced disease management in the near future.

**Take-home messages**

- Better understanding of the alterations in immunological tolerance is crucial for the effective therapy of autoimmune diseases.
- Despite the potent immunosuppressive medications, induction of tolerance remains a major goal in solid organ transplantation as well.
- Novel results on the modification of immune-regulatory processes and tolerogenic mechanisms may open new avenues in the treatment of autoimmune diseases as well as transplant rejection.

**Conflict of Interest**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that there is no conflict of interests regarding the publication of this paper.

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