

The homeostasis and heterogeneity of regulatory T cells in sepsis

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Abstract

Sepsis poses a critical threat to global health, mainly due to the disruption of immune homeostasis, which critically influences both early death and long-term adverse outcomes. Current evidence shows that regulatory T (Treg) cells—key mediators of adaptive immunity—play an essential role in maintaining immunological balance during sepsis progression. During the initial hyperinflammatory phase, Treg cells actively suppress excessive inflammation, reducing tissue damage. Paradoxically, in the subsequent immunosuppressive phase, expanded Treg populations may exacerbate immunosuppression by inhibiting effector cell function, ultimately leading to poorer clinical outcomes. Recent research has identified novel Treg-specific biomarkers in sepsis and explained how the septic environment affects Treg cell numbers and function through various signaling pathways. This review combines current understanding of the phenotypic features and roles of Treg cells in sepsis, examines the regulatory mechanisms controlling Treg dynamics within the inflammatory setting, and explores therapeutic strategies targeting Treg cells across different immune phases, emphasizing both existing challenges and future directions.

Keywords: Sepsis; regulatory T cell; Checkpoint; Immunotherapy

Highlights

- Treg cells exert dual-phase immunomodulatory functions in sepsis pathogenesis, critically suppressing excessive inflammation during the initial hyperinflammatory phase yet potentiating immunosuppression in the subsequent immunosuppressive phase.
- The mechanisms in which the septic inflammatory environment modulates the number and functions of Treg cells are elucidated.
- A summary of previous studies on the changes in Treg cells in sepsis and their relationship with patient prognosis through indicative markers is provided.
- Adopting differentiated targeted Treg intervention strategies based on the immune status of sepsis has potential clinical prospects, and recent advancements are briefly introduced.
- Despite promising preclinical advances in Treg biology, translating these findings into effective therapeutic approaches remains hindered by persistent challenges.

Background

Sepsis represents a critical syndrome of life-threatening organ dysfunction triggered by a dysregulated host reaction to severe infection. This condition exhibits marked pathophysiological complexity and clinical heterogeneity [1]. It contributes substantially to critical care morbidity and mortality, particularly within intensive care units (ICUs) [2]. Current evidence indicates that sepsis manifests as a complex and heterogeneous condition characterized by both pro-inflammatory and anti-inflammatory responses. Once sepsis occurs, the immune system is typically over-activated. Host pattern recognition receptors (PRRs) detect pathogen-associated molecular patterns (PAMPs) from invading microorganisms and damage-associated molecular patterns (DAMPs) released from injured tissues, leading to the release of a large number of inflammatory cytokines. These cytokines induce widespread endothelial damage, coagulation cascade activation, and microvascular thrombosis, ultimately leading to multiorgan dysfunction [3]. Successful pathogen clearance during the early phase enables

rapid immune homeostasis restoration. Conversely, persistent pathogen exposure drives immune network decompensation, shifting the system toward dominant immunosuppression [4]. The disordered immune system expresses a state of suppression, characterized by increased immune tolerance and an increased number and enhanced function of immunosuppressive cells [4, 5]. Epidemiological analyses indicate that 60%–70% of sepsis-related mortality occurs during the late phase, with ICU-acquired secondary infections constituting the predominant cause of death [6, 7]. Persistent immune suppression remains a critical determinant of poor long-term outcomes in sepsis survivors [8].

Treg cells are a specialized CD4⁺ T-lymphocyte subset essential for immune homeostasis by suppressing excessive immune responses, maintaining immune tolerance, and preventing autoimmune reactions [9]. During sepsis, these cells exhibit phase-dependent immunomodulatory functions: exerting protective effects in the initial hyperinflammatory phase while driving detrimental immunosuppression in

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the late phase. [6] The activation of Treg cells helps suppress excessive inflammatory responses, promote bacterial clearance, and reduce tissue damage [10]. At the same time, over-suppression by Treg cells may lead to increased immune tolerance, thereby inhibiting the function of effector T cells, weakening the body's ability to clear pathogens, and increasing the risk of secondary infections. Moreover, previous studies have shown that sepsis-induced pathological expansion and functional augmentation of Treg cells establish a permissive microenvironment for tumor immune evasion [11]. This phenomenon underscores the long-term health consequences of sepsis-mediated Treg dysregulation, which extends beyond acute infection management. Alterations in Treg frequency, distribution, and function during sepsis progression are driven by dysregulated inflammatory mediators, immunosuppressive metabolites, and interactions with other immune cells within distinct inflammatory niches. These factors modulate Treg dynamics through multiple interconnected mechanisms. Despite advances in characterizing Treg roles in sepsis, critical knowledge gaps persist regarding stage-specific regulatory mechanisms and intercellular interactions. Understanding the dynamics of Treg cells at different stages of the disease and how they interact with other immune cells is crucial for developing new therapeutic approaches.

This review delineates the immunopathological dynamics of Treg cells in sepsis and septic shock, with particular emphasis on their stage-specific functional plasticity. Concurrently, we discuss the interaction between Treg cells and other immune cell subsets. Critically, phase-targeted therapeutic interventions modulating Treg activity hold significant potential to rectify sepsis-induced immune imbalances. Optimizing sepsis treatment through precision modulation of Treg frequency and function represents a potential research frontier.

Review

Brief overview of Treg cells and its behavior in sepsis

As early as the 1970s, scientists first proposed the regulatory role of CD4⁺ T cells in immune responses, suggesting that these cells can control pro-inflammatory reactions and maintain immune homeostasis [12]. This group of cells, which exerts immune regulatory functions, was initially implicated in mediating self-tolerance, garnering significant interest from researchers. However, the absence of definitive molecular markers and functional characterization fueled substantial controversy throughout the late 1990s [13]. A critical breakthrough occurred in 1995 when Japanese immunologist Shimon Sakaguchi identified CD25 (IL-2 receptor α -chain) as a surface marker defining thymus-derived immunosuppressive cells. Sakaguchi's experiments demonstrated that T-cell suspensions lacking CD25⁺ cells could induce autoimmune diseases in mice. However, when these mice were subsequently treated with a suspension rich in CD25⁺ cells shortly after the initial infusion, the newly infused CD25⁺ cells effectively prevented the progression of early autoimmune pathology [14]. The study results also indicate that this population of CD4⁺CD25⁺ T cells with unique functions and phenotypes is primarily generated in the thymus [15]. The discovery of CD25 as a key marker, expressed in both humans and rodents, finally enabled researchers to isolate and study regulatory T cells [16, 17]. However, due to the upregulation of CD25 in

all activated T cells, its utility in isolating regulatory T cells for subsequent studies is limited. Parts of researchers at that time also suspected that this population of CD25-expressing Treg cells is merely an activated state of conventional CD4⁺ T cells, which may downregulate immune responses by competing with effector T cells for IL-2 [18]. More accurate identification and differentiation of Treg cells and subsequent studies on their function and mechanisms have been largely facilitated by research on the X-chromosome-encoded transcription factor Foxp3. Loss-of-function mutations in this gene have been identified in mice and human patients with IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome [19, 20]. Foxp3 plays a crucial role in the immune homeostasis regulation of T cells. Mutations in Foxp3 can lead to a fatal early-onset T cell-dependent lymphoproliferative immune dysregulation disease, manifesting as thyroiditis, diabetes, splenomegaly, lymphadenopathy, hemolytic anemia, exfoliative dermatitis, high IgE syndrome, and cytokine storm [21]. With further research, three studies from 2003 collectively established that the transcription factor Foxp3 uniquely defines Treg cells and is essential for their differentiation [22–24]. Shohei Hori, in collaboration with Sakaguchi, along with the laboratories of Alexander Rudensky and Fred Ramsdell, revealed in their research that the absence of Foxp3 leads to the overactivation of nonregulatory T cells, resulting in a fatal autoimmune disease. By analyzing the changes in the CD4⁺CD25⁺ T cell subsets in mixed bone marrow chimeras, thymus, and lymphoid organs following Foxp3 deficiency and wild-type bone marrow transplantation, it was found that Foxp3-deficient mice did not develop lymphoproliferative diseases or immune-mediated tissue damage. Moreover, CD25⁺ Treg cells were generated exclusively from Foxp3-sufficient precursor cells, not Foxp3-deficient precursors. These results indicate that Foxp3 is essential for differentiating Treg cells in the thymus [22]. Inhibiting Foxp3 expression experimentally alters Treg cell function, converting them into effector cells and triggering immune diseases [25]. Furthermore, the sustained expression of Foxp3 plays a crucial role in the normal suppressive function of mature Treg cells. Targeted deletion of Foxp3 in mature Treg cells leads to the loss of Treg suppressive function and characteristic cell surface markers and the acquisition of immune effector cell properties [26]. In all, Foxp3 has been widely recognized in the scientific community as a key factor in regulating the function of regulatory T cells, with Foxp3 driving the production of anti-inflammatory factors through the activation of associated genes. Over five decades of research have cemented Treg cells—defined by nuclear Foxp3 expression and surface CD25—as indispensable mediators of immune equilibrium and pathological dysregulation. Further studies have gradually revealed these cells essential roles and mechanisms in normal immune function and various disease processes [27].

Although Foxp3 serves as a prominent marker distinguishing Treg cells from other T cell subsets, transient activation of Foxp3 in nonregulatory T cells under certain conditions has raised questions about the unique definition of Treg cells [28]. This ambiguity necessitates complementary surface markers for precise identification. Researchers have identified low expression of CD127 in human peripheral blood as a novel marker for Treg cells [29]. Helios, an Ikaros transcription factor family member, is another crucial marker for identifying natural Treg cells and maintains the stability and suppressive function of Treg cells [30]. These markers

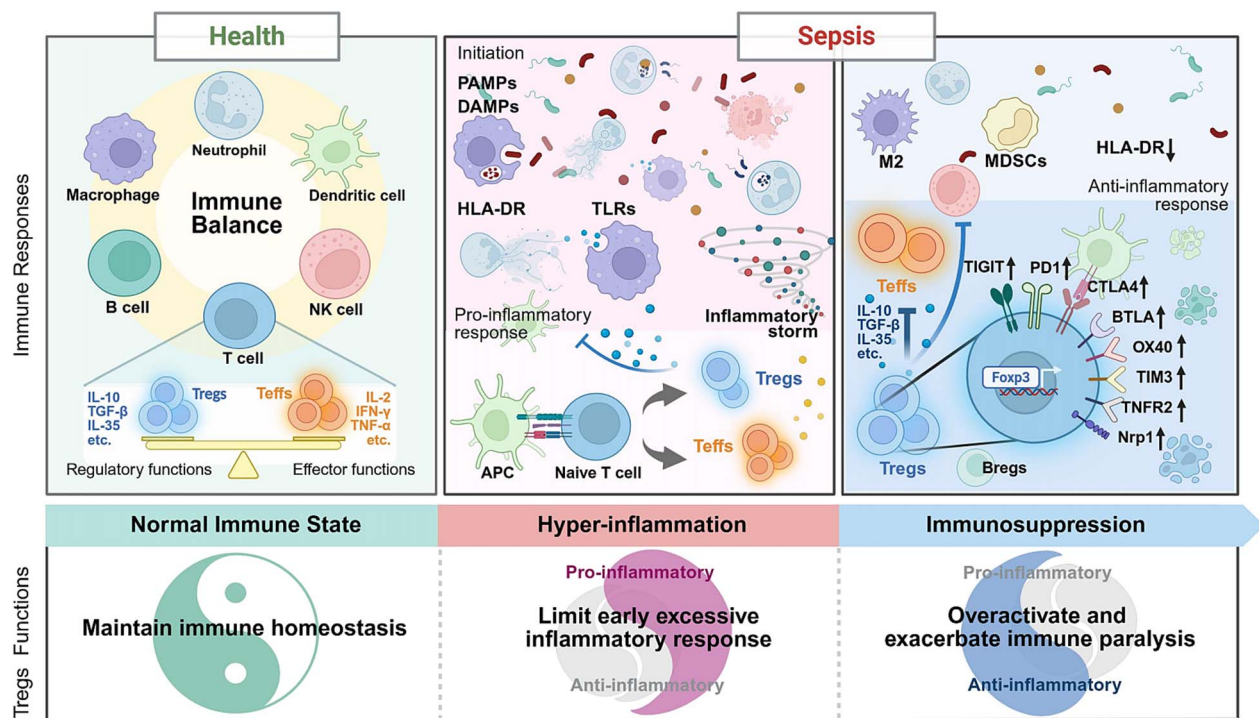


Figure 1. The functions of Tregs in immune homeostasis and immune response in sepsis. Treg cells are essential for maintaining immune balance under normal conditions by controlling immune responses. In the hyper-inflammatory stage of sepsis, they help reduce excessive inflammation by releasing inhibitory cytokines like IL-10 and TGF- β , thus protecting tissues from damage. However, during immunosuppression, Treg cells become overly active, worsening immune paralysis and contributing to complications associated with sepsis. *PAMP* pathogen-associated molecular patterns, *DAMP* damage-associated molecular patterns, *HLA-DR* human leukocyte antigen-DR, *TLR* Toll-like receptor, *APC* antigen-presenting cell, *MDSC* myeloid-derived suppressive cells, *NK* natural killer, *IL* interleukin, *TNF* tumor necrosis factor, *IFN* interferon

collectively enable stratified assessment of immune status in sepsis patients, with clinical implications for predicting the extent of disease progression and guiding therapeutic strategies. Moreover, Treg cells express both costimulatory and co-inhibitory molecules, as well as the chemokine receptor, which regulate their function and heterogeneity. Costimulatory molecules enhance Treg-mediated immune regulation, while immune checkpoints contribute to immune tolerance and the suppression of autoimmune responses [31]. These signaling pathways are essential for Treg cell development and function, particularly in sepsis. In the following sections, we will describe the specific changes and roles of each Treg cell subset in sepsis.

The heterogeneity of Treg cells in sepsis

Sepsis involves a biphasic immunopathological response characterized by simultaneous activation of hyperinflammatory and immunosuppressive mechanisms, which may occur sequentially or concurrently. Although Treg cells constitute a minor subset of the CD4⁺ T lymphocyte population (accounting for 5%–10% of the total peripheral blood CD4⁺ T lymphocyte population), their powerful immunomodulatory ability highlights their vital role in sepsis pathophysiology [27, 32]. The study of Treg cells in sepsis began with research into the immunoparalysis that postsepsis anti-inflammatory treatments could not alleviate [33]. Due to the identification of immuno-suppression CD4⁺CD25⁺ T cells in human peripheral blood [34], researchers have become interested in the role and variation of this cell in sepsis patients. Increasing evidence has demonstrated the dual role of Treg cells in sepsis. Studying the changes and functions of Treg

cells in sepsis is crucial for understanding the immunological condition of sepsis. (Figure 1).

Variations of Treg cells during sepsis

Mounting clinical evidence confirms a progressive increase in the relative proportion of Treg cells during sepsis progression (Table 1). In patients diagnosed with systemic inflammatory response syndrome (SIRS) or bacterial infectious sepsis, the proportion of CD4⁺CD25⁺Foxp3⁺ Treg cells in the peripheral blood circulation showed a significant increase [35]. Leveraging CD127 as a human Treg marker [29], researchers examined the proportion of CD4⁺CD25⁺CD127⁺ Treg cells in the peripheral blood of septic patients 3–7 days after sepsis onset. Compared to healthy individuals, the proportion of Treg cells in the peripheral blood of septic patients was significantly elevated [36]. Additionally, peripheral blood Treg proportions rise early post-trauma, compared to nonseptic trauma patients [37]. The dissociation between proportional and absolute Treg counts was later confirmed. Despite the proportion of Treg cells beginning to show a significant increase 3 days after the onset of sepsis, septic patients exhibit significantly reduced Treg absolute counts [38]. More clinical data proved that the proportion of Treg cells does not parallel the results of their absolute counts. Compared to healthy controls, the absolute count of Treg cells is significantly decreased in septic patients, with the lowest absolute count observed in patients with septic shock. Among septic patients, survivors have a higher absolute Treg cell count than nonsurvivors [39–42]. This suggests that Treg cells may play an essential role in the recovery of septic patients, a notion that has been validated in the cecal ligation and puncture (CLP) model

Table 1. The changes and characteristics of Treg cells in clinical sepsis patients

Markers of Tregs	Tregs numerical dynamics	Quantitative changes	Objects	Observation time	Specimen source	Immunological characteristics	Outcomes	Research type	Reference
CD4 ⁺ CD25 ⁺ Foxp3 ⁺	Treg was significantly elevated in trauma patients with sepsis complications	The percentage of CD4 ⁺ CD25 ⁺ cells 15.4 ± 2.8% in traumatic sepsis, 5.7 ± 1.2% in trauma hemorrhagic shock, and 4.5 ± 1.3% in healthy controls	114 trauma patients (with 25 patients developing sepsis within 30 days) and 50 healthy controls	within 8 h of trauma	Peripheral whole blood	Reduced T cell proliferation in trauma hemorrhagic shock patients as compared to control.		Observational study	[37]
CD4 ⁺ CD25 ^{high}	Tregs in survivors were higher than in nonsurvivors		87 patients with severe sepsis (60 survivors and 27 nonsurvivors), 30 healthy controls	within 48 h of admission to the ICU	PBMC	- Th1/CD4⁺ ratios and circulating Th1 lymphocyte counts in survivors were higher than in non-survivors. - Absolute counts of Th17 and Tregs in survivors were higher.	Treg lymphocytes were not directly associated with mortality in severe sepsis	Observational study	[42]
CD4 ⁺ CD25 ⁺ CD127 ⁻	Percentage increase, absolute number remained lower	Absolute number of Tregs (cells/ μ l): 27 (13–33) in septic shock, 43 (22–66) in nonseptic shock, and 65 (45–72) in healthy controls on day 3	43 shock patients (26 septic, 17 nonseptic), and 7 healthy volunteers	Within 12 h of admission, at Days 3, 5, and 7	Peripheral whole blood	No correlation was found between Treg cell levels and plasma cytokine (IL-2, IL-4, IL-5, IL 10, INF γ , TNF α , and TGF- β) concentrations		Observational study	[38]
CD4 ⁺ CD25 ⁺ CD127 ⁻	Percentage increase	The percentage of CD4 ⁺ CD25 ⁺ CD127 ⁻ cells: 12.0 ± 1.0% in patients vs. 6.8 ± 0.3% in healthy volunteers	30 septic shock patients and 17 healthy individuals	Once between 3 and 7 days after the onset of shock	Peripheral whole blood	- Reduced HLA-DR on their monocytes - A decreased lymphoproliferative response		Observational study	[36]
CD4 ⁺ CD25 ⁺	Percentage increase	The percentage of CD4 ⁺ CD25 ⁺ cells: 24 ± 3% in survival patients with septic shock and 38 ± 5% in nonsurvivors on Days 7–10	16 patients with septic shock and 36 healthy individuals	Days 1, 3, 5, 7–10	Peripheral whole blood	A marked elevation of circulating CD4⁺CD25⁺ T cells that were also CD45RO⁺ and CD69⁻ and overexpressed CTLA-4		Observational study	[45]

(continued)

Table 1. Continued

Markers of Tregs	Tregs numerical dynamics	Quantitative changes	Objects	Observation time	Specimen source	Immunological characteristics	Outcomes	Research type	Reference
CD4 ⁺ CD25 ⁺	Tregs of Day7 in survivors were higher than in nonsurvivors	The ratios of CD4 ⁺ CD25 ⁺ cells: 2.10% (0.80%, 3.10%) in the survival group vs. 1.80% (1.15%, 3.65%) in the death group on Day 1; 0.90% (0.30%, 2.80%) in the survival group vs. 5.70% (2.60%, 8.30%) in the death group on Day 7	28 patients diagnosed with sepsis (12 had severe trauma, 10 had septic shock, and 9 died)	Days 1 and 7 after hospitalization in the ICU	Periphery blood		Ratio of CD4 ⁺ CD25 ⁺ Treg cells in peripheral blood of patients with sepsis are associated with survival outcomes.	Observational study	[47]
CD4 ⁺ CD25 ⁺ CD127 ⁻	The percentages of Tregs in total CD4 ⁺ T-cells is significantly higher in severe sepsis than healthy controls. By Day 7, the percentage of Tregs progressively decreased in survivors, while it increased in nonsurvivors.	The percentages of Tregs in total CD4 ⁺ T-cells: mean, 4.97% in healthy control vs. 6.65% in patients with severe sepsis; 6.71 ± 2.49% in survivors, 6.99 ± 3.17% in nonsurvivors on Day 1; 5.94 ± 1.55% in survivors, 7.51 ± 1.61% in nonsurvivors on Day 7	101 patients with severe sepsis and 45 healthy volunteers	Days 1 and 7 during sepsis	Peripheral whole blood	• The expression of BTLA on Tregs was significantly higher in patients with severe sepsis compared with that in healthy controls. • BTLA expression on Tregs was higher in nonsurvivors than that in survivors.	Survivors had a lower percentage of Tregs and higher number of Tregs than nonsurvivors.	Observational study	[48]
CD4 ⁺ CD25 ⁺	Elevated levels of cytokines produced by Tregs and activation markers on Tregs' surface in septic patients.		106 patients with total burn surface area larger than 30%	Postburn Days 1, 3, 7, 14, and 21	Periphery blood		In septic patients, the levels of CTLA-4 and FOXP3 expression in the survival group were notably lower compared to those in the fatal outcome group between postburn Days 3 and 21.	Observational study	[51]
mRNA of T-bet; GATA-3; RORgammat (ROR γ t); FOXP3	Increased mRNA levels		80 patients with differing severities of sepsis (31 sepsis, 33 severe sepsis, and 16 septic shocks)	24 h after diagnosis	Peripheral arterial blood	• Higher Th1 and Th2 transcription factor and Higher IFN-γ, IL-4, and IL-10, in the peripheral blood of patients with sepsis and severe sepsis • The levels of T-bet, GATA-3, and IFN-γ were lower in patients with septic shock compared to those with sepsis		Observational study	[54]

using DEREg mice (DEpletion of REgulatory T cells) [43]. The increase of Treg cells during the immunosuppression of sepsis is now a widely accepted belief, which is closely related to septic patients' survival [4, 44]. This alteration in the peripheral blood circulation of sepsis patients was first reported by Monneret *et al.* in 2003. Their findings indicated that increased CD4⁺CD25⁺ Treg frequency in nonsurvivors perpetuates severe immunoparalysis, driving adverse clinical outcomes [45]. This trend is more significant in patients who died, accompanied by a notable increase in IL-10 levels [46]. The frequency of circulating Foxp3⁺ Treg cells among CD4⁺ T lymphocytes in nonsurvivors is significantly higher on the seventh day after sepsis compared to the first day [47]. Intriguingly, on the seventh day, survivors exhibited a lower Treg frequency but paradoxically higher absolute Treg counts relative to nonsurvivors [48].

Variations of Treg cells have also been identified across different populations. Single-cell immune profiling of paediatric sepsis shows that the proportion of peripheral blood Treg cells is increased during both the acute and recovery phases, with this pattern consistently observed among older individuals' children [49]. Furthermore, a clinical study demonstrated that children with neutropenia have a higher percentage of peripheral blood Treg cells in the early stages of sepsis compared to the non-neutropenic children group [50]. In severe burn-induced sepsis, the activation and maturation of Treg cells are higher in the early stages after the burn (on Days 1 and 3), as well as on Days 7, 14, and 21, compared to nonseptic patients. This shift fully enhances the immunosuppressive activity of Treg cells, ultimately leading to an immunosuppressive state in the patients [51].

The causes of Treg cells' numerical dynamics in sepsis are diverse. In terms of absolute counts, both lineages of CD4⁺ T cells (CD25⁺ and CD25⁻) were found to be diminished immediately after the onset of shock. While Treg cells quickly returned to levels observed in healthy donors, the number of CD4⁺CD25⁻ T lymphocytes remained significantly reduced. This indicates that the increase in the proportion of Treg cells following shock is not due to their proliferation but rather to the decrease in the number of CD4⁺CD25⁻ T lymphocytes [52]. T cell apoptosis is an essential cause of immunosuppression in sepsis. The increased proportion of Treg cells in sepsis may be explained by their resistance to apoptosis, which is mediated through the preferential overexpression of Bcl-2 compared to conventional effector T cells' lymphocytes [53]. Furthermore, this phenomenon is closely linked to the activation of the transcriptional regulatory network, as the mRNA expression levels of Treg-related transcription factors GATA-3, RORγt, and FOXP3 were increased in patients' peripheral blood 24 h after sepsis diagnosis [54]. Moreover, cytokines such as IL-33, IL-10, and TGF-β, as well as abnormal metabolites in the septic microenvironment, promote the expansion of Treg cells [55–58]. Other immune cells such as neutrophils and macrophages also promote the expansion of Treg cells through direct or indirect mechanism means [59–61]. These contents will be elaborated specifically in the following sections.

Subgroups of Treg in sepsis

Growing evidence indicates that Treg cells are not a single cell type but comprise multiple subsets with distinct functions and surface markers. Based on their differentiation process and anatomical location, Treg cells are currently classified

into thymus-derived Tregs (tTregs), peripherally induced Tregs (pTregs), induced Tregs (iTregs), and Th-like Tregs [56, 62].

The majority of tTregs develop in the thymus, whereas a smaller proportion of Treg cells originate from conventional T cells (Tconvs) or pTregs, maturing under specific conditions [63]. tTregs undergo negative selection in the thymic medulla and, under specific cytokine stimulation, further differentiate into CD4⁺CD25^{hi}Foxp3⁺ tTregs through the recognition of self-antigen peptides and interaction with dendritic cells. They help prevent autoimmune disease and maintain immune tolerance by recognizing and suppressing immune responses against self-antigens [64]. Functionally, tTregs mainly ensure self-tolerance and prevent autoimmune diseases. They achieve this by directly suppressing self-reactive T cells and releasing immunosuppressive factors like IL-10 and TGF-β to sustain immune homeostasis. pTregs are produced in peripheral lymphoid tissues and originate from CD4⁺Foxp3⁻ T cells. These cells turn into pTregs when they encounter antigens in the peripheral environment, in the presence of TGF-β and the absence of danger signals, through activation of the T cell receptor (TCR) [64]. They can also be induced *in vitro*. pTregs play a crucial role in peripheral immune responses by helping to control excessive immune reactions and preventing the onset of allergic and inflammatory diseases. They exhibit heterogeneity, including subtypes such as T regulatory 1 (Tr1) cells and Th3 cells, which produce distinct cytokines [65]. iTregs are generated *in vitro* or induced within the peripheral environment *in vivo*. Their formation typically depends on IL-2 and TGF-β but does not require intensive TCR stimulation. iTregs show relatively lower stability of Foxp3 expression, which can make them less stable than tTregs in certain situations and conditions [66]. Th-like Tregs, which display features similar to their respective T helper (Th) cell counterparts, can develop under specific environmental conditions, especially during infections like sepsis. They include Th1-like, Th2-like, Th17-like, and even follicular helper T (Tfh)-like Tregs. These subsets help regulate the immune response by colocalizing with their respective Th cell populations and responding to cytokine signals [67].

During the development of sepsis, tTregs exert their immunoregulatory function by suppressing the immune activity of effector T cells (Teff) and facilitating targeted transport [56]. Tregs can respond to stimuli such as cytokines, antigen presentation, and other immune signals in sepsis. iTregs can be induced by appropriate antigenic stimulation and specific microenvironmental signals. They are widely used in various pathological models, including sepsis [60]. Moreover, environmental factors can differentiate Tregs into various Th-like subsets, such as Th1, Th2, Th17, and even follicular helper T (Tfh) cells [67]. During sepsis, Th-like Tregs regulate the associated immune response by colocalizing with their corresponding Th cells [68]. In a murine polytrauma model, researchers found that splenectomy elevated 28-day survival from 62% to 92% in septic mice with secondary insult. Additionally, splenectomy effectively suppressed the release of inflammatory cytokines after CLP modeling and caused C5a levels to increase. Furthermore, splenectomy post-trauma elevated Treg frequency, driving immunosuppression via TGF-β-dependent Foxp3 induction and impairing antimicrobial immunity [69]. The above evidence suggests that circulating Tregs (iTregs) rather than splenic-derived natural Treg cells are critical in improving sepsis prognosis.

Table 2. Checkpoints of Tregs in sepsis

Checkpoint	Ligand	Signaling	Class	Function to Tregs
PD1	PD-L1	Notch pathway	Co-inhibitory receptor	• Increase Foxp3 expression • Induce Treg expansion • Enhance Treg's immunosuppressive ability.
CTLA-4	CD80/86		Co-inhibitory receptor	• Competitively bind to and reduces the expression of CD80/CD86 costimulatory molecules on APCs, thereby depriving Tconv cells of the necessary costimulatory signal.
BTLA	HVEM (CD270)		Co-inhibitory receptor	• Enhance Treg's suppressive function
TIM3	Ceacam-1 HMGB-1	STAT-3 phosphorylation IL10, EBI3, GZMB, PRF1, IL1R α , and CCR6 expression	Co-inhibitory receptor	• Regulate the balance between regulatory and effector T cells.
TIGIT	CD155 CD226 Nectin-2		Co-inhibitory receptor	• Leads to FOXP3 demethylation
OX40	OX40L	NF κ B, PI3K, ERK, and AKT signaling	Costimulatory molecule	• Maintain Treg's suppressive ability: suppress effector T cell proliferation or IFN-γ production.
Nrp1	SEMA3A SEMA4A TGF- β & TGF- β RI/II/III	Smad signaling neuropilin-1-semaphorin-4a axis		• Support the stability and functional maintenance of Tregs by regulating semaphorin-4a • Reduce apoptosis of Tregs and lower the methylation levels of Foxp3-TSDR • Involve the production of IL-10 and TGF-β in Treg cells
CD39 and CD73	ATP			• CD39 mediates the elimination of ATP-associated effects in Treg cells • CD73 mediates immune suppression by adenosine production

Checkpoints of Treg in sepsis

Treg cells co-express costimulatory/co-inhibitory molecules that orchestrate functional diversification and subset heterogeneity through downstream signaling. These molecules can serve as potential targets for distinguishing and identifying Treg subtypes [6]. Co-stimulatory molecules are vital for activating and differentiating T cells. These molecules also support Tregs, helping them effectively modulate immune responses. In contrast, immune checkpoints, known as co-inhibitory signaling pathways, such as CTLA-4, programmed cell death receptor 1 (PD-1), and T-cell immunoglobulin mucin 3 (TIM-3), induce T cell apoptosis, exhaustion, and immune tolerance. Immune checkpoint expression on Tregs governs their development and functional maturation, critically regulating immunosuppression in sepsis [6, 56] (Table 2).

Elevated expression of TIM-3, PD-1, and CTLA-4 on CD4⁺ T lymphocytes exhibits a significant positive correlation with sepsis severity. Notably, CD4⁺PD-1⁺ T cells demonstrate the strongest association and may serve as an independent risk factor for disease progression [70]. PD-1 co-inhibitory signaling through PD-L1 engagement suppresses T cell proliferation and cytokine secretion [71]. The PD-1/PD-L1 axis drives Treg cell expansion via Notch signaling potentiation and stabilizes their suppressive phenotype by suppressing asparaginyl endopeptidase (AEP) activity [72]. In clinical patients with severe sepsis and septic shock, Treg cells express higher PD-1 levels, which are positively correlated with poorer outcomes

[39, 40]. Splenectomy shields CLP mice from sepsis by reducing PD-1/PD-L1 and decreasing Tregs [69], while in early-phase septic animal models, PD-1⁺ Treg cells can alleviate lung tissue damage caused by acute inflammation [73, 74].

Foxp3⁺CD4⁺CD25⁺Tregs highly and constitutively express CTLA-4, which can bind to CD80/86 and prevent CD4⁺ T cells from overactivation, thereby helping Treg cells maintain immune tolerance [75]. In sepsis-induced immunosuppression, CTLA-4⁺ Tregs inhibit the function of effector T cells, thereby suppressing T cell proliferation, cytokine production, and other immune responses. Additionally, CTLA-4⁺ Tregs can form relatively stable immune synapses with antigen-presenting cells (APCs) and induce the upregulation of free PD-L1 on APCs, which effectively prevents naive T cell activation and causes effector T cell exhaustion and functional inhibition through dual inhibitory mechanisms [76]. Clinical studies show that increased CTLA-4⁺ Treg cell proportion is positively associated with sepsis severity, and elevated levels of CTLA-4⁺ Tregs are regarded as an independent risk factor for 28-day mortality in sepsis patients [77].

B and T lymphocyte attenuator (BTLA/CD272) functions as a co-inhibitory receptor that engages herpesvirus entry mediator (HVEM/CD270). It demonstrates sustained surface expression on Tregs producing IL-10, thereby suppressing CD4⁺ T cell effector functions [78]. Experimental evidence indicates that BTLA mediates CD4⁺ T cell depletion in the CLP-induced septic mouse model. Elevated BTLA on CD4⁺

T cells predicts susceptibility to hospital-acquired infections [79]. Furthermore, clinical evidence suggests that the increased expression of BTLA on Tregs enhances their suppressive function, and an increase in the number of BTLA⁺ Treg cells may indicate poor prognosis in patients with severe sepsis [48].

TIM3 plays a crucial role in regulating the immunosuppressive functions of Foxp3⁺ T cells [80, 81]. The stronger proliferative ability and inhibitory function of Tim-3⁺ Treg cells are related to the expression and phosphorylation of STAT-3, as well as the gene expressions of IL-10, EBI3, GZMB, PRF1, IL-1R α , and CCR6 [82]. During hepatitis C virus infection, TIM3-related signalling regulates the balance between regulatory and effector T cells [83]. During sepsis-associated acute lung injury (S-ALI), TIM-3⁺ Tregs upregulate the expression of IL-4 and IL-10 in a STAT-3-dependent manner, thereby resolving the inflammation [84].

T-cell immunoglobulin and ITIM domain (TIGIT) is a recently discovered coinhibitory molecule that delivers inhibitory signals into cells through its ITIM domain in the cytoplasmic tail. The two main recognized ligands are CD155 and CD226 (mainly expressed on APCs). Additionally, nectin-2 is a novel ligand for TIGIT [85, 86]. TIGIT⁺ CD4⁺ Foxp3⁺ Tregs can suppress Th1 and Th17 cells, serving as a key Treg subtype mediating immunosuppression [87, 88]. Upon binding to its ligand CD155, TIGIT suppresses TCR signaling pathways, thereby impairing antigen-induced T cell activation and promoting the secretion of the immunosuppressive molecule fibrinogen-like protein 2 (FGL2) [89]. Currently, reports on the regulation of Treg signals via TIGIT are still limited. One study suggests that the upregulation of TIGIT in Treg cells results in FOXP3 demethylation [90]. During sepsis, the significant expansion of TIGIT⁺ Treg cells indicates an increased susceptibility to secondary infections, with the ST2/IL-33 axis playing a crucial role in this process [91].

OX40 (CD134) is part of the tumor necrosis factor receptor superfamily (TNFRSF), a class of costimulatory molecules. It binds to the ligand OX40L (TNFSF4/CD252), supporting T cell proliferation, survival, and cytokine release through pathways like NF κ B, PI3K, ERK, and AKT signaling [92, 93]. Although OX40 is generally regarded as a molecule that promotes immune responses, it can also regulate immune tolerance in specific contexts. OX40 signaling has contrasting effects on Tregs, with functional outcomes depending on the inflammatory microenvironment and cytokine surroundings. Upon blockade of IL-4 and interferon (IFN)- γ , OX40 agonism, combined with TGF- β costimulation, encourages Treg expansion. Conversely, OX40 stimulation under IL-2 deprivation produces Tregs with reduced proliferative capacity and impaired suppressive function, a phenotype that can be reversed by exogenous IL-2 supplementation [94, 95]. OX40-deficient Tregs show impaired immunosuppressive function [96]. Early expansion of OX40⁺ Tregs in severe sepsis impairs effector T cell function, correlating with SOFA score progression and predicting 28-day mortality [97].

Nrp1 serves as a marker for tTreg cells, aiding in their differentiation from other types of Treg cells. It supports the stability and functional maintenance of Tregs by regulating semaphorin-4a. Under the influence of lipopolysaccharide (LPS), Nrp1 activates the Smad signaling pathway, working in conjunction with TGF- β 1 to maintain Treg stability [98, 99]. Elevated Nrp1 expression reduces Treg apoptosis and decreases methylation levels of Foxp3-TSDR, thereby promoting their stability. Additionally, research suggests that

Nrp1 expression is strongly linked to IL-10 and TGF- β production in Tregs during sepsis [100, 101]. Furthermore, activated latency-associated peptide (LAP)-TGF- β complex enhances the immunosuppressive function of TGF- β and promotes TGF- β -mediated Treg differentiation. At the same time, the formation of the TGF- β R1-NRP1 complex increases the bioactivity of TGF- β through a synergistic signaling boost mechanism [102, 103].

CD39, or nucleoside triphosphate diphosphohydrolase 1 (NTPDase 1), is an ectoenzyme that converts adenosine triphosphate (ATP) into adenosine monophosphate (AMP). When cells are damaged or die, they release ATP, which promotes inflammation. In contrast, CD39 helps counteract these effects by exerting anti-inflammatory actions [104]. Borsellino *et al.* pioneered the discovery of CD39 expression on immunosuppressive Foxp3⁺ Tregs, where TCR engagement potentiates its catalytic activity to eliminate ATP-driven proinflammatory effects, including P2 receptor-mediated cytotoxicity and dendritic cell maturation [105]. CD73 is an ecto-5'-nucleotidase that converts 5'-AMP into adenosine, and it is expressed on the surface of Tregs. CD73-expressing Treg cells mediate immune suppression by producing adenosine, which inhibits the proliferation and cytokine production of effector CD4⁺ T cells [106]. In sepsis, CD39⁺ Treg cells are upregulated during the immunosuppressive phase of the disease. This population exhibits higher levels of CD39 and PD-1, exerting inhibitory functions that may serve as a prognostic indicator of poor outcomes [107]. Moreover, increased adenosine in sepsis can upregulate the expression of CD39 and CD73 on the surface of Treg cells [108].

The role of Tregs in sepsis-associated tissue damage

While initial investigations into Treg biology during sepsis primarily focused on the peripheral circulation and spleen, current evidence reveals the diverse roles of Treg cells in sepsis-associated tissue damage across multiple organs. Especially during the early phase, the role of Tregs in reducing tissue damage has been gradually uncovered. Additionally, Tregs are also involved in organ dysfunction during the later stages of sepsis. (Figure 2).

Lung

Acute lung injury (ALI) represents acute hypoxemic respiratory failure triggered by noncardiogenic insults including trauma, sepsis, or toxic inhalation. This condition is defined by rapid-onset diffuse alveolar damage and dysfunctional alveolar-capillary barrier integrity, leading to uncontrolled pulmonary inflammation, protein-rich edema, and impaired gas exchange [109]. In the clinic, ALI is a common complication in patients with sepsis. Mounting evidence demonstrates the importance of CD4⁺CD25⁺Foxp3⁺ Tregs in mitigating acute inflammation in sepsis and improving outcomes in ALI/ARDS [61, 73, 110, 111]. *In vivo* evidence indicates that HMGB1 blockade or myeloid-specific phosphatase and tension homology deletion protein (PTEN) deletion attenuates pulmonary tissue injury by enhancing TGF- β secretion and expanding Tregs within the lung microenvironment. A recent study has shown the vital protective role of TNFR2 signaling pathway in Treg cell-mediated septic pneumococcal pneumonia by modulating $\gamma\delta$ T17 cell responses to IL-17A

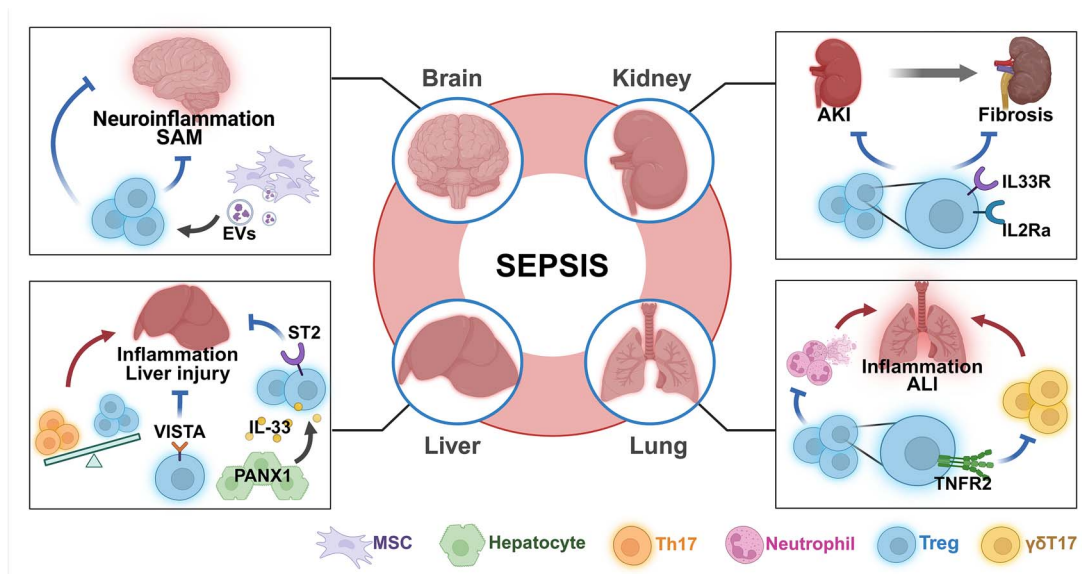


Figure 2. Tregs alleviate multiple organ tissue damage during acute inflammation of sepsis. During the acute inflammatory stage, Tregs help control excessive inflammation and prevent tissue damage. In the kidneys, IL33R⁺ and IL2Ra⁺ Tregs prevent AKI and subsequent fibrosis development. In the lungs, Tregs reduce neutrophil activity, while TNFR2⁺ Tregs inhibit Th17 cells to ease acute lung injury. In the brain, Tregs enhance SAM by lowering acute inflammation. In the liver, Tregs decrease hepatic inflammation and limit liver damage. SAM sepsis-associated encephalopathy, AKI acute kidney injury, ALI acute lung injury, EVs extracellular vesicles, MSCs mesenchymal stem cells

and encouraging the recruitment of neutrophils within the lungs. TNFR2⁺ Treg cells suppress $\gamma\delta$ T17 cell activation in the lung, thereby preventing excessive neutrophil infiltration and tissue injury. This immunoregulatory pathway may serve as an essential mechanism to avoid opportunistic pathogens, such as pneumococci, from invading lung tissues [112]. This evidence suggests that Treg cells, which exert protective effects during tissue damage in sepsis, may exhibit characteristic subpopulations. Additionally, previous studies have shown that Treg cells can reduce LPS-induced ALI by significantly decreasing neutrophil infiltration into the lungs and lowering lung cell apoptosis [73]. These cells may help reduce acute inflammation by interacting with other immune cells.

Kidney

Sepsis-associated acute kidney injury (S-AKI) is a common complication in patients with sepsis. It stems from a combination of factors, including reduced renal blood flow, heightened inflammatory responses, and cellular damage, which results in injury to the renal tubules and other parts of the kidney's structure [113]. Clinically, this presents as a sudden decline in renal function, characterized by decreased urine output and elevated levels of creatinine and blood urea nitrogen in the blood. Clinical analysis indicates that the dysregulation of Th17/Treg is associated with both the onset and severity of acute kidney injury (AKI) in sepsis patients. Furthermore, an increasing Th17/Treg ratio could serve as a potential predictive marker for sepsis-associated AKI [114]. The results of single-cell sequencing on the transition from AKI to chronic fibrosis reveal a significant increase in tissue-resident IL-33R⁺ and IL-2Ra⁺ Treg cells. This population can shield the kidneys from damage and fibrosis after injury. Transcriptomic analysis focusing on Tregs shows varying levels of upregulation in regeneration and pro-angiogenic pathways while also displaying markers of overstimulation and fibrosis in fibrotic tissue environments [115]. However, it is essential to note that this

change in Treg cells was observed in two acute ischemia-reperfusion injury (IRI) models. Given the differences in septic acute kidney injury compared to other types of kidney injuries [113], further validation is required to establish whether the subpopulation changes in Tregs contribute to their role after S-AKI.

Brain

Sepsis-associated encephalopathy (SAE) refers to brain dysfunction caused by sepsis, characterized by widespread impairment of cerebral function. This condition can cause a range of symptoms, including mild delirium and severe alterations in consciousness [116]. SAE correlates with persistent neurocognitive sequelae in sepsis survivors, primarily driven by infection-triggered neuroinflammation. This chronic condition, termed "sepsis brain", manifests through sustained microglial activation, oxidative mitochondrial damage, impaired cerebral glucose metabolism, and blood-brain barrier disruption, collectively contributing to long-term psychiatric and cognitive impairments [117, 118]. Recent studies have highlighted the role of infiltrating Tregs in the pathogenesis of SAE and related mental disorders. Utilizing a cecal slurry model, Saito *et al.* demonstrated that Tregs and Th2 cells infiltration ameliorate SAE and its neuropsychiatric sequelae through neuroinflammatory resolution in the chronic phase. [119] Additionally, another study has shown that exosomes derived from mesenchymal stem cells (MSCs) mitigate early brain injury in sepsis by increasing both the percentage and absolute numbers of Tregs, thereby reducing high levels of inflammation and immune response [120].

Liver

The liver plays a crucial role in immune regulation during sepsis by participating in bacterial clearance, producing acute-phase proteins, and regulating metabolism. However, it is also

a target organ for sepsis-related injuries, such as ischemic hepatitis, bile metabolism disorders, and drug-toxicity-induced damage. [121] Research indicates that Tregs are involved in the initial stages of septic liver inflammation and injury. The arginine deficiency present in sepsis can worsen liver inflammation by disturbing the Th17/Treg balance [122]. Additionally, VISTA⁺ Treg cells have been found to reduce levels of liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and pro-inflammatory factors in mice after sepsis, thereby reducing sepsis-associated liver injury [123]. The PANX1-IL-33 axis in hepatocytes modulates IL-33 secretion via the ATP-P2X7 pathway, thereby activating ST2⁺ Treg cells, mitigating endotoxemia-induced cytokine storm and hepatic injury [124].

Emerging evidence highlights the dual role of Tregs in septic pathophysiology. While current research primarily focuses on the protective functions of Treg expansion during the hyperinflammatory phase of sepsis, recent studies highlight their crucial role in late-phase organ dysfunction. [3, 4] Applying anti-CD25 to suppress Treg cell increase after sepsis demonstrated a beneficial effect in reducing multiple organ injury and preventing secondary chronic infection in mice during the immunosuppressive phase following CLP modeling [60, 125]. The mechanism by which Tregs directly mediate organ-specific damage during sepsis-induced immunoparalysis remains uncharacterized, constituting a critical barrier to targeted therapeutic development.

Tregs display tissue-specific adaptability to locally maintain immune homeostasis, as evidenced by recent research [126]. Emerging evidence suggests that tissue-resident Tregs drive sepsis-induced multi-organ dysfunction through organ-specific mechanisms in the lung, liver, kidney, muscle, brain, and myocardium [6]. A study shows that following CLP, changes in tissue-infiltrating and splenic-derived Treg cells do not follow the same pattern during acute *Pseudomonas aeruginosa* challenge in septic mice. In lung tissues, the count of Foxp3⁺ Treg cells nearly doubled by Day 3, then gradually decreased after that to Day 7 and returned to baseline levels. Conversely, Foxp3⁺ Treg cells in the spleen increased by 1.6 times on Day 3 and continued to rise subsequently [127]. This suggests that local inflammatory conditions during sepsis, such as hypoxia, DAMPs, and pathogen load, may influence the diverse phenotypes of Tregs, leading to distinct changes in tissue-resident Tregs compared to circulating Treg cells. Although the available evidence suggests that Treg cells contribute to sepsis-associated tissue injury, reports on tissue-specific Treg cells in sepsis-related tissue damage remain limited, and the underlying molecular mechanisms need further investigation.

Novel mechanisms for Treg regulation in sepsis

Regulation and mechanism of abnormal metabolites on Treg cells in sepsis

Adenosine is an essential naturally occurring metabolite that influences numerous immune functions by activating its specific receptors—A1, A2a, A2b, and A3—located on immune cells [57]. Circulating adenosine levels are elevated during the acute phase and play a crucial role in the development of immune suppression in sepsis by activating A2AR [128]. Adenosine or activated adenosine receptor signalling can promote Foxp3 expression in Treg cells through various mechanisms. The activation of JNK/AP-1 signaling mediates the upregulation of adenosine-induced Foxp3 expression in Treg

cells during sepsis [129]. A recent study found that high levels of adenosine in sepsis can activate the phosphorylation of element-binding protein (CREB) via the A2a receptor, thereby upregulating Foxp3 expression in Treg cells [130]. Furthermore, another report has indicated that the phosphorylation of CREB also plays a role in the A2AR-mediated induction of PD-L1 expression. Activation of A2AR *in vitro* can increase PD-L1 expression in Treg cells, thereby boosting their capacity to inhibit lymphocyte proliferation [131]. Previous studies have shown that during sepsis, Treg cells exposed to adenosine or the adenosine A2A receptor agonist CGS21680 demonstrate increased expression of surface molecules CD39 and CD73. This effect occurs through transcriptional regulation by E2F-1 and CREB, which also leads to increased intracellular adenosine production [108]. These results indicate that CREB signaling is essential in controlling adenosine-mediated functional pathways and surface receptor expression in Treg cells.

Sepsis patients have significantly elevated peripheral blood lactate levels, and clinical data show that PD-1 expression in Treg cells of sepsis patients is increased. Moreover, the percentage of PD-1⁺ Treg cells is positively correlated with lactate levels in sepsis patients, suggesting that lactate may induce inhibitory molecule expression in Treg cells [39]. Existing research indicates that lactate plays a crucial role in regulating the differentiation and function of Treg cells. *In vitro* lactate stimulation induces the differentiation of Naïve CD4⁺ T cells into Treg cells [58]. Additionally, lactate regulates the expression of surface co-inhibitory molecules on Treg cells through various mechanisms, thereby modulating their immunosuppressive function. Lactic acid enters Treg cells via monocarboxylate transporter 1 (MCT1), promoting the translocation of NFAT1 into the nucleus and increasing the expression of PD-1 [132]. Lactate is also confirmed to increase CTLA-4 expression through a splicing-related mechanism [133]. Another study found that lactate modulates the generation of Treg cells through epigenetic mechanisms. Lactate-mediated lactylation of Lys72 enhances the interaction between MOESIN and TGF- β receptor I, thereby promoting downstream SMAD3 signalling and enhancing Treg cell function [134]. Furthermore, a recent study has revealed that lactate promotes the transcription of MGAT1 by activating XBP1s (X-box binding protein one splicing factor) and interacts with the mitochondrial outer membrane translocase TOM70 receptor, ultimately enhancing the OXPHOS capacity of Treg mitochondria for transport [135]. Current research on the mechanisms underlying lactic acid-induced differentiation and enhanced inhibitory function of Treg cells primarily focuses on cancers [132–134, 136]. However, given the widespread presence of elevated lactic acid levels in clinical septic patients, and the potential connection between sustained lactic acid elevation and serious adverse outcomes related to immune suppression, further research into the specific mechanisms by which lactic acid influences Treg differentiation and function in sepsis could provide valuable insights.

Regulation and the following mechanism of Treg cells by other immune cells in sepsis

Neutrophils and neutrophil extracellular traps. The role of specific subsets of innate immune cells in recruiting Treg cells and supporting their immunosuppressive function is gradually being clarified. Researchers have identified a novel pathogenic neutrophil population with high CD200R expression in sepsis

models. This subset of neutrophils, which appears early in sepsis, is marked by elevated levels of Igf1. IGF-1 secreted by CD200R-high neutrophils stimulates the production of Treg cells, thereby promoting systemic immunosuppression [137]. Liao *et al.*'s study explained the role of Siglec-F⁺ neutrophils during the immunosuppressive phase, affecting splenic T lymphocytes and secondary infections in persistent inflammation, immunosuppression, and catabolism syndrome (PICS) mice. In terms of mechanism, the IL-10 secreted by Siglec-F⁺ neutrophils plays a vital role [59]. However, research into the relationship between this specific subset of neutrophils and Treg cells has not yet been conducted. The possible influence of this neutrophil subset on Treg cell differentiation and function, as well as the underlying mechanisms, warrants further investigation in future studies.

In addition to the newly discovered neutrophil subset capable of inducing Treg cell generation, extracellular traps released by neutrophils in sepsis also play a significant role in regulating Treg cells. NETs (neutrophil extracellular traps) are specialized structures primarily composed of DNA, forming a net-like framework. Current research reveals that besides the DNA scaffold from neutrophils, NETs also contain a range of complex components, including histones, antimicrobial peptides [such as β -defensins and cathelicidin (LL-37)], enzymes [such as elastase, neutrophil collagenase (MMP-9), and neutrophil elastase (NE)], oxidases [such as reactive oxygen species (ROS) produced by NADPH oxidase], and other antimicrobial proteins (such as thrombin and immunoglobulins) [138, 139]. A previous study has revealed that pathological NETosis in sepsis induces cholesterol-centric metabolic reprogramming in naïve CD4⁺ T cells via hyperactivated AKT/mTOR/SREBP2 signaling, thereby driving their differentiation into immunosuppressive Treg cells with enhanced functional capacity [60]. NET-driven Treg differentiation from naïve CD4⁺ T cells bridges innate and adaptive immunity [140]. Further research into the specific components of NETs that drive Treg cell differentiation may offer new clinical strategies for precisely targeting NETs and enhancing the management of sepsis-associated immune suppression.

Macrophages. The regulation of Treg cells by macrophages during sepsis is often mediated through TGF- β signaling released from macrophages. In the early inflammatory stage of sepsis, HMGB1 released by macrophages activates PTEN, which inhibits the PI3K/PDK1/Akt pathway and thereby reduces β -catenin activity. This decrease diminishes macrophage release of TGF- β , ultimately suppressing Treg induction [61]. Adipose-derived MSC-derived exosomes (ADMSC-Exos) promote TGF- β secretion in macrophages, which increases Treg proportion in CLP-mice spleen, effectively reducing sepsis-induced ALI in these mice [141]. Additionally, research indicates that Tim-3⁺Treg cells can promote M2 macrophage polarization by intervening in the expression of p-STAT3 signaling [84].

Dendritic cells. The sepsis process can induce spontaneous apoptosis of dendritic cells (DCs) [142]. Surviving immature dendritic cells inhibit their later maturation when stimulated with LPS by engulfing apoptotic dendritic cells. This process results in the upregulation of TGF- β 2 and the secretion of TGF- β 1, thereby facilitating Treg conversion [143].

Novel markers

As researchers delve deeper into Treg characteristics in sepsis, emerging markers that regulate Treg attributes and functions in sepsis have been identified. The downstream mechanisms involve directly influencing the expression of Foxp3, activating related receptor signaling, and modulating the inhibitory functional molecules of Treg cells. GPR174 regulates Treg suppressive function, and mice lacking Gpr174 show increased resistance to sepsis-induced inflammatory shock. Gpr174 deficiency upregulates CTLA-4 and IL-10 expression in Treg cells and protects mice from lung injury by promoting M2 macrophage polarization. Gpr174-deficient Tregs also encourage macrophage polarization to the M2 phenotype and reduce pro-inflammatory cytokine secretion *in vitro*. Furthermore, LysoPS negatively affects Treg cell accumulation and activity via GPR174. Therefore, GPR174 antagonism represents a promising strategy for inflammatory disease modulation [144, 145]. The stability of Tregs relies on the demethylation of specific CpG-rich regions within the Foxp3 locus, a process promoted by ten-eleven translocation (TET) dioxygenases [146, 147]. Wu *et al.* revealed that iron-regulatory genes are highly expressed in Treg cells, particularly ferritin heavy chain (FTH), which is crucial in supporting TET-mediated demethylation of the FOXP3 locus. By promoting the transcription of FOXP3, FTH helps maintain Treg cell lineage stability [148]. Recently, researchers discovered that the sepsis-induced upregulation of p53 promotes the expansion of Treg cells. Mechanistically, p53 can directly interact with the promoter regions of DNMT3a and TET2 genes, thereby regulating their transcriptional levels. This modulation of DNA methylation and demethylation processes subsequently regulates Foxp3 expression, maintaining Treg functionality [149]. Another study has found that activating β 1-adrenergic receptors enhances the suppressive function of Treg cells, promoting the progression of immune suppression in sepsis [150].

Other molecules

Cold-inducible RNA-binding protein (CIRP), released as a DAMP during sepsis, promotes Treg differentiation by activating TLR4 and downstream IL-2 signaling. Simultaneously, CIRP affects STAT5 to regulate Treg cell function, worsening late-stage immune suppression in sepsis [151]. The release of HMGB1 (High Mobility Group Box 1) initiates inflammation, and its sustained elevation drives immunosuppression in sepsis [152]. Researchers discovered that the HMGB1/PTEN/ β -catenin signaling pathway in macrophages controls the induction of Treg cells in an LPS-induced sepsis model of ALI [61]. However, another study has shown that during ALI, HMGB1-activated TLR4 signaling may worsen tissue injury in the acute inflammatory phase by preventing Treg differentiation [153]. Furthermore, complement C3 depletion in sepsis is associated with the expansion of Treg cells during abdominal sepsis [154]. The novel cytokine Metrnl shows a significant link between its serum levels in patients with clinical sepsis and mortality rates, with a higher risk of death in those with lower Metrnl levels. Metrnl may play a role in preventing and treating sepsis by boosting immune defence through promoting Treg cell differentiation, thereby increasing survival rates in mouse models [155] (Figure 3).

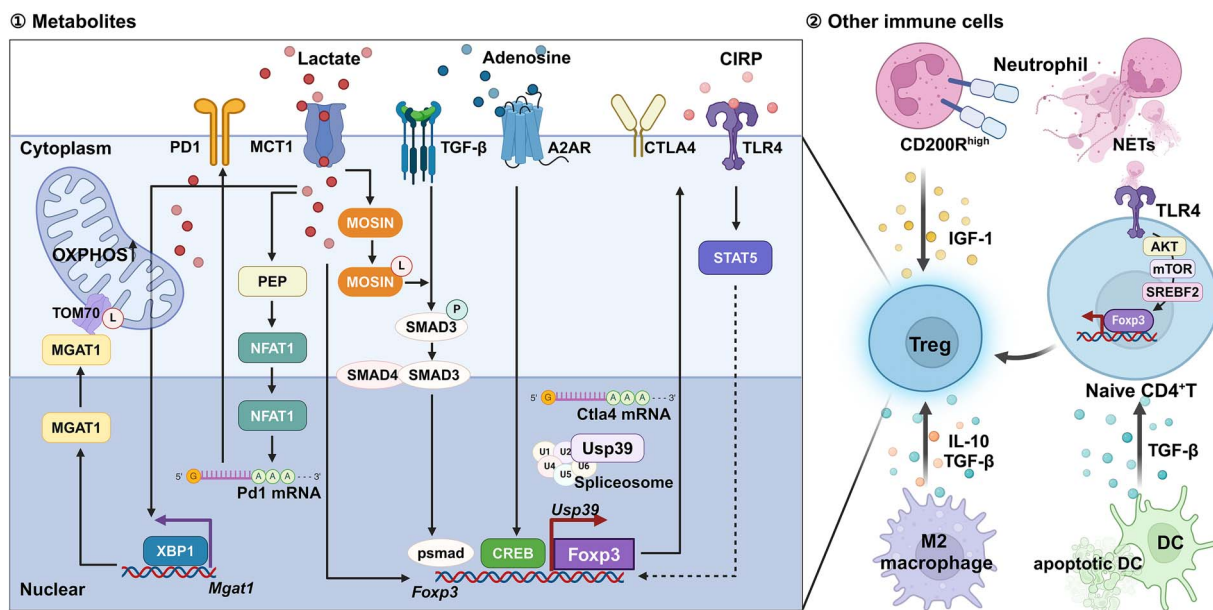


Figure 3. Novel insights into Treg modulation in sepsis. During sepsis, metabolites such as lactic acid and adenosine, along with inflammation-related factors like CIRP, are produced systemically as a result of inflammatory responses and tissue injury. These elements intricately affect Treg metabolism, their differentiation process, and the expression of surface inhibitory molecules via various molecular pathways. Furthermore, immune cells present in the septic environment—particularly neutrophils, macrophages, and DCs—play a role in modulating Treg differentiation and function by releasing immunoregulatory cytokines such as IL-10 and TGF- β . CIRP cold-inducible RNA-binding protein, IL-10 interleukin-10, TGF- β transforming growth factor-beta

Treatment targeting Treg cells in sepsis

Currently, sepsis management remains challenging due to the lack of effective therapies. Existing clinical strategies primarily focus on supportive care, including infection control, prompt administration of antibiotics, resuscitation, and support for organ function. Recent research has highlighted the potential of immunotherapy to enhance long-term outcomes for patients with sepsis. Patient-specific immunotherapies targeting unique immune profiles demonstrate significant clinical efficacy in preclinical and clinical settings [156]. Due to the distinct roles of Tregs at different stages of sepsis, immunotherapy targeting Tregs should be considered in light of the patient's immune status (Table 3).

Hyperinflammation status

Current evidence indicates that Treg expansion or functional enhancement during septic hyperinflammation attenuates excessive immune responses and ameliorates acute tissue injury. Some potential small-molecule drugs, biological agents, Treg adoptive transfer treatments, and cell-derived therapies can mitigate early inflammation and organ injury by enhancing the count and function of Treg cells during the acute inflammatory stage.

Drugs. PI3K p110 δ inhibitor, CAL-101, and Interleukin-2-induced T-cell kinase (ITK) inhibitors are validated not only to restore Treg cell numbers but also to enhance their functional capacity, playing a role in modulating immune responses and reducing inflammatory damage during the hyper-inflammatory stage [157, 158]. Ganoderma polysaccharides (G.PS) promoted CD4⁺ T cell differentiation into Treg cells through the p-STAT5 pathway, modulated inflammatory cytokines such as TNF α , IL-17A, IL-6, and IL-10, which significantly improved the survival rate of septic mice [159]. Berberine (BBR), a therapeutic agent recognized for its antioxidant, anti-inflammatory, and immunomodulatory

properties, significantly reduces lung injury by increasing the number of Treg cells in the spleen and lung tissues in the CLP model [160]. Moreover, a single dose of arginine administered at the onset of sepsis can reduce septic liver inflammation by regulating the Th/Treg balance [122]. In shock and sepsis models, ethyl pyruvate, a stabilized pyruvate derivative, attenuates oxidative stress and inflammation by enhancing Treg proliferation and suppressive function during CD4⁺CD25⁻ T-cell differentiation [161].

Cell transplanting treatments. In 2005, Heuer *et al.* first employed *in vitro*-induced Treg cells for adoptive transfer in a CLP mouse model. The results showed that mice receiving stimulated Treg cells experienced a significant increase in peritoneal mast cell populations and higher levels of TNF- α . Furthermore, the bacterial clearance ability of the treatment group mice was significantly improved, resulting in better survival rates [162]. *In vivo* experimental results demonstrate that the infusion of TIM3⁺ Treg cells can protect against structural lung injury in septic ALI by modulating M2 macrophage polarization, thereby reducing inflammatory infiltrates and effectively limiting the fibrotic process following septic lung injury [84]. Combining Treg cell therapy with PD-L1/PD-1 and Tim-3 agonists offers new therapeutic potential for promoting the resolution of ALI and lung repair in clinical settings [84, 163]. Moreover, adoptively transferred VISTA⁺ Treg cells attenuate sepsis-induced hepatic inflammation and injury in animal models [123].

Cell-derived therapies. Additional cell-based interventions mitigate early septic inflammation, primarily through Treg-mediated immunomodulation. One study showed that human adipose-derived mesenchymal stem cells (hASCs) can partially upregulate Treg cells and IL-10, thereby improving the early inflammatory response in sepsis induced by LPS or CLP modeling [164]. Bone marrow mesenchymal stem

Table 3. Treatment targeting Tregs in sepsis

Immune status	Methods	Trial	Species	Treatments	Regulation to Tregs	Outcomes	References
Pro-inflammation	Drugs	<i>In vivo</i>	Mice	CAL-101(PI3K p110 δ inhibitor)	Restore Treg cell numbers and enhance Treg function	Reduce inflammatory injury	[157]
		<i>In vivo</i>	Mice	Interleukin-2-induced T-cell kinase inhibitors	Restore Treg cell numbers and enhance Treg function	Reduce inflammatory injury	[158]
		<i>In vivo</i>	Mice	Ganoderma polysaccharides	Facilitated CD4 ⁺ T cell differentiation into regulatory T cells		[159]
		<i>In vivo</i>	Mice	Berberine	Increase Treg population	Alleviate lung injury	[160]
		<i>In vivo</i>	Mice	Arginine	Regulate the Th/Treg balance	Alleviate liver inflammation	
		<i>In vitro</i>		Ethyl pyruvate	Enhance Treg proliferation and suppressive function		[161]
	Cell-transplanting treatments	<i>In vivo</i>	Mice	<i>In vitro</i> -induced Tregs		Increase peritoneal mast cell populations and elevated TNF- α levels, enhance bacterial clearance capacity and survival rates	[162]
		<i>In vivo</i>	Mice	TIM3 ⁺ Tregs		Alleviate structural lung injury	[84]
		<i>In vivo</i>	Mice	VISTA ⁺ Tregs		Reduce liver inflammation and injury	[123]
	Cell-derived therapies	<i>In vivo</i>	Mice	Human adipose-derived mesenchymal stem cells	Increase Treg proportion and IL-10 expression	Alleviate the early inflammatory response	[164]
		<i>In vivo</i>	Mice	An immunosuppressive natural microvesicle mimetic	Enhance Treg levels	Reduce inflammatory injury	[168]
Immuno-suppression	Checkpoint-targeted therapies	<i>In vivo</i>	Mice	Combination therapy of anti-PD-L1 antibody with probiotics	Enhance Th17/Treg balance	Increased the 7-day survival rate	[169]
		<i>In vivo</i>	Human	BMS-936559 (PD-L1 inhibitor)		Reverse immunosuppressive status by restoring immune biomarkers	[170]
		<i>In vivo</i>	Mice	TGF- β or IL-10 antibodies			[172]
		<i>In vivo</i>	Mice	Anti-CD25	Reduce Treg cell numbers	Alleviate tissue damage and inflammation	[60]
	Drugs	<i>In vitro</i>		Curcumin	Downregulate CTLA-4 and inhibit Treg function		[173]
		<i>In vivo</i>	Mice	<i>Codonopsis pilosula</i> polysaccharide	Inhibit Treg Foxp3 expression		[174]
		<i>In vivo</i>	Mice	Astragalus polysaccharides	Decrease Treg proportion	Attenuate weight loss and kidney injury	[175]
		<i>In vivo</i>	Mice	Nicotinamide ribose	Suppress Treg proliferation	Mitigate the depletion of splenic mononuclear cells and T lymphocytes	[176]
		<i>In vivo</i>	Mice	ZM241385 (A2AR antagonist)	Inhibit Treg PD-L1 expression	Enhance long-term prognosis	[131]
		<i>In vivo</i>	Mice	Artesunate	Inhibit Treg activation	Reestablishing immune homeostasis	[177]
		<i>In vivo</i>	Human	Polymyxin B-immobilized fiber	Reduce the Treg number and serum IL-10 levels	Improve sepsis-induced immunosuppression	[178]
		<i>In vivo</i>	Mice	BMDC transplantation	Reduces Treg proliferation and differentiation	Enhance the survival rate	[180]
	Cell transplanting treatments						

cells (BMMSCs) and umbilical cord mesenchymal stem cells (UCMSCs) have also been shown to exert beneficial effects in alleviating the early inflammatory response induced by CLP through the upregulation of Treg cell number and function [165]. Cells isolated from human amniotic membrane cells (HAMCs) have the potential to generate and regulate Treg cells, thereby alleviating sepsis-related inflammation. [166] Autologous cord blood mononuclear cells (ACBMNC) intervention can improve late-onset sepsis (LOS) in very preterm infants by increasing the proportion of Treg cells [167]. Microvesicles can be applied to manage inflammatory responses induced by sepsis infection, thereby maintaining immune homeostasis. In addition, endotoxin-tolerant DC-derived microvesicle mimetics generated via extrusion elevate Treg populations through miR-155-3p upregulation [168]. Despite promising preclinical findings from laboratory studies, significant translational hurdles persist in translating these results into clinical applications.

Immunosuppression status

Checkpoint-targeted therapies. Anti-PD-L1 treatment improves the immunoregulatory state during septic immunosuppression by modulating the balance of Treg cells. As research progresses, combination therapies involving PD-L1 have been proposed for application during the immunosuppressive phase. Combining anti-PD-L1 antibody with probiotics synergistically augments septic mouse survival by Day 7 through dual immunomodulation: suppressing pro-inflammatory cytokines while elevating anti-inflammatory IL-10, concurrently ameliorating oxidative stress and lung injury via PI3K/AKT axis suppression. This regimen uniquely optimizes Th17/Treg balance and accelerates polymorphonuclear neutrophil apoptosis, outperforming monotherapies [169]. Immune checkpoint-based therapies have shown promising clinical potential in septic patients. A Phase Ib randomized controlled trial (RCT) in sepsis-induced immunosuppression demonstrated favorable tolerability of PD-L1 inhibitor BMS-936559, with dose-dependent reversal of immune dysfunction by reactivating immune biomarkers. Nevertheless, large-scale trials must validate the durability of safety and efficacy in this critically ill cohort (NCT02576457) [170]. Despite experimental and clinical evidence linking Treg cells' upregulation of immunosuppressive checkpoints, including CTLA-4 and BTLA, to late-phase immunosuppression and poor prognosis in patients, targeted therapies against these molecules remain inadequately validated. Current evidence indicates that sepsis-induced immunosuppression requires targeted synergy of immune checkpoint inhibitors with adjuvant immunomodulators, such as lysophosphatidic acid, IL-7, IL-15, IFN, and FMS-like tyrosine kinase 3 ligand (FLT3L), with individualized treatment plans tailored to each patient [171]. In CLP-induced septic mice, the application of TGF- β or IL-10 antibodies for neutralization reduces Treg percentage and improves the survival rate [172]. Moreover, although reports indicate that the use of the monoclonal antibody anti-CD25 to reduce Treg cell numbers can effectively alleviate tissue damage and inflammation during the immune suppression phase of sepsis in CLP-induced mouse models, as well as increase the survival rate of septic mice [60], there is currently no robust clinical evidence to suggest that patients in sepsis would benefit from the application of anti-CD25 in clinical settings.

Drugs. In addition to immune checkpoint inhibitors, certain specific compounds or receptor agonists have also shown therapeutic effects targeting Treg cells in animal experiments. *In vitro* experiments demonstrate that curcumin can inhibit Treg function by downregulating CTLA-4, thereby suppressing cell-cell contact, inhibiting the secretion of inhibitory cytokines [173]. Another component isolated from traditional Chinese herbs, *Codonopsis pilosula* polysaccharide, may partially rebalance immune homeostasis and ameliorates sepsis outcomes by inhibiting the expression of Foxp3 on Treg cells through TLR4 signalling [174]. Moreover, Astragalus polysaccharides (APS) have been reported to attenuate immunosuppression in polymicrobial sepsis by downregulating Treg [175]. A notable decrease in NAD⁺ levels and its downstream molecule, SIRT1, is found within T cells in sepsis. Zhao *et al.* verified that the immediate administration of nicotinamide ribose (NR), an NAD⁺ precursor, following cecal ligation and puncture, significantly enhances NAD⁺ and SIRT1 levels. NR supplementation mitigates the depletion of splenic mononuclear cells and T lymphocytes during sepsis, while also boosting CD4⁺ and CD8⁺ T cell counts. Furthermore, NR suppresses the proliferation of Treg cells among CD4⁺ T cells in sepsis [176]. As is known, circulating adenosine levels modulate Treg cell differentiation and function via adenosine receptors during sepsis. *In vivo* studies indicate that A2AR regulates the suppression of splenic regulatory T cells, promoting sepsis-induced immune suppression. A2AR blockade improves CD4⁺ T cell homeostasis through a spleen-dependent mechanism, inhibits PD-L1 expression in Treg cells, and reduces their capacity to suppress lymphocyte proliferation. Administration of the A2AR antagonist ZM241385 effectively enhances long-term prognosis in CLP mice [131]. Artesunate (ART) can inhibit the activation of Treg cells, alleviating the immunosuppressive state of sepsis and reestablishing immune homeostasis in the host [177]. In addition, clinical research results based on sepsis patients with intra-abdominal infection foci show that treatment with polymyxin B-immobilized fiber (PMX-F) for 24 h can significantly improve sepsis-induced immunosuppression by reducing the number of Treg cells and serum IL-10 levels [178, 179].

Cell-transplanting treatments. Recent animal studies have shown the potential for using cell transplantation strategies during the immunosuppressive phase of sepsis. In the CLP model of septic mice, transplanting bone marrow-derived dendritic cells (BMDCs) increases DC counts and improves sepsis outcomes. This approach reduces the proliferation and differentiation of splenic Treg cells and CD4⁺ CD25⁺ Foxp3⁺ Treg cells, leading to a notable increase in survival rates among septic animal subjects [180].

Challenge and future perspectives

The variability in pro-inflammatory and immunosuppressive responses among individual sepsis patients presents significant challenges for the successful implementation of immunotherapy. Precisely identifying the optimal therapeutic window for targeting Treg cells in sepsis remains a crucial clinical issue. Current evidence highlights the dual roles of Treg cells: in hyperinflammatory states, Treg cells help alleviate systemic inflammatory response syndrome, while excessive Treg activity in later stages may worsen immunosuppression. This temporal duality necessitates biomarker-guided stratification,

such as monitoring monocyte HLA-DR expression or plasma cytokine profiles (e.g. IL-10, TGF- β concentration), to identify immune-paralyzed patients who may benefit from Treg modulation. However, establishing a unified criterion for the immune status of sepsis patients in clinical practice remains controversial. Employing machine learning and artificial intelligence to determine immune profiles and develop personalized treatment strategies shows considerable potential for clinical application [181]. Meanwhile, despite substantial preclinical findings demonstrating the potential therapeutic efficacy of various molecular agents and cellular therapies in modulating Treg-mediated immune homeostasis during different stages of sepsis, current research remains predominantly preclinical. Large-scale RCTs are still crucial for validating clinical efficacy and establishing evidence-based therapeutic protocols.

Conclusions

The role of Treg cells in sepsis is intricate, as they can have both protective and immunosuppressive effects, which vary depending on the disease stage. During sepsis progression, abnormal metabolites, DAMPs, and other immune cells regulate the changes in the number and function of Treg cells through various mechanisms, further affecting immune homeostasis. Current research suggests that Treg cells and Treg cells with specific markers may have potential value in predicting the prognosis of sepsis patients. While standard treatments for sepsis continue to focus on infection control and supportive care, targeted immunotherapies that modulate Treg cell function present an exciting opportunity to improve outcomes in septic patients. However, given the dual role of Treg cells at different stages of sepsis, choosing the right timing for treatment remains a significant challenge. Personalized approaches, tailored to an individual's immune status, are likely to be the most effective way to harness the beneficial aspects of Treg cells while reducing their potential for immune suppression. Further studies must optimize these strategies to validate their clinical safety and therapeutic efficacy.

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Conflict of interest

None declared.

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References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M. *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801–10. <https://doi.org/10.1001/jama.2016.0287>.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR. *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395:200–11. [https://doi.org/10.1016/S0140-6736\(19\)32989-7](https://doi.org/10.1016/S0140-6736(19)32989-7).
3. van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. *Immunity* 2021;54:2450–64. <https://doi.org/10.1016/j.immuni.2021.10.012>.
4. Liu D, Huang SY, Sun JH, Zhang HC, Cai QL, Gao C. *et al.* Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options. *Mil Med Res* 2022;9:56. <https://doi.org/10.1186/s40779-022-00422-y>.
5. Venet F, Monneret G. Advances in the understanding and treatment of sepsis-induced immunosuppression. *Nat Rev Nephrol* 2018;14:121–37. <https://doi.org/10.1038/nrneph.2017.165>.
6. Gao YL, Yao Y, Zhang X, Chen F, Meng XL, Chen XS. *et al.* Regulatory T cells: angels or demons in the pathophysiology of sepsis? *Front Immunol* 2022;13:829210. <https://doi.org/10.3389/fimmu.2022.829210>.
7. Daviaud F, Grimaldi D, Dechartres A, Charpentier J, Geri G, Marin N. *et al.* Timing and causes of death in septic shock. *Ann Intensive Care* 2015;5:16. <https://doi.org/10.1186/s13613-015-0058-8>.
8. Martin-Loeches I, Singer M, Leone M. Sepsis: key insights, future directions, and immediate goals. A review and expert opinion. *Intensive Care Med* 2024;50:2043–9. <https://doi.org/10.1007/s00134-024-07694-z>.
9. Savage PA, Klawon DEJ, Miller CH. Regulatory T cell development. *Annu Rev Immunol* 2020;38:421–53. <https://doi.org/10.1146/annurev-immunol-100219-020937>.
10. Okeke EB, Okwor I, Mou Z, Jia P, Uzonna JE. CD4+CD25+ regulatory T cells attenuate lipopolysaccharide-induced systemic inflammatory responses and promotes survival in murine *Escherichia coli* infection. *Shock* 2013;40:65–73. <https://doi.org/10.1097/SHK.0b013e318296e65b>.
11. Cavassani KA, Carson WF, Moreira AP, Wen H, Schaller MA, Ishii M. *et al.* The post sepsis-induced expansion and enhanced function of regulatory T cells create an environment to potentiate tumor growth. *Blood* 2010;115:4403–11. <https://doi.org/10.1182/blood-2009-09-241083>.
12. Gershon RK, Kondo K. Cell interactions in the induction of tolerance: the role of thymic lymphocytes. *Immunology* 1970;18:723–37.
13. Sakaguchi S. Regulatory T cells: key controllers of immunologic self-tolerance. *Cell* 2000;101:455–8. [https://doi.org/10.1016/S0092-8674\(00\)80856-9](https://doi.org/10.1016/S0092-8674(00)80856-9).
14. Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor α -chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol* 1995;155:1151–64. <https://doi.org/10.4049/jimmunol.155.3.1151>.
15. Itoh M, Takahashi T, Sakaguchi N, Kuniyasu Y, Shimizu J, Otsuka F. *et al.* Thymus and autoimmunity: production of CD25+CD4+ naturally anergic and suppressive T cells as a key function of the thymus in maintaining immunologic self-tolerance. *J Immunol* 1999;162:5317–26. <https://doi.org/10.4049/jimmunol.162.9.5317>.
16. Shevach EM. Certified professionals: CD4(+)CD25(+) suppressor T cells. *J Exp Med* 2001;193:F41–6. <https://doi.org/10.1084/jem.193.11.F41>.
17. Sakaguchi S. Naturally arising CD4+ regulatory t cells for immunologic self-tolerance and negative control of immune

- responses. *Annu Rev Immunol* 2004;22:531–62. <https://doi.org/10.1146/annurev.immunol.21.120601.141122>.
18. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. *Annu Rev Immunol* 2012;30:531–64. <https://doi.org/10.1146/annurev.immunol.25.022106.141623>.
 19. Wildin RS, Ramsdell F, Peake J, Faravelli F, Casanova JL, Buist N. *et al.* X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. *Nat Genet* 2001;27:18–20. <https://doi.org/10.1038/83707>.
 20. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L. *et al.* The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* 2001;27:20–1. <https://doi.org/10.1038/83713>.
 21. Gambineri E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. *Curr Opin Rheumatol* 2003;15:430–5. <https://doi.org/10.1097/00002281-200307000-00010>.
 22. Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. *Nat Immunol* 2003;4:330–6. <https://doi.org/10.1038/ni904>.
 23. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* 2003;299:1057–61. <https://doi.org/10.1126/science.1079490>.
 24. Khattri R, Cox T, Yasayko SA, Ramsdell F. An essential role for Scurfin in CD4+CD25+ T regulatory cells. *Nat Immunol* 2003;4:337–42. <https://doi.org/10.1038/ni909>.
 25. Wan YY, Flavell RA. Regulatory T-cell functions are subverted and converted owing to attenuated Foxp3 expression. *Nature* 2007;445:766–70. <https://doi.org/10.1038/nature05479>.
 26. Williams LM, Rudensky AY. Maintenance of the Foxp3-dependent developmental program in mature regulatory T cells requires continued expression of Foxp3. *Nat Immunol* 2007;8:277–84. <https://doi.org/10.1038/ni1437>.
 27. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T cells and human disease. *Annu Rev Immunol* 2020;38:541–66. <https://doi.org/10.1146/annurev-immunol-042718-041717>.
 28. Hori S. FOXP3 as a master regulator of T(reg) cells. *Nat Rev Immunol* 2021;21:618–9. <https://doi.org/10.1038/s41577-021-00598-9>.
 29. Liu W, Putnam AL, Xu-Yu Z, Szot GL, Lee MR, Zhu S. *et al.* CD127 expression inversely correlates with Foxp3 and suppressive function of human CD4+ T reg cells. *J Exp Med* 2006;203:1701–11. <https://doi.org/10.1084/jem.20060772>.
 30. Thornton AM, Korty PE, Tran DQ, Wohlfert EA, Murray PE, Belkaid Y. *et al.* Expression of Helios, an Ikaros transcription factor family member, differentiates thymic-derived from peripherally induced Foxp3+ T regulatory cells. *J Immunol* 2010;184:3433–41. <https://doi.org/10.4049/jimmunol.0904028>.
 31. Węgrzyn AS, Kedzierska AE, Obojski A. Identification and classification of distinct surface markers of T regulatory cells. *Front Immunol* 2022;13:1055805.
 32. Cao C, Ma T, Chai YF, Shou ST. The role of regulatory T cells in immune dysfunction during sepsis. *World J Emerg Med* 2015;6:5–9. <https://doi.org/10.5847/wjem.j.1920-8642.2015.01.001>.
 33. Kox WJ, Volk T, Kox SN, Volk HD. Immunomodulatory therapies in sepsis. *Intensive Care Med* 2000;26 Suppl 1:S124–8. <https://doi.org/10.1007/s001340051129>.
 34. Dieckmann D, Bruett CH, Ploettner H, Lutz MB, Schuler G. Human CD4(+)CD25(+) regulatory, contact-dependent T cells induce interleukin 10-producing, contact-independent type 1-like regulatory T cells [corrected]. *J Exp Med* 2002;196:247–53. <https://doi.org/10.1084/jem.20020642>.
 35. Leng FY, Liu JL, Liu ZJ, Yin JY, Qu HP. Increased proportion of CD4(+)CD25(+)Foxp3(+) regulatory T cells during early-stage sepsis in ICU patients. *J Microbiol Immunol Infect* 2013;46:338–44. <https://doi.org/10.1016/j.jmii.2012.06.012>.
 36. Venet F, Chung CS, Kherouf H, Geeraert A, Malcus C, Poitevin F. *et al.* Increased circulating regulatory T cells (CD4(+)CD25(+)CD127 (-)) contribute to lymphocyte anergy in septic shock patients. *Intensive Care Med* 2009;35:678–86. <https://doi.org/10.1007/s00134-008-1337-8>.
 37. Gupta DL, Bhoi S, Mohan T, Galwankar S, Rao DN. Coexistence of Th1/Th2 and Th17/Treg imbalances in patients with post traumatic sepsis. *Cytokine* 2016;88:214–21. <https://doi.org/10.1016/j.cyt.2016.09.010>.
 38. Hein F, Massin F, Cravoisy-Popovic A, Barraud D, Levy B, Bollaert PE. *et al.* The relationship between CD4+CD25+CD127-regulatory T cells and inflammatory response and outcome during shock states. *Crit Care* 2010;14:R19. <https://doi.org/10.1186/cc8876>.
 39. Liu Q, An L, Qi Z, Zhao Y, Li C. Increased expression of programmed cell Death-1 in regulatory T cells of patients with severe sepsis and septic shock: An observational clinical study. *Scand J Immunol* 2017;86:408–17. <https://doi.org/10.1111/sji.12612>.
 40. Jiang W, Li X, Ding H, Wang K, Liu X, Wang Q. *et al.* PD-1 in Tregs predicts the survival in sepsis patients using sepsis-3 criteria: a prospective, two-stage study. *Int Immunopharmacol* 2020;89:107175. <https://doi.org/10.1016/j.intimp.2020.107175>.
 41. Carvelli J, Piperoglou C, Bourenne J, Farnarier C, Banzet N, Demerlé C. *et al.* Imbalance of circulating innate lymphoid cell subpopulations in patients with septic shock. *Front Immunol* 2019;10:2179. <https://doi.org/10.3389/fimmu.2019.02179>.
 42. Wu HP, Chung K, Lin CY, Jiang BY, Chuang DY, Liu YC. Associations of T helper 1, 2, 17 and regulatory T lymphocytes with mortality in severe sepsis. *Inflamm Res* 2013;62:751–63. <https://doi.org/10.1007/s00011-013-0630-3>.
 43. Kühnhorn F, Rath M, Schmoekel K, Cziupka K, Nguyen HH, Hildebrandt P. *et al.* Foxp3+ regulatory T cells are required for recovery from severe sepsis. *PLoS One* 2013;8:e65109. <https://doi.org/10.1371/journal.pone.0065109>.
 44. Pei F, Yao RQ, Ren C, Bahrami S, Billiar TR, Chaudry IH. *et al.* Expert consensus on the monitoring and treatment of sepsis-induced immunosuppression. *Mil Med Res* 2022;9:74. <https://doi.org/10.1186/s40779-022-00430-y>.
 45. Monneret G, Debar AL, Venet F, Bohe J, Hequet O, Biennu J. *et al.* Marked elevation of human circulating CD4+CD25+ regulatory T cells in sepsis-induced immunoparalysis. *Crit Care Med* 2003;31:2068–71. <https://doi.org/10.1097/01.CCM.0000069345.78884.0F>.
 46. Lu X, Song CY, Wang P, Li L, Lin LY, Jiang S. *et al.* The clinical trajectory of peripheral blood immune cell subsets, T-cell activation, and cytokines in septic patients. *Inflamm Res* 2024;73:145–55. <https://doi.org/10.1007/s00011-023-01825-w>.
 47. Chen K, Zhou QX, Shan HW, Li WF, Lin ZF. Prognostic value of CD4(+)CD25(+) Tregs as a valuable biomarker for patients with sepsis in ICU. *World J Emerg Med* 2015;6:40–3. <https://doi.org/10.5847/wjem.j.1920-8642.2015.01.007>.
 48. Liu Q, Lu Y, An L, Li CS. B- and T-lymphocyte attenuator expression on regulatory T-cells in patients with severe sepsis. *Chin Med J* 2018;131:2637–9. <https://doi.org/10.4103/0366-6999.244104>.
 49. Alhamdan F, Koutsogiannaki S, Yuki K. The landscape of immune dysregulation in pediatric sepsis at a single-cell resolution. *Clin Immunol* 2024;262:110175. <https://doi.org/10.1016/j.clim.2024.110175>.
 50. Yin F, Xi YL, Wang Y, Li BR, Qian J, Ren H. *et al.* The clinical outcomes and biomarker features of severe sepsis/septic shock with severe neutropenia: a retrospective cohort study. *Transl Pediatr* 2021;10:464–73. <https://doi.org/10.21037/tp-20-230>.
 51. Huang LF, Yao YM, Dong N, Yu Y, He LX, Sheng ZY. Association between regulatory T cell activity and sepsis and outcome of

- severely burned patients: a prospective, observational study. *Crit Care* 2010;14:R3. <https://doi.org/10.1186/cc8232>.
52. Venet F, Pachot A, Debard AL, Bohé J, Bienvenu J, Lepape A. *et al.* Increased percentage of CD4+CD25+ regulatory T cells during septic shock is due to the decrease of CD4+CD25- lymphocytes. *Crit Care Med* 2004;32:2329–31. <https://doi.org/10.1097/01.CCM.0000145999.42971.4B>.
 53. He W, Xiao K, Fang M, Xie L. Immune cell number, phenotype, and function in the elderly with sepsis. *Aging Dis* 2021;12: 277–96. <https://doi.org/10.14336/AD.2020.0627>.
 54. Li J, Li M, Su L, Wang H, Xiao K, Deng J. *et al.* Alterations of T helper lymphocyte subpopulations in sepsis, severe sepsis, and septic shock: a prospective observational study. *Inflammation* 2015;38:995–1002. <https://doi.org/10.1007/s10753-014-0063-3>.
 55. Nascimento DC, Melo PH, Piñeros AR, Ferreira RG, Colón DF, Donate PB. *et al.* IL-33 contributes to sepsis-induced long-term immunosuppression by expanding the regulatory T cell population. *Nat Commun* 2017;8:14919. <https://doi.org/10.1038/ncomms14919>.
 56. Huang S, Liu D, Han L, Deng J, Wang Z, Jiang J. *et al.* Decoding the potential role of regulatory T cells in sepsis-induced immunosuppression. *Eur J Immunol* 2024;54:e2350730.
 57. Zhang T, Yu-Jing L, Ma T. The immunomodulatory function of adenosine in sepsis. *Front Immunol* 2022;13:936547. <https://doi.org/10.3389/fimmu.2022.936547>.
 58. Zhang YT, Xing ML, Fang HH, Li WD, Wu L, Chen ZP. Effects of lactate on metabolism and differentiation of CD4(+)T cells. *Mol Immunol* 2023;154:96–107. <https://doi.org/10.1016/j.molimm.2022.12.015>.
 59. Liao C, Luo S, Liu X, Zhang L, Xie P, Zhou W. *et al.* Siglec-F(+) neutrophils in the spleen induce immunosuppression following acute infection. *Theranostics* 2024;14:2589–604. <https://doi.org/10.7150/thno.93812>.
 60. Shi Y, Wu D, Wang Y, Shao Y, Zeng F, Zhou D. *et al.* Treg and neutrophil extracellular trap interaction contributes to the development of immunosuppression in sepsis. *JCI Insight* 2024;9:e180132. <https://doi.org/10.1172/jci.insight.180132>.
 61. Zhou M, Fang H, Du M, Li C, Tang R, Liu H. *et al.* The modulation of regulatory T cells via HMGB1/PTEN/beta-catenin Axis in LPS induced acute lung injury. *Front Immunol* 2019;10:1612. <https://doi.org/10.3389/fimmu.2019.01612>.
 62. Shevach EM, Thornton AM. rTregs, pTregs, and iTregs: similarities and differences. *Immunol Rev* 2014;259:88–102. <https://doi.org/10.1111/immr.12160>.
 63. Russler-Germain EV, Rengarajan S, Hsieh CS. Antigen-specific regulatory T-cell responses to intestinal microbiota. *Mucosal Immunol* 2017;10:1375–86. <https://doi.org/10.1038/mi.2017.65>.
 64. Yang WY, Shao Y, Lopez-Pastrana J, Mai J, Wang H, Yang XF. Pathological conditions re-shape physiological Tregs into pathological Tregs. *Burns Trauma* 2015;3:1. <https://doi.org/10.1186/s41038-015-0001-0>.
 65. van der Veeken J, Campbell C, Pritykin Y, Schizas M, Verter J, Hu W. *et al.* Genetic tracing reveals transcription factor Foxp3-dependent and Foxp3-independent functionality of peripherally induced Treg cells. *Immunity* 2022;55:1173–1184.e7. <https://doi.org/10.1016/j.immuni.2022.05.010>.
 66. Kanamori M, Nakatsukasa H, Okada M, Lu Q, Yoshimura A. Induced regulatory T cells: their development, stability, and applications. *Trends Immunol* 2016;37:803–11. <https://doi.org/10.1016/j.it.2016.08.012>.
 67. Duhén T, Duhén R, Lanzavecchia A, Sallusto F, Campbell DJ. Functionally distinct subsets of human FOXP3+ Treg cells that phenotypically mirror effector Th cells. *Blood* 2012;119: 4430–40. <https://doi.org/10.1182/blood-2011-11-392324>.
 68. Hoeppli RE, MacDonald KN, Leclair P, Fung VCW, Mojibian M, Gillies J. *et al.* Tailoring the homing capacity of human Tregs for directed migration to sites of Th1-inflammation or intestinal regions. *Am J Transplant* 2019;19:62–76. <https://doi.org/10.1111/ajt.14936>.
 69. Drechsler S, Zipperle J, Rademann P, Jafarmadar M, Klotz A, Bahrami S. *et al.* Splenectomy modulates early immunoinflammatory responses to trauma-hemorrhage and protects mice against secondary sepsis. *Sci Rep* 2018;8:14890. <https://doi.org/10.1038/s41598-018-33232-1>.
 70. Gao DN, Yang ZX, Qi QH. Roles of PD-1, Tim-3 and CTLA-4 in immunoregulation in regulatory T cells among patients with sepsis. *Int J Clin Exp Med* 2015;8:18998–9005.
 71. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010;236:219–42. <https://doi.org/10.1111/j.1600-065X.2010.00923.x>.
 72. Cai J, Wang D, Zhang G, Guo X. The role of PD-1/PD-L1 Axis in Treg development and function: implications for cancer immunotherapy. *Onco Targets Ther* 2019;Volume 12:8437–45. <https://doi.org/10.2147/OTT.S221340>.
 73. Tang L, Bai J, Chung CS, Lomas-Neira J, Chen Y, Huang X. *et al.* Programmed cell death receptor ligand 1 modulates the regulatory T cells' capacity to repress shock/sepsis-induced indirect acute lung injury by recruiting phosphatase SRC homology region 2 domain-containing phosphatase 1. *Shock* 2015;43: 47–54. <https://doi.org/10.1097/SHK.0000000000000247>.
 74. Tang L, Bai J, Chung CS, Lomas-Neira J, Chen Y, Huang X. *et al.* Active players in resolution of shock/sepsis induced indirect lung injury: immunomodulatory effects of Tregs and PD-1. *J Leukoc Biol* 2014;96:809–20. <https://doi.org/10.1189/jlb.4MA1213-647RR>.
 75. Hossen MM, Ma Y, Yin Z, Xia Y, Du J, Huang JY. *et al.* Current understanding of CTLA-4: from mechanism to autoimmune diseases. *Front Immunol* 2023;14:1198365. <https://doi.org/10.3389/fimmu.2023.1198365>.
 76. Tekguc M, Wing JB, Osaki M, Long J, Sakaguchi S. Treg-expressed CTLA-4 depletes CD80/CD86 by trogocytosis, releasing free PD-L1 on antigen-presenting cells. *Proc Natl Acad Sci USA* 2021;118:e2023739118. <https://doi.org/10.1073/pnas.2023739118>.
 77. Wang L, Zhang Z, Chen X, Yu F, Huang H, Shen X. *et al.* Relationship between the expression of PD-1 and CTLA-4 on T lymphocytes and the severity and prognosis of sepsis. *Int J Gen Med* 2023;16:1513–25. <https://doi.org/10.2147/IJGM.S402586>.
 78. McBride MA, Patil TK, Bohannon JK, Hernandez A, Sherwood ER, Patil NK. Immune checkpoints: novel therapeutic targets to attenuate sepsis-induced immunosuppression. *Front Immunol* 2020;11:624272. <https://doi.org/10.3389/fimmu.2020.624272>.
 79. Shubin NJ, Monaghan SF, Heffernan DS, Chung CS, Ayala A. B and T lymphocyte attenuator expression on CD4+ T-cells associates with sepsis and subsequent infections in ICU patients. *Crit Care* 2013;17:R276. <https://doi.org/10.1186/cc13131>.
 80. Gupta S, Thornley TB, Gao W, Larocca R, Turka LA, Kuchroo VK. *et al.* Allograft rejection is restrained by short-lived TIM-3+PD-1+Foxp3+ Tregs. *J Clin Invest* 2012;122:2395–404. <https://doi.org/10.1172/JCI45138>.
 81. Sakuishi K, Ngiow SF, Sullivan JM, Teng MW, Kuchroo VK, Smyth MJ. *et al.* TIM3(+)FOXP3(+) regulatory T cells are tissue-specific promoters of T-cell dysfunction in cancer. *Onco Targets Ther* 2013;2:e23849.
 82. Gautron AS, Dominguez-Villar M, de Marcken M, Hafler DA. Enhanced suppressor function of TIM-3+ FoxP3+ regulatory T cells. *Eur J Immunol* 2014;44:2703–11. <https://doi.org/10.1002/eji.201344392>.
 83. Moorman JP, Wang JM, Zhang Y, Ji XJ, Ma CJ, Wu XY. *et al.* Tim-3 pathway controls regulatory and effector T cell balance during hepatitis C virus infection. *J Immunol* 2012;189:755–66. <https://doi.org/10.4049/jimmunol.1200162>.
 84. Liu X, Jiang S, Zhang Q, Xu S, Bao X, Cao W. *et al.* Tim-3 regulates Tregs' ability to resolve the inflammation and proliferation of acute lung injury by modulating macrophages

- polarization. *Shock* 2018;50:455–64. <https://doi.org/10.1097/SHK.0000000000001070>.
85. Deuss FA, Gully BS, Rossjohn J, Berry R. Recognition of nectin-2 by the natural killer cell receptor T cell immunoglobulin and ITIM domain (TIGIT). *J Biol Chem* 2017;292:11413–22. <https://doi.org/10.1074/jbc.M117.786483>.
 86. Johnston RJ, Comps-Agrar L, Hackney J, Yu X, Huseni M, Yang Y. *et al.* The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. *Cancer Cell* 2014;26:923–37. <https://doi.org/10.1016/j.ccell.2014.10.018>.
 87. Joller N, Lozano E, Burkett PR, Patel B, Xiao S, Zhu C. *et al.* Treg cells expressing the coinhibitory molecule TIGIT selectively inhibit proinflammatory Th1 and Th17 cell responses. *Immunity* 2014;40:569–81. <https://doi.org/10.1016/j.immuni.2014.02.012>.
 88. Lucca LE, Axisa PP, Singer ER, Nolan NM, Dominguez-Villar M, Hafler DA. TIGIT signaling restores suppressor function of Th1 Tregs. *JCI Insight* 2019;4:e124427. <https://doi.org/10.1172/jci.insight.124427>.
 89. Lee DJ. The relationship between TIGIT(+) regulatory T cells and autoimmune disease. *Int Immunopharmacol* 2020;83:106378. <https://doi.org/10.1016/j.intimp.2020.106378>.
 90. Zhang Y, Maksimovic J, Naselli G, Qian J, Chopin M, Blewitt ME. *et al.* Genome-wide DNA methylation analysis identifies hypomethylated genes regulated by FOXP3 in human regulatory T cells. *Blood* 2013;122:2823–36. <https://doi.org/10.1182/blood-2013-02-481788>.
 91. de Lima MHF, Hiroki CH, de Fatima BV, Cebinelli GCM, Santos J, Rosa MH. *et al.* Sepsis-induced immunosuppression is marked by an expansion of a highly suppressive repertoire of FOXP3+ T-regulatory cells expressing TIGIT. *J Infect Dis* 2022;225:531–41. <https://doi.org/10.1093/infdis/jiab405>.
 92. Liu YC, Shou ST, Chai YF. Immune checkpoints in sepsis: new hopes and challenges. *Int Rev Immunol* 2022;41:207–16. <https://doi.org/10.1080/08830185.2021.1884247>.
 93. Webb GJ, Hirschfield GM, Lane PJ. OX40, OX40L and autoimmunity: a comprehensive review. *Clin Rev Allergy Immunol* 2016;50:312–32. <https://doi.org/10.1007/s12016-015-8498-3>.
 94. Ruby CE, Yates MA, Hirschhorn-Cymerman D, Chlebeck P, Wolchok JD, Houghton AN. *et al.* Cutting edge: OX40 agonists can drive regulatory T cell expansion if the cytokine milieu is right. *J Immunol* 2009;183:4853–7. <https://doi.org/10.4049/jimmunol.10901112>.
 95. Xiao X, Gong W, Demirci G, Liu W, Spoerl S, Chu X. *et al.* New insights on OX40 in the control of T cell immunity and immune tolerance in vivo. *J Immunol* 2012;188:892–901. <https://doi.org/10.4049/jimmunol.1101373>.
 96. Vu MD, Xiao X, Gao W, Degauque N, Chen M, Kroemer A. *et al.* OX40 costimulation turns off Foxp3+ Tregs. *Blood* 2007;110:2501–10. <https://doi.org/10.1182/blood-2007-01-070748>.
 97. Lu Y, An L, Liu Q, Li C. Expression and clinical correlations of costimulatory molecules on peripheral T lymphocyte subsets of early-stage severe sepsis: a prospective observational study. *Shock* 2018;49:631–40. <https://doi.org/10.1097/SHK.0000000000001017>.
 98. Delgoffe GM, Woo SR, Turnis ME, Gravano DM, Guy C, Overacre AE. *et al.* Stability and function of regulatory T cells is maintained by a neuropilin-1-semaphorin-4a axis. *Nature* 2013;501:252–6. <https://doi.org/10.1038/nature12428>.
 99. Xu J, Li X, Yuan Q, Wang C, Xu L, Wei X. *et al.* The semaphorin 4A-neuropilin 1 axis alleviates kidney ischemia reperfusion injury by promoting the stability and function of regulatory T cells. *Kidney Int* 2021;100:1268–81. <https://doi.org/10.1016/j.kint.2021.08.023>.
 100. Gao Y, Zhang X, Wang Z, Qiu Y, Liu Y, Shou S. *et al.* The contribution of neuropilin-1 in the stability of CD4(+) CD25(+) regulatory T cells through the TGF- β 1/Smads signaling pathway in the presence of lipopolysaccharides. *Immun Inflamm Dis* 2022;10:143–54. <https://doi.org/10.1002/iid3.551>.
 101. Gao YL, Wang CX, Wang ZY, Li WJ, Liu YC, Shou ST. *et al.* Targeting Neuropilin-1 suppresses the stability of CD4(+) CD25(+) regulatory T cells via the NF- κ B Signaling pathway in sepsis. *Infect Immun* 2021;89:e00399–20.
 102. Glinka Y, Prud'homme GJ. Neuropilin-1 is a receptor for transforming growth factor beta-1, activates its latent form, and promotes regulatory T cell activity. *J Leukoc Biol* 2008;84:302–10. <https://doi.org/10.1189/jlb.0208090>.
 103. Glinka Y, Stoilova S, Mohammed N, Prud'homme GJ. Neuropilin-1 exerts co-receptor function for TGF- β -1 on the membrane of cancer cells and enhances responses to both latent and active TGF- β . *Carcinogenesis* 2011;32:613–21.
 104. Mizumoto N, Kumamoto T, Robson SC, Sévigny J, Matsue H, Enjyoji K. *et al.* CD39 is the dominant Langerhans cell-associated ecto-NTPDase: modulatory roles in inflammation and immune responsiveness. *Nat Med* 2002;8:358–65. <https://doi.org/10.1038/nm0402-358>.
 105. Borsellino G, Kleinewietfeld M, Di Mitri D, Sternjak A, Diamantini A, Giometto R. *et al.* Expression of ectonucleotidase CD39 by Foxp3+ Treg cells: hydrolysis of extracellular ATP and immune suppression. *Blood* 2007;110:1225–32. <https://doi.org/10.1182/blood-2006-12-064527>.
 106. Kobie JJ, Shah PR, Yang L, Rebhahn JA, Fowell DJ, Mosmann TR. T regulatory and primed uncommitted CD4 T cells express CD73, which suppresses effector CD4 T cells by converting 5'-adenosine monophosphate to adenosine. *J Immunol* 2006;177:6780–6. <https://doi.org/10.4049/jimmunol.177.10.6780>.
 107. Huang H, Xu R, Lin F, Bao C, Wang S, Ji C. *et al.* High circulating CD39(+) regulatory T cells predict poor survival for sepsis patients. *Int J Infect Dis* 2015;30:57–63. <https://doi.org/10.1016/j.ijid.2014.11.006>.
 108. Bao R, Shui X, Hou J, Li J, Deng X, Zhu X. *et al.* Adenosine and the adenosine A2A receptor agonist, CGS21680, upregulate CD39 and CD73 expression through E2F-1 and CREB in regulatory T cells isolated from septic mice. *Int J Mol Med* 2016;38:969–75. <https://doi.org/10.3892/ijmm.2016.2679>.
 109. Kumar V. Pulmonary innate immune response determines the outcome of inflammation during pneumonia and sepsis-associated acute lung injury. *Front Immunol* 2020;11:1722. <https://doi.org/10.3389/fimmu.2020.01722>.
 110. Xia H, Wang F, Wang M, Wang J, Sun S, Chen M. *et al.* Maresin1 ameliorates acute lung injury induced by sepsis through regulating Th17/Treg balance. *Life Sci* 2020;254:117773. <https://doi.org/10.1016/j.lfs.2020.117773>.
 111. Zhao J, Liu Y, Hu JN, Peng M, Dong N, Zhu XM. *et al.* Autocrine regulation of Interleukin-3 in the activity of regulatory T cells and its effectiveness in the pathophysiology of sepsis. *J Infect Dis* 2021;223:893–904. <https://doi.org/10.1093/infdis/jiaa441>.
 112. Xu R, Jacques LC, Khandaker S, Beentjes D, Leon-Rios M, Wei X. *et al.* TNFR2(+) regulatory T cells protect against bacteremic pneumococcal pneumonia by suppressing IL-17A-producing $\gamma\delta$ T cells in the lung. *Cell Rep* 2023;42:112054. <https://doi.org/10.1016/j.celrep.2023.112054>.
 113. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019;96:1083–99. <https://doi.org/10.1016/j.kint.2019.05.026>.
 114. Zhou X, Yao J, Lin J, Liu J, Dong L, Duan M. Th17/regulatory T-cell imbalance and acute kidney injury in patients with sepsis. *J Clin Med* 2022;11:4027. <https://doi.org/10.3390/jcm11144027>.
 115. do Valle Duraes F, Lafont A, Beibel M, Martin K, Darribat K, Cuttat R. *et al.* Immune cell landscaping reveals a protective role for regulatory T cells during kidney injury and fibrosis. *JCI Insight* 2020;5:e130651.
 116. Chung HY, Wickel J, Brunkhorst FM, Geis C. Sepsis-associated encephalopathy: from delirium to dementia? *J Clin Med* 2020;9:703. <https://doi.org/10.3390/jcm9030703>.
 117. Ren C, Yao RQ, Zhang H, Feng YW, Yao YM. Sepsis-associated encephalopathy: a vicious cycle of immunosuppression.

- J Neuroinflammation* 2020;17:14. <https://doi.org/10.1186/s12974-020-1701-3>.
118. Sonnevile R, de Montmollin E, Poujade J, Garrouste-Orgeas M, Souweine B, Darmon M. *et al.* Potentially modifiable factors contributing to sepsis-associated encephalopathy. *Intensive Care Med* 2017;43:1075–84. <https://doi.org/10.1007/s00134-017-4807-z>.
 119. Saito M, Fujinami Y, Ono Y, Ohyama S, Fujioka K, Yamashita K. *et al.* Infiltrated regulatory T cells and Th2 cells in the brain contribute to attenuation of sepsis-associated encephalopathy and alleviation of mental impairments in mice with polymicrobial sepsis. *Brain Behav Immun* 2021;92:25–38. <https://doi.org/10.1016/j.bbi.2020.11.010>.
 120. Chang CL, Chen HH, Chen KH, Chiang JY, Li YC, Lin HS. *et al.* Adipose-derived mesenchymal stem cell-derived exosomes markedly protected the brain against sepsis syndrome induced injury in rat. *Am J Transl Res* 2019;11:3955–71.
 121. Strnad P, Tacke F, Koch A, Trautwein C. Liver - guardian, modifier and target of sepsis. *Nat Rev Gastroenterol Hepatol* 2017;14:55–66. <https://doi.org/10.1038/nrgastro.2016.168>.
 122. Yeh CL, Tanuseputero SA, Wu JM, Tseng YR, Yang PJ, Lee PC. *et al.* Intravenous arginine administration benefits CD4(+) T-cell homeostasis and attenuates liver inflammation in mice with polymicrobial sepsis. *Nutrients* 2020;12:1047. <https://doi.org/10.3390/nu12041047>.
 123. Gray CC, Biron-Girard B, Wakeley ME, Chung CS, Chen Y, Quiles-Ramirez Y. *et al.* Negative immune checkpoint protein, VISTA, regulates the CD4(+) T(reg) population during sepsis progression to promote acute sepsis recovery and survival. *Front Immunol* 2022;13:861670. <https://doi.org/10.3389/fimmu.2022.861670>.
 124. Wang P, Shi B, Wang C, Wang Y, Que W, Jiang Z. *et al.* Hepatic pannexin-1 mediates ST2(+) regulatory T cells promoting resolution of inflammation in lipopolysaccharide-induced endotoxemia. *Clin Transl Med* 2022;12:e849. <https://doi.org/10.1002/ctm2.849>.
 125. Huo R, Wang L, Wang X, Zhao Y, Wang Y, Zhao X. *et al.* Removal of regulatory T cells prevents secondary chronic infection but increases the mortality of subsequent sub-acute infection in sepsis mice. *Oncotarget* 2016;7:10962–75. <https://doi.org/10.18632/oncotarget.7682>.
 126. Huppert LA, Green MD, Kim L, Chow C, Leyfman Y, Daud AI. *et al.* Tissue-specific Tregs in cancer metastasis: opportunities for precision immunotherapy. *Cell Mol Immunol* 2022;19:33–45. <https://doi.org/10.1038/s41423-021-00742-4>.
 127. Hu ZQ, Yao YM, Chen W, Bian JL, Zhao LJ, Chen LW. *et al.* Partial depletion of regulatory T cells enhances host inflammatory response against acute *Pseudomonas aeruginosa* infection after sepsis. *Inflammation* 2018;41:1780–90. <https://doi.org/10.1007/s10753-018-0821-8>.
 128. Nemeth ZH, Csoka B, Wilmanski J, Xu D, Lu Q, Ledent C. *et al.* Adenosine A2A receptor inactivation increases survival in polymicrobial sepsis. *J Immunol* 2006;176:5616–26. <https://doi.org/10.4049/jimmunol.176.9.5616>.
 129. Bao R, Hou J, Li Y, Bian J, Deng X, Zhu X. *et al.* Adenosine promotes Foxp3 expression in Treg cells in sepsis model by activating JNK/AP-1 pathway. *Am J Transl Res* 2016;8:2284–92.
 130. Zhang T, Fu W, Liu D, He Y, Wang J, Ma T. Adenosine influences Foxp3 expression of T regs via the A2ar/Creb pathway in a mouse model of sepsis. *Shock* 2024;61:924–33.
 131. Zhang T, Zhao J, Zheng T, Fu W, Ma T. Adenosine 2A receptor antagonists promote lymphocyte proliferation in sepsis by inhibiting Treg expression of PD-L1 in spleen. *Immunology* 2024;171:566–82. <https://doi.org/10.1111/imm.13744>.
 132. Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y. *et al.* Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. *Cancer Cell* 2022;40:201–218.e9. <https://doi.org/10.1016/j.ccc.2022.01.001>.
 133. Ding R, Yu X, Hu Z, Dong Y, Huang H, Zhang Y. *et al.* Lactate modulates RNA splicing to promote CTLA-4 expression in tumor-infiltrating regulatory T cells. *Immunity* 2024;57:528–540.e6. <https://doi.org/10.1016/j.immuni.2024.01.019>.
 134. Gu J, Zhou J, Chen Q, Xu X, Gao J, Li X. *et al.* Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF- β signaling in regulatory T cells. *Cell Rep* 2022;39:110986. <https://doi.org/10.1016/j.celrep.2022.110986>.
 135. Zhou J, Gu J, Qian Q, Zhang Y, Huang T, Li X. *et al.* Lactate supports Treg function and immune balance via MGAT1 effects on N-glycosylation in the mitochondria. *J Clin Invest* 2024;134:e175897. <https://doi.org/10.1172/JCI175897>.
 136. Watson MJ, Vignali PDA, Mullett SJ, Overacre-Delgoffe AE, Peralta RM, Grebinoski S. *et al.* Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. *Nature* 2021;591:645–51. <https://doi.org/10.1038/s41586-020-03045-2>.
 137. Kim YS, Jeong YS, Bae GH, Kang JH, Lee M, Zabel BA. *et al.* CD200R(high) neutrophils with dysfunctional autophagy establish systemic immunosuppression by increasing regulatory T cells. *Cell Mol Immunol* 2024;21:349–61. <https://doi.org/10.1038/s41423-024-01136-y>.
 138. Zhang H, Wang Y, Qu M, Li W, Wu D, Cata JP. *et al.* Neutrophil, neutrophil extracellular traps and endothelial cell dysfunction in sepsis. *Clin Transl Med* 2023;13:e1170. <https://doi.org/10.1002/ctm2.1170>.
 139. Kumar S, Payal N, Srivastava VK, Kaushik S, Saxena J, Jyoti A. Neutrophil extracellular traps and organ dysfunction in sepsis. *Clin Chim Acta* 2021;523:152–62. <https://doi.org/10.1016/j.cca.2021.09.012>.
 140. Wang H, Zhang H, Wang Y, Brown ZJ, Xia Y, Huang Z. *et al.* Regulatory T-cell and neutrophil extracellular trap interaction contributes to carcinogenesis in non-alcoholic steatohepatitis. *J Hepatol* 2021;75:1271–83. <https://doi.org/10.1016/j.jhep.2021.07.032>.
 141. Chen Y, Wang L, Liu M, Zhao J, Xu X, Wei D. *et al.* Mechanism of exosomes from adipose-derived mesenchymal stem cells on sepsis-induced acute lung injury by promoting TGF-beta secretion in macrophages. *Surgery* 2023;174:1208–19. <https://doi.org/10.1016/j.surg.2023.06.017>.
 142. Zheng LY, Duan Y, He PY, Wu MY, Wei ST, Du XH. *et al.* Dysregulated dendritic cells in sepsis: functional impairment and regulated cell death. *Cell Mol Biol Lett* 2024;29:81. <https://doi.org/10.1186/s11658-024-00602-9>.
 143. Kushwah R, Wu J, Oliver JR, Jiang G, Zhang J, Siminovitch KA. *et al.* Uptake of apoptotic DC converts immature DC into tolerogenic DC that induce differentiation of Foxp3+ Treg. *Eur J Immunol* 2010;40:1022–35. <https://doi.org/10.1002/eji.200939782>.
 144. Barnes MJ, Li CM, Xu Y, An J, Huang Y, Cyster JG. The lysophosphatidylserine receptor GPR174 constrains regulatory T cell development and function. *J Exp Med* 2015;212:1011–20. <https://doi.org/10.1084/jem.20141827>.
 145. Qiu D, Chu X, Hua L, Yang Y, Li K, Han Y. *et al.* Gpr174-deficient regulatory T cells decrease cytokine storm in septic mice. *Cell Death Dis* 2019;10:233. <https://doi.org/10.1038/s41419-019-1462-z>.
 146. Yue X, Lio CJ, Samaniego-Castruita D, Li X, Rao A. Loss of TET2 and TET3 in regulatory T cells unleashes effector function. *Nat Commun* 2019;10:2011. <https://doi.org/10.1038/s41467-019-09541-y>.
 147. Nakatsukasa H, Oda M, Yin J, Chikuma S, Ito M, Koga-Iizuka M. *et al.* Loss of TET proteins in regulatory T cells promotes abnormal proliferation, Foxp3 destabilization and IL-17 expression. *Int Immunol* 2019;31:335–47. <https://doi.org/10.1093/intimm/dxz008>.
 148. Wu Q, Carlos AR, Braza F, Bergman ML, Kitoko JZ, Bastos-Amador P. *et al.* Ferritin heavy chain supports stability and

- function of the regulatory T cell lineage. *EMBO J* 2024;43:1445–83. <https://doi.org/10.1038/s44318-024-00064-x>.
149. Zhang H, Wu T, Ren C, Dong N, Wu Y, Yao Y. p53 promotes the expansion of regulatory T cells via DNMT3a- and TET2- mediated Foxp3 expression in sepsis. *Burns Trauma* 2023;11:tkad021.
 150. Durand M, Hagimont E, Louis H, Asfar P, Fripiat JP, Singer M. *et al.* The β 1 -adrenergic receptor contributes to sepsis-induced immunosuppression through modulation of regulatory T-cell inhibitory function. *Crit Care Med* 2022;50:e707–18. <https://doi.org/10.1097/CCM.0000000000005503>.
 151. Wu Z, Liu X, Huang W, Chen J, Li S, Chao J. *et al.* CIRP increases Foxp3(+) regulatory T cells and inhibits development of Th17 cells by enhancing TLR4-IL-2 signaling in the late phase of sepsis. *Int Immunopharmacol* 2024;132:111924. <https://doi.org/10.1016/j.intimp.2024.111924>.
 152. Li L, Lu YQ. The regulatory role of high-mobility group protein 1 in sepsis-related immunity. *Front Immunol* 2020;11:601815. <https://doi.org/10.3389/fimmu.2020.601815>.
 153. Zhou M, Zhang Y, Tang R, Liu H, Du M, Gao Z. *et al.* HMGB1/TLR4 Signaling affects regulatory T cells in acute lung injury. *J Inflamm Res* 2021;14:1551–61. <https://doi.org/10.2147/JIR.S302967>.
 154. Yuan Y, Yan D, Han G, Gu G, Ren J. Complement C3 depletion links to the expansion of regulatory T cells and compromises T-cell immunity in human abdominal sepsis: a prospective pilot study. *J Crit Care* 2013;28:1032–8. <https://doi.org/10.1016/j.jcrc.2013.09.007>.
 155. Chen X, Chen X, Yang Y, Luo N, Yang J, Zhong L. *et al.* Protective role of the novel cytokine Metrnl/ interleukin-41 in host immunity defense during sepsis by promoting macrophage recruitment and modulating Treg/Th17 immune cell balance. *Clin Immunol* 2023;254:109690. <https://doi.org/10.1016/j.clim.2023.109690>.
 156. Slim MA, van Mourik N, Bakkerus L, Fuller K, Acharya L, Gianidis T. *et al.* Towards personalized medicine: a scoping review of immunotherapy in sepsis. *Crit Care* 2024;28:183. <https://doi.org/10.1186/s13054-024-04964-6>.
 157. Zhang S, Shan J, Jie Y, Zhang X, Zhu M, Shen J. *et al.* Inhibition of PI3K p110delta rebalanced Th17/Treg and reduced macrophages pyroptosis in LPS-induced sepsis. *Mol Immunol* 2024;170:110–8. <https://doi.org/10.1016/j.molimm.2024.04.008>.
 158. Nadeem A, Al-Harbi NO, Ahmad SF, Al-Harbi MM, Alhamed AS, Alfardan AS. *et al.* Blockade of interleukin-2-inducible T-cell kinase signaling attenuates acute lung injury in mice through adjustment of pulmonary Th17/Treg immune responses and reduction of oxidative stress. *Int Immunopharmacol* 2020;83:106369. <https://doi.org/10.1016/j.intimp.2020.106369>.
 159. Xiong W, Xia J, Peng X, Tan Y, Chen W, Zhou M. *et al.* Novel therapeutic role of Ganoderma polysaccharides in a septic mouse model - the key role of macrophages. *Heliyon* 2024;10:e26732. <https://doi.org/10.1016/j.heliyon.2024.e26732>.
 160. Chen L, Liu X, Wang X, Lu Z, Ye Y. Berberine alleviates acute lung injury in septic mice by modulating Treg/Th17 homeostasis and downregulating NF-kappaB Signaling. *Drug Des Devel Ther* 2023;17:1139–51. <https://doi.org/10.2147/DDDT.S401293>.
 161. Koprivica I, Gajic D, Pejnovic N, Paunovic V, Saksida T, Stojanovic I. Ethyl pyruvate promotes proliferation of regulatory T cells by increasing glycolysis. *Molecules* 2020;25:4112. <https://doi.org/10.3390/molecules25184112>.
 162. Heuer JG, Zhang T, Zhao J, Ding C, Cramer M, Justen KL. *et al.* Adoptive transfer of in vitro-stimulated CD4+CD25+ regulatory T cells increases bacterial clearance and improves survival in polymicrobial sepsis. *J Immunol* 2005;174:7141–6. <https://doi.org/10.4049/jimmunol.174.11.7141>.
 163. Song H, Zhou Y, Li G, Bai J. Regulatory T cells contribute to the recovery of acute lung injury by upregulating Tim-3. *Inflammation* 2015;38:1267–72. <https://doi.org/10.1007/s10753-014-0096-7>.
 164. Gonzalez-Rey E, Anderson P, González MA, Rico L, Büscher D, Delgado M. Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis. *Gut* 2009;58:929–39. <https://doi.org/10.1136/gut.2008.168534>.
 165. Chao YH, Wu HP, Wu KH, Tsai YG, Peng CT, Lin KC. *et al.* An increase in CD3+CD4+CD25+ regulatory T cells after administration of umbilical cord-derived mesenchymal stem cells during sepsis. *PLoS One* 2014;9:e110338. <https://doi.org/10.1371/journal.pone.0110338>.
 166. Parolini O, Souza-Moreira L, O'Valle F, Magatti M, Hernandez-Cortes P, Gonzalez-Rey E. *et al.* Therapeutic effect of human amniotic membrane-derived cells on experimental arthritis and other inflammatory disorders. *Arthritis Rheumatol* 2014;66:327–39. <https://doi.org/10.1002/art.38206>.
 167. Zhuxiao R, Shuo Y, Jiangxue H, Jingjun P, Qi Z, Zhu W. *et al.* Antimicrobial peptide LL37 and regulatory T cell associated with late-onset sepsis in very preterm infants. *iScience* 2024;27:109780. <https://doi.org/10.1016/j.isci.2024.109780>.
 168. Lin M, Lei S, Chai Y, Xu J, Wang Y, Wu C. *et al.* Immunosuppressive microvesicles-mimetic derived from tolerant dendritic cells to target T-lymphocytes for inflammation diseases therapy. *J Nanobiotechnology* 2024;22:201. <https://doi.org/10.1186/s12951-024-02470-z>.
 169. Sun L, Fang K, Yang Z. Combination therapy with probiotics and anti-PD-L1 antibody synergistically ameliorates sepsis in mouse model. *Heliyon* 2024;10:e31747. <https://doi.org/10.1016/j.heliyon.2024.e31747>.
 170. Hotchkiss RS, Colston E, Yende S, Angus DC, Moldawer LL, Crouser ED. *et al.* Immune checkpoint inhibition in sepsis: a phase 1b randomized, placebo-controlled, single ascending dose study of Antiprogrammed cell death-ligand 1 antibody (BMS-936559). *Crit Care Med* 2019;47:632–42. <https://doi.org/10.1097/CCM.0000000000003685>.
 171. Patil NK, Guo Y, Luan L, Sherwood ER. Targeting immune cell checkpoints during sepsis. *Int J Mol Sci* 2017;18:2413. <https://doi.org/10.3390/ijms18112413>.
 172. Hiraki S, Ono S, Tsujimoto H, Kinoshita M, Takahata R, Miyazaki H. *et al.* Neutralization of interleukin-10 or transforming growth factor- β decreases the percentages of CD4+ CD25+ Foxp3+ regulatory T cells in septic mice, thereby leading to an improved survival. *Surgery* 2012;151:313–22. <https://doi.org/10.1016/j.surg.2011.07.019>.
 173. Zhao GJ, Lu ZQ, Tang LM, Wu ZS, Wang DW, Zheng JY. *et al.* Curcumin inhibits suppressive capacity of naturally occurring CD4+CD25+ regulatory T cells in mice in vitro. *Int Immunopharmacol* 2012;14:99–106. <https://doi.org/10.1016/j.intimp.2012.06.016>.
 174. Zheng YS, Wu ZS, Ni HB, Ke L, Tong ZH, Li WQ. *et al.* Codonopsis pilosula polysaccharide attenuates cecal ligation and puncture sepsis via circuiting regulatory T cells in mice. *Shock* 2014;41:250–5. <https://doi.org/10.1097/SHK.0000000000000091>.
 175. Hou YC, Wu JM, Wang MY, Wu MH, Chen KY, Yeh SL. *et al.* Modulatory effects of astragalus polysaccharides on T-cell polarization in mice with polymicrobial sepsis. *Mediat Inflamm* 2015;2015:826319. <https://doi.org/10.1155/2015/826319>.
 176. Zhao GJ, Yang XY, Zhang C, Dong W, Dong FB, Zhang J. *et al.* Supplementation WITH NICOTINAMIDE RIBOSIDE ATTENUATES T CELL EXHAUSTION AND IMPROVES SURVIVAL IN SEPSIS. *Shock* 2023;60:238–47. <https://doi.org/10.1097/SHK.0000000000002153>.
 177. Chen J, He X, Bai Y, Liu J, Wong YK, Xie L. *et al.* Single-cell transcriptome analysis reveals the regulatory effects of artemunate on splenic immune cells in polymicrobial sepsis. *J Pharm Anal* 2023;13:817–29. <https://doi.org/10.1016/j.jpha.2023.02.006>.
 178. Ono S, Kimura A, Hiraki S, Takahata R, Tsujimoto H, Kinoshita M. *et al.* Removal of increased circulating CD4+CD25+Foxp3+ regulatory T cells in patients with septic shock using hemoperfusion with polymyxin B-immobilized fibers. *Surgery* 2013;153:262–71. <https://doi.org/10.1016/j.surg.2012.06.023>.

179. Shoji H, Opal SM. Therapeutic rationale for endotoxin removal with polymyxin B immobilized Fiber column (PMX) for septic shock. *Int J Mol Sci* 2021;22:2228. <https://doi.org/10.3390/ijms22042228>.
180. Wang HW, Yang W, Gao L, Kang JR, Qin JJ, Liu YP. *et al.* Adoptive transfer of bone marrow-derived dendritic cells decreases inhibitory and regulatory T-cell differentiation and improves survival in murine polymicrobial sepsis. *Immunology* 2015;145: 50–9. <https://doi.org/10.1111/imm.12423>.
181. Cajander S, Kox M, Scicluna BP, Weigand MA, Mora RA, Flohé SB. *et al.* Profiling the dysregulated immune response in sepsis: overcoming challenges to achieve the goal of precision medicine. *Lancet Respir Med* 2024;12:305–22. [https://doi.org/10.1016/S2213-2600\(23\)00330-2](https://doi.org/10.1016/S2213-2600(23)00330-2).