frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 06 February 2024
DOI 10.3389/fimmu.2024.1328193

OPEN ACCESS

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RECEIVED 26 October 2023
ACCEPTED 16 January 2024
PUBLISHED 06 February 2024

CITATION
Goldmann O, Nwofor OV, Chen Q and Medina E (2024) Mechanisms underlying immunosuppression by regulatory cells. *Front. Immunol.* 15:1328193. doi: 10.3389/fimmu.2024.1328193

Mechanisms underlying immunosuppression by regulatory cells

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Regulatory cells, such as regulatory T cells (Tregs), regulatory B cells (Bregs), and myeloid-derived suppressor cells (MDSCs), play a crucial role in preserving immune tolerance and controlling immune responses during infections to prevent excessive immune activation. However, pathogens have developed strategies to hijack these regulatory cells to decrease the overall effectiveness of the immune response and persist within the host. Consequently, therapeutic targeting of these immunosuppressive mechanisms during infection can reinvigorate the immune response and improve the infection outcome. The suppressive mechanisms of regulatory cells are not only numerous but also redundant, reflecting the complexity of the regulatory network in modulating the immune responses. The context of the immune response, such as the type of pathogen or tissue involved, further influences the regulatory mechanisms involved. Examples of these immunosuppressive mechanisms include the production of inhibitory cytokines such as interleukin 10 (IL-10) and transforming growth factor beta (TGF-β) that inhibit the production of pro-inflammatory cytokines and dampen the activation and proliferation of effector T cells. In addition, regulatory cells utilize inhibitory receptors like cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) to engage with their respective effector cells, thereby suppressing their function. An alternative approach involves the modulation of metabolic reprogramming in effector immune cells to limit their activation and proliferation. In this review, we provide an overview of the major mechanisms mediating the immunosuppressive effect of the different regulatory cell subsets in the context of infection.

KEYWORDS

regulatory T cells, regulatory B cells, myeloid-derived suppressor cells, immunosuppressive mechanisms, infection

1 Introduction

The immune system plays an essential role in host defense against pathogens. However, the immune response during infection needs to be properly regulated in order to effectively eliminate the infecting agent while also avoiding the detrimental effect of an excessive inflammatory reaction. Achieving this balance is important for the maintenance of immune homeostasis and preventing autoimmunity. For example, failure to control hyperinflammatory responses can lead to a cytokine storm that ultimately results in death (1). On the other hand, excessive dampening of the immune response poses a risk, potentially hindering the clearance of pathogens and contributing to the chronicity of infection (2, 3). In order to prevent both excessive responses and chronic infections, the immune system has evolved several mechanisms orchestrated by diverse subsets of regulatory cells for regulating the intensity and duration of immune reactions. However, because these regulatory mechanisms are mostly immunosuppressive, many pathogens have evolved strategies to hijack the regulatory mechanisms of the host for their own advantage, thus generating conditions that ensure their survival and persistence within the host. Therefore, in the context of infection, adjunctive therapeutic approaches that aim to ameliorate or modulate these suppressive mechanisms may be beneficial for improving the infection outcome.

The most prominent regulatory cell subsets include regulatory T cells (Tregs), regulatory B cells (Bregs), and myeloid-derived suppressor cells (MDSCs). Tregs are a specialized population of T cells that regulate the activity of CD4+ and CD8+ T cells as well as natural killer (NK) cells and are an essential component for the proper functioning of the immune system (4, 5). They play a pivotal role in preventing autoimmune diseases by dampening the responses of self-reactive lymphocytes (6, 7). Tregs are characterized by the expression of CD4 and the interleukin-2 receptor α-chain (IL-2Rα), commonly known as CD25 (4). A defining feature of Tregs is the expression of the forkhead box transcription factor Foxp3, a master regulator that plays a critical role in their development and function (8–10). Tregs also control the immune response to infectious pathogens, and in this context, their activity is not always beneficial (11). For example, Tregs can hinder the development of sterilizing immunity against specific pathogens by preventing an effective immune response (11, 12).

While B cells are typically recognized for their role in initiating a humoral immune response through the production of antigen-specific antibodies (13), a distinct subset called regulatory B cells (Breg cells) deviates from this conventional function and contributes to immune regulation (14–16). Whereas the regulatory function of Bregs is critical for the maintenance of immune balance, it can also benefit certain pathogens (17).

MDSCs are immature myeloid cells with vigorous immune-suppressive activity involved in suppression of effective immune responses in many pathological conditions, including cancer, chronic inflammation, autoimmunity, and infections (18, 19). Various pathogens, including viruses, bacteria, and parasites, promote the expansion of MDSCs (20). The ability of MDSCs to dampen effector T-cell responses contributes to their immunosuppressive nature, impacting the overall efficacy of the immune system (21). This, in turn, favors pathogen persistence and the risk of chronicity following acute infection.

In the context of infection, interfering with the inhibitory mechanisms of regulatory cells may assist in the clearance of pathogens. However, a complete understanding of these immunosuppressive mechanisms is required prior to exploiting these novel therapeutic strategies. In this article, we review the mechanisms used by the different regulatory cell types to mediate immunosuppression.

2 Mechanisms of Treg-mediated immunosuppression

Tregs inhibit proliferation and production of cytokines after ligation of the receptor [T-cell receptor (TCR)] in effector CD4+ as well as the cytotoxic effect of CD8+ T cells (22, 23). While the main function of Tregs is to prevent excessive immune activation and the maintenance of tolerance to self-antigens (7), they have also been shown to have a significant negative impact on the immune responses to pathogens (11, 12, 24, 25). The diverse functions of Tregs are reflected in the existence of several types, each designated based on their source, generation, and effector mechanisms. The two major subsets identified are the thymus-derived naturally occurring Foxp3+ regulatory T cells (nTregs) and inducible regulatory T cells (iTregs), which develop from peripheral conventional CD4+ T cells in response to stimulus such as microbial products (26). Although both nTregs and iTregs play a significant role in infections due to their ability to control the intensity and duration of the effector responses, natural Tregs play a major role in mediating tolerance to self-antigens and inducible Tregs are the main players in the induction of tolerance to pathogens (27).

Tregs play a crucial and nuanced role in the immune response to various infections (12, 25). For example, in the case of infections caused by *Mycobacterium tuberculosis*, Tregs hinder an effective immune response against the pathogen by inhibiting the production of cytokines like interferon gamma (IFN-γ) or interleukin 17 (IL-17), which are essential for controlling *M. tuberculosis* (28). Indeed, Tregs are expanded in patients infected with *M. tuberculosis* and compromise protective IFN-γ responses and bacterial killing by macrophages (29–31). High amounts of Tregs capable of suppressing antigen-specific production of INF-γ by effector T cells have been found in patients with active tuberculosis (29, 32–34). Tregs have been also shown to expand and restrict bacterial clearance in the lungs of *M. tuberculosis*-infected mice (35). The Tregs arising in *M. tuberculosis*-infected mice proliferated faster than effector T cells and induced delayed recruitment of effector T cells into the infected lungs (36). Tregs have been also shown to suppress protective immunity in other bacterial infections, including those by *Streptococcus pneumoniae* (37), *Salmonella* (38), *Helicobacter pylori* (39), and *Listeria monocytogenes* (40). Tregs play also an important role in the outcome of acute and chronic viral infections, including herpes simplex virus (HSV) (41), human immunodeficiency virus (HIV) (42), hepatitis B virus

(HBV) (43), and hepatitis C virus (HCV) (44). Strategies that temporarily dampen the immune-suppressive mechanisms of Tregs could enhance the efficacy of infection therapies, allowing the immune system to mount a more robust response to the infecting agents.

Studies in humans and experimental models have revealed that Treg cells employ a variety of mechanisms to suppress immune responses, in both cell contact-dependent and cell contact-independent manners (45, 46). These mechanisms include a) production of suppressive cytokines such as IL-10, transforming growth factor beta (TGF-β), and IL-35; b) induction of cytolysis in effector cells; c) suppression of immune cells or function indirectly by modulating antigen-presenting cells; d) suppression of T cells via IL-2 consumption; and e) generation of immunosuppressive environments through adenosine production (45–47) (Figure 1). The different suppressive mechanisms of Tregs are described in more detail in the following sections.

2.1 Production of suppressive cytokines

The suppressive cytokines TGF-β and IL-10 have been reported to be involved in Treg-mediated immunosuppression (48–50). The engagement of IL-10 with its receptor on monocytes and macrophages triggers the activation of the Janus kinase/signal transduce and activator of transcription (JAK/STAT) signaling cascade (51). The activation of this pathway by IL-10 results in profound changes in expression of immunomodulatory genes that lead to the inhibition of pro-inflammatory mediator production, decreased antigen presentation capacity, and impaired phagocytosis (51). TGF-β signaling involves activation of suppressor of mothers against decapentaplegic (SMAD) transcription factors (52). TGF-β blocks T helper type 1 (Th1) differentiation and effector functions (53) and silences the expression of IL-2, which is required for T-cell proliferation (54). Furthermore, TGF-β inhibits the antigen presentation capacity of dendritic cells by suppressing expression of major histocompatibility complex (MHC) class II genes (55). Several studies have also reported the ability of Tregs to suppress CD8+ T-lymphocyte cytotoxicity via TGF-β (50, 56) and to suppress differentiation of CD4+ T cells into Th1 effectors (57). Furthermore, TGF-β produced by Tregs induces infectious tolerance by further promoting naive T cells to become immunosuppressive cells, thus leading to long-term propagation of the effects provoked by Tregs (58–61).

Contrary to the perception of TGF-β as a dominant mechanism of Treg suppression, some studies have presented challenges to this notion (62, 63). The findings that the addition of anti-IL-10 or anti-TGF-β antibodies did not impact the suppressive effect of human Treg cells in *in vitro* assays imply that Treg-mediated suppression may involve alternative mechanisms beyond the classical role attributed to IL-10 or TGF-β (64). The diverse functions of IL-10 and TGF-β in Treg-induced suppression in different specific pathologies may provide an explanation for these discrepancies. Addressing these discrepancies and understanding the specific

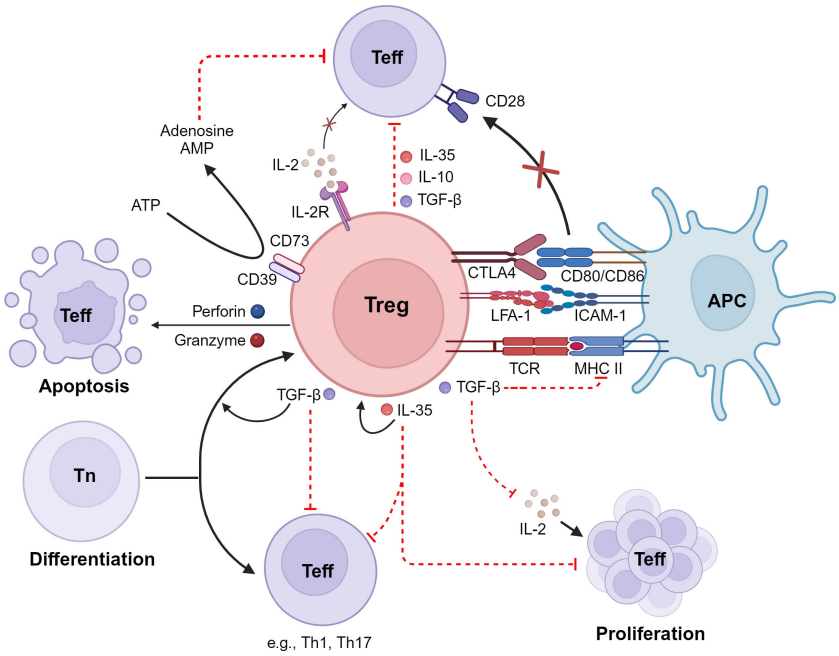

FIGURE 1
Immunosuppressive mechanisms of Tregs. Tregs inhibit effector T cells (Teff) by 1) the release of inhibitory cytokines, including IL-10, TGF-β, and IL-35; 2) exerting of cytotoxic effects on Teff as well as on antigen-presenting cells (APCs); 3) interference with Teff proliferation via consumption and depletion of IL-2; 4) metabolic disruption; and 5) interference with differentiation of naive T cells (Tn) into Teff. LFA-1, lymphocyte function-associated antigen 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; IDO, indoleamine 2,3-dioxygenase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate. Created with BioRender.com.

conditions under which these cytokines operate is crucial for a better understanding of Treg function.

IL-35 is an additional inhibitory cytokine that contributes to Treg function (65). IL-35 not only has the ability to directly suppress effector T-cell effector functions and proliferation (65), but it is also able to propagate infectious tolerance by expanding a vigorous population of inducible Tregs (66). Furthermore, IL-35 produced by Tregs can inhibit the capacity of CD4+ T cells to differentiate into Th17 effector cells (67).

2.2 Induction of cytolysis in effector cells

Activated human natural Treg cells have been shown to exert cytotoxic activity against various cell types, including monocytes, dendritic cells, and CD4+ and CD8+ T cells (68). This cytotoxic effect is mediated by the perforin/granzyme pathway and is dependent on CD18 adhesive interactions (68). In the perforin/granzyme pathway, perforin and granzymes synergize to mediate apoptosis of target cells such T cells, monocytes, and dendritic cells (69). Thus, perforin induces pores in the target cell membrane and granzymes induce cell death after diffusing into the intracellular compartment through the perforin pores (69). Natural Tregs have been shown to predominantly express granzyme A, whereas iTregs express granzyme B upon activation, but both exert cytotoxicity against autologous targets via perforin (68). Granzyme A and B differ in their target cell-killing mechanism. Granzyme A induces a caspase-independent form of cell death that includes apoptotic features such as DNA damage (70). In contrast, granzyme B triggers apoptosis through a different route by directly cleaving caspases and caspase substrates (71). The differential modes of action of granzyme A and granzyme B exemplify the adaptability of Tregs in utilizing various cytotoxic mechanisms based on the specific context and the nature of the target cell.

2.3 Modulation of antigen-presenting cell function

Tregs can also inhibit immune responses by modulating the activity of antigen-presenting cells such as dendritic cells (72–74). In this regard, it has been reported that antigen-specific Tregs can inhibit antigen presentation to T cells by strongly binding to dendritic cells (72). This tight interaction reduces the capacity of dendritic cells to present antigens by promoting the removal of cognate peptide/MHC class II complex (72). Adhesion of Tregs to dendritic cells is mediated by lymphocyte function-associated antigen 1 (LFA-1), which exhibits an extraordinarily high strength binding as a consequence of a reduced calpain activities within these cells (73). The decreased calpain activities result in a deficiency in the normal process of integrin recycling, leading to sustained presence of LFA-1 on the cell surface. Consequently, Tregs exhibit prolonged binding to dendritic cells, limiting the physical interactions of dendritic cells with cognate conventional T cells and thereby reducing the capacity of dendritic cells to prime T cells (73).

Co-stimulation by CD28 binding to CD80 and CD86 expressed by antigen-presenting cells is essential for effective T-cell expansion and differentiation (75). Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) can also bind CD80 and CD86 on antigen-presenting cells, but in contrast to CD28, this molecule is a negative regulator and inhibits T-cell responses (76). Tregs express high levels of CTLA-4, which seems to be an important means of immunosuppression (77–80). Several mechanisms that mediate the inhibitory activity of CTLA-4 have been proposed, including the downregulation of ligand expression and transmission of inhibitory signals (76, 81). Furthermore, CTLA-4 has a superior affinity for CD80 and CD86 molecules than for CD28 (82). By outcompeting with CD28, CTLA-4 downregulates the co-stimulatory signals required for optimal activation of conventional T cells. Tregs can also induce tolerogenic dendritic cells through CTLA-4 engagement-induced tryptophan catabolism (83, 84). Thus, Tregs can stimulate dendritic cells to produce the enzyme indoleamine 2,3-dioxygenase (IDO), which catabolizes the conversion of tryptophan to kynurenine, which is toxic to T cells (85).

2.4 Other immunosuppressive mechanisms

Tregs are extremely dependent on IL-2 for their maintenance and functionality, but they lack the capability to produce IL-2 themselves (86–88). Therefore, Tregs rely on the external supply of IL-2, typically provided by activated effector T cells and other immune cells in their microenvironment. Since IL-2 is also critical for the survival and proliferation of effector T cells (89), it has been suggested that one mechanism of Treg suppression of effector T-cell activation is by depriving effector T cells of IL-2 (90–92). An additional suppressing mechanism of Tregs is mediated by the release of high levels of adenosine in the extracellular environment (93). Tregs, in contrast to conventional T cells, express high amounts of CD39 and CD73 on the cell surface, which are nucleotidases capable of producing extracellular adenosine from adenosine triphosphate (ATP) (94–96). Thus, the coordinated action of CD39 and CD72 allows Tregs to generate extracellular adenosine from ATP. The interaction of extracellular adenosine with the adenosine A2A receptor on conventional T cells results in increased cyclic adenosine monophosphate (cAMP) levels, subsequent activation of protein kinase A, and inhibition of T-cell activation (97–99).

3 Mechanisms of Breg-mediated immunosuppression

B cells are typically known for their role in the adaptive immune response, including antigen presentation, cytokine secretion, and production of pathogen-specific antibodies (100). However, a subset of B cells with immunomodulatory activity has been identified and termed Bregs (15, 16). Identifying specific phenotypic markers for Bregs has been a challenge, and the characterization of these cells is an area of ongoing research

(101). However, several B-cell subsets with regulatory functions have been reported in humans and mice based on their capacity to inhibit effective immune responses *in vivo* or *in vitro* (102). The main Breg subsets identified in humans include CD19+CD24+CD38+ (103) and CD19+CD24^{hi}CD27+ (104), and in mice, CD19+CD5+CD1d^{hi} (105), CD5+CD19+B220^{low} (106), and CD19+CD25+CD1d^{hi} IgM^{hi}CD5^{-}CD23^{-}Tim-1^{-} (107). Nevertheless, it is important to note that, rather than relying solely on surface markers, the identification of Bregs is often based on functional assays, such as the ability to produce IL-10 or inhibit immune responses. Ongoing research is focused on gaining a deeper understanding of Breg biology, refining phenotypic markers and identifying markers that are consistently associated with regulatory functions across different contexts.

Generation of Bregs has been reported in a number of infectious diseases, including bacterial, viral, and parasitic infections (108). For example, Bregs have been shown to be involved in the pathogenesis of chronic HBV infection (109) and also to inhibit CD8+ T-cell proliferation and production of IFN-γ in patients infected with HIV (110). Bregs have been implicated in hampering the clearance of hepatitis B virus through the production of IL-10 (111). Also, during bacterial infections such as that by *L. monocytogenes*, expansion of Bregs that inhibit pathogen eradication has been observed in experimental infection in mice (112). A rapid accumulation of Bregs has also been detected in mice infected with *Salmonella typhimurium*, which was detrimental for the course of infection because they inhibited the protective activity mediated by CD4+ T cells, NK cells, and neutrophils (113).

Several mechanisms underlying the regulatory activity of Bregs have been described, including skewing T-cell differentiation toward Tregs (114–116). This skewing process seems to take place by a direct cell–cell interaction between Bregs and T cells as suggested by the requirement of the expression of CD40 and MHC class II (105, 117, 118). It has also been reported that Bregs enter the T-cell zone in lymphoid organs and make more frequent and longer contacts with both CD4+ and CD8+ T cells through direct cognate interaction compared to non-Breg (119). The increased and prolonged interaction between Bregs and T cells reduces the subsequent contacts between T cells and dendritic cells and thereby hinders the process of antigen presentation and subsequent T-cell activation (119). Bregs can also regulate humoral immunity by modulating the activity of follicular helper T cells, which is a population of T cells involved in the activation and differentiation of B cells into antibody-producing plasma cells (120). This effect is mediated by the expression of high levels of programmed death-ligand 1 (PD-L1) on Bregs that binds to PD-1 on T cells (120, 121). Binding of PD-1 to its ligand PD-L1 induces inhibition of the functionality and proliferation of effector T cells (122). However, most of the suppressive activities of Bregs are mediated by the release of high amounts of IL-10. Thus, Bregs can thwart differentiation of T cells toward Th1 or Th17 by inhibition of cytokine production by dendritic cells (123, 124) and promote Th2 cells and Foxp3+ Tregs by producing IL-10 (125, 126). It has been shown that Bregs produce IL-10 after interaction with *Leishmania major*, which leads to downregulation of IL-12 production by dendritic cells, thereby supporting Th2 responses that are detrimental for the proper control of this pathogen (127). Other studies have indicated that direct interaction between Bregs and dendritic cells results in IL-10-mediated deactivation of the dendritic cells, which can result in the suppression of CD8+ T cells (128). Accordingly, by producing IL-10, Bregs have been shown to contribute to the T-cell impairment observed during HIV (110) and chronic hepatitis B virus (109) infections.

In addition to the release of IL-10, Bregs can also modulate the immune response through the production of other suppressive cytokines such TGF-β and IL-35 (106, 129) as well as other immunomodulatory molecules such as adenosine (130, 131) and heat shock protein 70 (132). The different inhibitory mechanisms of Bregs are illustrated in Figure 2.

4 Suppressive mechanisms of MDSCs

MDSCs are considered an atypical population of myeloid cells that appear in many pathological disorders, including cancer, autoimmune diseases, and chronic infections, and exert strong suppressive activity on T cells (133). MDSCs originate from common myeloid progenitors but they do not undergo full maturation and remain in an immature differentiation status (19, 134). Phenotypically, MDSCs are commonly divided into two different subsets, monocytic and granulocytic, based on the expression of CD14+CD11b+CD33+HLA-DR− and CD15+CD11b+CD33+HLA-DR-, respectively, in humans (135). The phenotypic markers for murine monocytic MDSCs are CD11b+Ly6C+Ly6G^{low} and CD11b+Ly6C^{low}Ly6G+ for granulocytic MDSC (135). However, these markers are not exclusive to MDSCs and are also expressed by mature monocytes, neutrophils, and other hematopoietic precursor lineages (136). Additional markers such as the chemokine CCL6 have been identified in the murine system that enable to discriminate immature granulocytes precursors (Ly6G^{+}CCL6^{-}) from mature neutrophils (Ly6G^{+}CCL6^{+}) (134). Despite the additional markers, differentiation of MDSCs from other myeloid cells based on these phenotypic markers is rather challenging and functional assays that confirm their immunosuppressive activity are essential for a more definitive assessment. Furthermore, while monocytic and granulocytic subsets are commonly recognized, additional subsets and phenotypic variations have been described in various studies (137). The high degree of heterogeneity within the MDSC population has been clearly illustrated in the single-cell RNA sequencing (RNA-seq) analysis of MDSCs generated in mice during chronic *Staphylococcus aureus* infection performed in our laboratory. This analysis shows that the population of MDSCs comprised a continuum of myeloid cell precursors in different differentiation stages (134). The spectrum of myeloid cell precursors within the MDSC population can extend to earlier stages of myeloid differentiation, involving common myeloid progenitors. Expansion of MDSCs in the context of infection may be associated with emergency granulopoiesis, which involves a rapid release of immature myeloid cells into the circulation in response to the need for an elevated production of myeloid cells to combat the infection (134).

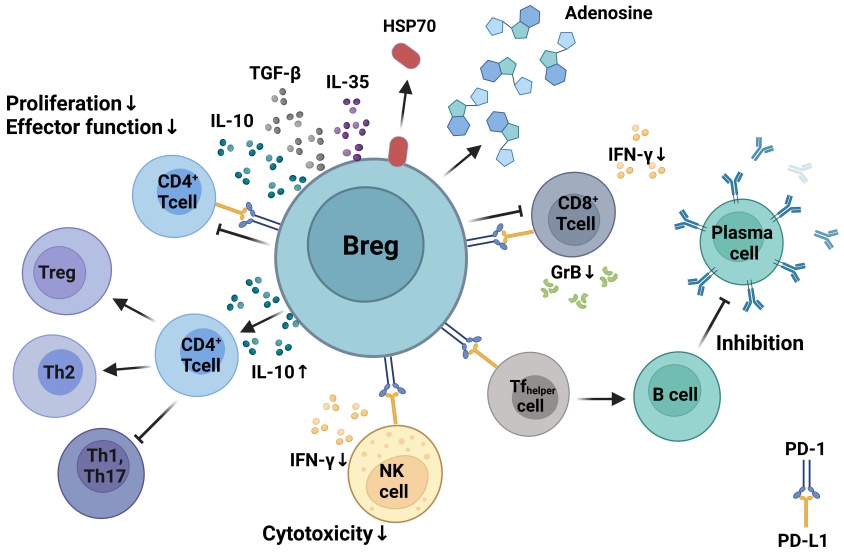

FIGURE 2
Mechanisms of Breg immunosuppression. Bregs can inhibit the proliferation, differentiation, and functionality of CD4+ and CD8+ T cells via production of IL-10. Bregs can regulate humoral immunity by modulating the activity of follicular T-helper cells via expression of programmed death-ligand 1 (PD-L1) that binds to PD-1 on T cells. Bregs inhibit CD8+ and CD4+ T-cell proliferation and differentiation by producing inhibitory molecules such as IL-10, TGF-β, adenosine, and heat shock protein 70. Bregs inhibit IFN-γ production and suppress the cytotoxicity of CD8+ T cells and NK cells. Created with BioRender.com.

MDSCs are known for their ability to suppress various components of the immune system, extending beyond T cells (138–142). They can exert inhibitory effects on other immune cell types, including B cells and NK cells (138–142). Many pathogens, including bacteria and viruses, promote expansion of MDSCs as a means of suppressing the immune response mounted by the host (20). In this regard, expansion of MDSCs has been associated with tuberculosis progression in humans (143) and mice (144, 145). The induction of MDSCs in response to *M. tuberculosis* has been implicated in the impaired ability of the host to eliminate the bacterium, thereby contributing to the development of tuberculosis disease (143). MDSCs have been reported to play an important role in chronic infections caused by *S. aureus*, a notorious pathogen known for its ability to cause challenging and difficult-to-treat chronic infections (146, 147). Thus, expansion of MDSCs has been linked to progressive dysfunction of T cells and failure to eliminate *S. aureus* in murine models of staphylococcal chronic abscess (146). In infected prosthetic joints, MDSCs have been shown to inhibit the pro-inflammatory activity of monocytes/macrophages, thereby facilitating the chronicity of *S. aureus* orthopedic biofilm infection (147). Increased frequency of MDSCs that inhibit protective T-cell responses via nitric oxide production has been also reported in mice infected with *Salmonella enterica* serovar Typhimurium (148).

The generation of MDSCs in many viral infections seems to contribute to the establishment of a chronic course (149, 150). Thus, immunosuppression of T-cell responses mediated by reactive oxygen species (ROS) produced by MDSCs has been shown to initiate and maintain HCV persistence (151). MDSCs also inhibit the production of IFN-γ, a key cytokine involved in anti-viral defense, by natural killer cells in patients infected with HCV via an arginase-1-dependent mechanism (140). Several studies have also reported elevated numbers of MDSCs in patients with chronic HIV infection, which dampen anti-HIV T-cell-mediated immune responses (152, 153) and promote the development of Tregs (154). An increased frequency of MDSCs has been observed in the peripheral blood of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), particularly those with severe disease (155). The expansion of MDSCs in SARS-CoV-2-infected patients appears to correlate with the severity of respiratory symptoms and the need for intensive care (155).

The mechanisms implicated in the suppressive activity of MDSC in the context of infections are described in the following section and summarized in Figures 3A, B.

4.1 Suppression mediated by arginine metabolism

L-Arginine is an essential amino acid that is critical for body physiology because it is required for protein synthesis and for the production of nitric oxide, creatine, and polyamines (156). L-Arginine accessibility is crucial for activation and proper functionality of T cells (157). Arginine can be metabolized either to nitric oxide by the activity of the nitric oxide synthase or to urea and L-ornithine by the activity of arginase enzymes (158). Metabolism of L-arginine by arginase-1 has been reported to be a substantial mechanism of MDSC suppression of T-cell responses by depleting L-arginine in the T-cell microenvironment (159, 160). L-Arginine starvation hampers T-cell responses by provoking an

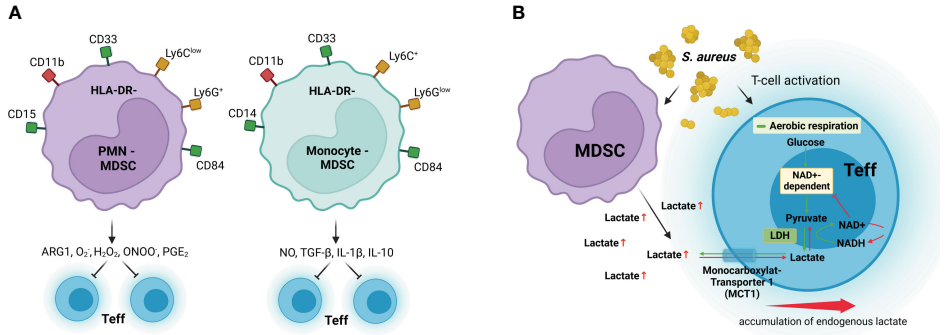

FIGURE 3
MDSC immunosuppressive mechanisms. **(A)** Granulocytic MDSCs (PMN-MDSC) preferentially use arginase 1 (ARG1), reactive oxygen species such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$) to inhibit effector T-cell (Teff) responses, whereas monocytic MDSCs (Monocyte-MDSC) preferentially use nitric oxide (NO), inhibitory cytokines such as TGF-β and IL-10, and the receptors CTLA-4 and PD-1, which induce anergy and apoptosis after binding their respective receptors in Teff. **(B)** MDSCs inhibit T-cell activation by excretion of high levels of lactate, which results in discontinuous glycolysis and impedes NAD+ regeneration from NADH in Teff. LDH, lactate dehydrogenase; NAD+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; MCT1, monocarboxylate transporter 1. Surface receptors of human MDSCs are shown in green and red, and surface receptors for murine MDSCs are shown in yellow and red. Created with BioRender.com.

arrest in the proliferation of activated T cells (161) as well as by reducing the expression of the CD3ζ chain (162, 163).

4.2 Suppression mediated by nitric oxide and reactive oxygen species

Nitric oxide produced in large amounts by MDSCs via arginase activity can suppress T-cell responses (164) and can obstruct T-cell migration by inhibiting vascular expression of E-selectin (165). Furthermore, nitric oxide has been suggested to trigger suppression of T-cell responses by altering key molecules in the signaling pathway induced after IL-2 binding to its surface receptor (166). Nitric oxide can also affect the stability of the IL-2 messenger RNA (mRNA), resulting in reduced IL-2 release by T cells (167).

MDSCs can also generate high levels of ROS, including hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and superoxide ($O2^-$), which can have damaging effects on nucleic acids, lipids, and proteins (168). Thus, ROS produced by MDSCs have been shown to suppress antigen-specific CD8+ T cells by inducing alterations in the T-cell receptor that impair the capacity of CD8+ T cells to bind MHC class I on antigen-presenting cells (169). MDSCs are capable of avoiding the toxic effects of the high levels of ROS that they generate by upregulating series of genes via nuclear factor erythroid 2-related factor 2 (Nrf2) that mitigate oxidative stress (170).

Similar to other regulatory cell populations described in the previous sections, MDSCs can also suppress T-cell responses by production of inhibitory cytokines such as IL-10 and TGF-β (141, 171, 172). For example, it has been reported that TGF-β produced by MDSCs hinders the functionality of NK cells by inhibiting their capacity to produce IFN-γ as well as their cytotoxic activity (141). Furthermore, MDSCs were shown to be able to induce other immunosuppressive cells such as Tregs in HIV-infected individuals (154).

4.3 Suppression by altering T-cell metabolism

Upon antigen recognition and activation via TCR, effector T cells proliferate extensively and develop effector functions. Through the activation process, T cells need to reprogram their metabolism from oxidative phosphorylation toward aerobic glycolysis to ensure the bioenergetic demands required for cell division and production of effector molecules (173–175). Glycolysis is the major pathway of glucose metabolism. In resting cells and under aerobic conditions, glucose is usually converted into pyruvate, which is further oxidized to generate acetyl-coenzyme A, which enters the mitochondria and undergoes further oxidation in the citric acid cycle. In the absence of oxygen, pyruvate is converted to lactate instead of entering the mitochondria to undergo oxidation. In proliferating cells, a significant portion of pyruvate is converted to lactate in the cytoplasm even in the presence of oxygen rather than entering the mitochondria and undergoing complete oxidation. This reaction is known as "aerobic glycolysis" (175). This is considered an adaptation to the rapid growth and high energy demands of proliferating cells (173–175). By using aerobic glycolysis, cells can quickly generate ATP and metabolic intermediates needed for the synthesis of macromolecules such as nucleotides, amino acids, and lipids, which are crucial for cell proliferation (173–175). During the conversion of pyruvate to lactate in aerobic glycolysis, reduced nicotinamide adenine dinucleotide (NADH) donates electrons to pyruvate, converting it to lactate and regenerating oxidized nicotinamide adenine dinucleotide (NAD+) (175). This process is essential during glycolysis and other metabolic pathways where NAD+ serves as a crucial cofactor for many enzymes (175). At the same time, the excess of lactate produced during aerobic glycolysis in proliferating cells needs to be exported from the cells to prevent the buildup of lactate, which could otherwise inhibit glycolysis. This export is facilitated by proton-linked monocarboxylate transporters that are dependent on a concentration gradient. Our group has reported that MDSCs generated during chronic *S. aureus*

infection in mice exhibit elevated glycolytic activity and release a high amount of lactate in the extracellular microenvironment (134). In further studies, we demonstrated that the high levels of lactate discharged by MDSCs change the transmembrane concentration gradient and inhibit lactate removal by activated CD4+ T cells (176). This results in an intracellular buildup of lactate that hinders the regeneration of NAD+, inhibits the activity of NAD-dependent glycolytic enzymes, and discontinues glycolysis (176). Therefore, an important mechanism of T-cell immunosuppression by MDSCs is disturbing their capacity to undergo metabolic reprogramming.

5 Clinical relevance and future perspectives

Targeting regulatory cells could be an attractive option for the therapy of infectious diseases, in particular those with a chronic course. However, elimination of regulatory cells could lead to immune dysregulation, contributing to the development of autoimmune diseases, inflammatory conditions, and risk of tissue damage caused by an overactive immune system. Therefore, modulation of the mechanisms mediating the immune-suppressive effect of regulatory cells may provide a more nuanced approach compared to direct elimination of these cells. For example, several regulatory cell subsets often exert their suppressive effects through the secretion of immunosuppressive cytokines, such as IL-10 and TGF-β. Targeting these cytokines or their receptors could be a strategy to modulate their suppressive activity. Surface molecules on regulatory cells, such as CTLA-4 and PD-1, are involved in immune suppression. Blocking these molecules or their ligands can disrupt the inhibitory signals. These strategies would enable the fine-tuning of the immune response to infection, promoting an appropriate and controlled reaction to pathogens while maintaining immune homeostasis. Additionally, targeting specific mechanisms should be context specific and consider the individual characteristics of the different infections. In this regard, precision medicine approaches that target suppressive mechanisms in a controlled and selective manner are desired. However, considering the wide spectrum of immunosuppressive mechanisms with redundant and overlapping functions in the different subsets of regulatory cells, it is possible to anticipate that one single strategy might not be sufficient to mount proper immune responses and effective immunotherapies will require multifaceted approaches. Therefore, effective immunotherapies will require combinatorial regimens to restore cell effector functions and improve the infection outcome by not only mitigating the effect of immunosuppressive mechanisms but also incorporating methods to control tissue damage produced by excessive inflammation.

The complexity of the regulatory network in most infections is a challenging yet crucial area of research. Understanding the intricate details of the immune regulatory mechanisms during infections can unveil critically important features that can inform the development of targeted therapies and enhance our ability to manipulate immune responses for improved outcomes in infectious diseases, in particular those with a persistent or chronic course.

Author contributions

OG: Writing – review & editing, Conceptualization, Writing – original draft. ON: Writing – review & editing, Writing – original draft. QC: Writing – review & editing, Writing – original draft. EM: Funding acquisition, Writing – original draft, Conceptualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by funding provided by the Deutsche Forschungsgemeinschaft (DFG, German research Foundation) - SFB 1583/1 - Project number: 492620490 and ME 187/6-1 - Project number: 514602564.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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