

Dampening antiviral immunity can protect the host

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Viral infections are very common, and in most cases, the virus is well controlled and eliminated by the immune system. Nevertheless, in some cases, damage of the host tissue inflicted by the virus itself or by the elicited immune response may result in severe disease courses. Thus, regulatory mechanisms are necessary to control virus-induced and immune pathology. This ensures immune responses are elicited in a potent but controlled manner. In this review, we will outline how immune regulation may contribute to this process. We focus on regulatory T cells and co-inhibitory receptors and outline how these two regulatory immune components allow for and may even promote potent but not pathologic immune responses. By enabling a balanced immune response, regulatory mechanisms can thus contribute to pathogen control as well as tissue and host protection.

Introduction

The main function of the immune system is to protect the body from infections that could cause damage and disease. To achieve this, the immune system uses several layers of defense ranging from physical barriers to specific recognition of individual antigens by the adaptive immune system. To cope with the diversity of pathogens, the mammalian immune system has evolved sophisticated recombination strategies to allow for the generation of an immense repertoire of antigen receptors, enabling it to recognize virtually all foreign antigens [1]. This enables the immune system to recognize pathogens it has never encountered before and protect the individual from infections.

Generally, protection from infections is achieved through elimination of the pathogen. However, clearance of pathogens, particularly viruses that reside and replicate inside the host's cells, does not come without

a price and, under certain circumstances, dampening of the immune response can be necessary to prevent collateral damage even if this impairs pathogen clearance (Fig. 1). On one hand, if viral infections are widespread, full elimination of the pathogen will cause massive tissue damage that could harm the host. In these cases, coexistence with a virus may be preferable for the individual. Indeed, this is a common occurrence and adults are estimated to carry approximately 8–12 chronic viral infections [2]. On the other hand, an overabounding but often unfocused immune response is the basis for the severe outcomes observed in patients infected with influenza virus, hepatitis A virus, respiratory syncytial virus (RSV), or the latest SARS-CoV-2 virus causing coronavirus disease (COVID)-19 [3–6]. Thus, a focused and controlled immune response is necessary to prevent a severe disease course. Several

Abbreviations

COVID, coronavirus disease; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HSV, herpes simplex virus; Lag-3, lymphocyte-activation gene 3; LCMV, lymphocytic choriomeningitis virus; PD-1, programmed cell death protein 1; RSV, respiratory syncytial virus; Th, T helper cell; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; Tim-3, T-cell immunoglobulin and mucin domain-containing protein 3; Treg, regulatory T cell.

regulatory mechanisms are in place to ensure immune responses are elicited in a controlled manner, including the control of immune responses by regulatory T cells (Tregs) and the fine-tuning of T cell activation through co-inhibitory receptors.

In this review, we will highlight how these regulatory mechanisms of the immune system can play a key role in establishing optimal conditions for host defense despite the fact that they are generally associated with inhibition of immunity. We will focus on Tregs and co-inhibitory receptors and outline how these two regulatory immune components allow and may even promote potent but not pathologic immune responses and thus contribute to tissue and host protection.

Role of regulatory T cells in infections

Regulatory T cells are a distinct subset of CD4⁺ T helper cells that play an essential role in maintaining immune tolerance and homeostasis by restraining autoimmune responses and excessive inflammation. Characterized by expression of the transcription factor Foxp3 and high levels of CD25 (IL-2R α), Tregs have been divided into thymically derived Tregs (tTregs) and peripherally induced Tregs (pTregs) according to their source [7,8]. Equipped with various inhibitory receptors and immunosuppressive molecules and cytokines, Tregs can efficiently inhibit the activation and effector functions of both innate and adaptive immune cells, and their dysfunction results in

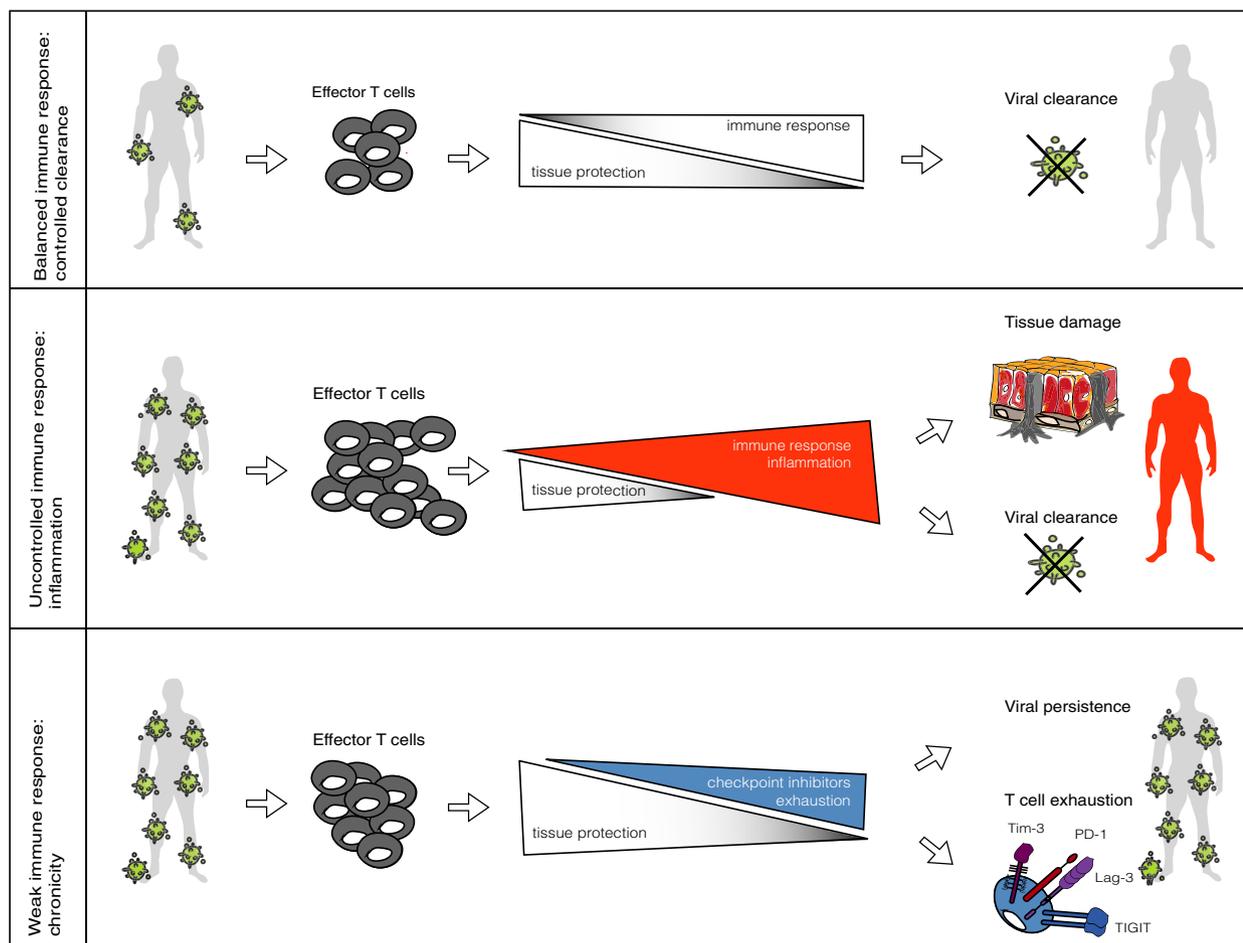


Fig. 1. Possible outcomes of anti-viral immunity. (Top) A balanced immune response following a moderate viral infection is cleared by a controlled effector T cell response and restoration of homeostasis. (Middle) Infection with a high viral dose results in a stronger effector T cell expansion, which clears the virus but also causes tissue damage due to the high dissemination of the virus or a dysregulated immune response due to the impaired regulatory pathways. (Bottom) High viral loads may also result in upregulation of checkpoint inhibitors and T cell exhaustion leading to a dampened immune response and viral persistence but less immune pathology.

autoimmune diseases and can lead to uncontrolled inflammation upon infection [9].

Even though Tregs play a critical role in limiting pathologic inflammation, their excessive number or function can also restrain the immune response required to eradicate pathogens and may promote their persistence (Fig. 2, left). For instance, persistence of *Leishmania major* in the skin requires the presence of CD4⁺CD25⁺ Tregs [10]. Similarly, reduction of Tregs in herpes simplex virus (HSV) or Friend virus infection markedly increases the virus-specific CD8⁺ T cell response and the rate of viral clearance, while adoptive transfer of Tregs impairs the CD8⁺ T cell response and prolongs viral persistence [11,12]. Hence, Tregs can contribute to the establishment of persistent infections by suppressing CD8⁺ T cell responses. Indeed, Tregs have been shown to promote CD8⁺ T cell dysfunction and foster viral persistence in chronic lymphocytic choriomeningitis virus (LCMV) infection [13]. Similar correlations can be observed in chronic viral infections in patients, where enhanced Treg frequencies are associated with persistence of HIV, hepatitis A and B virus, and disease progression [14–16].

On the flip side, Tregs can dampen excessive and persistent inflammatory responses induced upon infection, which, if uncontrolled, can have profound negative consequences for the host (Fig. 2, left) [4,6]. In RSV, influenza and SARS-CoV-2 infections, excessive immune activation contributes to severe disease courses and severely ill patients show reduced Treg numbers in peripheral blood [17–21]. RSV is the leading cause of respiratory infection in young children throughout the world and is also gaining more attention as a pathogen of the elderly [22]. In RSV infection models, Tregs with an activated phenotype have been found to accumulate in the lung and draining lymph nodes and their depletion increases disease severity, likely due to enhanced TNF- α production by CD8⁺ T cells [23]. Several molecules have been identified as crucial mediators for Treg-mediated regulation but during RSV infection, Treg-mediated cytotoxicity appears to play a key role in limiting disease severity [24]. Tregs found in the lungs of RSV infected mice express high levels of the cytotoxic mediator granzyme B and the degranulation marker CD107a. Furthermore, mice in which Tregs lack granzyme B show

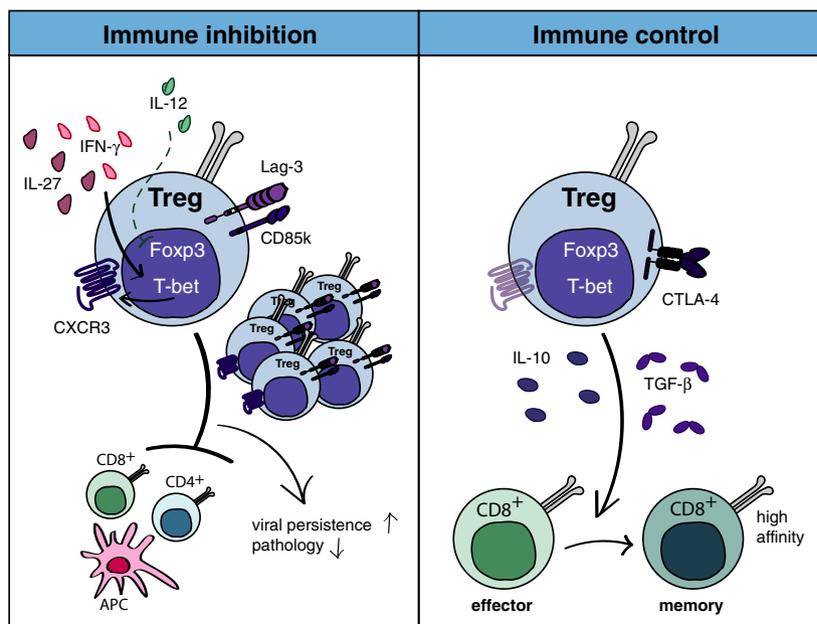


Fig. 2. Effects of Tregs in antiviral immune responses. During type 1 immune responses, such as those elicited upon viral infection, Tregs can act as potent suppressors of immunity (left) and exhibit tailored immune control to properly guide effector responses (right). (Left) Tregs specialize in response to IFN- γ and IL-27 to co-express T-bet together with Foxp3 as well as the chemokine receptor CXCR3 and the co-inhibitory receptors CD85k and Lag-3. Tregs show increasing responsiveness to IL-12 as the immune response progresses, which eventually inhibits Treg function. Treg specialization in response to type 1 cytokines as well as high Treg numbers can result in excessive suppression of effector responses, leading to viral persistence but also reduced immune pathology. (Right) Treg-mediated inhibition through CTLA-4, IL-10, and TGF- β focuses the CD8⁺ effector T cell response and supports the differentiation of high affinity memory CD8⁺ T cells.

enhanced weight loss and cell infiltration in the lung upon RSV infection. Conversely, IL-2 immune complex treatment, which expands Tregs and boosts their granzyme B expression, reduces disease severity without affecting viral clearance [24]. Tregs thus control RSV-induced immunopathology but not viral persistence through cytotoxicity-mediated immune suppression of CD8⁺ T cells. Whether Tregs employ the same mechanisms to dampen disease severity upon influenza infection and in COVID-19 patients or whether other tissue protective functions may be dominant in these settings remains to be determined.

Although the tissue protective role of Tregs in infections is well documented, it is still unclear whether this effect is mediated through tTregs or whether pTregs induced upon infection contribute to control of immunopathology. We showed in a recent study that pTregs generated in the periphery are critical for preventing collateral colitis triggered by chronic LCMV infection [25]. Nevertheless, given that pTregs generally play an important role in maintaining intestinal homeostasis [26], it remains to be determined whether pTregs induced upon infection also control immune pathology at other sites.

Interestingly, in addition to suppressing excessive immune responses and inflammation, Tregs also play a direct role in tissue repair and maintenance. During influenza infection, Tregs were shown to produce amphiregulin, a ligand for epidermal growth factor receptor, in response to stimulation with the alarmins IL-33 and IL-18 and thereby facilitate tissue repair [27]. Interestingly, this noncanonical Treg function is independent of their classical suppressive activity and does not affect the antiviral immune response during influenza infection [27]. Increased Treg frequencies also correlate with milder disease course in patients infected with West Nile virus or Dengue virus, and hence, Tregs likely also dampen immunopathology in humans during viral infection [28,29]. However, whether this is mediated through suppression of inflammation or direct tissue protective effects will have to be addressed in future studies.

Infection-induced changes in Tregs

Infections result in the activation of innate and adaptive immune cells and the induction of cytokines and other effector molecules to combat the infection. At the same time, the ongoing immune response also initiates the specialization of Tregs. Intracellular pathogens generally induce type 1 responses, where antigen presenting cell-derived IL-12 drives the differentiation of naive CD4⁺ T cells into type 1 T helper (Th1) cells.

Type 1 immune responses are dominated by IFN- γ , which not only promotes and mediates effector cell responses but also directly acts on Tregs to induce their functional specialization [30,31]. Even though exposure to high concentrations of IFN- γ can reduce the suppressive capacity of Tregs [32], IFN- γ (as well as IL-27) also drives the specialization of Tregs into type 1 Tregs, which are essential for effective suppression of Th1 responses (Fig. 2, left) [30,31,33]. Type 1 Tregs are characterized by the expression of the Th1 master regulator T-bet and the chemokine receptor CXCR3. IFN- γ and IL-27 signal through STAT1 to induce T-bet expression, which in turn drives expression of CXCR3 [34]. Different from Th1 cells, type 1 Tregs show delayed and low expression of IL-12R β 2 upon infection and exposure to IFN- γ and are thus less responsive to IL-12, which reduces their suppressive function [34]. At the early stage of infection, the low responsiveness to IL-12 prevents type 1 Treg instability and loss of their suppressive function. With the gradual acquisition of IL-12R β 2 expression over the course of infection, Tregs increasingly respond to IL-12, which then drives Treg contraction at the late stage of infection [35].

At steady state, the T-bet⁺ CXCR3⁺ type 1 Tregs are already present and gradually accumulate after birth [33,34]. Similar to effector T cells, type 1 Tregs are extensively expanded upon infections with pathogens eliciting a Th1 response in both lymphoid and nonlymphoid organs and then contract again once the infection is resolved [30,31,33,36,37]. With the mirrored expression of chemokine receptors, the specialized type 1 Tregs are thought to be optimally equipped to migrate to the same inflammatory sites as the effector Th1 cells and control local immune responses efficiently. Although mice with Treg-specific T-bet deficiency show mild or no Th1 cell activation at steady state [33,38,39], they have a higher susceptibility to induced autoimmunity and present with exacerbated diabetes and insulinitis in nonobese diabetic mice [40] and enhanced leukocyte infiltration in the kidneys of mice with induced nephritis [41].

In humans, CXCR3 can also mark a Th1-like subset of memory CD4⁺CD25⁺CD127^{-/low} Tregs that expresses T-bet and high levels of FOXP3 and Helios [42]. They can be generated from naive Tregs under Th1-polarizing conditions and maintain their stability and suppressive activity *in vitro*. Similar to mouse Tregs, IL-12 signaling can hamper human Treg function and induce IFN- γ production [42–44]. In addition, the type 1 Treg-specific molecules CD85k and granzyme K are induced in human Tregs upon influenza vaccination [36], which induces a Th1 response,

suggesting human Treg cells are responsive to antigen challenge and may also participate in immune regulation during infections in humans.

Importantly, type 1 Tregs are also essential for ensuring controlled Th1 immune response during infections, as adoptive transfer of type 1 Tregs alleviates pathology and prevents acute lethality of *Toxoplasma gondii*-infected IL-27 KO mice and *Mycobacterium tuberculosis* infected scurfy mice [30,31]. Type 1 Tregs thus seem to play a key role in preventing pathology caused by excessive type 1 immune responses.

Tregs can promote viral clearance

Tregs are generally associated with suppression of immunity and hence pathogen persistence [10,14]. Nevertheless, in some situations, Treg depletion unexpectedly results in reduced antiviral immunity and impaired virus clearance [45]. Studies in HSV infection models revealed that Tregs modulate chemokine expression in lymphoid organs and local tissues to promote the homing of effector cells to the site of infection [45]. Similarly, Tregs promote CD8⁺ T cell influx into the lung upon RSV infection, while Treg depletion results in a delayed viral clearance [46]. Interestingly, in addition to regulating effector cell trafficking, Tregs can improve the quality of the CD8⁺ T cell response by limiting low-affinity CD8⁺ T cell expansion [47]. Furthermore, type 1 Tregs play an essential role in the establishment of CD8⁺ tissue resident memory T cells through providing TGF- β , a key cytokine for the differentiation of CD8⁺ effector T cells into tissue resident memory T cells [38,48]. Finally, Treg-derived IL-10 and cytotoxic T-lymphocyte antigen 4 (CTLA-4) contribute to the transition from effector to memory CD8⁺ T cell by insulating them from pro-inflammatory signals and promoting their quiescence (Fig. 2, right) [49,50]. As such, transient depletion of Tregs during CD8⁺ T cell contraction impairs CD8⁺ memory T cell generation [50]. Tregs thus play an important role in promoting controlled T cell responses upon viral infections and can thereby quite unexpectedly enhance antiviral immunity (Fig. 2, right). This positive effect of Tregs on anti-pathogen immunity is in line with the emerging role of Tregs in actively promoting tissue integrity [27,51].

Co-inhibitory receptors in viral infections: an overview

Co-stimulatory and co-inhibitory receptor molecules play a fundamental role in the regulation of the

immune response to viral infections. Their delicate and balanced crosstalk is a major player in ensuring a controlled immune response to pathogens. Co-signaling molecules are cell surface glycoproteins that can modulate and adapt the immune response by positively and negatively regulating T cell receptor (TCR) signals, thus affecting the priming, expansion, differentiation, and functional maturation of the adaptive immune system [52]. The first line of co-inhibitory receptors includes CTLA-4 and programmed cell death protein 1 (PD-1), which act as global regulators of the threshold for T cell activation [53–55]. In addition, there is a more recently discovered new generation of co-inhibitory receptors, including T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), lymphocyte-activation gene 3 (Lag-3), and T cell immunoglobulin mucin-3 (Tim-3) [56–59], which have more subtle effects on T cell activation and seem to act predominantly in peripheral tissues [59]. Among other signals, T cell activation through interaction with their cognate antigen induces the transient expression of many co-inhibitory receptors [60–63]. This built-in regulation of the TCR signal prevents sustained T cell stimulation and thereby limits excessive T cell activation and tissue damage. During infections, co-inhibitory receptors are also highly expressed on exhausted virus-specific T cells and activated Tregs [36,64]. The concomitant upregulation of co-inhibitory receptors with T cell activation allows for the induction of a potent but controlled immune response during viral infection and re-establishment of immune homeostasis upon resolution of the inflammatory state. Moreover, co-inhibitory receptors such as TIGIT and CTLA-4 additionally induce the secretion of anti-inflammatory cytokines such as IL-10 and TGF- β , which additionally contribute to reducing tissue inflammation and pathology [60,65].

The network through which T cell activation is kept under control is very complex: It includes the interaction of positive and negative co-signaling receptors with several different ligands that, in turn, can be shared between the stimulatory and inhibitory receptors but with different affinities. For example, the co-inhibitory receptor PD-1 interacts with its ligands PD-L1 and PD-L2, while PD-L1 binds the co-inhibitory receptors PD-1 as well as the co-stimulatory receptor CD80 [55]. In addition, PD-1–PD-L1 and PD-1–PD-L2 interactions can have distinct effects on pathogen directed immune responses [66,67]. Similarly, TIGIT shares its ligands CD155 (PVR) and CD112 with the co-stimulatory receptor CD226 (also called DNAM-1) but binds them with much higher affinity [56,68–70]. Hence, depending on the receptor and ligand

expression pattern, multiple interactions and downstream effects on signaling pathways can be induced (for reviews, see Ref. [71] and Ref. [72]). The network of these molecules and their effects during viral infection are thus quite intricate but generally ensure the induction of potent yet controlled immune responses and the maintenance of tissue homeostasis.

Co-inhibitory receptors are highly upregulated and implicated in persistent infections, such as, for example, HIV or the LCMV model in mice [64,73]. In addition, they have been reported to be highly expressed during excessive immune responses, such as those observed in severe cases of influenza or COVID-19, caused by infection with SARS-CoV-2, which has been rapidly spreading globally over the course of the last year [74,75]. Here, co-inhibitory receptors are induced in response to the massive immune activation in order to dampen the immune response and allow for return to immune homeostasis [76]. In the following, we will outline the role of co-inhibitory receptors specifically in chronic infections and the induction of T cell exhaustion as well as their newly suggested intrinsic role in tissue protection and in limiting tissue pathology during viral infections.

T cell exhaustion

Infections result in exposure of the immune system to antigens for variable periods of time. In acute infections, effector T cells give rise to memory cells once the virus is cleared. Chronic infection settings, instead, are characterized by a prolonged and persistent exposure of the immune system to antigens. This leads to progressive loss of the effector functions of T cells, driving them toward the so-called exhausted phenotype [77]. T cell exhaustion was first defined in 1993 by Moskophidis and colleagues as they showed impaired cytotoxic T cell function upon chronic LCMV infection in mice [78]. Since then, exhaustion has been further defined and associated with reduced proliferation of T cells, decreased cytokine production and impaired effector function that results from persistent exposure to high levels of antigen [77]. Furthermore, exhausted T cells are marked by expression of multiple inhibitory receptors and a distinct transcriptional and metabolic program [79–84]. Through this mechanism, the immune response to overwhelming amounts of antigen, such as those found upon chronic infection but also in cancer and autoimmunity, is blunted to protect the host from immunopathology but also allows for pathogen persistence (Fig. 1) [85].

Overexpression of multiple co-inhibitory receptors, such as PD-1, CTLA-4, Lag-3, Tim-3, TIGIT and

others, is a hallmark of exhausted T cells [64,86–88]. Their engagement by their respective ligands reduces T cell activation and effector function and thereby acts as a physiological mechanism to dampen the immune response. Based on the fact that PD-1 is more highly expressed on exhausted cells than other co-inhibitory receptors, it was initially suggested as the driver of T cell exhaustion [79]. However, further studies revealed that while PD-1 is an important hallmark of T cell dysfunction, it does not itself drive exhaustion [89]. Nevertheless, PD-1 and other co-inhibitory receptors enforce the dysfunctional phenotype as blockade of PD-1 alone or in combination with other co-inhibitory receptors reverses exhaustion and revitalizes T cells, enabling them to clear persisting viral infections [64,73,79,90].

The impact of exhaustion on the strength of the immune response is further highlighted by the success of checkpoint therapy in cancer patients. Ligands of some of these co-inhibitory receptors (or immune checkpoints) are upregulated by cancer cells as a strategy of immune evasion [91,92]. Additionally, parallel to chronic infections, continuous tumor antigen exposure results in exhaustion and upregulation of co-inhibitory receptors on tumor-specific T cells [93]. Targeting of PD-1 and CTLA-4 with checkpoint blockers revitalizes exhausted T cells and enables potent anti-tumor immunity [94,95]. This approach has revolutionized cancer therapy and was recognized with the Nobel prize in Medicine awarded to James P. Allison and Tasuku Honjo in 2018 [96].

Exhaustion thus is a state of hypo-function of T cells that might be needed to limit immune activation and preserve antigen-specific T cells under chronic stimulation but at the same time prevents pathogen clearance and potent anti-tumor responses. Overall, the negative consequences of T cell exhaustion in cancer and infectious diseases are clear, but it is important to point out that in the context of excessive immune responses upon chronic or widespread viral infections, T cell exhaustion has a positive impact on the general condition of the host as it prevents tissue damage and immunopathology (Fig. 1) [78,97]. Indeed, clonal exhaustion can act as a mechanism to protect the host against severe immunopathology and mortality resulting from an excessive CD8⁺ T cell response [97–99]. For instance, infection with an intermediate dose of LCMV induces limited T cell exhaustion resulting in massive immunopathology and high mortality. In contrast, high dose infection results in strong T cell exhaustion but only limited tissue pathology [98]. Hence, although extensive clonal exhaustion is associated with virus persistence [78], it can also be beneficial

by reducing pathology and mortality caused by overwhelming CD8⁺ T cell responses. Again, this also becomes apparent in checkpoint therapy as it is often accompanied by massive side effects resulting from severe immunopathology, which can be even more pronounced than the damage caused by the tumor itself [100]. Thus, while T cell exhaustion allows for virus persistence and tumor progression, it also has positive effects through limiting tissue damage and immunopathology. Finding the sweet spot for enabling an effective immune response without causing immune pathology still remains unsolved but deepening our understanding of T cell exhaustion may prove to be a good starting point to reach this goal.

Limiting immunopathology

Following viral infections, the immune response is activated to eliminate the pathogen. However, in widespread infections, this targeting of infected cells will also damage a considerable proportion of the infected organ (Fig. 1). In addition, soluble inflammatory mediators will not only act on infected but also on the surrounding cells potentially causing tissue damage [101,102]. Indeed, in several infectious settings, such as, for example, LCMV or RSV, the anti-viral immune response causes more damage to the host than viral infection itself [6,103].

Many components of the immune system cooperate to avoid hyper-activation of the immune system to maintain self-tolerance but also limit peripheral tissue damage during viral infection. Co-inhibitory receptors and Tregs play an essential role in this regulatory process and enable the immune system to limit viral infection while still ensuring tissue protection. The aforementioned co-inhibitory molecules, PD-1 and TIGIT, are among the main players within this network. As discussed in detail in the last section, these co-inhibitory receptors play an important role in T cell exhaustion and thereby facilitate viral persistence but also limit tissue pathology. In addition, they also dampen pathological immune responses independently of T cell exhaustion. The PD-1 ligand PD-L1 is widely expressed in peripheral, nonhematopoietic tissues, suggesting a role of PD-1 in preventing tissue inflammation and limiting tissue damage [55]. In contrast to CTLA-4, PD-1 deficiency in itself is not lethal in mice [54,104]. However, PD-1-deficient mice have a higher susceptibility to autoimmune diseases and tissue damage [105,106]. In addition, the immunopathology often observed as a side effect of checkpoint therapy targeting the PD-1/PD-L1 pathway in cancer patients is not only caused by an

overshooting of the revived tumor-specific T cells but also by releasing the brakes on self-reactive T cells that cause tissue damage [107,108]. This tissue protective function of PD-1 is also observed in infectious settings as LCMV infection is lethal in PD-1-deficient mice due to severe CD8⁺ T cell-mediated damage to the blood vasculature [109]. PD-1 therefore seems to not only limit immune pathology by contributing to T cell exhaustion but also fulfill a direct protective role in peripheral tissues.

In addition to limiting effector T cell function, co-inhibitory receptor engagement has also been linked to the production of anti-inflammatory cytokines, such as IL-10. As such, PD-1 promotes IL-10 production by myeloid cells and is highly expressed on IL-10-producing T cells, including exhausted cells, Tr1 cells, and Tregs [55,110,111]. Moreover, the TIGIT pathway has been closely linked to IL-10 production as TIGIT indirectly induces IL-10 production in dendritic cells through engagement of its ligand CD155 as well as directly inducing IL-10 in Tregs [56,60]. TIGIT-induced IL-10 also plays a role in limiting tissue pathology upon viral infection as TIGIT engagement through an agonistic antibody reduced pathology upon both acute LCMV and influenza infection in an IL-10-dependent manner [112]. TIGIT engagement resulted in significantly decreased liver or lung damage, respectively, with a concomitant increase in IL-10 expression. Interestingly, targeting TIGIT during viral infection only restricted tissue damage but had no effect on viral clearance. Conversely, enhanced tissue damage was observed in fulminant hepatitis if TIGIT was blocked [113], which is in line with our own findings upon administration of blocking anti-TIGIT antibody during LCMV infection [112]. Moreover, TIGIT was shown to play an important role in maintaining immune tolerance and preventing tissue damage in a model for chronic hepatitis and hepatocellular carcinoma [114]. These recent studies uncover an active role of co-inhibitory receptors in limiting immune pathology and their active involvement in tissue protection during immune responses to viral infection. As such, these co-inhibitory receptors seem to contribute to disease tolerance, a term that defines a defense strategy that restricts tissue damage to maintain host fitness without affecting the pathogen burden (reviewed in Ref. [115] and Ref. [116]). The discovery of a possible role of co-inhibitory receptors in limiting immune pathology through a coordinated network of co-stimulatory and co-inhibitory signals may even facilitate new therapeutic approaches to treat infection-induced immunopathologies.

Concluding remarks

The immune system mostly responds to viral infections by mounting a balanced and effective immune response that allows for control and elimination of the virus but causes limited, if any, tissue damage (Fig. 3). Immune regulation may limit this process and allow for viral persistence and potentially virus-induced pathology. Nevertheless, it has become clear that these regulatory processes can also have many beneficial effects for the host such as limiting excessive immunity to prevent immune pathology. Furthermore, Tregs and co-inhibitory receptors ensure potent but controlled immune responses that allow for a balanced immune response. Finally, both Tregs and co-inhibitory receptors have the intrinsic ability to promote tissue protection and repair to limit pathology and contribute to disease tolerance.

While a healthy immune system is able to mount an appropriate immune response upon most challenges, infections with certain viruses such as influenza, RSV or the latest SARS-CoV-2 can cause great harm, especially in young children or the elderly, where an immature or aging immune system is often not able to mount a potent but balanced immune response. Harnessing the ability of regulatory receptors or cells to promote tissue protection, while maintaining the ability of the immune system to clear the pathogen itself could thus potentially bring great clinical benefit to those at risk.

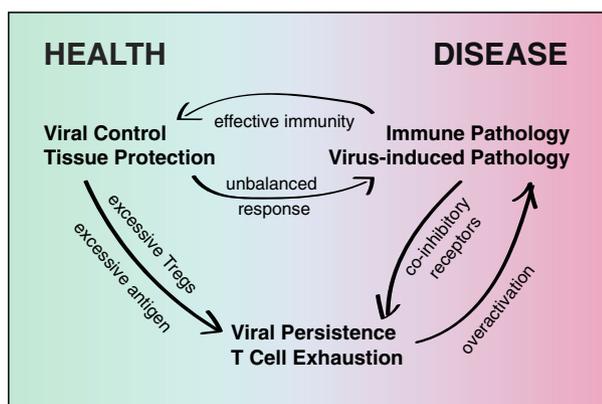


Fig. 3. Overview of the regulatory processes during viral infections. A balanced antiviral immune response allows for viral control while preserving the host tissues. In widespread infections, T cell exhaustion may allow for viral persistence but prevents immune pathology, which results from excessive immune activation. At the same time, limited or unfocused antiviral immunity may result in virus-induced pathology due to overwhelming dissemination of lytic virus.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

NJ conceptualized the manuscript; CP, K-CK, and NJ wrote the manuscript.

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