Published in final edited form as:
Curr Opin Immunol. 2010 June ; 22(3): 397–401. doi:10.1016/j.coi.2010.03.007.

Role of PD-1 in regulating acute infections

Keturah E. Brown[1], **Gordon J. Freeman**[2], **E. John Wherry**[3], and **Arlene H. Sharpe**[1]

Keturah E. Brown: keturah_brown@student.hms.harvard.edu; Gordon J. Freeman: gordon_freeman@dfci.harvard.edu; E. John Wherry: jwherry@wistar.org; Arlene H. Sharpe: arlene_sharpe@hms.harvard.edu

[1] Department of Pathology, Harvard Medical School, NRB 77 Avenue Louis Pasteur, Boston, MA 02115, USA

[2] Department of Medical Oncology, Dana Farber Cancer Center, Department of Medicine, Harvard Medical School, 44 Binney Street Boston, MA 02115

[3] Immunology Program, The Wistar Institute, 3601 Spruce Street, Philadelphia, PA 19104, USA

Summary

While the role of PD-1 in inhibiting immunity during chronic infections is well established, its functions during acute infections are much less clear. The PD-1 pathway can dampen CD8 T cell responses during some acute infections and restrain responses by “helpless” CD8 memory T cells. An emerging role for PD-1 in innate immunity has been revealed by recent studies showing that PD-1 can limit function of DC and macrophages as well as T cell independent B cell responses. Thus, PD-1 can influence adaptive immune responses during acute infections, though precisely how this regulation occurs is only just beginning to be appreciated.

Introduction

T cell responses are regulated by the balance of positive and negative regulatory pathways. Negative regulatory pathways are crucial for peripheral self-tolerance and prevent autoimmunity, and can function through signals delivered by cell surface inhibitory receptors, immunoregulatory cytokines, and regulatory T cells (Treg). These regulatory pathways also play an important role in the response to pathogens. Inhibitory receptors have received considerable attention recently for their role during chronic viral infections [1–3]. PD-1, an inhibitory receptor in the CD28 family, is highly expressed on dysfunctional CD8 and CD4 T cells during chronic infections including LCMV, HIV, HCV, and HBV and contributes to dampening antiviral T cell immunity [1–3].

The expression of inhibitory receptors by T cells is not unique to chronic infections, however, and T cell activation in many settings results in the upregulation of inhibitory molecules such as PD-1, CTLA-4, TIM-3, BTLA, LAG-3, CD244, and CD160 [4]. Early studies suggested that negative regulatory pathways are important to limit developing effector T cell responses and perhaps curb tissue damage [3,5,6]. Recent studies, however, suggest that the role of inhibitory receptors during acute infections is more complex. This review will focus on

Correspondence to: Arlene H. Sharpe, arlene_sharpe@hms.harvard.edu.

Conflicts of interest

GJF, AHS and EJW have patents and receive patent royalties related to PD-1.

emerging data showing roles for PD-1 and its ligands in modulating effector and memory T cell responses during acute infections. To provide a context for these studies, we first will outline the stages of T cell differentiation and introduce the PD-1 pathway.

Effector and Memory T cell differentiation following acute infections

The best understood developmental signals guiding T cell activation and differentiation are Signal 1 from antigen-TCR, Signal 2 from costimulation, and Signal 3 from inflammatory cytokines. The generation of effector and memory T cells can roughly be divided into four stages: 1) initial activation of naïve T cells by professional APC; 2) expansion, differentiation, and dispersal of effector T cells; 3) contraction of the effector response; and 4) establishment of a stable memory T cell population. Inhibitory receptors may be involved in each of these stages, though exactly how is only beginning to be understood.

Initial activation

Following infection, pattern recognition molecules of the innate immune system result in dendritic cell activation. Early following infection, naïve T cells interact with activated dendritic cells that present microbial antigens, resulting in delivery of TCR signals in combination with costimulatory signals to naïve T cells, the most effective combination for T cell activation. Costimulation during initial TCR engagement lowers the threshold for T cell activation and augments survival of the newly activated T cells [7]. Costimulation also can stabilize cytokine mRNAs, alter the transcriptional profile of T cells, and impact T cell differentiation [8].

Following T cell activation, a number of inhibitory receptors can be upregulated. One of the best studied, PD-1, is upregulated within 24–72 hours of TCR stimulation. Since PD-1 upregulation occurs after many costimulatory pathways have been engaged, one possible role for this inhibitory receptor is to help attenuate or shut off developing effector T cell responses. The expression of PD-1 ligands is also dynamic and regulated by the inflammatory milieu. PD-L1 and PD-L2 are upregulated on many cell types including professional APC [6]. The precise role of PD-1 in this phase of early T cell activation remains to be fully defined.

Expansion, differentiation and dispersal

After initial priming by professional APC, effector functions are acquired and antigen-specific T cells divide vigorously for the next ~1 week [9]. As few as several hundred resting naïve precursors can give rise to ~10^7 highly functional CD8+ T cells. These effector T cells distribute throughout the body to lymphoid and non-lymphoid tissues [9].

Subsets with different fate potential exist within the developing T cell population. Terminally differentiated effector T cells are highly activated and potent mediators of immunity, but lack the ability to develop into long-lived, self-renewing memory T cells [10,11]. Memory precursors also exist in the effector T cell population [10–12] and possess the ability to perform effector functions, but also have the capacity to further differentiate into a long-term memory population. Inflammation can regulate the overall “strength of signal” transmitted to a T cell during priming [10,13] and may be mediated by altering the balance of positive and negative costimulatory molecules. Influencing the strength of signal, in turn, can alter the proportion of effector T cells in different subsets and impact memory T cell differentiation over time [10, 14–16]. Thus, integration of signals provided by antigen/TCR, costimulatory pathways and inflammation shapes T cell fates. How specific inhibitory receptors impact fate decisions between terminally differentiated effector T cells and memory precursors is not fully understood.

Contraction and memory

Following control of acute infection the majority (>90%) of activated effector CD8 T cells dies by apoptosis. This contraction can involve both Bim and Fas, but growth factor withdrawal, as well as inhibitory receptors, have been implicated in terminating T cell responses [17,18]. As the surviving effector CD8 T cells differentiate into memory T cells, they acquire a resting phenotype, but have the capacity to rapidly reactivate effector functions. The early memory CD8 T cell pool resembles effector memory T cells (T_{EM}: $CD62L_{Lo}CCR7_{Lo}$, low IL-2 production). Over time this T_{EM} population gradually converts to a more central memory-like (T_{CM}) CD8 T cell population ($CD62L_{Hi}CCR7_{Hi}$, high IL-2 production) due to both loss of terminally differentiated T cells and further differentiation of some T_{EM} into T_{CM} [9,19]. T_{CM} are endowed with key memory properties such as high proliferative capacity, greater protective capacity, and long-term antigen-independent self-renewal [20]. The rate and efficiency of differentiation during the memory phase can be influenced by initial antigen dose and duration, tissue microenvironment, and inflammation [19], but exactly how inhibitory receptors influence memory T cell formation and/or maintenance remains poorly defined.

Role of PD-1:PD-L1/PD-L2 Pathway During Acute Infection

Introduction to PD-1

The Programmed Death (PD)-1 receptor has two ligands, PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273). PD-1 is inducibly expressed on CD4 and CD8 T cells, NKT cells, B cells, monocytes, and some DC subsets upon activation [6,21]. The PD-1 ligands differ in their expression [6,21]. PD-L2 is inducibly expressed on DCs, macrophages, peritoneal B1 B cells, and bone marrow (BM)-derived mast cells. PD-L1 is expressed on B cells, DCs, macrophages, BM-derived mast cells, and T cells, and is further upregulated upon activation. PD-L1 is also expressed on a variety of nonhematopoietic cell types. Upon ligation of PD-1 to either PD-L1 or PD-L2, TCR signaling is attenuated [6,21], providing at least one mechanism for suppression of T cell responses.

The discovery of a critical role for the PD-1:PD-L1 pathway in exhaustion of CD8 T cells during chronic LCMV infection in mice [5] has catalyzed studies that have demonstrated a role for this pathway in regulating immune responses to chronic viral infections in mice, primates, and humans [1–3]. While much work on the PD-1 pathway has focused on understanding the role of this pathway in chronic infections, tolerance and cancer, recent work has demonstrated that this pathway also plays a key role in regulating anti-microbial responses to acute infections (Table 1).

Regulation of T cell function during acute infections

In a study of rabies virus infection in mice, the PD-1 pathway negatively regulated antiviral T cell responses in the brain [22]. PD-L1 expressed on neurons during infection led to increased apoptosis of PD-1+ CD8 T cells infiltrating the CNS, thereby inhibiting T cell responses. Infection of PD-$L1^{-/-}$ mice resulted in decreased disease severity and mortality and decreased viral load in the CNS. This study indicates a role for PD-1:PD-L1 interactions in dampening CD8 T cell responses during rabies virus infection, and possibly serving to protect the CNS from immunopathology.

Another study examined the role of the PD-1 pathway in regulating T cell responses to the fungal pathogen *Histoplasma capsulatum* (HC), which replicates in macrophages [23]. PD-$1^{-/-}$ mice cleared fungal infection from their lungs completely while their WT counterparts had delayed or less effective control of this infection. PD-$1^{-/-}$ mice survived infection with 10 times the lethal dose of HC in WT mice. Additionally, PD-1 blockade in WT mice during otherwise lethal HC infection led to increased survival. These data suggest that the PD-1:PD-

L1 interaction dampens T cell responses during anti-fungal immune responses by blocking efficient T cell priming and the acquisition of effector function. Due to the expression of PD-1 on both T cells and macrophages, further investigation will be required to determine the cell type responsible for inhibition of T cell responses [23].

PD-L1 on naïve T cells might also influence appropriate maturation of DC during viral infection. When WT and PD-L1$^{-/-}$ mice were intranasally infected with influenza virus, PD-L1$^{-/-}$ mice generated a lower percentage of virus-specific CD8 T cells compared to WT [24]. This quantitative defect in CD8 responses of PDL1 $^{-/-}$ mice could be rescued by adoptive transfer of either WT naïve CD8 T cells, WT DCs, or DCs from RAG$^{-/-}$ that had been previously injected with WT naïve CD8 T cells. These data suggest that PD-L1 on the T cell is important for appropriate DC maturation, and that without it, less optimal DC activation occurs, resulting in suboptimal priming of antiviral CD8 T cell responses. While reduced CD8 T cell responses in the absence of PD-L1 are somewhat counterintuitive, the precise mechanism for this T cell intrinsic function of PD-L1 remains to be determined. It is unclear if PD-L1 deficiency in this setting could change the ability to control viral infection or duration of T cell interaction with DC and antigen exposure, which could impact quantity or quality of antiviral T cell responses. Furthermore, the effect of T cell expressed PD-L1 on other cell types (e.g. alveolar macrophages or airway epithelial cells) remains to be explored. Rowe et al. also found that blocking PD-L1 during acute *Listeria monocytogenes* infection led to reduced, rather than enhanced, antibacterial T cell responses during primary infection [25]. Whether PD-L1 in this setting truly provides a positive signal, prevents overstimulation of T cells, or has a more direct role in antibacterial immunity such as by affecting the activation status of infected macrophages is unclear. However, the authors did demonstrate an impact on T cell memory as PD-L1 blockade compromised the recall response and ability to control secondary bacterial infection.

The role of PD-1 in regulating function and maintenance of memory CD8 T cells generated in response to acute infection is only beginning to be understood. One study examined mice intranasally infected with vaccinia virus (VV) to determine when and how CD4 T cell help is required to generate efficient functional memory CD8 T cells [26]. Importantly, increased PD-1 expression (both frequency and MFI) was observed on unhelped memory CD8 T cells versus memory CD8 T cells primed in the presence of CD4 T cells. PD-1 expression could be reduced to WT levels if help was provided by agonistic anti-CD40 mAb administered during priming. PD-1 blockade during rechallenge enhanced expansion of “helpless” memory CD8 T cells, indicating that PD-1 limits responses by “helpless” memory CD8 T cells generated during microbial infection, perhaps by PD-1-mediated inhibition of IL-2 production, since addition of exogenous IL-2 also rescued “helpless” CD8 expansion.

Regulation of innate immune responses during acute infections

The PD-1 pathway also can have a role in regulating functions of cells other than T cells. For example, PD-1 expression was induced on a subset of myeloid DC in spleens of *Listeria monocytogenes*-infected mice [27]. PD-1$^{-/-}$ DC were more effective than wild-type DC in innate protection of mice against lethal *L. monocytogenes* infection even when adoptively transferred into Rag-1$^{-/-}$ recipients, likely because of increased IL-12 and TNF production by PD-1$^{-/-}$ DC. Additionally, in the RAW264.7 mouse macrophage cell line, PD-1 engagement has been shown to downregulate LPS-mediated IL-12 release [28]. Taken together, these studies suggest that PD-1 may provide an important negative feedback mechanism to attenuate innate immune inflammatory responses and tissue damage elicited by TLR and cytokine signaling.

The emerging role for PD-1 in attenuating innate immune responses to pathogens is further demonstrated in a mouse model of bacterial sepsis [29]. PD-1$^{-/-}$ mice were protected from early death, had a significantly greater capacity to clear bacteria than WT mice, and lower

levels of proinflammatory cytokines. Severe sepsis is associated with macrophage dysfunction manifest as reduced bactericidal activity, decreased inflammatory cytokine production and impaired APC function. PD-1 upregulation was much more rapid on macrophages than on T or B cells during sepsis and appeared to mediate macrophage dysfunction. PD-$1^{-/-}$ macrophages did not exhibit sepsis-associated dysfunction. Resistance of PD-$1^{-/-}$ mice to sepsis was abrogated by clondronate liposome depletion of macrophages. These studies identify PD-1 as a critical regulator of the outcome of sepsis. PD-1 may also serve as a useful biomarker to indicate macrophage function during sepsis, since PD-1 is significantly increased on monocytes from septic shock patients. Thus, PD-1 has a critical role in regulating the balance between protective immunity and immunopathology during sepsis, and blockade may provide a new strategy for treatment of sepsis.

Concluding Remarks

The PD-1:PD-L pathway is best know for its ability to negatively regulate immune responses. Most of the evidence for this role, however, comes from models of tolerance, cancer or chronic infections. Recent studies are revealing clear roles for this pathway during acute infections. While many studies demonstrate a negative regulatory role for this pathway during acute infections, there are also some situations where an intact PD-1 pathway appears to enhance, rather than inhibit, immunity. The mechanism for this potential positive role of the inhibitory receptor is not yet clear and future experiments are needed to clarify whether this pathway can provide a positive signal under some circumstances, whether attenuating antigen-receptor signaling via inhibitory receptors during some infections prevents overstimulation of activated T (or B) cells, or whether expression of PD-1 and PD-L1 on non-lymphocytes (e.g. DC, macrophages) plays a critical role in these settings, perhaps by increased production of NO or other oxygen radicals that could lead to killing of effector T cells [30].

While we have focused mainly on T cell responses in this review, there is also clearly a role for the PD-1 pathway on other cell types. We have discussed recent work showing that PD-1 or PD-L1 on cells of the innate immune system can impact anti-microbial immunity. However, PD-1 (and perhaps PD-L1 or PDL2) can influence B cell responses [31], though whether this effect is directly mediated by PD-1, PD-L1, or PD-L2 on the T or B cell or through effects on PD-1+ T_{FH} cells is not entirely clear [32]. Several of the recent studies discussed here also illustrate the potential direct regulation of DC and macrophages by the PD-1 pathway, suggesting that interventions based on PD-1 pathway disruption might be more complicated to interpret than just an effect on T cells. These observations also indicate, however, that the potential therapeutic benefit of modulating this pathway might be substantially more broad than previously considered.

Further work is clearly needed to fully understand the importance of the PD-1 pathway in regulating immune responses at each phase of the primary immune response during acute infection. The possible impact on T cell memory suggested by several studies also indicates that manipulating these pathways might not only have utility for regulating the response during primary infection, but also in actively modulating the quantity and/or quality of T cell memory.

Acknowledgments

This work was supported by grants from the National Institutes of Health (NIH), BAA-05-11 and P01 AI078897 (to AHS, GJF and EJW), P01 AI56299 (to AHS and GJF), 1U19A1082630 (to GJF and EJW), A108080192 and HL92565 (to GJF), and AI071309 (to EJW), and grants from the Dana Foundation and Ellison Medical Foundation (to EJW). Because of space restrictions, we were able to cite only a fraction of the relevant literature and apologize to colleagues whose contributions may not be appropriately acknowledged.

REFERENCES AND ANNOTATIONS

1. Crawford A, Wherry EJ. The diversity of costimulatory and inhibitory receptor pathways and the regulation of antiviral T cell responses. Curr Opin Immunol 2009;21:179–186.
2. Kaufmann DE, Walker BD. PD-1 and CTLA-4 inhibitory cosignaling pathways in HIV infection and the potential for therapeutic intervention. J Immunol 2009;182:5891–5897.
3. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol 2007;8:239–245.
4. Blackburn SD, Shin H, Haining WN, Zou T, Workman CJ, Polley A, Betts MR, Freeman GJ, Vignali DA, Wherry EJ. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. Nat Immunol 2009;10:29–37.
5. Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, Freeman GJ, Ahmed R. Restoring function in exhausted CD8 T cells during chronic viral infection. Nature 2006;439:682–687. [PubMed: 16382236]
6. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704. [PubMed: 18173375]
7. Linsley PS, Nadler SG. The clinical utility of inhibiting CD28-mediated costimulation. Immunol Rev 2009;229:307–321. [PubMed: 19426230]
8. Rudd CE, Taylor A, Schneider H. CD28 and CTLA-4 coreceptor expression and signal transduction. Immunol Rev 2009;229:12–26. [PubMed: 19426212]
9. Virgin HW, Wherry EJ, Ahmed R. Redefining chronic viral infection. Cell 2009;138:30–50. [PubMed: 19596234]
10. Joshi NS, Cui W, Chandele A, Lee HK, Urso DR, Hagman J, Gapin L, Kaech SM. Inflammation directs memory precursor and short-lived effector CD8(+) T cell fates via the graded expression of T-bet transcription factor. Immunity 2007;27:281–295. [PubMed: 17723218]
11. Sarkar S, Kalia V, Haining WN, Konieczny BT, Subramaniam S, Ahmed R. Functional and genomic profiling of effector CD8 T cell subsets with distinct memory fates. J Exp Med 2008;205:625–640. [PubMed: 18316415]
12. Kaech SM, Tan JT, Wherry EJ, Konieczny BT, Surh CD, Ahmed R. Selective expression of the interleukin 7 receptor identifies effector CD8 T cells that give rise to long-lived memory cells. Nat Immunol 2003;4:1191–1198. [PubMed: 14625547]
13. Haring JS, Harty JT. Aberrant contraction of antigen-specific CD4 T cells after infection in the absence of gamma interferon or its receptor. Infect Immun 2006;74:6252–6263. [PubMed: 16966404]
14. Badovinac VP, Haring JS, Harty JT. Initial T cell receptor transgenic cell precursor frequency dictates critical aspects of the CD8(+) T cell response to infection. Immunity 2007;26:827–841. [PubMed: 17555991]
15. Badovinac VP, Messingham KA, Jabbari A, Haring JS, Harty JT. Accelerated CD8+ T-cell memory and prime-boost response after dendritic-cell vaccination. Nat Med 2005;11:748–756. [PubMed: 15951824]
16. Sarkar S, Teichgraber V, Kalia V, Polley A, Masopust D, Harrington LE, Ahmed R, Wherry EJ. Strength of stimulus and clonal competition impact the rate of memory CD8 T cell differentiation. J Immunol 2007;179:6704–6714. [PubMed: 17982060]
17. D'Cruz LM, Rubinstein MP, Goldrath AW. Surviving the crash: transitioning from effector to memory CD8+ T cell. Semin Immunol 2009;21:92–98. [PubMed: 19269192]
18. Hand TW, Kaech SM. Intrinsic and extrinsic control of effector T cell survival and memory T cell development. Immunol Res 2009;45:46–61. [PubMed: 18629449]
19. Kaech SM, Wherry EJ. Heterogeneity and cell-fate decisions in effector and memory CD8+ T cell differentiation during viral infection. Immunity 2007;27:393–405. [PubMed: 17892848]
20. Wherry EJ, Teichgraber V, Becker TC, Masopust D, Kaech SM, Antia R, von Andrian UH, Ahmed R. Lineage relationship and protective immunity of memory CD8 T cell subsets. Nat Immunol 2003;4:225–234. [PubMed: 12563257]
21. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19:813–824. [PubMed: 17606980]

22. Lafon M, Megret F, Meuth SG, Simon O, Velandia Romero ML, Lafage M, Chen L, Alexopoulou L, Flavell RA, Prehaud C, et al. Detrimental contribution of the immuno-inhibitor B7-H1 to rabies virus encephalitis. J Immunol 2008;180:7506–7515. This study confirms expression of PD-L1 on murine neurons following rabies infection and demonstrates the importance of this costimulatory molecule in regulating the survival of CD8 T cells infiltrating the CNS (and therefore disease severity/progression). [PubMed: 18490751]

23. Lazar-Molnar E, Gacser A, Freeman GJ, Almo SC, Nathenson SG, Nosanchuk JD. The PD-1/PD-L costimulatory pathway critically affects host resistance to the pathogenic fungus Histoplasma capsulatum. Proc Natl Acad Sci U S A 2008;105:2658–2663. This paper furthers the role of the PD-1:PD-ligand pathway in regulating the response to microbial infection by demonstrating a significant role for PD-1 in dampening the immune response to *Histoplasma capsulatum* (fungal pathogen). [PubMed: 18268348]

24. Talay O, Shen CH, Chen L, Chen J. B7-H1 (PD-L1) on T cells is required for Tcell-mediated conditioning of dendritic cell maturation. Proc Natl Acad Sci U S A 2009;106:2741–2746. [PubMed: 19202065]

25. Rowe JH, Johanns TM, Ertelt JM, Way SS. PDL-1 blockade impedes T cell expansion and protective immunity primed by attenuated Listeria monocytogenes. J Immunol 2008;180:7553–7557. [PubMed: 18490756]

26. Fuse S, Tsai CY, Molloy MJ, Allie SR, Zhang W, Yagita H, Usherwood EJ. Recall responses by helpless memory CD8+ T cells are restricted by the upregulation of PD-1. J Immunol 2009;182:4244–4254. This study describes a role for the PD-1 pathway in regulating the “helpless” recall response of CD8 memory T cells (generated in the absence of CD4 T cell help). The study demonstrates that blockade of the pathway during recall responses of “helpless memory CD8 T cells” enhances the functionality of the cells, implicating PD-1-mediated inhibition as a mechanism for helplessness. [PubMed: 19299723]

27. Yao S, Wang S, Zhu Y, Luo L, Zhu G, Flies S, Xu H, Ruff W, Broadwater M, Choi IH, et al. PD-1 on dendritic cells impedes innate immunity against bacterial infection. Blood 2009;113:5811–5818. This paper describes a direct role for PD-1 in negatively regulating the function of dendritic cells during *Listeria* infection, and suggests that upregulation of PD-1 on dendritic cells during infection contributes to the dampening of the innate immune response. [PubMed: 19339692]

28. Cho HY, Choi EK, Lee SW, Jung KO, Seo SK, Choi IW, Park SG, Choi I, Lee SW. Programmed death-1 receptor negatively regulates LPS-mediated IL-12 production and differentiation of murine macrophage RAW264.7 cells. Immunol Lett 2009;127:39–47. [PubMed: 19723542]

29. Huang X, Venet F, Wang YL, Lepape A, Yuan Z, Chen Y, Swan R, Kherouf H, Monneret G, Chung CS, et al. PD-1 expression by macrophages plays a pathologic role in altering microbial clearance and the innate inflammatory response to sepsis. Proc Natl Acad Sci U S A 2009;106:6303–6308. This paper demonstrates a novel role for the PD-1 pathway in inhibiting macrophage function during sepsis, thereby suggesting the PD-1 pathway as a potential therapeutic target for treatment of sepsis. [PubMed: 19332785]

30. Yamazaki T, Akiba H, Koyanagi A, Azuma M, Yagita H, Okumura K. Blockade of B7-H1 on macrophages suppresses CD4+ T cell proliferation by augmenting IFN-gamma-induced nitric oxide production. J Immunol 2005;175:1586–1592. [PubMed: 16034097]

31. Haas KM, Poe JC, Tedder TF. CD21/35 promotes protective immunity to Streptococcus pneumoniae through a complement-independent but CD19-dependent pathway that regulates PD-1 expression. J Immunol 2009;183:3661–3671. [PubMed: 19710450]

32. Velu V, Titanji K, Zhu B, Husain S, Pladevega A, Lai L, Vanderford TH, Chennareddi L, Silvestri G, Freeman GJ, et al. Enhancing SIV-specific immunity in vivo by PD-1 blockade. Nature 2009;458:206–210. [PubMed: 19078956]

Table 1

Examples of the role of CTLA-4 and PD-1 pathways during acute infection Infection Pathway Cell types regulated Reference

Rabies virus	PD-L1	CD8 T cells	[22]
Histoplasma capsulatum			
	PD-1	T cells	[23]
Influenza virus	PD-L1	DC/T cells	[24]
Listeria monocytogenes			
	PD-L1	CD8 T cells	[25]
Vaccinia virus	PD-1	Unhelped memory CD8 T cells	[26]
Listeria monocytogenes			
	PD-1	DC	[27]
Sepsis (multiple bacterial *sp*.)			
	PD-1	Macrophages	[29]