HHS Public Access

Author manuscript

Curr Opin Immunol. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

Curr Opin Immunol. 2023 February ; 80: 102283. doi:10.1016/j.coi.2023.102283.

Immune Checkpoint Receptors in Autoimmunity

Kelly P. Burke[1,2], **Dillon G. Patterson**[2], **Dan Liang**[2], **Arlene H. Sharpe**[2,3,4,*]

[1)]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

[2)]Department of Immunology, Blavatnik Institute, Harvard Medical School, Boston, MA USA

[3)]Evergrande Center for Immunological Diseases, Harvard Medical School and Brigham and Women's Hospital, Boston MA USA

[4)]Broad Institute of MIT and Harvard, Cambridge, MA, USA

Abstract

Immune checkpoint receptors such as PD-1, CTLA-4, LAG3, and TIGIT have distinct and overlapping inhibitory functions that regulate T cell activation, differentiation, and function. These inhibitory receptors also mediate tolerance, and dysregulation of these receptors can result in a breach of tolerance and the development of autoimmune syndromes. Similarly, antibody blockade of immune checkpoint receptors or their ligands for cancer immunotherapy may trigger a spectrum of organ inflammation that resembles autoimmunity, termed immune-related adverse events (irAE). In this review, we discuss recent advances in the regulation of autoimmunity by immune checkpoint receptors. We highlight coordinated gene expression programs linking checkpoint receptors, heterogeneity within autoreactive T cell populations, parallels between irAE and autoimmunity, and bidirectional functional interactions between immune checkpoint receptors and their ligands.

Introduction

Signaling through the T cell receptor (TCR) drives multiple downstream processes, including T cell activation, differentiation, proliferation, and release of effector cytokines and chemokines. In turn, this process upregulates the expression of inhibitory immune checkpoint receptors such as PD-1, CTLA-4, or LAG3, which oppose signals through costimulatory receptors and serve as critical rheostats to abrogate or temper TCR signaling. These receptors play critical roles to shutdown effector T cell responses to limit immunopathology during infection or tissue inflammation, thereby maintaining homeostasis and preserving tissue integrity. Importantly, although these checkpoint receptors are expressed on both CD4+ and CD8+ T cells, among other immune cells, some of their

[*]Correspondence: Arlene H. Sharpe, Arlene_Sharpe@hms.harvard.edu, Mailing address: 77 Avenue Louis Pasteur, NRB 837, Boston, MA 02115.

Author Contributions: K.P.B., D.G.P., D.L, and A.H.S. wrote the manuscript. K.P.B. and A.H.S edited the manuscript.

ligands may be expressed on both hematopoietic and non-hematopoietic cells, as well as tumor cells (Table 1). Notably, ligands such as PD-L1 may be upregulated within the tumor microenvironment on tumor cells and hematopoietic cells [1]. Thus, these immune checkpoint receptors regulate responses in lymphoid tissues (e.g., spleen and lymph nodes), peripheral tissues and the tumor microenvironment.

Over the past decade, blockade of these inhibitory immune checkpoint receptors has been used to augment anti-tumor T cell effector functions and has revolutionized cancer care. In contrast, in both human autoimmune diseases and experimental mouse models of autoimmunity, where pathologic effector cells functionally surpass suppression by regulatory cells, the functions of immune checkpoint receptors are impaired, underscoring their importance in tolerance. Genetic studies have revealed the important roles of checkpoint inhibitors in both the induction and maintenance of peripheral T cell tolerance. For example, genetic deletion of *Pdcd1* (encoding PD-1) or *Lag3* accelerated type 1 diabetes (T1D) in the non-obese diabetic (NOD) mouse model [2,3]. Likewise, loss-of-function mutations in either *CTLA4* or *LRBA*, which alters trafficking of CTLA-4 to the cell membrane, leads to human autoimmune syndromes with parallels to the *Ctla4* knockout mouse model [4]. Similarly, polymorphisms in *CTLA4 or PDCD1* are associated with the development of multiple autoimmune diseases [5,6]. Moreover, immune checkpoint receptors can exert differing effects on pathogenic effector cells or regulatory T cells [7–9], revealing further ways these receptors control T cell tolerance and autoimmunity. To this end, a recent study of single-cell expression quantitative trait loci (sc-eQTL) demonstrated the effects of genetic variants of *CTLA4* and *PDCD1* on their transcriptional expression in different CD4+ T cell types [10].

In this review, we focus on recent advances in understanding immune checkpoint receptors on effector cells in the context of autoimmunity. We first discuss the discovery of gene programs that coordinate expression of checkpoint receptors. Next, we highlight recent work identifying autoreactive T cells with features of T cell exhaustion and anatomic locations of reservoirs of autoreactive T cells. We then discuss parallels between immune checkpoint blockade-induced immune-related adverse events and autoimmunity. Finally, we summarize recent studies on bidirectional functional interactions between immune checkpoint receptors and their ligands, and the implications of these interactions for tolerance and autoimmunity.

Coordinated expression of checkpoint receptors on T cells

Loss of a single checkpoint receptor has been associated with compensatory upregulation of other inhibitory molecules in models of chronic viral infection, tumor and autoimmunity [7,8,11,12], suggesting an underlying shared regulation of checkpoint receptors. Using a murine tumor model, Chihara et al. identified a shared gene regulatory program of costimulatory and coinhibitory checkpoint molecules (including *Ctla4*, *Lag3*, *Havcr2* (encoding TIM-3), *Icos*) across multiple states of T cell hyporesponsiveness, including autoimmunity, that was driven by IL-27 signaling [13]. Intriguingly, although *Pdcd1* was identified as part of this gene program transcriptionally, its protein expression was not affected by loss of IL-27, highlighting potential regulatory differences among checkpoint receptors. As IL-27 is at least partially regulated by IFN-β, Sumida et al. assessed the effects

of both IL-27 and IFN-β on induction of coinhibitory receptor expression in human T cells [14]. In both in vitro experiments and within an in vivo dataset, IFN-β induced expression of PD-1, TIM-3, and LAG3 but inhibited expression of TIGIT, with these effects driven by different interferon-specific gene modules [14]. These types of systems biology approaches have the ability to highlight regulatory mechanisms shared across diseases and identify novel therapeutic targets.

Heterogeneity of autoreactive CD8+ T cells at sites of inflammation

In the periphery, autoreactive T cells may be presented with self-antigen and continuously stimulated. Persistent stimulation with self-antigen has similarities with chronic viral infection, where continuous T cell receptor signaling leads to a dysfunctional CD8+ T cell program, known as T cell exhaustion. T cell exhaustion is characterized by transcriptional and epigenetic changes leading to elevated expression of inhibitory receptors, and loss of proliferative capacity, cytokine production, and cytotoxicity [15–17]. Substantial heterogeneity exists among exhausted CD8+ T cells, including a self-renewing stem-like population that give rise to terminally differentiated subsets expressing high levels of the co-inhibitory molecules PD-1, TIM-3, and LAG3, among others [18–21].

Intriguingly, a subset of pathogenic T cells expressing hallmarks of terminally exhausted T cells (PD-1, LAG3, TOX) and a self-renewing stem-like population (TCF1) have recently been described in multiple autoimmune models, including a model of chronic CNS inflammation [22] and T1D in NOD mice [23,24]. In a model of chronic CNS inflammation, the transcription factor TOX was dispensable for the initial expansion of autoreactive CD8+ T cells but required for their persistence in the tissue. Notably, the presence of TOX was required for the expression of PD-1, TIGIT, and LAG3, suggesting a role for TOX in controlling autoreactive CD8+ T cell differentiation and survival [22]. Likewise, a subset of infiltrating CD8+ T cell population in pancreatic islets at the time of diabetes expressed PD-1, TOX, TIGIT, and LAG3 [24]. Within this exhausted-like subset, LAG3 restricted progression of diabetes, in part by limiting proliferation and effector function [24]. Together, these studies suggest the presence of immune checkpoint molecules may promote the long-term survival and tissue adaptation of autoreactive T cells. Further studies are needed to define how autoreactive cells with features of T cell exhaustion arise relative to the more numerous autoreactive pathogenic cells. Importantly, these disease models show significant differences in patterns of checkpoint receptor expression and T cell functionality, including cytokine production, compared to exhausted T cells in chronic viral infection or malignancy. The differences between chronic infection and cancer versus autoimmunity suggest a nuanced context-specific role for each checkpoint receptor in regulating T cell activation, differentiation, and trafficking to target organs following chronic stimulation.

The reservoir of autoreactive T cells

Two recent studies identified a reservoir of stem-like autoreactive T cells that are maintained outside the site of organ inflammation. Transcriptional profiling of antigen-specific autoreactive CD8+ T cells from pancreatic LN (pLN) and pancreas of mice with T1D identified a transition from stem-like $TCF1^{hi}$ “autoimmune progenitors” in pLN to $TCF1^{lo}$ “autoimmune mediators” in pLN and pancreas [25], pointing to a progenitor pool

within the pLN. Likewise, paired scRNA-/TCR-seq of Th17 cells from the CNS, peripheral lymphoid organs, and intestinal tissues from EAE mice found a TCF1^{hi}SLAMF6^{+} stem-like subset in the spleen with clonotypes shared with homeostatic Th17 cells in the intestinal tissues [26]. The stem-like subset continuously gave rise to a CXCR6^{+} pathogenic Th17 population also seen in the draining LN and CNS [26], pointing to a migratory role of Th17 cells originating from the gut. In both settings, upregulation of PD-1 and several other co-inhibitory receptors (TIGIT, TIM-3 or LAG3) occurred during the “progenitor” to “mediator” transition [25] or were highly expressed on pathogenic autoreactive T cells in the CNS [26]. Further work is needed to determine the roles of interactions between checkpoint receptors and their ligands in the generation and/or maintenance of autoreactive stem-like cells, as well as their differentiation into pathogenic effector cells.

Parallels to immune-related adverse events with immune checkpoint blockade

A subset of cancer patients treated with antibodies blocking PD-1/PD-L1 or CTLA-4 pathways will develop irAEs. Clinically, irAEs may manifest as inflammation in any organ, most commonly dermatologic, gastrointestinal, pulmonary, and endocrine. The pattern of organ involvement may overlap but is generally distinct between anti-CTLA-4 and anti-PD-1/PD-L1. Notably, combination therapy increases the incidence and severity of irAEs. These toxicities range from mild to life-threatening, requiring immunosuppression and/or treatment discontinuation, either of which may adversely impact therapeutic outcome [27–29]. Multiple mechanisms have been proposed, including a pre-existing susceptibility to autoimmunity, generation of a new self-reactive repertoire, or aberrant presentation of self-antigen in the tumor microenvironment.

Two recent publications profiling checkpoint-inhibitor induced colitis [30] and inflammatory arthritis [31] shed light on differing trafficking patterns of inflammatory irAE-associated T cells. Both studies showed significant tissue infiltration of highly proliferative Th1-like CD4+ T cells and cytotoxic CD8+ T cells expressing high levels of checkpoint receptor genes (*Pdcd1*, *Lag3*, *Havcr2*, and *Ctla4*). Intriguingly, TCR repertoire analysis showed shared clonal origin among CD8+ effector T cells at the site of the colitis with gut tissue resident memory (T_{RM} cells, suggesting clonal expansion arising from a T_{RM} population [30]. These findings were corroborated by flow cytometry, bulk RNA-sequencing, and single-cell RNA sequencing in a separate cohort of patients with anti-CTLA-4/anti-PD-1 associated colitis and gastritis, which similarly demonstrated enrichment of an activated CD8+ T_{RM} population expressing high levels of PD-1, LAG3 and CTLA-4 with high production of IFNγ, a signature distinct from ulcerative colitis [32].

Studies examining checkpoint-induced inflammatory arthritis showed shared clonality between a CD8+CX3CR1^{hi} effector phenotype in the peripheral blood and CXCR3+CXCRL6+$^{high/low}$ effector memory or terminally differentiated effector memory CD8+ in the synovial fluid [31]. These findings imply active trafficking and differentiation from the peripheral blood to the synovial fluid. Recent work in preclinical mouse arthritis models demonstrated a role for both expansion of T_{RM} in a previously inflamed joint and influx of cells from the periphery [33]. Similarly, single cell analyses from patients with rheumatoid arthritis demonstrated a shared presence of granzyme K-expressing CD8+

T cells between the peripheral blood, inflamed synovial tissue, and synovial fluid [34]. Collectively, these studies suggest that in tissues that lack a T_{RM} population, such as the synovium, trafficking of T cells from the peripheral blood to the inflamed tissue plays a significant role.

Corticosteroids are the mainstay and first-line treatment for severe irAE with organ-specific immunosuppressive strategies employed to treat steroid-refractory irAE. It remains to be understood how the genesis of the immune infiltrate differs to drive steroid-refractoriness. Notably, the study of immune checkpoint-related arthritis identified an increase in Th17 cells in the synovial fluid of subjects treated with combination anti-CTLA-4/anti-PD-1 therapy compared to those subjects treated with anti-PD-1 alone, and the presence of Th17 cells made the inflammatory arthritis less likely to be steroid responsive [31]. How combination therapy would preferentially drive the presence of Th17 cells is unclear.

Immune Checkpoint Ligand Reverse Signaling

Recent work indicates there may be bidirectional functional interactions between immune checkpoint receptors and their ligands. While signaling through the immune checkpoint receptors into T cells is well established, emerging data show that reverse signaling through the ligands of immune checkpoint receptors, such as PD-L1, can exert cell-intrinsic effects. Much of the biology related to this reverse signaling comes from studies of ligand signaling within tumor cells [35]. Deletion of the PD-L1 cytoplasmic tail in tumor cells increased susceptibility to T-cell mediated lysis, indicating PD-L1 plays a critical cell intrinsic role in shielding tumor cells against killing [36]. PD-L1 signaling in tumor cells modulates cell proliferation and motility, mammalian target of rapamycin complex 1 (mTORC1) activation, autophagy, survival, and interferon cytotoxicity [37–40]. Signaling proteins bind the cytoplasmic tail of PD-L1 to transmit biochemical signals [41]. In a tumor model, oncogenic signaling through EGFR recruited phospholipase C-γ1 (PLC-γ1) to the cytoplasmic tail of PD-L1, led to increased protein kinase C activation, Rho GTPases, and calcium flux; and resulted in increased cell motility and invasiveness [42]. Further studies are needed to determine whether similar signaling pathways are activated in non-hematopoietic cells during autoimmunity. For example, PD-L1 upregulation on beta islet cells in the T1D mouse model is driven by IFN expression and has a protective effect on cell survival [43]. This effect could be due, at least in part, to PD-L1 signaling in beta cells.

The PD1-PD-L1 axis also drives cell-intrinsic effects within myeloid cells [44]. Deletion of PD-L1 on DC results in exacerbated EAE through impaired initial activation of CD4+ T cells [45]. PD-L1 is required for proper chemokine mediated dermal dendritic cell migration to the draining lymph node, which is dependent on a three amino acid sequence within the cytoplasmic tail of PD-L1 [46]. Mice containing a deletion in this motif exhibit impaired CCR7 signaling, ultimately hampering CCL21 G protein activation, actin polymerization, and ERK phosphorylation. Defects in dendritic cell migration resulted in reduced T cell priming in infection models requiring dendritic cell trafficking to the lymph node [46]. Collectively, these studies underscore the diverse functions of PD-1/PD-L1 bidirectional signaling events on immune cells and cancer.

Conclusions and future directions

Immune checkpoint receptors such as PD-1, CTLA-4 and LAG3 collectively serve as a rheostat to balance protective immunity, tolerance, immune-mediated tissue damage and homeostasis. They can regulate T cell activation, and fine-tune T cell fates and functions with roles dependent on anatomic location (lymphoid and peripheral tissues), specific immune checkpoint receptor, and T cell type. The presence of genetic polymorphisms in immune checkpoint molecules in humans may layer additional complexity to this rheostat. Given these genetic polymorphisms, targeting immune checkpoint receptors, either by agonistic or antagonistic antibodies, may affect tolerance differently across individuals and provide one explanation for the differing presentations and likelihood of developing immune related adverse events. Further understanding of the multifaceted functions of immune checkpoint receptors and the impact of these genetic polymorphism may provide insights into how to best modulate these pathways to suppress pathologic responses during autoimmunity and promote anti-tumor immunity while limiting irAEs.

Acknowledgments:

We greatly acknowledge thoughtful conversation with K.E. Pauken. 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 acknowledged.

Funding:

This work was supported by NIH 5P50CA127003 and P01 CA236749 (to A.H.S.).

K.P.B. was supported by funding from the 2021 AACR-Bristol Myers Squibb Immuno-oncology Research Fellowship, Grant 21–40-15-BURK.

Conflict of Interest Statement:

Arlene Sharpe currently has funding from Quark, Merck, AbbVie, Moderna and Vertex unrelated to the submitted work. She serves on advisory boards for Surface Oncology, SQZ Biotechnologies, Selecta, Elpiscience, Monopteros, Bicara, Fibrogen, and Alixis. She also is on scientific advisory boards for the Massachusetts General Cancer Center, Program in Cellular and Molecular Medicine at Boston Children's Hospital, the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center, Glaxo Smith Kline and Janssen. She is an academic editor for the Journal of Experimental Medicine. A.H.S. has patents/pending royalties on the PD-1 pathway from Roche and Novartis.

REFERENCES

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Sharpe AH, Pauken KE: The diverse functions of the PD1 inhibitory pathway. Nat Rev Immunol 2017.
2. Wang J, Yoshida T, Nakaki F, Hiai H, Okazaki T, Honjo T: Establishment of NOD-Pdcd1−/− mice as an efficient animal model of type I diabetes. Proc Natl Acad Sci U S A 2005, 102:11823–11828. [PubMed: 16087865]
3. Bettini M, Szymczak-Workman AL, Forbes K, Castellaw AH, Selby M, Pan X, Drake CG, Korman AJ, Vignali DA: Cutting edge: accelerated autoimmune diabetes in the absence of LAG-3. J Immunol 2011, 187:3493–3498. [PubMed: 21873518]

4. Lo B, Fritz JM, Su HC, Uzel G, Jordan MB, Lenardo MJ: CHAI and LATAIE: new genetic diseases of CTLA-4 checkpoint insufficiency. Blood 2016, 128:1037–1042. [PubMed: 27418640]
5. Zamani MR, Aslani S, Salmaninejad A, Javan MR, Rezaei N: PD-1/PD-L and autoimmunity: A growing relationship. Cell Immunol 2016, 310:27–41. [PubMed: 27660198]
6. Wicker LS, Clark J, Fraser HI, Garner VE, Gonzalez-Munoz A, Healy B, Howlett S, Hunter K, Rainbow D, Rosa RL, et al. : Type 1 diabetes genes and pathways shared by humans and NOD mice. J Autoimmun 2005, 25 Suppl:29–33. [PubMed: 16257508]
7. Zhang Q, Chikina M, Szymczak-Workman AL, Horne W, Kolls JK, Vignali KM, Normolle D, Bettini M, Workman CJ, Vignali DAA: LAG3 limits regulatory T cell proliferation and function in autoimmune diabetes. Sci Immunol 2017, 2.
8. Tan CL, Kuchroo JR, Sage PT, Liang D, Francisco LM, Buck J, Thaker YR, Zhang Q, McArdel SL, Juneja VR, et al. : PD-1 restraint of regulatory T cell suppressive activity is critical for immune tolerance. J Exp Med 2021, 218.
9. Lucca LE, Dominguez-Villar M: Modulation of regulatory T cell function and stability by co-inhibitory receptors. Nat Rev Immunol 2020, 20:680–693. [PubMed: 32269380]
10. Schmiedel BJ, Gonzalez-Colin C, Fajardo V, Rocha J, Madrigal A, Ramirez-Suastegui C, Bhattacharyya S, Simon H, Greenbaum JA, Peters B, et al. : Single-cell eQTL analysis of activated T cell subsets reveals activation and cell type-dependent effects of disease-risk variants. Sci Immunol 2022, 7:eabm2508.
11. Paterson AM, Lovitch SB, Sage PT, Juneja VR, Lee Y, Trombley JD, Arancibia-Cárcamo CV, Sobel RA, Rudensky AY, Kuchroo VK, et al. : Deletion of CTLA-4 on regulatory T cells during adulthood leads to resistance to autoimmunity. J Exp Med 2015, 212:1603–1621. [PubMed: 26371185]
12. Odorizzi PM, Pauken KE, Paley MA, Sharpe A, Wherry EJ: Genetic absence of PD-1 promotes accumulation of terminally differentiated exhausted CD8+ T cells. J Exp Med 2015, 212:1125–1137. [PubMed: 26034050]
13. Chihara N, Madi A, Kondo T, Zhang H, Acharya N, Singer M, Nyman J, Marjanovic ND, Kowalczyk MS, Wang C, et al. : Induction and transcriptional regulation of the co-inhibitory gene module in T cells. Nature 2018, 558:454–459. [PubMed: 29899446]
14. Sumida TS, Dulberg S, Schupp JC, Lincoln MR, Stillwell HA, Axisa PP, Comi M, Unterman A, Kaminski N, Madi A, et al. : Type I interferon transcriptional network regulates expression of coinhibitory receptors in human T cells. Nat Immunol 2022, 23:632–642. [PubMed: 35301508] •The authors identify two distinct transcription factor networks in response to IFN-beta that differentially control the coinhibitory molecules PD-1, TIM-3, and LAG3 separately from TIGIT.
15. 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. [PubMed: 19043418]
16. 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]
17. Wherry EJ, Ha SJ, Kaech SM, Haining WN, Sarkar S, Kalia V, Subramaniam S, Blattman JN, Barber DL, Ahmed R: Molecular signature of CD8+ T cell exhaustion during chronic viral infection. Immunity 2007, 27:670–684. [PubMed: 17950003]
18. Miller BC, Sen DR, Al Abosy R, Bi K, Virkud YV, LaFleur MW, Yates KB, Lako A, Felt K, Naik GS, et al. : Subsets of exhausted CD8. Nat Immunol 2019, 20:326–336. [PubMed: 30778252]
19. Sade-Feldman M, Yizhak K, Bjorgaard SL, Ray JP, de Boer CG, Jenkins RW, Lieb DJ, Chen JH, Frederick DT, Barzily-Rokni M, et al. : Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma. Cell 2018, 175:998–1013.e1020. [PubMed: 30388456]
20. Siddiqui I, Schaeuble K, Chennupati V, Fuertes Marraco SA, Calderon-Copete S, Pais Ferreira D, Carmona SJ, Scarpellino L, Gfeller D, Pradervand S, et al. : Intratumoral Tcf1(+)PD-1(+)CD8(+) T Cells with Stem-like Properties Promote Tumor Control in Response to Vaccination and Checkpoint Blockade Immunotherapy. Immunity 2019, 50:195–211 e110. [PubMed: 30635237]

21. Im SJ, Hashimoto M, Gerner MY, Lee J, Kissick HT, Burger MC, Shan Q, Hale JS, Nasti TH, Sharpe AH, et al. : Defining CD8+ T cells that provide the proliferative burst after PD-1 therapy. Nature 2016, 537:417–421. [PubMed: 27501248]

22. Page N, Lemeille S, Vincenti I, Klimek B, Mariotte A, Wagner I, Di Liberto G, Kaye J, Merkler D: Persistence of self-reactive CD8+ T cells in the CNS requires TOX-dependent chromatin remodeling. Nature Communications 2021, 12:1009. •In a model of chronic CNS inflammation, the authors demonstrate changes in transcription and chromatin accessibility of several genes associated with T cell exhaustion and that expression of TOX in self-reactive cells is required for downstream persistence of these cells.

23. Zakharov PN, Hu H, Wan X, Unanue ER: Single-cell RNA sequencing of murine islets shows high cellular complexity at all stages of autoimmune diabetes. J Exp Med 2020, 217.

24. Grebinoski S, Zhang Q, Cillo AR, Manne S, Xiao H, Brunazzi EA, Tabib T, Cardello C, Lian CG, Murphy GF, et al. : Autoreactive CD8+ T cells are restrained by an exhaustionlike program that is maintained by LAG3. Nature Immunology 2022, 23:868–877. [PubMed: 35618829] • Using the NOD model, the authors identify a subset of autoreactive CD8+ T cells that have features of T cell exhaustion. Deletion of LAG3 on CD8+ T cells accelerated the onset of diabetes, at least partially through a combination of increased cell numbers and increased effector function.

25. Gearty SV, Dündar F, Zumbo P, Espinosa-Carrasco G, Shakiba M, Sanchez-Rivera FJ, Socci ND, Trivedi P, Lowe SW, Lauer P, et al. : An autoimmune stem-like CD8 T cell population drives type 1 diabetes. Nature 2022, 602:156–161. [PubMed: 34847567] •• The authors identify a self-renewing CD8+ T cell population that originates in the lymph node, undergoes further differentiation and trafficks to the pancreas and is sufficient to drive the development of type I diabetes in the NOD model.

26. Schnell A, Huang L, Singer M, Singaraju A, Barilla RM, Regan BML, Bollhagen A, Thakore PI, Dionne D, Delorey TM, et al. : Stem-like intestinal Th17 cells give rise to pathogenic effector T cells during autoimmunity. Cell 2021, 184:6281–6298.e6223. [PubMed: 34875227] • Using single cell RNA-sequencing, the authors identify a homeostatic population of Th17 cells shared between the intestine and the spleen. A subset of this homeostatic population can give rise to the pathogenic cells that induce CNS pathology in EAE.

27. Burke KP, Grebinoski S, Sharpe AH, Vignali DAA: Understanding adverse events of immunotherapy: A mechanistic perspective. J Exp Med 2021, 218.

28. Pauken KE, Dougan M, Rose NR, Lichtman AH, Sharpe AH: Adverse Events Following Cancer Immunotherapy: Obstacles and Opportunities. Trends Immunol 2019, 40:511–523. [PubMed: 31053497]

29. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, Izzeddine H, Marabelle A, Champiat S, Berdelou A, et al. : Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016, 13:473–486. [PubMed: 27141885]

30. Luoma AM, Suo S, Williams HL, Sharova T, Sullivan K, Manos M, Bowling P, Hodi FS, Rahma O, Sullivan RJ, et al. : Molecular Pathways of Colon Inflammation Induced by Cancer Immunotherapy. Cell 2020, 182:655–671 e622. [PubMed: 32603654] ••The authors performed single cell RNA-sequencing with paired T cell receptor sequencing on colon biopsies from subjects treated with immune checkpoint inhibitors who did or did not have immune-related checkpoint colitis. Importantly, they identify an enrichment in CD8+ cytotoxic effector cells in patients with ICB-colitis; these CD8+ cytotoxic effector cells are clonally related to tissue resident CD8+ memory population.

31. Kim ST, Chu Y, Misoi M, Suarez-Almazor ME, Tayar JH, Lu H, Buni M, Kramer J, Rodriguez E, Hussain Z, et al. : Distinct molecular and immune hallmarks of inflammatory arthritis induced by immune checkpoint inhibitors for cancer therapy. Nat Commun 2022, 13:1970. ••The authors performed single cell RNA-sequencing with paired T cell receptor sequencing from paired peripheral blood and synovial fluid from subjects with immune-checkpoint-associated arthritis. They identified enrichment in Th1-like CD4+ and CD8+ T cells in blood and synovial fluid from subjects with ICB-associated arthritis compared to osteoarthritis. Th17 cells were enriched in synovial fluid from combination checkpoint blockade compared to single agent anti-PD-1 therapy.

32. Sasson SC, Slevin SM, Cheung VTF, Nassiri I, Olsson-Brown A, Fryer E, Ferreira RC, Trzupek D, Gupta T, Al-Hillawi L, et al. : Interferon-Gamma-Producing CD8(+) Tissue Resident Memory T

Cells Are a Targetable Hallmark of Immune Checkpoint Inhibitor-Colitis. Gastroenterology 2021, 161:1229–1244 e1229. [PubMed: 34147519]

33. Chang MH, Levescot A, Nelson-Maney N, Blaustein RB, Winden KD, Morris A, Wactor A, Balu S, Grieshaber-Bouyer R, Wei K, et al. : Arthritis flares mediated by tissue-resident memory T cells in the joint. Cell Rep 2021, 37:109902.
34. Jonsson AH, Zhang F, Dunlap G, Gomez-Rivas E, Watts GFM, Faust HJ, Rupani KV, Mears JR, Meednu N, Wang R, et al. : Granzyme K(+) CD8 T cells form a core population in inflamed human tissue. Sci Transl Med 2022, 14:eabo0686.
35. Kornepati AVR, Vadlamudi RK, Curiel TJ: Programmed death ligand 1 signals in cancer cells. Nat Rev Cancer 2022, 22:174–189. [PubMed: 35031777]
36. Azuma T, Yao S, Zhu G, Flies AS, Flies SJ, Chen L: B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood 2008, 111:3635–3643. [PubMed: 18223165]
37. Zhang D, Reyes RM, Osta E, Kari S, Gupta HB, Padron AS, Kornepati AVR, Kancharla A, Sun X, Deng Y, et al. : Bladder cancer cell-intrinsic PD-L1 signals promote mTOR and autophagy activation that can be inhibited to improve cytotoxic chemotherapy. Cancer Med 2021, 10:2137–2152. [PubMed: 33626233]
38. Clark CA, Gupta HB, Sareddy G, Pandeswara S, Lao S, Yuan B, Drerup JM, Padron A, Conejo-Garcia J, Murthy K, et al. : Tumor-Intrinsic PD-L1 Signals Regulate Cell Growth, Pathogenesis, and Autophagy in Ovarian Cancer and Melanoma. Cancer Res 2016, 76:.
39. Feng D, Qin B, Pal K, Sun L, Dutta S, Dong H, Liu X, Mukhopadhyay D, Huang S, Sinicrope FA: BRAF(V600E)-induced, tumor intrinsic PD-L1 can regulate chemotherapy-induced apoptosis in human colon cancer cells and in tumor xenografts. Oncogene 2019, 38:6752–6766. [PubMed: 31406255]
40. Gato-Canas M, Zuazo M, Arasanz H, Ibanez-Vea M, Lorenzo L, Fernandez-Hinojal G, Vera R, Smerdou C, Martisova E, Arozarena I, et al. : PDL1 Signals through Conserved Sequence Motifs to Overcome Interferon-Mediated Cytotoxicity. Cell Rep 2017, 20:1818–1829. [PubMed: 28834746]
41. Escors D, Gato-Canas M, Zuazo M, Arasanz H, Garcia-Granda MJ, Vera R, Kochan G: The intracellular signalosome of PD-L1 in cancer cells. Signal Transduct Target Ther 2018, 3:26. [PubMed: 30275987]
42. Ghosh S, Nataraj NB, Noronha A, Patkar S, Sekar A, Mukherjee S, Winograd-Katz S, Kramarski L, Verma A, Lindzen M, et al. : PD-L1 recruits phospholipase C and enhances tumorigenicity of lung tumors harboring mutant forms of EGFR. Cell Rep 2021, 35:109181.
43. Osum KC, Burrack AL, Martinov T, Sahli NL, Mitchell JS, Tucker CG, Pauken KE, Papas K, Appakalai B, Spanier JA, et al. : Interferon-gamma drives programmed death-ligand 1 expression on islet beta cells to limit T cell function during autoimmune diabetes. Sci Rep 2018, 8:8295. [PubMed: 29844327]
44. Liu X, Hogg GD, DeNardo DG: Rethinking immune checkpoint blockade: ‘Beyond the T cell’. J Immunother Cancer 2021, 9.
45. Sage PT, Schildberg FA, Sobel RA, Kuchroo VK, Freeman GJ, Sharpe AH: Dendritic Cell PD-L1 Limits Autoimmunity and Follicular T Cell Differentiation and Function. J Immunol 2018, 200:2592–2602. [PubMed: 29531164]
46. Lucas ED, Schafer JB, Matsuda J, Kraus M, Burchill MA, Tamburini BAJ: PD-L1 Reverse Signaling in Dermal Dendritic Cells Promotes Dendritic Cell Migration Required for Skin Immunity. Cell Rep 2020, 33:108258. • The authors identify a threonine-serine-serine (TSS) motif on PD-L1 required for effective dendritic cell migration from the skin to the lymph node. This indicates a role for reverse ligand signaling through the PD-1/PD-L1 axis.
47. Baumeister SH, Freeman GJ, Dranoff G, Sharpe AH: Coinhibitory Pathways in Immunotherapy for Cancer. Annu Rev Immunol 2016, 34:539–573. [PubMed: 26927206]
48. Yang Y, Li X, Ma Z, Wang C, Yang Q, Byrne-Steele M, Hong R, Min Q, Zhou G, Cheng Y, et al. : CTLA-4 expression by B-1a B cells is essential for immune tolerance. Nat Commun 2021, 12:525. [PubMed: 33483505]
49. Anderson AC, Joller N, Kuchroo VK: Lag-3, Tim-3, and TIGIT: Co-inhibitory Receptors with Specialized Functions in Immune Regulation. Immunity 2016, 44:989–1004. [PubMed: 27192565]

50. Andrews LP, Yano H, Vignali DAA: Inhibitory receptors and ligands beyond PD-1, PD-L1 and CTLA-4: breakthroughs or backups. Nat Immunol 2019, 20:1425–1434. [PubMed: 31611702]

51. Harjunpaa H, Guillerey C: TIGIT as an emerging immune checkpoint. Clin Exp Immunol 2020, 200:108–119. [PubMed: 31828774]

Table 1:

Selected immune checkpoint receptors, their cell-type-specific expression patterns, and ligands in non-tumor tissue.

Immune checkpoint receptor (Alternate name, *Gene name*)	**Cell types expressing receptor**	**Immune checkpoint ligand (*Gene name*)**	**Cell types expressing ligand**	**Ref**
PD-1 (*Pdcd1*) CD279	T cells B cells NK cells Myeloid	PD-L1 (B7-H1; CD274)	Hematopoietic (antigenpresenting cells, T cells, B cells) Non-hematopoietic (e.g., vascular endothelial cells, pancreatic islets, liver non-parenchymal cells, placental syncytiotrophoblasts)	[1]
		PD-L2 (B7-DC; CD273)	Hematopoietic (dendritic cells, macrophages, some B cells, some mast cells, Th2 CD4+ cells); non-hematopoietic (lung epithelial cells)	
CTLA-4 (*Ctla4*) CD152	T cells B1a cells	B7–1 (*Cd80*)	Hematopoietic (antigen presenting cells)	[47,48]
		B7–2 (*Cd86*)		
LAG3 (*Lag3*) CD223	T cells NK cells NKT B cells	MHC-II	Hematopoietic (antigenpresenting cells, T cells, B cells, macrophages)	[49,50]
		Galectin-3	Non-hematopoietic tissues (e.g., epithelial cells, endothelial cells)	
		LSECtin	Liver	
		FGL-1	Liver	
TIGIT (*Tigit*) WUCAM, VSIG9, VSTM3	T cells NK cells Gamma-delta T cells	CD115 (*Pvr*)	Hematopoietic (antigenpresenting cells, T cells, B cells, macrophages) Non-hematopoietic cells	[49,51]
		CD112 (PVRL2; Nectin-2)		
		CD113 (PVRL3; Nectin-3)	Non-hematopoietic cells	