Co-inhibitory receptors and tolerance

Adel Mohammadzadeh[1]

[1]Urmia University of Medical Sciences

May 5, 2020

Abstract

Maintaining immune tolerance is a dynamic biological process which is provided by various types of tolerance mechanisms. In the light of the remarkable role of co-inhibitory receptors for switching-off the immune system, the potential impact of these receptors in controlling auto-reactivity is needed to be interrogated. Recent investigations suggested that the dysregulation of co-inhibitory receptors in chronic immune responses including cancer and chronic infections can result in immunological consequences called exhaustion. Exhaustion confer a potent "switch-off" mechanism for immune response. Using both co-inhibitory receptors and transcription factors in controlling T cells behavior, this review provide an overview of the potential effects of co-inhibitory receptors in maintaining tolerance and discuss how impaired co-inhibitory receptors might results in autoimmunity.

Key messages

- Early expression of co-inhibitory receptors on activated T cell, indicated the unique role of co-inhibitory receptors in controlling of T cells
- T cells exhaustion is a successful mechanism in controlling immune response in the case of cancers and chronic viral infections generally because of the highly expressed co-inhibitory receptors
- There is a significant correlations between co-inhibitory receptors and transcription factors
- Dysregulation or down-regulation of co-inhibitory receptors can foster autoimmunity
- Profiling and monitoring of the major T cell transcription factors along with surface expressed co-inhibitory receptors in chronic inflammatory condition can result in better prognoses and treatment protocols
- In order to make a reasonable prediction of the immune system's behavior during chronic inflammation such as autoimmunity, co-inhibitory receptors as well as the transcription factor's profile represent good candidates.

Introduction

T cells activation is a multistep process involving an interaction of T cell receptor (TCR)-complex with MHC-peptide and expression of co-stimulatory receptors along with cytokine milieu that is also necessary for directing T cell's fate [1].[1] The interaction of co-stimulatory receptors, CD28 superfamily, on T cells with B7 family ligands (B7.1/CD80, B7.2/CD86) on the surface of antigen presenting cells (APCs) serve a critical step in T cells activation[2]. Engagement of CD28 with B7 family ligands results in regulation of several important cellular signaling pathways which are important for cell survival by producing anti-apoptotic proteins such as Bcl-xL[3]. In contrast to CD28 and ICOS (inducible co-stimulator/ CD278), the other members of this family including CTLA-4 (cytotoxic T lymphocyte antigen 4/CD152), PD-1 (programmed death-1/CD279), B-and T-lymphocyte attenuator (BTLA/CD272), LAG-3 (lymphocyte-activation gene-3/CD223), Tim-3 (T cell immunoglobulin and mucin 3/ or hepatitis A virus cellular receptor 2 or HAVCR2), VISTA (a programmed death-1 homologue (PD-1H, also called V-domain Ig suppressor of T cell activation) and 2B4 (CD244) are involved in down-regulation of the immune response [4]. Alongside co-stimulatory receptors, activation leads

a significant up-regulation of co-inhibitory receptors on the surface of activated T cells that occur following antigen encounter [5]. Co-inhibitory receptors serve as breaks or "immune checkpoints" that are mainly used to rein T cells. Although, the role of co-inhibitory receptors as a major players for T cell exhaustion is comprehensively investigated in cancers [6] and chronic viral infections [7], but their exquisite role during autoimmunity are not explored well. Based on the recently published articles in chronic viral infection, cancer and autoimmune disease, this review highlights the unique role of co-inhibitory receptors mainly CTLA-4 and PD-1 and transcription factors such as AP-1 and NFAT in regulating of immune response as well as explores the role of transcription factors in directing T cells fate during a chronic immune response.

Co-inhibitory receptors as important players in T cell exhaustion

In response to chronic viral infections such as HIV, HCV and cancers, our immune system undergoes many dramatic changes both morphologically and genetically in which a hypo-responsiveness state occurs that is called exhaustion. Characteristically exhausted T cells fail to produce IFN-γ and TNF-α and IL-2 in response to common T cell stimulators and consequently lost their proliferation capacity [8]. Although the molecular mechanisms that control T cell exhaustion are not completely discovered, but several complex interplay between genetic and environmental factors, including chronic exposure to antigen, decreasing of CD4+T cells, expression of multiple inhibitory receptors, presence of unique inhibitory cytokines such as IL-10 and TGF-β [9, 10], type I interferon signaling [11], myeloid derived suppressor cells (MDSC) [12], transcription factors [13] and quality of T cell receptor engagement [14] have been designated to this process. Note that there are other requirements such as the nature of antigens, for example clone 13 vs Armstrong of lymphocytic choriomeningitis virus (LCMV) [15], different genetic factors [16, 17], epigenetic [18] and the metabolic mood of T cells [19] that must be regarded as effective players in this event.

High level and sustained expression of multiple co-inhibitory receptors such as CTLA-4, PD-1, LAG-3, CD160 and TIM3 are considered as hallmarks of T cell exhaustion [10]. Thus, T cells exhaustion during chronic viral infections and cancer seems to be a potent switch-off mechanism that reflects the amenable capability of the immune system. Consequently, both cancer and chronic viral infections use co-inhibitory receptors as an evolutionary escape mechanism to control the immune response [9]. Indeed, for instance, the emerging of immune-check point antibodies emphasize the unique role of co-inhibitory receptors as important players in regulating immune response.

The unique role of the co-inhibitory receptors in sustaining tolerance

Owing to the randomly generated T-cell receptors, it is well accepted that all individuals have degrees of self-recognition [20] (BOX 1). Since central tolerance appears to be not enough to delete all self-reactive T cells, peripheral tolerance mechanisms such as anergy and regulatory T cells are necessary to maintain self-tolerance [21].

A complex interplay between gens and environmental factors are involved in autoimmunity.

The contribution of certain types of human leukocyte antigen (HLA) and non-HLA as a genetic risk factors with different autoimmune diseases have been established. Of note, the expression of HLA-DRB1 alleles are strongly associated with multiple sclerosis (MS) [22] and rheumatoid arthritis, and strong association of HLA-DQB1 with type 1 diabetes (T1D), HLA-DQ2/DQ8 in celiac disease and HLA-B27 with ankylosing spondylitis (AS) have been documented [23]. However in addition to genetic predisposition, the environmental factors such as infectious agents, particularly viral infections, are thought to play important role in instructing auto-reactivity. Infections can provoke self-reactivity by several mechanisms such as molecular mimicry, epitope spreading, and bystander activation and so on. Among the environmental factors, infections are of particular interest to autoimmunity owing to their ability to provide pathogen associated molecular patterns (PAMPs) for induction of co-stimulatory receptors [24]. Thus, if tolerance mechanisms fail to regulate such developing pathogenic self-reactive lymphocytes, then the autoimmune disease would be expected [25]. Given the plenty of evidence that has now accumulated to demonstrate that antibodies against co-inhibitory receptors prompt a range of immune-related adverse events (IRAE), strongly suggests that co-inhibitory receptors does indeed play a role in maintaining self-tolerance [26]. Significant differences

in expression and composition of co-inhibitory receptors such as CTLA-4, PD-1, and TIM-3 and TIGIT on the surface of various types of T cells could have profound effects on the outcome of autoimmune disease [27, 28]. Indeed, the pattern of co-inhibitory receptors expressed by anergic T cells showed significant overlap with regulatory and exhausted T cells [29]. This indicates that these receptors are of particular importance to block auto-reactivity. Therefore, expression of co-inhibitory receptors on T cells are pivotal for restricting harmful clones of T cells which might be developed under different conditions particularly after exposure to infectious agents [24, 30]. This is why the expression of co-inhibitory receptors are often followed by cellular activation [31].

BOX 1 Immune-regulation is necessary for tolerance

Failure in discriminating self from non-self can favors an inflammatory response against self-antigens that can results in autoimmunity [32]. Although self-reactivity is necessary for the generation of regulatory T cells [33]. It is evident that, self- tolerance mainly results from a composite of central and peripheral mechanisms. Having established that central tolerance by clonal deletion and peripheral tolerance by anergy, ignorance and regulatory cells are fundamental to maintain self- tolerance [32], there is another important factor, immune-regulation, which is key to ensuring that everything runs well [34]. Because of the randomly generated nature of T cell receptors, the net result of the thymus selection might not be expected to be an effective process. Consequently, some of the potentially auto-reactive clones can escape from thymus selection. So, the presence of auto-reactive T lymphocytes in various degrees would be expected [35]. In addition, repeated encounters with different pathogens can foster bystander activation of T cells, which can promote auto-reactivity [36, 37]. Besides that, although anergic T cells are not supposed to normally attack self-antigens, depending on the presence of pathogen associated molecular pattern (PAMP) and damage associated molecular pattern (DAMP), they could be reinvigorated against self [38, 39]. The other potential reason for increasing auto-reactive T cells throughout the entire lifetime is cell plasticity especially among the CD4 T cells subtypes [40, 41]. Thus, it could be argued that we can expect more auto-reactive T cells during the entire lifetime (Figure 3) It is not surprising, therefore, that the co-inhibitory receptors (immune checkpoints) introduced as an important regulatory mechanism for maintaining self-tolerance [42].

CTLA-4

The Cytotoxic T lymphocyte antigen-4 (CTLA-4/CD152) co-inhibitory receptor is present on many cells types including regulatory, anergic, and newly activated T cells which can represses the T cells proliferation and production of IL-2 and IFN-g [43]. To emphasize the role of CTLA-4 as a unique negative regulator of activated T cells, it should be noted that both CD28 and CTLA-4 mutually can bind to the same ligands B7.1 (CD80) and B7.2 (CD86), while the affinity of CTLA-4 to B7.1 and B7.2 is higher than CD28. This competitive based binding to B7 ligands emphasizes the importance of checking effect of CTLA-4 on CD28 signaling pathway. Continuous expression of CTLA-4 on regulatory T cells (Tregs) and its interaction with dendritic cells (DCs) serve as "off switches" for T cell activation. In addition, CTLA-4 might be involved in T cell receptor (TCR) signaling termination by mechanisms such as recruitment of Src homology 2 (SH2) domain-containing phosphatase-1/2 (SHP-1/SHP-2) protein tyrosine phosphatases and protein phosphatase 2A (PP2A) to the TCR complex. CTLA-4 can also augment the expression of casitas-B-lineage lymphoma (Cbl)-b protein, an E3 ubiquitin ligase, to oppose the activation of T cells [44]. Interestingly, CTLA-4 is also capable to diminish the contact time between DC and T cells. On the other hand, CTLA-4 has a role in regulating the immunological synapse. Furthermore, the interaction of CTLA-4 with B7 ligands induce a "reverse" signaling through the induction of indoleamine 2,3-dioxygenase (IDO), which can degrades tryptophan, to inhibit T-cell proliferation [45, 46]. It has been reported that mice with CTLA-4 deficiency fail to control infiltrated auto-reactive T cells and die soon because of the complications in heart and pancreas [47]. This study provide a relative evidence to support the tissue specific role for CTLA-4 on controlling auto-reactive pathogenic T cells [48]. Moreover, mice with CTLA-4 deficiency developed multi-organ autoimmunity that can results in lethal inflammatory condition such as diabetes and experimental autoimmune encephalomyelitis (EAE/ animal model of multiple sclerosis) [49]. For instance, alternative spliced form of CTLA-4 leads to type 1 diabetes (T1D) in non-obese diabetes (NOD) mice that is attributed

to deficient MYPPPY motif of CTLA-4 [50]. In humans, germ line haploinsufficiency in CTLA-4 is related to increase in auto-reactive T and B cells and cause dysregulation of Tregs [51] suggesting that CTLA-4 has critical functions in regulating auto-reactivity. Persistent expression of CTLA-4 on Tregs, represent the valuable role of CTLA-4 in the maintaining tolerance [52]. The expression pattern of CTLA-4 on CD4+ and CD8+ T cells are not quite similar and it is higher in CD4+T cells [53]. And finally, because of the importance of the PI3K/Akt signaling pathway in cell survival and proliferation [54], the ability to regulate PI3K/Akt is of strategic importance of CTLA-4 in controlling T cells proliferation [55-57].

PD-1

The other widely distributed inhibitory receptor on the surface of immune cells is PD-1(programmed cell death -1/CD279) [58]. PD-1 expression on naïve T cells is low but it is often up-regulated on activated T cells and constitutively express on Treg cells to maintain their survival and suppressive capacity. Given that the PD-1 is widely distributed on both adaptive and innate immune cells such as DCs, B and T cell and activated monocytes [59], its deficiency would has detrimental consequences; this is why many patients with different types of cancers that treated with mAbs against PD-1 such as nivolumab and pembrolizumab are often experienced IRAE [60]. It has been demonstrated that the development of induced Tregs (iTregs) is significantly diminished in PD-1 deficient mice [61] and this could results in autoimmune disease such as T1D, systemic lupus erythematosus (SLE) and induce EAE in mice [62-64]. Although there is no doubt that PD-1 is potent regulator of immune response, but the underling molecular mechanisms of action of PD-1 is not completely revealed (Figure 1). With two unique motifs i.e., immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM) in its cytoplasmic domain [65], it seems that PD-1 plays a respected role in controlling TCR by recruiting phosphatases to tyrosine-based inhibitory motifs [66]. The important issue that might makes PD-1 as a key modulator of immune response is its interaction with two ligands, including PD-L1 (B7-H1/CD274), PD-L2 (B7-DC/CD273), which are implicated in controlling of T cell responses with a different mechanisms [27, 58, 67, 68]. Of striking significance is the ability of PD-1 to induce different signalosom though the utilizing of different loops with the distinct binding kinetics and thermodynamic features to PD-L1 and PD-L2 [69]. Similar to CTLA-4, PD-1 can reduce TCR signaling by recruitments of SHP-2 and inhibit phosphorylation of ZAP70 and PKC-ϑ and PI3K and Akt signaling pathways [70]. In addition to attenuate TCR signaling, PD-1 is also exert its inhibitory function by regulating various transcription factors including T-bet, GATA-3 and Eomes and STAT3, NF-ϰB, AP-1, and NFATc1 that can antagonize signal transduction events in immune cells [71-73]. From the metabolic points of view, unlike CTLA-4, ligation of PD-1 to its ligands stimulate fatty-acid oxidation and lipid catabolism to limits T-cell activity toward inactive states like exhaustion and memory cells [74]. In addition to CTLA-4 and PD-1, several recent studies supporting the respected role of other members of co-inhibitory receptors such as TIM-3, LAG-3 in maintaining tolerance [75].

TIM-3

TIM-3 expressed on the surface of many cell types, particularly on activated CD4+ T cells. TIM-3 is relatively promiscuous molecule that can bind to various ligands such as Galectin-9, high-mobility group box-1 (HMBG-1), phosphatidyl serine (PS) and carcinoembryonic antigen-related cell adhesion molecule-1(CEACAM-1) [76, 77]. The function of TIM-3 depends on its intact cytoplasmic domain. HLA-B associated transcript 3 (Bat-3) plays as a regulatory element for TIM-3 signaling (Figure 1). By following the interaction of TIM-3 with its ligands, Fyn recruited to the cytoplasmic domain of TIM-3 and subsequently Bat-3 can be released which induce T cell energy [78]. Nonetheless, with releasing Bat-3, Lck recruited to the cytoplasmic domain of TIM-3 then TIM-3 tends to be a rather active receptor owing to the absence of its ligands [77]. In particular, regulatory cytokines such as IFN-β and IL-27 stimulate the expression of TIM-3 [79, 80]. A specific role for TIM-3 in modulating subtypes of T cells has been demonstrated. It seems that TIM-3 has a considerable effect on CD4+T cells, but not Th17 cell, and prevent IFN-g production in EAE mice [81]. Suggesting that some of these co-inhibitory receptors, such as TIM-3, might act as a relatively unique regulator of T cells.

LAG-3

LAG-3, another co-inhibitory family member, is widely expressed by many different cell types and its signals can also suppress T-cell response. Similar to TIM-3, LAG-3 has several ligands, which are of particular interest because these ligands such as MHC II, and both Galectin-3 and LSECtin are involved in the regulation of CD4+T cells and CD8+T cells, respectively [82, 83]. This type of competitive and selective mode of action may play a critical role in eliminating auto-reactive CD4+ T cells by its antagonistic effects in controlling TCR. LAG-3 has a highly conserved KIEELE motif in its cytoplasmic domain which is thought to be essential for the suppression of auto-reactive T-cells [84], as its deletion results in a uncontrolled expansion of T cells in periphery [85]. Recently it has been found that a LAG-3–specific humanized agonist Ab, IMP761, can prevent T cell proliferation through abolition of TCR signaling and NFAT [86]. However, LAG-3 does not appear to play an instructive role during steady state condition, rather, it is appears to have a suppressive effects on T cells proliferation [87].

VISTA, BTLA and TIGIT

Another co-inhibitory receptor which can suppress immune responses of activated T-cells is VISTA. The known ligand for VISTA is P-selectin glycoprotein ligand-1 (PSGL-1) and it found that VISTA selectively inhibit T cell functions in a PH dependent manner [88, 89]. The regulatory function of VISTA have been reported in several autoimmune mice model such as SLE [90] and in T cell mediated autoimmune disease including EAE or modulation of alloreactive T cells in graft versus host disease (GvHD) [91] (Table 1). Another effective co-inhibitory receptor similar to CTLA-4 and PD-1 that has a several ligands is BTLA which is expressed on many cell types [92]. BTLA exhibit an inhibitory properties when interaction with the herpes virus entry mediator (HVEM), a TNF receptor superfamily member 14 (TNFRSF14) is provided. Nevertheless, engagement with CD160 appears to function in a cell-specific manner which might be either activating receptor, on NK cells, or inhibitory receptor on T cells. Whereas interaction of BTLA with LIGHT (TNFSF14, CD258) and lymphotoxin-α (LTβR), the other ligands, appear to enhance inflammatory responses [93]. Similar to PD-1, BTLA has both inhibition motifs ITIM and ITSM in its cytoplasmic domain which are necessary for recruitment SHP-1 and SHP-2 [94]. Akin to PD-1 and BTLA, T cell Ig and ITIM domain (TIGIT) is widely expressed by many cell types. NK cells, peripheral memory and regulatory T cells as well as activated CD4+T cells express TIGIT. And CD155 (poliovirus receptor) is a well-known ligand for it [95]. Remarkably, the presence of an Ig-like V-type domain and an ITIM in its cytoplasmic domain, TIGIT can trigger a negative signaling events to regulate immune response. Indeed, experiments using agonistic anti-TIGIT mAb have shown promising effects in controlling T-cell-mediated immune responses in EAE mice. Engagement of TIGIT with CD155 leads to down regulation of well-known inflammatory cytokine, IFN-g, and T-bet, GATA-3, retinoic acid-related orphan receptor-c (RORc) and IFN regulatory factor-4 (IRF-4) transcription factors [96]. Together, in part, these data indicates that a complex multi-layered interaction of co-inhibitory receptors and their ligands with various transcription factors are in play to regulate self-reactivity. And accumulating data indicate that self-reactive T cells that are present in the periphery of autoimmune patients usually pose a threat, in part, due to the lack of co-inhibitory receptors or dysregulated expression pattern of these molecules [75].

Transcription factors and co-inhibitory receptors are important determining factors in T cells behavior

Many of investigations showed that the transcription factors are important regulators of T cells behavior [122]. Indeed transcription factors such as activator protein-1 (AP-1) and NFkB have central role in various aspects of cell biology including T cell survival, activation, differentiation, memory and exhaustion or T cell lineages differentiation [123, 124]. So analyzing and profiling of the pattern of transcription factors and determining their relationship to the co-inhibitory receptors can provide highly reliable interpretations in the context of chronic immune response (Figure 2). Activation of T cell leads to signal transductions via different pathways. TCR engagement derive the activation of the enzyme phospholipase C (PLCg1) which can produce IP3 and DAG (diacylglycerol) from the membrane lipid called PIP2 (phosphatidylinositol 4, 5 bisphosphate). DAG can then promote protein kinase C (PKC) activation. As a results of IP3 activity, calcium can be released from endoplasmic reticulum (ER) and bind to calmodulin and then NFAT can be localized in to nucleus

because of the dephosphorylating activity of calcineurin. This pathway warranted the production of IL-2 and even transcription factor NFκB. Another important signaling pathway that are needed for IL-2 production is Ras/ Mitogen Activated Protein Kinases (MAPK) pathway. The recruitment of the GRB2/SOS complex to the plasma membrane by phosphorylated LAT and ZAP-70, the Ras-GTP/Raf/MAPK/MEK/ERK1 and Elk1 kinases pathway will be initiated that result in c-Fos/AP-1 production [125]. In addition to TCR signaling, CD28 also capable to induce AP-1expression via PI3 kinase pathway [126]. Both Ap-1 and NFAT act synergistically to induce robust and effective immune responses. But, as immune response proceeds, the function and utility of these transcription factors will be changed. And altered expression of AP-1 and NFkB is considered as hallmark characteristics of tolerant T cells [127, 128].

Although the expression of multiple inhibitory receptors on the surface of T cells could result in exhaustion phenotype [27], some other activated, regulatory, anergic and memory T cells can also express shared co-inhibitory receptors [129], thereby making it difficult to select them as an exclusive marker to exhaustion. For example, in addition to newly activated T cells, PD-1 is also up-regulated on follicular helper T cells (T_{FH})[130] and regulatory T cells [131]. Similarly, not only CTLA-4 can express on the surface of the newly activated T cells, but it could be detectable on Tregs and anergic T cells as well [132, 133] (Figure 2). Therefore, in order to reconcile the behavior of immune system especially during chronic inflammatory conditions, real-time analyzing of both co-inhibitory receptors and their transcriptome is indispensable. Of note, the expression of CTLA-4 is up-regulated by nuclear factor of activated T-cells (NFAT) which is expressed following T cell activation [14]. Foxp-3, another important transcription factor which is major transcription factor of Tregs and as well expressed on newly activated T cells, can also increases the expression of CTLA-4 [134, 135]. Reduced expression of AP-1 impairs T cell functionality. As in the absence of AP-1, NFAT mediate T cell exhaustion and anergy [14, 72]. Short-lived expression of AP-1 might be a clever adaptation that is designed to reduce T cells proliferation either by immune system itself or some viruses during chronic inflammatory situation. However, the regulatory effects of NFAT in directing T cells fate does not end there. Recent studies have revealed an essential role for the down-stream transcription factors of NFAT in T cells unresponsiveness.

The importance of NFATc1 for the development of unresponsiveness states can be stressed by its direct effect on TIM-3 expression [14]. While TCF-1 decreases the expression of TIM-3 [136].

And, co-expression of high-mobility group (HMG)-box transcription factors TOX, TOX2 and NR4A facilitate PD-1 and TIM-3 mediated inactivation of tumor infiltration T cells (TILs), leading to exhaustion [137]. These findings suggested that different combinations of transcription factors support the different types of immune response and T cells behavior.

During a chronic inflammatory response, regulated cooperation of IRF4, BATF and NFATc1 strongly derive T cells toward exhaustion, while high amount expression of IRF4 restrict the establishment of memory cell phenotype. Increased expression of IRF4 resulted in amplified expression of PD-1, TIM-3, LAG-3, TIGIT and CTLA-4 which are important for maintaining T cell unresponsiveness. Consequently, these cooperative activity of NFATc1, IRF4 and BATF repress TCF-1 that is necessary for memory and T cell functionality [13, 14].

It has been shown that several transcriptional factors, including c-Fos/AP-1, NFATc1, FOXO1, STAT3, and IRF4 increase PD-1 expression while BLIMP-1 and T-bet limit PD-1 expression [138]. It will be of interest to elaborate the exquisite role of transcription factors network mainly NFAT in controlling activation vs hyporesponsivness state of the immune system to have a successful immunotherapeutic approaches [139].

In this regard, it is of particular interest to note that both newly activated T and anergic T cells express early growth response gene-2 (Egr-2) and T-bet. Egr-1/2-deficient mice display marked reduction in LAG-3 and 4-1BB on CD8 TILs [140]. And Egr2/3 deficient T cells showed enhanced expression of inflammatory transcription factors such as Id3, Tcf1 and RORγt which can lead to loss of self-tolerance. The outcome may well depend upon the different condition [141]. The role of Egr2/3 are complex and not always advantageous, such as exhausted CD8+T cells in tumor microenvironment.

Even the pattern of co-inhibitory receptors and transcription factors expression between exhausted CD4+ and CD8+T cells is different, for example; during chronic viral infection, expression of Helios and ID2 became dominant in the case of CD4+ exhausted T cells [142, 143]. Recent studies have revealed that the expression of Helios and Egr-2 are not restricted to CD4+T cells, as they are expressed by exhausted CD8+T cells too [140, 144]. A study of Irf4-deficient CD4+T cells in an experimental model of cardiac allograft has indicated that in the absence of IRF4, a profound increase in the expression of PD-1 and Helios occur and resulted in defective Th1 and Th17 development [145]. This diversity even goes beyond, as recent report have been classified the exhausted T cells to a diverse subset based on disease-specific features and their functionality [18]. According to these results, assessing and estimating the behavior of the T cells in different situations could reveal a clear vision in predicting of highly dynamic nature of the immune response.

Concluding Remarks

It seems that exhaustion is an important mechanism for the suppression of an effective immune response in the case of cancer and chronic viral infections, which appears to be achieved, in part, via the expression of co-inhibitory receptors. Accordingly, with regard the importance of co-inhibitory receptors as a potent immune regulators, dysregulation and genetic deletion of these receptors could result in aberrant activation of T cells [146, 147]. Decoding the role of co-inhibitory receptors can provide fundamental support in designing successful treatment approaches for the management of autoimmune diseases [148]. The importance of co-inhibitory receptors in multiple autoimmune diseases such as multiple sclerosis (MS) [149] inflammatory bowel disease (IBD) and systemic lupus erythematous (SLE) is demonstrated [148] (table 1). Moreover, in the autoimmune disease with a bad prognosis the expression of co-inhibitory receptors are significantly down-regulated [150, 151]. Suggesting that evaluation of these receptors and their expression pattern during an autoimmune disease could have a potential prognostic values and subsequently could predict clinical outcomes of the autoimmune disease [148].

Funding and Conflict of Interest

This research did not receive any specific grant from funding agencies. The author declares no conflict of interest.

References

1 Corthay A. A three-cell model for activation of naive T helper cells. Scandinavian journal of immunology 2006; **2** :93-96.

2 Schnell A, Bod L, Madi A, Kuchroo VK. The yin and yang of co-inhibitory receptors: toward anti-tumor immunity without autoimmunity. Cell Research 2020.

3 Watts TH. Staying Alive: T Cell Costimulation, CD28, and Bcl-x_L. The Journal of Immunology 2010; **7** :3785-3787.

4 Okoye IS, Houghton M, Tyrrell L, Barakat K, Elahi S. Coinhibitory Receptor Expression and Immune Checkpoint Blockade: Maintaining a Balance in CD8+ T Cell Responses to Chronic Viral Infections and Cancer. Frontiers in Immunology 2017;**1215** .

5 Fuertes Marraco SA, Neubert NJ, Verdeil G, Speiser DE. Inhibitory Receptors Beyond T Cell Exhaustion. Frontiers in immunology 2015; 310.

6 Turnis ME, Andrews LP, Vignali DA. Inhibitory receptors as targets for cancer immunotherapy. European journal of immunology 2015; **7** :1892-1905.

7 Yasuma-Mitobe K, Matsuoka M. The Roles of Coinhibitory Receptors in Pathogenesis of Human Retroviral Infections. Frontiers in immunology 2018; 2755.

8 Wherry EJ, Blattman JN, Murali-Krishna K, van der Most R, Ahmed R. Viral persistence alters CD8 T-cell immunodominance and tissue distribution and results in distinct stages of functional impairment.

Journal of virology 2003;**8** :4911-4927.

9 Attanasio J, Wherry EJ. Costimulatory and Coinhibitory Receptor Pathways in Infectious Disease. Immunity 2016; **5** :1052-1068.

10 Zarour HM. Reversing T-cell Dysfunction and Exhaustion in Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 2016;**8** :1856-1864.

11 Oldstone MB. A Jekyll and Hyde Profile: Type 1 Interferon Signaling Plays a Prominent Role in the Initiation and Maintenance of a Persistent Virus Infection. The Journal of infectious diseases 2015; S31-36.

12 Weber R, Fleming V, Hu X, Nagibin V, Groth C, Altevogt P, Utikal J, Umansky V. Myeloid-Derived Suppressor Cells Hinder the Anti-Cancer Activity of Immune Checkpoint Inhibitors. Frontiers in immunology 2018; 1310.

13 Man K, Gabriel SS, Liao Y, Gloury R, Preston S, Henstridge DC, Pellegrini M, Zehn D, Berberich-Siebelt F, Febbraio MA *et al* . Transcription Factor IRF4 Promotes CD8(+) T Cell Exhaustion and Limits the Development of Memory-like T Cells during Chronic Infection. Immunity 2017; **6** :1129-1141 e1125.

14 Martinez GJ, Pereira RM, Aijo T, Kim EY, Marangoni F, Pipkin ME, Togher S, Heissmeyer V, Zhang YC, Crotty S *et al* . The transcription factor NFAT promotes exhaustion of activated CD8(+) T cells. Immunity 2015; **2** :265-278.

15 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; **4** :670-684.

16 Maruhashi T, Okazaki IM, Sugiura D, Takahashi S, Maeda TK, Shimizu K, Okazaki T. LAG-3 inhibits the activation of CD4(+) T cells that recognize stable pMHCII through its conformation-dependent recognition of pMHCII. Nature immunology 2018;**12** :1415-1426.

17 Mognol GP, Spreafico R, Wong V, Scott-Browne JP, Togher S, Hoffmann A, Hogan PG, Rao A, Trifari S. Exhaustion-associated regulatory regions in CD8(+) tumor-infiltrating T cells. Proceedings of the National Academy of Sciences of the United States of America 2017; **13** :E2776-E2785.

18 Bengsch B, Ohtani T, Khan O, Setty M, Manne S, O'Brien S, Gherardini PF, Herati RS, Huang AC, Chang KM*et al* . Epigenomic-Guided Mass Cytometry Profiling Reveals Disease-Specific Features of Exhausted CD8 T Cells. Immunity 2018;**5** :1029-1045 e1025.

19 McKinney EF, Smith KGC. Metabolic exhaustion in infection, cancer and autoimmunity. Nature immunology 2018; **3** :213-221.

20 Kim HO, Cho JH. T Cell's Sense of Self: a Role of Self-Recognition in Shaping Functional Competence of Naive T Cells. Immune network 2017; **4** :201-213.

21 Mueller DL. Mechanisms maintaining peripheral tolerance. Nature immunology 2010; **1** :21-27.

22 Mack SJ, Udell J, Cohen F, Osoegawa K, Hawbecker SK, Noonan DA, Ladner MB, Goodridge D, Trachtenberg EA, Oksenberg JR *et al* . High resolution HLA analysis reveals independent class I haplotypes and amino-acid motifs protective for multiple sclerosis. Genes & Immunity 2019; **4** :308-326.

23 Dendrou CA, Petersen J, Rossjohn J, Fugger L. HLA variation and disease. Nature Reviews Immunology 2018;**5** :325-339.

24 Ercolini AM, Miller SD. The role of infections in autoimmune disease. Clinical and experimental immunology 2009; **1** :1-15.

25 Xing Y, Hogquist KA. T-cell tolerance: central and peripheral. Cold Spring Harbor perspectives in biology 2012; **6** .

26 Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. Journal for ImmunoTherapy of Cancer 2019; **1** :306.

27 Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nature reviews Immunology 2015; **8** :486-499.

28 Jain N, Nguyen H, Chambers C, Kang J. Dual function of CTLA-4 in regulatory T cells and conventional T cells to prevent multiorgan autoimmunity. Proceedings of the National Academy of Sciences of the United States of America 2010;**4** :1524-1528.

29 Kalekar LA, Schmiel SE, Nandiwada SL, Lam WY, Barsness LO, Zhang N, Stritesky GL, Malhotra D, Pauken KE, Linehan JL *et al* . CD4+ T cell anergy prevents autoimmunity and generates regulatory T cell precursors. Nature immunology 2016;**3** :304-314.

30 Yong J, Tian J, Dang H, Wu T-T, Atkinson MA, Sun R, Kaufman DL. Increased risk for T cell autoreactivity to ß-cell antigens in the mice expressing the Avy obesity-associated gene. Scientific Reports 2019; **1** :4269.

31 Boussiotis VA, Charest A. Immunotherapies for malignant glioma. Oncogene 2018;**9** :1121-1141.

32 Goodnow CC, Sprent J, de St Groth BF, Vinuesa CG. Cellular and genetic mechanisms of self tolerance and autoimmunity. Nature 2005; **7042** :590-597.

33 Kronenberg M, Rudensky A. Regulation of immunity by self-reactive T cells. Nature 2005;**7042** :598-604.

34 Lehman HK. Autoimmunity and Immune Dysregulation in Primary Immune Deficiency Disorders. Current allergy and asthma reports 2015; **9** :53.

35 Richards DM, Ruggiero E, Hofer A-C, Sefrin JP, Schmidt M, von Kalle C, Feuerer M. The Contained Self-Reactive Peripheral T Cell Repertoire: Size, Diversity, and Cellular Composition. The Journal of Immunology 2015;**5** :2067-2079.

36 Nogai A, Siffrin V, Bonhagen K, Pfueller CF, Hohnstein T, Volkmer-Engert R, Brück W, Stadelmann C, Kamradt T. Lipopolysaccharide Injection Induces Relapses of Experimental Autoimmune Encephalomyelitis in Nontransgenic Mice via Bystander Activation of Autoreactive CD4⁺ Cells. The Journal of Immunology 2005; **2** :959-966.

37 van Aalst S, Ludwig IS, van der Zee R, van Eden W, Broere F. Bystander activation of irrelevant CD4+ T cells following antigen-specific vaccination occurs in the presence and absence of adjuvant. PLOS ONE 2017; **5** :e0177365.

38 Kubo T, Hatton RD, Oliver J, Liu X, Elson CO, Weaver CT. Regulatory T Cell Suppression and Anergy Are Differentially Regulated by Proinflammatory Cytokines Produced by TLR-Activated Dendritic Cells. The Journal of Immunology 2004;**12** :7249-7258.

39 Valdor R, Macian F. Induction and stability of the anergic phenotype in T cells. Seminars in immunology 2013; **4** :313-320.

40 Qiu R, Zhou L, Ma Y, Zhou L, Liang T, Shi L, Long J, Yuan D. Regulatory T Cell Plasticity and Stability and Autoimmune Diseases. Clinical reviews in allergy & immunology 2020;**1** :52-70.

41 Stadhouders R, Lubberts E, Hendriks RW. A cellular and molecular view of T helper 17 cell plasticity in autoimmunity. J Autoimmun 2018; 1-15.

42 Spallarossa P, Meliota G, Brunelli C, Arboscello E, Ameri P, Dessalvi CC, Grossi F, Deidda M, Mele D, Sarocchi M *et al* . Potential cardiac risk of immune-checkpoint blockade as anticancer treatment: What we know, what we do not know, and what we can do to prevent adverse effects. Medicinal Research Reviews 2018; **5** :1447-1468.

43 Alegre M-L, Frauwirth KA, Thompson CB. T-cell regulation by CD28 and CTLA-4. Nature Reviews Immunology 2001; **3** :220-228.

44 Li D, Gal I, Vermes C, Alegre ML, Chong AS, Chen L, Shao Q, Adarichev V, Xu X, Koreny T *et al* . Cutting edge: Cbl-b: one of the key molecules tuning CD28- and CTLA-4-mediated T cell costimulation. Journal of immunology 2004;**12** :7135-7139.

45 Boasso A, Herbeuval JP, Hardy AW, Winkler C, Shearer GM. Regulation of indoleamine 2,3-dioxygenase and tryptophanyl-tRNA-synthetase by CTLA-4-Fc in human CD4+ T cells. Blood 2005; **4** :1574-1581.

46 Grohmann U, Orabona C, Fallarino F, Vacca C, Calcinaro F, Falorni A, Candeloro P, Belladonna ML, Bianchi R, Fioretti MC *et al* . CTLA-4–Ig regulates tryptophan catabolism in vivo. Nature immunology 2002; **11** :1097-1101.

47 Klocke K, Sakaguchi S, Holmdahl R, Wing K. Induction of autoimmune disease by deletion of CTLA-4 in mice in adulthood. Proceedings of the National Academy of Sciences of the United States of America 2016; **17** :E2383-2392.

48 Paterson AM, Sharpe AH. Taming tissue-specific T cells: CTLA-4 reins in self-reactive T cells. Nature immunology 2010; **2** :109-111.

49 Verma N, Burns SO, Walker LSK, Sansom DM. Immune deficiency and autoimmunity in patients with CTLA-4 (CD152) mutations. Clinical and experimental immunology 2017;**1** :1-7.

50 Vijayakrishnan L, Slavik JM, Illés Z, Greenwald RJ, Rainbow D, Greve B, Peterson LB, Hafler DA, Freeman GJ, Sharpe AH *et al* . An Autoimmune Disease-Associated CTLA-4 Splice Variant Lacking the B7 Binding Domain Signals Negatively in T Cells. Immunity 2004; **5** :563-575.

51 Kuehn HS, Ouyang W, Lo B, Deenick EK, Niemela JE, Avery DT, Schickel J-N, Tran DQ, Stoddard J, Zhang Y*et al* . Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science 2014; **6204** :1623-1627.

52 Wing JB, Ise W, Kurosaki T, Sakaguchi S. Regulatory T cells control antigen-specific expansion of Tfh cell number and humoral immune responses via the coreceptor CTLA-4. Immunity 2014; **6** :1013-1025.

53 Chan DV, Gibson HM, Aufiero BM, Wilson AJ, Hafner MS, Mi QS, Wong HK. Differential CTLA-4 expression in human CD4+ versus CD8+ T cells is associated with increased NFAT1 and inhibition of CD4+ proliferation. Genes and immunity 2014;**1** :25-32.

54 Chan KT, Blake S, Zhu H, Kang J, Trigos AS, Madhamshettiwar PB, Diesch J, Paavolainen L, Horvath P, Hannan RD *et al* . A functional genetic screen defines the AKT-induced senescence signaling network. Cell Death & Differentiation 2020; **2** :725-741.

55 Wang CJ, Heuts F, Ovcinnikovs V, Wardzinski L, Bowers C, Schmidt EM, Kogimtzis A, Kenefeck R, Sansom DM, Walker LSK. CTLA-4 controls follicular helper T-cell differentiation by regulating the strength of CD28 engagement. Proceedings of the National Academy of Sciences 2015; **2** :524-529.

56 Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, Linsley PS, Thompson CB, Riley JL. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Molecular and cellular biology 2005;**21** :9543-9553.

57 Olsson C, Riesbeck K, Dohlsten M, Michaelsson E. CTLA-4 ligation suppresses CD28-induced NF-kappaB and AP-1 activity in mouse T cell blasts. The Journal of biological chemistry 1999; **20** :14400-14405.

58 Schildberg FA, Klein SR, Freeman GJ, Sharpe AH. Coinhibitory Pathways in the B7-CD28 Ligand-Receptor Family. Immunity 2016; **5** :955-972.

59 Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunological reviews 2010; 219-242.

60 Danlos FX, Voisin AL, Dyevre V, Michot JM, Routier E, Taillade L, Champiat S, Aspeslagh S, Haroche J, Albiges L *et al* . Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. European journal of cancer 2018; 21-29.

61 Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, Sharpe AH. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. The Journal of experimental medicine 2009; **13** :3015-3029.

62 Dinesh RK, Hahn BH, Singh RP. PD-1, gender, and autoimmunity. Autoimmunity reviews 2010;**8** :583-587.

63 Kasagi S, Kawano S, Okazaki T, Honjo T, Morinobu A, Hatachi S, Shimatani K, Tanaka Y, Minato N, Kumagai S. Anti-Programmed Cell Death 1 Antibody Reduces CD4⁺PD-1⁺ T Cells and Relieves the Lupus-Like Nephritis of NZB/W F1 Mice. The Journal of Immunology 2010; **5** :2337-2347.

64 Kroner A, Schwab N, Ip CW, Ortler S, Gobel K, Nave KA, Maurer M, Martini R, Wiendl H. Accelerated course of experimental autoimmune encephalomyelitis in PD-1-deficient central nervous system myelin mutants. The American journal of pathology 2009;**6** :2290-2299.

65 Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. The EMBO journal 1992; **11** :3887-3895.

66 Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. The Journal of Immunology 2004; **2** :945-954.

67 Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007; **1** :111-122.

68 Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. Frontiers in oncology 2018; 86.

69 Lyu N, Wang K, Zhang F, Qin H, Zhao Y, Wu R, Si Y, Wang L. Recognition of PDL1/L2 by different induced-fit mechanisms of PD1: a comparative study of molecular dynamics simulations. Physical chemistry chemical physics : PCCP 2020;**3** :1276-1287.

70 Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, Qiu Y, Jussif JM, Carter LL, Wood CR*et al* . PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS letters 2004; **1-3** :37-41.

71 Zerdes I, Matikas A, Bergh J, Rassidakis GZ, Foukakis T. Genetic, transcriptional and post-translational regulation of the programmed death protein ligand 1 in cancer: biology and clinical correlations. Oncogene 2018;**34** :4639-4661.

72 Atsaves V, Leventaki V, Rassidakis GZ, Claret FX. AP-1 Transcription Factors as Regulators of Immune Responses in Cancer. Cancers 2019; **7** .

73 Oestreich KJ, Yoon H, Ahmed R, Boss JM. NFATc1 regulates PD-1 expression upon T cell activation. Journal of immunology 2008; **7** :4832-4839.

74 Bengsch B, Johnson AL, Kurachi M, Odorizzi PM, Pauken KE, Attanasio J, Stelekati E, McLane LM, Paley MA, Delgoffe GM *et al* . Bioenergetic Insufficiencies Due to Metabolic Alterations Regulated by the Inhibitory Receptor PD-1 Are an Early Driver of CD8(+) T Cell Exhaustion. Immunity 2016; **2** :358-373.

75 Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: Co-inhibitory Receptors with Specialized Functions in Immune Regulation. Immunity 2016; **5** :989-1004.

76 Huang Y-H, Zhu C, Kondo Y, Anderson AC, Gandhi A, Russell A, Dougan SK, Petersen B-S, Melum E, Pertel T *et al* . CEACAM1 regulates TIM-3-mediated tolerance and exhaustion. Nature 2015; **7534** :386-390.

77 Wolf Y, Anderson AC, Kuchroo VK. TIM3 comes of age as an inhibitory receptor. Nature Reviews Immunology 2019.

78 Rangachari M, Zhu C, Sakuishi K, Xiao S, Karman J, Chen A, Angin M, Wakeham A, Greenfield EA, Sobel RA*et al* . Bat3 promotes T cell responses and autoimmunity by repressing Tim-3–mediated cell death and exhaustion. Nature Medicine 2012; **9** :1394-1400.

79 Zhu C, Sakuishi K, Xiao S, Sun Z, Zaghouani S, Gu G, Wang C, Tan DJ, Wu C, Rangachari M *et al* . An IL-27/NFIL3 signalling axis drives Tim-3 and IL-10 expression and T-cell dysfunction. Nature Communications 2015; **1** :6072.

80 Boivin N, Baillargeon J, Doss PM, Roy AP, Rangachari M. Interferon-beta suppresses murine Th1 cell function in the absence of antigen-presenting cells. PLoS One 2015;**4** :e0124802.

81 Lee SY, Goverman JM. The influence of T cell Ig mucin-3 signaling on central nervous system autoimmune disease is determined by the effector function of the pathogenic T cells. Journal of immunology 2013; **10** :4991-4999.

82 Xu F, Liu J, Liu D, Liu B, Wang M, Hu Z, Du X, Tang L, He F. LSECtin expressed on melanoma cells promotes tumor progression by inhibiting antitumor T-cell responses. Cancer research 2014; **13** :3418-3428.

83 Solinas C, Migliori E, De Silva P, Willard-Gallo K: LAG3: The Biological Processes That Motivate Targeting This Immune Checkpoint Molecule in Human Cancer. In: Cancers. vol.**11** ; 2019.

84 Workman CJ, Dugger KJ, Vignali DAA. Cutting Edge: Molecular Analysis of the Negative Regulatory Function of Lymphocyte Activation Gene-3. The Journal of Immunology 2002; **10** :5392-5395.

85 Jha V, Workman CJ, McGaha TL, Li L, Vas J, Vignali DAA, Monestier M. Lymphocyte Activation Gene-3 (LAG-3) Negatively Regulates Environmentally-Induced Autoimmunity. PLOS ONE 2014; **8** :e104484.

86 Angin M, Brignone C, Triebel F. A LAG-3–Specific Agonist Antibody for the Treatment of T Cell–Induced Autoimmune Diseases. The Journal of Immunology 2020; ji1900823.

87 Workman CJ, Vignali DA. The CD4-related molecule, LAG-3 (CD223), regulates the expansion of activated T cells. European journal of immunology 2003;**4** :970-979.

88 Kelly PN. VISTA is a pH-selective checkpoint. Science 2019; **6467** :834-835.

89 Johnston RJ, Su LJ, Pinckney J, Critton D, Boyer E, Krishnakumar A, Corbett M, Rankin AL, Dibella R, Campbell L *et al* . VISTA is an acidic pH-selective ligand for PSGL-1. Nature 2019; **7779** :565-570.

90 Han X, Vesely MD, Yang W, Sanmamed MF, Badri T, Alawa J, López-Giráldez F, Gaule P, Lee SW, Zhang J-P*et al* . PD-1H (VISTA)–mediated suppression of autoimmunity in systemic and cutaneous lupus erythematosus. Science Translational Medicine 2019; **522** :eaax1159.

91 Flies DB, Higuchi T, Chen L. Mechanistic Assessment of PD-1H Coinhibitory Receptor-Induced T Cell Tolerance to Allogeneic Antigens. Journal of immunology 2015;**11** :5294-5304.

92 Watanabe N, Gavrieli M, Sedy JR, Yang J, Fallarino F, Loftin SK, Hurchla MA, Zimmerman N, Sim J, Zang X*et al* . BTLA is a lymphocyte inhibitory receptor with similarities to CTLA-4 and PD-1. Nature immunology 2003; **7** :670-679.

93 del Rio ML, Lucas CL, Buhler L, Rayat G, Rodriguez-Barbosa JI. HVEM/LIGHT/BTLA/CD160 cosignaling pathways as targets for immune regulation. Journal of leukocyte biology 2010; **2** :223-235.

94 Yu X, Zheng Y, Mao R, Su Z, Zhang J. BTLA/HVEM Signaling: Milestones in Research and Role in Chronic Hepatitis B Virus Infection. Frontiers in Immunology 2019; **617** .

95 Yu X, Harden K, C Gonzalez L, Francesco M, Chiang E, Irving B, Tom I, Ivelja S, Refino CJ, Clark H*et al* . The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. Nature immunology 2009; **1** :48-57.

96 Lozano E, Dominguez-Villar M, Kuchroo V, Hafler DA. The TIGIT/CD226 axis regulates human T cell function. Journal of immunology 2012; **8** :3869-3875.

97 Lei C, Dongqing Z, Yeqing S, Oaks MK, Lishan C, Jianzhong J, Jie Q, Fang D, Ningli L, Xinghai H *et al* . Association of the CTLA-4 gene with rheumatoid arthritis in Chinese Han population. European Journal of Human Genetics 2005;**7** :823-828.

98 Flores-Borja F, Jury EC, Mauri C, Ehrenstein MR. Defects in CTLA-4 are associated with abnormal regulatory T cell function in rheumatoid arthritis. Proceedings of the National Academy of Sciences 2008; **49** :19396-19401.

99 Gerdes LA, Held K, Beltran E, Berking C, Prinz JC, Junker A, Tietze JK, Ertl-Wagner B, Straube A, Kumpfel T *et al* . CTLA4 as Immunological Checkpoint in the Development of Multiple Sclerosis. Annals of neurology 2016;**2** :294-300.

100 Barreto M, Santos E, Ferreira R, Fesel C, Fontes MF, Pereira C, Martins B, Andreia R, Viana JF, Crespo F*et al* . Evidence for CTLA4 as a susceptibility gene for systemic lupus erythematosus. European Journal of Human Genetics 2004;**8** :620-626.

101 Curran CS, Gupta S, Sanz I, Sharon E. PD-1 immunobiology in systemic lupus erythematosus. Journal of Autoimmunity 2019; 1-9.

102 Zhang N, Tu J, Wang X, Chu Q. Programmed cell death-1/programmed cell death ligand-1 checkpoint inhibitors: differences in mechanism of action. Immunotherapy 2019;**5** :429-441.

103 Bartosinska J, Zakrzewska E, Krol A, Raczkiewicz D, Purkot J, Majdan M, Krasowska D, Chodorowska G, Giannopoulos K. Differential expression of programmed death 1 (PD-1) on CD4+ and CD8+ T cells in rheumatoid arthritis and psoriatic arthritis. Polish archives of internal medicine 2017; **12** :815-822.

104 Trabattoni D, Saresella M, Pacei M, Marventano I, Mendozzi L, Rovaris M, Caputo D, Borelli M, Clerici M. Costimulatory Pathways in Multiple Sclerosis: Distinctive Expression of PD-1 and PD-L1 in Patients with Different Patterns of Disease. The Journal of Immunology 2009; **8** :4984-4993.

105 Clotman K, Janssens K, Specenier P, Weets I, De Block CEM. Programmed Cell Death-1 Inhibitor–Induced Type 1 Diabetes Mellitus. The Journal of Clinical Endocrinology & Metabolism 2018; **9** :3144-3154.

106 Zheng H, Guo X, Tian Q, Li H, Zhu Y. Distinct role of Tim-3 in systemic lupus erythematosus and clear cell renal cell carcinoma. Int J Clin Exp Med 2015;**5** :7029-7038.

107 Lee J, Oh JM, Hwang JW, Ahn JK, Bae EK, Won J, Koh EM, Cha HS. Expression of human TIM-3 and its correlation with disease activity in rheumatoid arthritis. Scandinavian journal of rheumatology 2011; **5** :334-340.

108 Brück P, Ramos-Lopez E, Bartsch W, Böhme A, Badenhoop K. TIM-3 polymorphisms in type 1 diabetes families. Journal of Human Genetics 2008; **6** :559-564.

109 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. Science immunology 2017;**9** :eaah4569.

110 Zhang Z, Duvefelt K, Svensson F, Masterman T, Jonasdottir G, Salter H, Emahazion T, Hellgren D, Falk G, Olsson T *et al* . Two genes encoding immune-regulatory molecules (LAG3 and IL7R) confer susceptibility to multiple sclerosis. Genes & Immunity 2005; **2** :145-152.

111 Nakachi S, Sumitomo S, Tsuchida Y, Tsuchiya H, Kono M, Kato R, Sakurai K, Hanata N, Nagafuchi Y, Tateishi S *et al* . Interleukin-10-producing LAG3(+) regulatory T cells are associated with disease activity and abatacept treatment in rheumatoid arthritis. Arthritis research & therapy 2017; **1** :97.

112 Kato R, Sumitomo S, Tsuchida Y, Tsuchiya H, Nakachi S, Sakurai K, Hanata N, Nagafuchi Y, Kubo K, Tateishi S *et al* . CD4(+)CD25(+)LAG3(+) T Cells With a Feature of Th17 Cells Associated With Systemic Lupus Erythematosus Disease Activity. Frontiers in immunology 2019; 1619-1619.

113 Slater BT, Han X, Chen L, Xiong Y. Structural insight into T cell coinhibition by PD-1H (VISTA). Proceedings of the National Academy of Sciences 2020;**3** :1648-1657.

114 Ceeraz S, Sergent PA, Plummer SF, Schned AR, Pechenick D, Burns CM, Noelle RJ. VISTA Deficiency Accelerates the Development of Fatal Murine Lupus Nephritis. Arthritis & rheumatology 2017; **4** :814-825.

115 Borggrewe M, Grit C, Den Dunnen WFA, Burm SM, Bajramovic JJ, Noelle RJ, Eggen BJL, Laman JD. VISTA expression by microglia decreases during inflammation and is differentially regulated in CNS diseases. Glia 2018;**12** :2645-2658.

116 Li N, Xu W, Yuan Y, Ayithan N, Imai Y, Wu X, Miller H, Olson M, Feng Y, Huang YH *et al* . Immune-checkpoint protein VISTA critically regulates the IL-23/IL-17 inflammatory axis. Scientific Reports 2017; **1** :1485.

117 Yang B, Huang Z, Feng W, Wei W, Zhang J, Liao Y, Li L, Liu X, Wu Z, Cai B *et al* . The Expression of LIGHT Was Increased and the Expression of HVEM and BTLA Were Decreased in the T Cells of Patients with Rheumatoid Arthritis. PLOS ONE 2016; **5** :e0155345.

118 Piancone F, Saresella M, Marventano I, La Rosa F, Zoppis M, Agostini S, Longhi R, Caputo D, Mendozzi L, Rovaris M *et al* . B Lymphocytes in Multiple Sclerosis: Bregs and BTLA/CD272 Expressing-CD19+ Lymphocytes Modulate Disease Severity. Scientific Reports 2016; **1** :29699.

119 Inuo M, Ihara K, Matsuo T, Kohno H, Hara T. Association study between B- and T-lymphocyte attenuator gene and type 1 diabetes mellitus or systemic lupus erythematosus in the Japanese population. International journal of immunogenetics 2009;**1** :65-68.

120 Lowther D, Ramanan S, DeBartolo D, Park C, Duan X, Hafler D, Pitt D. The TIGIT/CD226/CD155 axis is differentially expressed in MS and glioblastoma: implications for autoimmunity and tumor immune escape. (P4.043). Neurology 2015;**14 Supplement** :P4.043.

121 Luo Q, Deng Z, Xu C, Zeng L, Ye J, Li X, Guo Y, Huang Z, Li J. Elevated Expression of Immunoreceptor Tyrosine-Based Inhibitory Motif (TIGIT) on T Lymphocytes is Correlated with Disease Activity in Rheumatoid Arthritis. Med Sci Monit 2017; 1232-1241.

122 Li P, Spolski R, Liao W, Leonard WJ. Complex interactions of transcription factors in mediating cytokine biology in T cells. Immunological reviews 2014; **1** :141-156.

123 Wulczyn FG, Krappmann D, Scheidereit C. The NF-ϰB/Rel and IϰB gene families: mediators of immune response and inflammation. Journal of Molecular Medicine 1996;**12** :749-769.

124 Whitmarsh AJ, Davis RJ. Transcription factor AP-1 regulation by mitogen-activated protein kinase signal transduction pathways. Journal of Molecular Medicine 1996;**10** :589-607.

125 Cantrell DA. T-cell antigen receptor signal transduction. Immunology 2002; **4** :369-374.

126 Riha P, Rudd CE. CD28 co-signaling in the adaptive immune response. Self/nonself 2010;**3** :231-240.

127 Anderson PO, Manzo BA, Sundstedt A, Minaee S, Symonds A, Khalid S, Rodriguez-Cabezas ME, Nicolson K, Li S, Wraith DC *et al* . Persistent antigenic stimulation alters the transcription program in T cells, resulting in antigen-specific tolerance. European journal of immunology 2006; **6** :1374-1385.

128 Schwartz RH. T Cell Anergy. Annual Review of Immunology 2003; **1** :305-334.

129 Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nature Reviews Immunology 2015; **8** :486-499.

130 Shi J, Hou S, Fang Q, Liu X, Liu X, Qi H. PD-1 Controls Follicular T Helper Cell Positioning and Function. Immunity 2018; **2** :264-274 e264.

131 Sambucci M, Gargano F, De Rosa V, De Bardi M, Picozza M, Placido R, Ruggieri S, Capone A, Gasperini C, Matarese G *et al* . FoxP3 isoforms and PD-1 expression by T regulatory cells in multiple sclerosis. Scientific reports 2018;**1** :3674.

132 Kalekar LA, Mueller DL. Relationship between CD4 Regulatory T Cells and Anergy In Vivo. Journal of immunology 2017; **7** :2527-2533.

133 Jago CB, Yates J, Camara NO, Lechler RI, Lombardi G. Differential expression of CTLA-4 among T cell subsets. Clinical and experimental immunology 2004; **3** :463-471.

134 Walker LS. Treg and CTLA-4: two intertwining pathways to immune tolerance. Journal of autoimmunity 2013; 49-57.

135 Wu Y, Borde M, Heissmeyer V, Feuerer M, Lapan AD, Stroud JC, Bates DL, Guo L, Han A, Ziegler SF*et al* . FOXP3 controls regulatory T cell function through cooperation with NFAT. Cell 2006; **2** :375-387.

136 Wu T, Ji Y, Moseman EA, Xu HC, Manglani M, Kirby M, Anderson SM, Handon R, Kenyon E, Elkahloun A*et al* . The TCF1-Bcl6 axis counteracts type I interferon to repress exhaustion and maintain T cell stemness. Science immunology 2016; **6** .

137 Seo H, Chen J, González-Avalos E, Samaniego-Castruita D, Das A, Wang YH, López-Moyado IF, Georges RO, Zhang W, Onodera A *et al* . TOX and TOX2 transcription factors cooperate with NR4A transcription factors to impose CD8⁺ T cell exhaustion. Proceedings of the National Academy of Sciences 2019;**25** :12410-12415.

138 Bally APR, Austin JW, Boss JM. Genetic and Epigenetic Regulation of PD-1 Expression. Journal of immunology (Baltimore, Md : 1950) 2016; **6** :2431-2437.

139 Mognol GP, González-Avalos E, Ghosh S, Spreafico R, Gudlur A, Rao A, Damoiseaux R, Hogan PG. Targeting the NFAT:AP-1 transcriptional complex on DNA with a small-molecule inhibitor. Proceedings of the National Academy of Sciences 2019;**20** :9959-9968.

140 Williams JB, Horton BL, Zheng Y, Duan Y, Powell JD, Gajewski TF. The EGR2 targets LAG-3 and 4-1BB describe and regulate dysfunctional antigen-specific CD8+ T cells in the tumor microenvironment. The Journal of experimental medicine 2017;**2** :381-400.

141 Omodho B, Miao T, Symonds ALJ, Singh R, Li S, Wang P. Transcription factors early growth response gene (Egr) 2 and 3 control inflammatory responses of tolerant T cells. Immunity, inflammation and disease 2018; **2** :221-233.

142 Getnet D, Grosso JF, Goldberg MV, Harris TJ, Yen HR, Bruno TC, Durham NM, Hipkiss EL, Pyle KJ, Wada S*et al* . A role for the transcription factor Helios in human CD4(+)CD25(+) regulatory T cells. Molecular immunology 2010;**7-8** :1595-1600.

143 Crawford A, Angelosanto JM, Kao C, Doering TA, Odorizzi PM, Barnett BE, Wherry EJ. Molecular and transcriptional basis of CD4(+) T cell dysfunction during chronic infection. Immunity 2014; **2** :289-302.

144 Scott-Browne JP, Lopez-Moyado IF, Trifari S, Wong V, Chavez L, Rao A, Pereira RM. Dynamic Changes in Chromatin Accessibility Occur in CD8(+) T Cells Responding to Viral Infection. Immunity 2016; **6** :1327-1340.

145 Wu J, Zhang H, Shi X, Xiao X, Fan Y, Minze LJ, Wang J, Ghobrial RM, Xia J, Sciammas R *et al* . Ablation of Transcription Factor IRF4 Promotes Transplant Acceptance by Driving Allogenic CD4(+) T

Cell Dysfunction. Immunity 2017;**6** :1114-1128 e1116.

146 Moulton VR, Tsokos GC. T cell signaling abnormalities contribute to aberrant immune cell function and autoimmunity. The Journal of clinical investigation 2015;**6** :2220-2227.

147 Rosenblum MD, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. The Journal of clinical investigation 2015; **6** :2228-2233.

148 McKinney EF, Lee JC, Jayne DR, Lyons PA, Smith KG. T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. Nature 2015;**7562** :612-616.

149 Mohammadzadeh A, Rad IA, Ahmadi-Salmasi B. CTLA-4, PD-1 and TIM-3 expression predominantly downregulated in MS patients. Journal of neuroimmunology 2018; 105-108.

150 Zhang Q, Vignali DA. Co-stimulatory and Co-inhibitory Pathways in Autoimmunity. Immunity 2016; **5** :1034-1051.

151 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;**7710** :454-459.

Figure legends

Table 1. Mechanisms of action of well-known co-inhibitory receptors and related autoimmune disease

Abbreviations: CTLA-4 : Cytotoxic T-Lymphocyte Antigen 4;**PD-1** : Programmed cell death protein 1; **PD-L1** : Programmed cell death 1 ligand 1; **TIM-3** : T cell Immunoglobulin Mucin-3**; LAG-3** : Lymphocyte-Activation Gene 3; **ζ** : cluster of differentiation 3 zeta-chain; **ZAP-70** : Zeta-chain-associated protein kinase 70; **PP2A** : Protein phosphatase 2; **BTLA** : B- and T-lymphocyte Attenuator;**Bat3** - Human Leukocyte Antigen B (HLA-B)-associated Transcript 3; **HVEM** : Herpes Virus Entry Mediator; **SHP-1/2** /: Src homology 2-containing tyrosine phosphatase 1/2/; **ITIM** - Immunoreceptor Tyrosine-based Inhibition Motif; **ITSM** : Immunoreceptor Tyrosine-based Switch Motif; **Lck** : Lymphocyte-specific protein tyrosine kinase; **MHC II** : Major Histocompatibility Complex II; **TIGIT** : T-cell immunoreceptor with immunoglobulin and ITIM domains; **PVR** : Poliovirus receptor;**VISTA** : V-domain Ig suppressor of **T cell** activation;**LIGHT** : Lymphotoxin-like, exhibits inducible expression, and competes with herpes simplex virus glycoprotein D for HVEM;**PI3K** : Phosphoinositide 3-kinase; **SLE** : Systemic Lupus erythematous; **RA** : Rheumatoid Arthritis; **MS** : Multiple Sclerosis; T1D: type I diabetes.

Fig 1. Mechanisms of co-inhibitory receptors dominance at the molecular level. Several known and un-known mechanisms including controlling of transcription factors, recruitment of phosphatases, having inhibitory motifs in cytoplasmic domain, and interaction with different avidity to their ligands and so on, are considered as molecular mechanisms regarding the co-inhibitory receptors mode of actions.

Fig 2. T cells differentiation and phenotypes in chronic immune response based on co-inhibitory receptors and transcription factor's profile. Following the activation of T cells, they could undergo divers differentiation steps under the controle of different profile of transcription factors and consequently show different patterns of phenotyps.

Fig 3. The probability of auto-reactivity and self-tolerance during lifetime. Several factors are involved in increasing of auto-reactivity such as infection, molecular mimicry and bystander activation, genes and immune dysregulation (BOX 1).

Hosted file

`Table 1.docx` available at https://authorea.com/users/304729/articles/435285-co-inhibitory-receptors-and-tolerance

Hosted file

Fig 1..tif available at https://authorea.com/users/304729/articles/435285-co-inhibitory-receptors-and-tolerance

Hosted file

Fig 2..tif available at https://authorea.com/users/304729/articles/435285-co-inhibitory-receptors-and-tolerance

Hosted file

Fig 3..tif available at https://authorea.com/users/304729/articles/435285-co-inhibitory-receptors-and-tolerance