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CD160 expression defines a uniquely exhausted subset of T lymphocytes in HTLV-1 infection

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ABSTRACT

HTLV-1 infection is a life-long retroviral infection. Chronic viral antigenic stimulation induces persistent infection which results in a clinically asymptomatic carrier state. Only a minor proportion of infected individuals develop adult T cell leukemia/lymphoma (ATLL) or HTLV-1-associated myelopathy/tropical spastic myelopathy (HAM/TSP). This is dependent on a balance of host and genetic factors. CD8+ cytotoxic T lymphocyte function is important in the immune response against viral infection; however, the contribution of CD160 receptor associated with CD8+ T lymphocytes is unclear. Thus, we sought to decipher its role on CTL function in HTLV-1 infection. Here, we report high frequencies of CD160 on CD8+ T cells, with significantly higher levels on HTLV-1 specific CD8+ T cells. Intercepting the CD160 pathway via blockade of the receptor or its ligand, herpes virus entry mediator (HVEM) resulted in improved perforin production and CD107a degranulation of HTLV-1 specific CD8+ T cells. Analysis of the CD160-expressing CD8+ cells demonstrated a unique subset associated with a highly differentiated effector memory based on CD45RA and CCR7 co-expression, increased expression of inhibitory molecules, 2B4 and PD1. Altogether, these results suggest a role for CD160/HVEM pathway in regulating immune response against HTLV-1 infection which may prove promising in the development of immune therapies for the treatment of HTLV-1 infection and other associated disorders.

1. Introduction

Human T-cell lymphotropic virus-1 (HTLV-1) belongs to the Retroviridae family and is the etiologic agent of HTLV-1 infection. HTLV-1 infection is endemic in the Caribbean, Southern Japan, Central and South America and West Africa [1]. Persistence of HTLV-1 infection results in an asymptomatic carrier (AC) state due to repetitive antigenic stimulation. Over a period of 40–60 years, a minor population of infected individuals eventually develop adult T cell lymphoma/leukemia (ATLL), HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) or a host of other inflammatory diseases [2–4]. ATLL is characterized by monoclonal transformation of malignant cells which results in functional deficiency of CD8+ cytotoxic T cells. This dysfunction is observed in a minor proportion of carrier subjects [5,6]. It is noteworthy that prognosis of ATLL is very poor with best available therapy [low with poor treatment response]. Recent studies on melanoma have focused on the role of PD1 in the pathogenesis of ATLL. In vivo and in vitro blockade of PD1 has been shown to result in restoration of function, a promising study that has progressed to different phases of clinical trials [7–9].

CD8+ cytotoxic T lymphocyte (CTL) plays an important role in immune response to viral infections. In fact, the efficiency of CTL response is an important determinant of the onset of ATLL. However, CTL response to HTLV-1 infection is impaired due to continuous exposure to viral antigens, which results in repeated activation and further impaired function [10,11]. Functional impairment of CTL is associated with expression of inhibitory receptors, which results in T-cell exhaustion and persistence of infection. A number of selectively up-regulated receptors have been identified to contribute to T-cell exhaustion In T-cell exhaustion including: PD1 (Programmed cell death receptor-1), Natural-killer cell receptor (2B4), T-cell immunoglobulin and mucin protein-3 (Tim-3) and CD160 among others. The interaction between these receptors and their ligands has a negative effect on CTL effector function resulting in modulation of CTL response. Blockade of this interaction results in improved function marked by cytokine production and proliferation ability in the case of PD1, 2B4, Tim-3 [12–14]. Therefore, we sought to investigate the role of CD160 in the

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modulation of the immune response to HTLV-1 infection. CD160 is a glycosylphosphatidylinositol (GPI)-anchored member of the immunoglobulin superfamily expressed on CD8+ T cells, NK cells, and CD4+ T cells in humans. The major form of CD160 is the GPI-anchored disulfide linked multimer that contains a single immunoglobulin like domain, but lacks immunoreceptor tyrosine based activation motifs (ITAMs). CD160 has been shown to bind to herpes virus entry mediator (HVEM), a ligand to which it competitively shares a binding site with B and T lymphocyte attenuator (BTLA). HVEM is expressed on T cells, B cells, Natural killer (NK) cells, monocytes and melanoma cells [15–17]. Recent studies have shown a relationship between CD160 expression and progressive decrease in functional activity in a mouse model of chronic Lymphocytic choriomeningitic virus (LCMV), Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections [18–22].

To determine the role of CD160, we assessed the expression of CD160 on CD8+ T cells from HTLV-1 infected individuals (ATLL and AC) compared to uninfected sero-negative controls. We also assessed CD160 expression on HTLV-1 specific CD8+ T cells, and the effect of intercepting the receptor ligand interaction on cytokine production.

2. Materials and methods

2.1. Subjects

Cryopreserved peripheral blood mononuclear cells (PBMCs) from 11 ATLL, 21 asymptomatic carriers and 12 HTLV-1 sero-negative uninfected controls in the same demographic area were obtained from Kagoshima University Hospital. All subjects gave informed consent prior to biological sample collection. This study was approved by the local Ethics Committee of Kagoshima University and performed in accordance with the Declaration of Helsinki for experiments involving humans.

2.2. Surface receptor staining

Cryopreserved samples were thawed and washed with complete-RPMI 1640 (to which 10% FCS was added) and then stained with monoclonal antibodies conjugated with relevant fluorophores of different channels: Alexa Fluor 488, FITC, PE, PerCP and APC. Antibodies to CD160 (clone BY55, eBioscience, Biolegend), BTLA (CD272, clone M1H26, Biolegend), 2B4 (CD244, C1.7, Biolegend), PD1 (CD279, Biolegend), HVEM (all Biolegend, San Diego, CA), CD4, CD8 (both BD Bioscience), CD25 (BD Bioscience).

Isotype controls were incorporated where appropriate to gate out non-specific populations. In the case of CD160, isotype control to CD160 AF488, isotype IgM k FITC (BD Pharmingen) was used as both fluorophores are in the same FL1channel, in line with the manufacturer's instruction.

For intracellular staining, PBMCs were washed with phosphate buffer solution (PBS), permeabilised with FACS Permeabilising solution 2 (BD, San Diego CA) for 10 min, washed, suspended in saponin in PBS solution for 10 min, and then incubated with appropriate staining antibodies. All steps were performed at room temperature.

2.3. Tetramer analyses

Prior to surface receptor staining, PBMCs were incubated with appropriate tetramer antibodies for 15 mins at room temperature. All tetramers were obtained from MBL, Nagoya, Japan: HLA-A*2402 Tax 301-309 (tetramer-SFHSLHLLF), HLA-A*0201 Tax 11-19 (tetramer-LLFGYPVYV), HLA-A*0201 EBV BMLF-1 (GLCTLVAML) and HLA-A*2402 EBV BRLF1 (TYPVLEEMF).

2.4. Functional assays

Thawed PBMCs were washed in 10% FCS RPMI and then stimulated with relevant HLA-restricted peptides in the presence of Brefeldin A (Sigma Aldrich (for perforin) or monensin (Biolegend, SanDiego, CA (for CD107a)) as protein transport inhibitors and CD107a for 5 h at 37 °C prior to staining for appropriate antibodies. Where required purified antibody to HVEM ((Clone 122, Biolegend)) was incorporated and production of CD107a (Southern Biotech) or perforin (BD Pharmingen, San Diego, CA) in the different conditions analyzed after permeabilising and staining with relevant antibodies.

2.5. Flow cytometry

Cells were analyzed by a FACS Calibur flow cytometry (BD Biosciences, San Jose, CA). 1×10^5 events were collected for cell surface studies and 7×10^4 events for functional assays. Data analysis was performed using Cell Quest software (BD Biosciences, San Jose, CA). Gating was done using the forward scatter/side scatter gating and % CD8+ T cells gated for subsequent analyses.

2.6. Statistical analysis

All flow cytometric analyses were done using Flowjo (v 7.6.5) and graphic representations and statistical analyses were performed on Graph Pad Prism (v.6.01). For tests of statistical significance, Mann–Whitney and Wilcoxon-matched pairs test were used for unpaired and paired samples, respectively as shown in the legends accompanying the figures.

3. Results

3.1. Increased CD160 frequency on total CD8 T cells

To investigate the role of CD160 in CD8+ T lymphocyte exhaustion during HTLV-1 infection, we analyzed CD160 expression on CD8+ T cells from HTLV-1 infected [11 ATLL and 21 asymptomatic carriers) patients compared to sero-negative controls [12 HDs]. We observed significantly elevated frequencies of CD160 on HTLV-1 infected subjects compared to sero-negative controls, HDs [Mean ± S.E (standard error), ATLL = 31.4 ± 6.6% ($p < 0.005$); AC = 27.6 ± 3.7% ($p < 0.0005$); HD = 9.7 ± 1.46%, Fig. 1A–C]. There was no difference in CD160 expression between ACs and ATLL subjects ($p = 0.6364$).

3.2. CD160 up-regulation on HTLV-1-specific CD8+ T cells

Next, we evaluated the expression of CD160 on HTLV-1 specific CD8+ T cells in infected subjects with detectable virus-specific tetramer cluster ($\geqslant 0.05$). HLA-A*0201 and *2402 were the dominant tetramers in our cohort. Our analysis showed a high CD160 frequency on HTLV-1 specific CD8+ T cells (ATLL (5) = 66.0 ± 39.3%; AC (9) = 69.2 ± 33.8%). Similarly, on virus-specific CD8+ T cells in persistent latent infection with EBV, high levels of CD160 expression was detected (EBV-specific ATLL (6) = 85.6 ± 19.6%, AC (9) = 73.9 ± 28.9%, HD (5) = 56.2 ± 11.1%. Significantly higher expression was observed on ATLL compared to HD, ($p < 0.05$) (Fig. 1D and E).

Compared to total CD8+ T cells, higher levels of CD160 were detected on HTLV-1 specific CD8+ T cells both ATLL (31.4 ± 22%: 66.0 ± 39.3%, $p = 0.1101$, not significant) and AC (27.6 ± 16.7%:

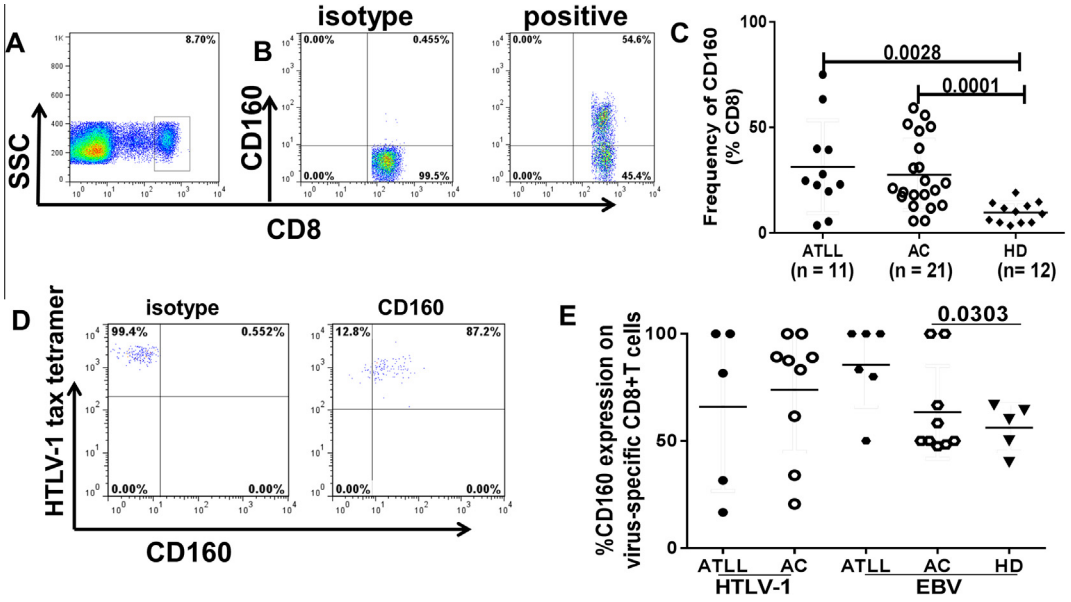

Fig. 1. Frequency of CD160 expression on total CD8+ T and virus-specific CD8+ T cells. (A) Representative dot plot illustrating gating strategy for CD8+ bright population, (B) isotype control and positive staining of CD160, (C) scatter plot summary of frequency of CD160 expression on total CD8+ T cells in the three groups, ATLL (11), AC (21) and healthy individuals (12) respectively, (D) representative dot plot showing CD160 expression on tetramer specific CD8+ T cells, control and positive staining, (E) summary plot showing similarly high CD160 expression on HTLV-1- and EBV-specific CD8+ T cell in HTLV-1 infected compared to healthy donors. *p*-Values by Mann–Whitney test.

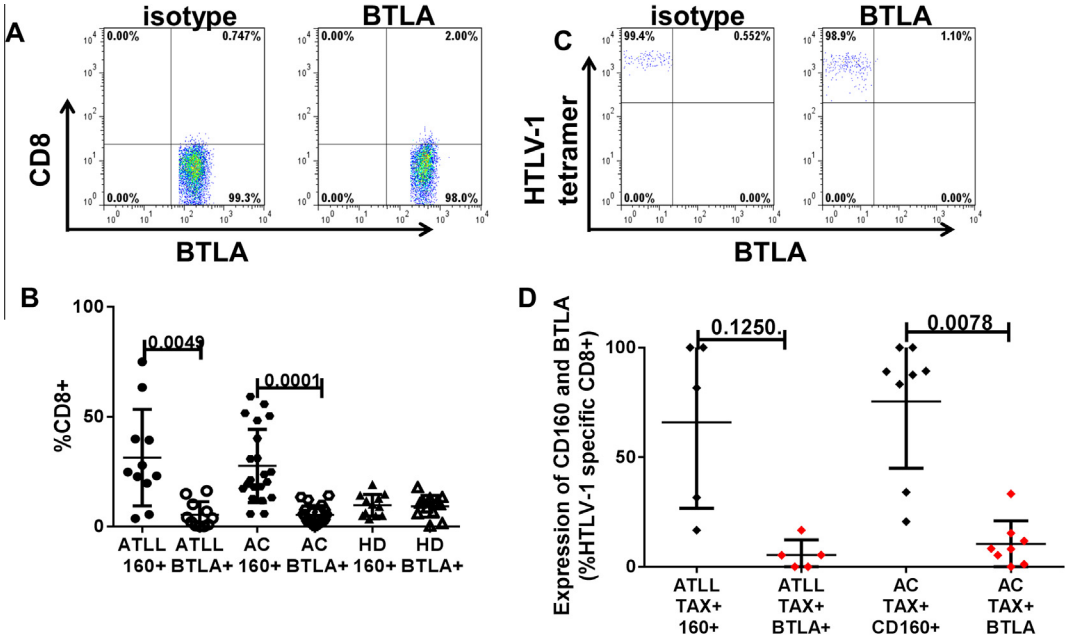

Fig. 2. Increased levels of CD160 compared to BTLA on total CD8+ and virus-specific CD8+ T cells in ATLL and AC. Dot plot representation of gating strategy for BTLA on (A) total CD8, (B) HTLV-1 specific CD8+ T cells. Scatter plot comparison of BTLA and CD160 expression on (C) %CD8+ (D) HTLV-1 specific CD8+ T cells. Indicated *p*-values by Wilcoxon matched pairs test.

73.9 ± 28.9%, $p < 0.0005$, (Supplementary Fig. 2A), demonstrating a role for CD160 in HTLV-1 infection in both ATLL and AC.

3.3. Higher expression of CD160 than BTLA on total CD8+ T cells and HTLV-1 specific CD8+ T cells

CD160 and BTLA have been shown to demonstrate competitive binding for the ligand HVEM in mediating co-inhibition. We sought to determine the levels of the two receptors in same subjects and in turn determine the dominant pathway in HTLV-1 infection. In HTLV-1 infected cohort (11 ATLL and 21 ACs), we observed a statistically higher CD160: BTLA proportion on total CD8+ T cells. ATLL, 31.4 ± 22.0%: 5.4 ± 5.9%, $p < 0.005$; AC, 27.6 ± 16.7%: 5.3 ± 4.2%, $p < 0.0005$, in contrast to HDs (9.7 ± 4.9%: 9.2 ± 5.0%; $p = 0.7334$) in which comparable levels of expression of the two receptors were observed (Fig. 2A and B).

This analysis was also performed for HTLV-1 specific CD8+ T cells. CD160 expression was again higher as compared to BTLA expression in ATLL, (66.0 ± 39.3%: 5.5 ± 6.8%, $p = 0.125$) and AC, (75.5 ± 30%: 10.4 ± 10.6%, $p < 0.05$). Of the 5 ATLL and 8 AC subjects for whom we could demonstrate a tetramer cluster, 2 ATLL and 1 AC subject showed no expression of BTLA in the analysis of

HTLV-1 specific CD8+ T cells. BTLA expression was generally low in both groups (Fig. 2C and D).

3.4. Memory compartmentalization of CD160+CD8+ T cells

CD45RA and CCR7 co-expression is a standard marker of memory. Hence, we examined CD160+CD8+T cells for CD45RA+CCR7+ co-expression in ACs compared to healthy controls to demarcate the memory compartment characterizing CD160 expressing CD8+ T cells.

In both groups, CD160+CD8+ T cells were predominantly of the terminally differentiated compartment (TDEM: CD45RA+CCR7−) and effector memory (EM: CD45RA−CCR7−), although significantly higher in ACs compared to HDs ($p < 0.05$) in the TDEM compartment. A lower frequency was observed in other compartments, effector (CD45RA−CCR7+) and naïve (CCR7+CD45RA+) compartments with the lowest expression in central memory (Supplementary Fig. 2B). Thus, CD160 expression delineates a highly differentiated subset of CD8+ T cells.

3.5. CD160 expressing HTLV-1 specific CD8+ T cells upregulate PD1 and 2B4

Increasing evidence in recent studies has attributed an inhibitory role to PD1 and 2B4. Thus, we investigated the relationship between these molecules and CD160. We examined the expression of these molecules on CD160+CD8+ T cells relative to CD160−CD8+ T cells. Increased levels of 2B4 on CD160+CD8+ in both ATLL and AC relative to CD160-CD8+ T cells (ATLL: 88.6 ± 13.4%, $p < 0.05$; AC: 93.2 ± 3.8%, $p < 0.05$) were detected. In contrast, PD1 expression levels was significantly lower on CD160+CD8+ T cells compared to CD160−CD8+ T cells in both ATLL and AC (ATLL: 13.9 ± 13.6%, $p < 0.05$; 9.5 ± 8.1%, $p < 0.05$) Fig. 3C and D. There was no difference between ATLL and AC subjects. Extending this analysis to HTLV-1 specific CD8+ T cells, a similar trend of 2B4 and PD1 expression was observed with significant up-regulation compared to total CD8+ T cells in AC subjects as shown in Supplementary Fig. 1B. However, preferential up-regulation of 2B4 compared to PD1 was observed on total and virus-specific CD8+ T cells. Taken together, these results suggest a highly exhausted subset in part due to the expression of CD160, which also likely indicates the degree to which CD160 expressing CD8+ T cells are exhausted.

3.6. High frequency of Herpes virus entry mediator (HVEM) on CD4+ and CD4+CD25+ subsets

Receptor–ligand interaction influences the eventual outcome of signaling in cells. Screening the ligand expression on tumor cells helps determine the suitability of intercepting receptor-ligand interaction. In HTLV-1 infection, ATLL cells are mainly tumor cells with a characteristic CD4+ expression, some of which express CD25 giving rise to a CD4+CD25+ phenotype. Thus, we analyzed the expression of the CD160 ligand, HVEM on CD4+ and CD4+CD25+ cells. Analysis of the mean fluorescence intensity revealed a significantly higher HVEM expression on ATLLs compared to ACs on CD4+ only (74.7 ± 11.6%: 44.5 ± 14.2%; $p = 0.0005$) or CD4+ CD25+ T cells (75.0 ± 14.6%: 45.7 ± 17.2%; $p = 0.005$) (Supplementary Fig. 3). We detected no difference in HVEM expression between CD4+ and CD4+CD25+ T cells in the individual groups.

3.7. CD160 inhibits effector function of HTLV-1 specific CD8+ T cells

The CTL quality largely determines response to infection. This can be assessed in terms of ability to produce effectors, perforin, CD107a among others. Furthermore, interaction of receptors with their ligands has been shown to negate effector abilities of T cells.

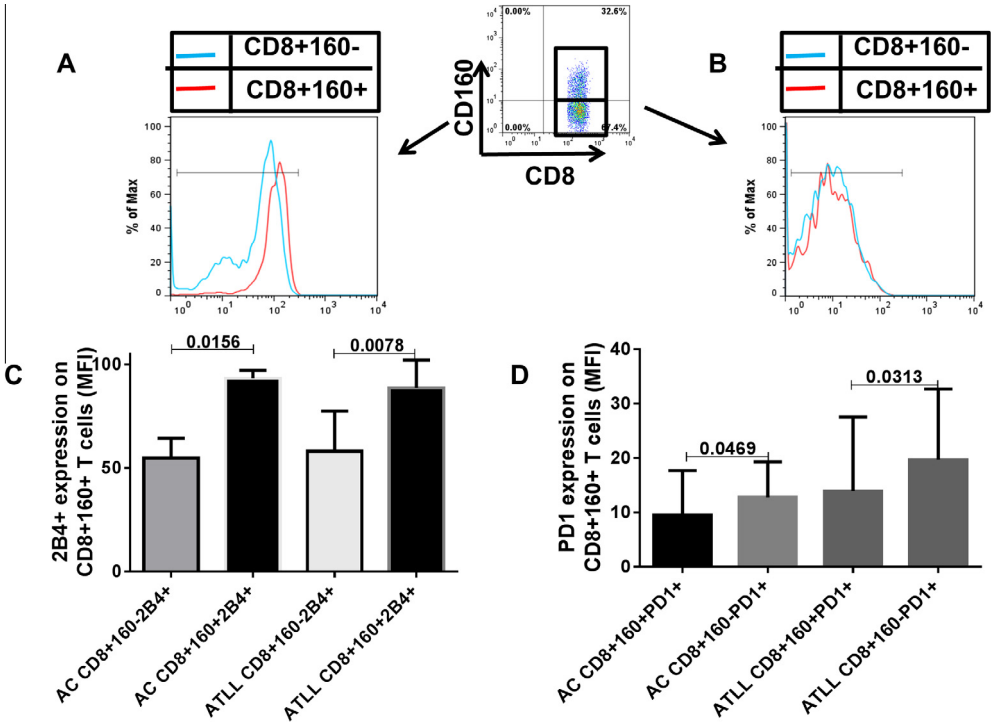

Fig. 3. Comparison of 2B4 and PD1 on CD8+160+ and CD8+160− T cells in AC and ATLL. Representative mean fluorescence intensity plot of (A) 2B4, (B) PD1 on CD8+160− and CD8+160+ in blue and red respectively. Data summary showed (C) Significantly higher expression of 2B4 on CD8+160+ compared to CD8+160− in both ATLL and AC, (D) in contrast, PD1 expression was observed although lower on CD8+160+ compared to CD8+160− cells. *p*-Values by Wilcoxon matched pairs test.

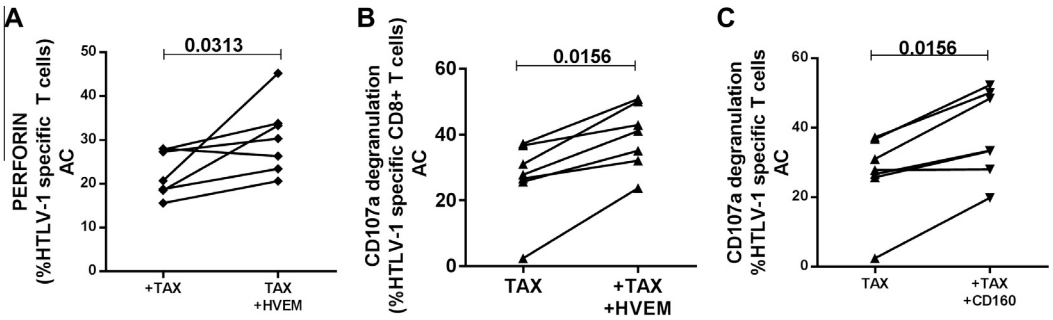

Fig. 4. Perforin production and CD107a degranulation ability of HTLV-specific CD8+ T cells on addition of anti-HVEM antibodies post short-term peptide stimulation and incubation in AC. (A) Increased perforin production on addition of anti-HVEM antibody compared to peptide stimulation alone. Significant improvement in CD107a degranulation ability on HTLV-1 specific CD8+ T cell on addition of (B) anti-HVEM and (C) anti-CD160 antibodies compared to stimulation alone in AC (7 independent experiments). Comparison of blockade using either anti-HVEM or anti-CD160 antibodies showed no difference in CD107a degranulation ability on HTLV-1 specific CD8+ T cells, however was increased in both cases compared to peptide stimulation alone. *p*-Values by Wilcoxon matched pairs test.

We have previously shown improvement in effector function after intercepting receptor-ligand interaction between 2B4/CD48 and PD1/PDL1 [12,13]. Based on HVEM expression on CD4+ and CD4+CD25+ T cells, HVEM blockade seemed an appropriate target for intercepting CD160 interaction.

Thus, we examined the effect of blocking CD160 pathway via ligand, HVEM blockade in response to peptide stimulation. We analyzed the capacity of HTLV-1 specific CD8+ T cells to degranulate CD107a and produce perforin post short-term stimulation.

Simultaneous tax stimulation and addition of anti-HVEM antibodies significantly improved CD107a degranulation (39.4%) and perforin expression (30.4%) on HTLV-1 tetramer specific CD8+ T cells as compared to tax-stimulation alone in AC (7 independent experiments) Fig. 4A and B. Blockade using anti-CD160 antibodies revealed similarly significant improvement in CD107a degranulation (37.9%) compared to controls (Fig. 4).

Blockade of either CD160 or HVEM using relevant antibodies showed no difference in CD107a degranulation for HTLV-1 specific CD8+ T cells, rather, comparable CD107a levels were observed.

4. Discussion

The underlying mechanisms for impairment of CD8+ T cell function in HTLV-1 infection is still unclear [5]. Here, we demonstrate a uniquely exhausted CD160+CD8+ T cell subset and a role for CD160/HVEM pathway in HTLV-1 infection. Our data shows an involvement of CD160 in regulating the immune response to persistent infections as demonstrated by the similarly high expression of CD160 on other latent virus-specific cells. The expression of inhibitory receptors, 2B4 and PD1 on CD160+CD8+ T cells confirms a dysfunctional state of this subset.

CD160+ CD8+ T cells were more of the terminally differentiated compartment as shown by CD45RA and CCR7 co-expression profile. In this context, differentiation could be associated with up-regulation of inhibitory receptors with consequent dysfunction or reduction in effector function.

The similarly increased levels of expression of CD160 on CD8+ and HTLV-1 specific CD8+ T cells in both ATLL and AC individuals may well support the generalized dysfunction associated with HTLV-1 infection regardless of presentation. This observation was not unique to HTLV-1 as similarly high levels were observed on EBV-specific CD8+ T cells, although higher on ATLLs, suggesting a role for CD160 in modulating response to viral infections. Also, HVEM expression has been postulated to be associated with disease outcome and tumorigenesis [23]. The increased HVEM frequencies observed in ATLL compared to AC may further explain the poor clinical outcome observed in ATLL.

CTL function directly correlates with the number of inhibitory receptors expressed [20,21]. Based on our findings, CD160+CD8+ T cells were preferentially positive for 2B4 relative to PD1. This could indicate interdependence more with 2B4 relative to PD1 receptor and cooperative synergy among these receptors in inhibiting CTL effector function. However, whether this synergy is positive or negative, beneficial to the host or virus, needs to be addressed. Furthermore, it would be interesting to determine at what phase this molecules are acquired and expressed. Also, inhibitory function has been alluded to several receptors. On the other hand, exhausted dysfunctional T cells may selectively up-regulate certain receptors which may be more beneficial for viral persistence. Analysis of the different viral infections to examine this will be helpful in developing infection targeted therapeutic strategies. It is reasonable then to infer that CD160+ expressing CD8+ T cells comprise a subset with overlapping function in HTLV-1 infection.

Receptor–ligand interactions are indispensable in regulation of immune response [24] Thus, intercepting this interaction can augment antiviral effector functions resulting in promising outcomes in clinical trials [9]. Studies from our group [12,13] have shown CTLs from HTLV-1 infected subjects to be dysfunctional regardless of the presentation, with an augmentation of function after ligand blockade. In this study, CD160/HVEM blockade resulted in increased levels of CD107a degranulation and perforin production. This suggests a role for CD160/HVEM pathway in the response to HTLV-1 infection. Thus, HTLV-1 specific CD8+ T cells could utilize the CD160/HVEM pathway as a means of inhibiting host response, in turn enhancing infection persistence. Improved function of HTLV-1 specific CD8+ T cells post peptide stimulation alone agrees with a previous study which showed a retention of function in the face of exhaustion [6]. Introduction of HVEM antibodies led to a further increase in CD8+ CTL effector function comparable to the addition of antibodies to CD160.

Our findings herewith favor an inhibitory function for CD160 on CD8+ CTLs in HTLV-1 infection. High expression of receptor in addition to expression of other co-inhibitory molecules may be an immune evasion mechanism, aimed at ensuring persistence of the infection in the presence of chronic antigen stimulation and impaired effector function via the CD160/HVEM pathway.

Our data also indicates a role for CD160 in the impairment or exhaustion of CTL function, and consequent reduction in antiviral efficacy. CD160 could be a valuable marker for delineating highly exhausted CD8+ T cell population. Notably, the expression of other inhibitory receptors on the CD160+ subset brings to the fore the need for caution in developing immune interventions based on intercepting pathways. Furthermore, this knowledge may be utilized in development of immune therapies to help improve effector function.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.09.084.

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