JLB

Review

CD57$^+$ T lymphocytes and functional immune deficiency

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RECEIVED AUGUST 23, 2009; REVISED SEPTEMBER 16, 2009; ACCEPTED SEPTEMBER 18, 2009. DOI: 10.1189/jlb.0809566

ABSTRACT

CD57$^+$ expression in T lymphocytes has been recognized for decades as a marker of in vitro replicative senescence. In recent years, accumulating evidences have pointed on the utility of this marker to measure functional immune deficiency in patients with autoimmune disease, infectious diseases, and cancers. We review here the relevant literature and implications in clinical settings. *J. Leukoc. Biol.* 87: 107–116; 2010.

Introduction

The CD57 antigen (**Fig. 1**) is a terminally sulfated glycan carbohydrate epitope (glycoepitope) that was first described in 1981 on HNK cells [2], and it is also called HNK-1, LEU-7, or L2 [3]. The HNK-1 epitope is expressed by a variety of cell types in the vertebrate nervous system, where its cell type-specific expression patterns change during neural development. The HNK-1 determinant is composed of a GlcA attached in α1–3 linkage to a terminal galactose. This structure is synthesized by specific glucuronosyltransferases that act on terminal (poly)-*N*-acetyl-lactosamine units of N-glycans. Glucuronylation is followed by 3-*O*-sulfation of the GlcA by one or more specific sulfotransferases. The HNK-1 epitope has also been described on *O*-glycans of glycoproteins, on proteoglycans, and on glycolipids. Two different GlcA transferases participate in HNK-1 GlcA addition: GlcAT-P and GlcAT-S [4–6] (a third enzyme, GlcAT-D, has been suggested to be involved [7]). They have very different activities for glycoprotein or glycolipid substrates in vitro and thus, may generate functionally different HNK-1 epitopes in vivo.

The HNK-1 epitope is present on a variety of neuronal cell glycoproteins, including neural cell adhesion molecule, contactin, myelin-associated glycoprotein, 5′-nucleotidase [1], ICAM5 [8], L1, and P0 (the major glycoprotein of peripheral nerve myelin [9–11]). Accordingly, the first mouse anti-CD57 mAb, M6764, was produced against the crude membrane fractions of the neural tubes [12]. There is evidence that HNK-1 can function as a ligand for laminin [13], L-selectin, P- selectin [14], and a cerebellar adhesion protein, termed amphoterin. HNK-1 has also been shown to mediate homotypic adhesive interactions involving P0. HNK-1-dependent adhesive interactions have been implicated in cell migration processes involving cell–cell and cell–matrix interactions and are proposed to participate in reinnervation of muscles by motor neurons.

Expression of CD57 is also found on T-lineage lymphocytes, where it is currently considered a marker-replicative senescence ("clonal exhaustion" [15]), i.e., a high susceptibility to activation-induced cell death and the inability to undergo new cell-division cycles despite preserved ability to secrete cytokines upon encounter with their cognate antigen [16]. The phenotypes associated with replicatively senescent CD8$^+$ T lymphocytes are not well defined [17, 18] but are generally attributed to lack of CD28 or expression of CD57 [19–24]. This proliferative defect had been shown in all lymphocyte subsets, which express CD57 (CD4$^+$ and CD8$^+$ T lymphocytes and NK cells) and with some relevant exception [25], was not overcome by addition of IL-2 or IL-15. Despite neural crest and T-lineage restriction, in chickens, CD57 is considered as a B cell activation marker for bursal lymphocytes [26].

Doubts about real replicative inability of CD57$^+$ T lymphocytes were first raised when Chong et al. [27] demonstrated that CD8$^+$CD57$^+$ T lymphocytes are capable of rapid expansion using multiple techniques (including ^{3}H-thymidine uptake, flow cytometric bead-based enumeration, and standard hemocytometer counting). Previous reports can be explained by marked inhibition of activation-induced expansion and increased 7-amino-actinomycin D uptake by CD8$^+$CD57$^+$ T lymphocytes following treatment with CFSE, a dye used previously to measure their proliferation, combined with specific media requirements for the growth of this cell subset. The ability of

Abbreviations: ATG=antithymocyte globulin, B-CLL=B cell chronic lymphocytic leukemia, CD62L=CD62 ligand, FL=follicular lymphoma, GC=germinal center, GlcA=3-*O*-sulfated glucuronic acid, HAART=highly active antiviral therapy, HCMV=human CMV, HCV=hepatitis C virus, HNK-1=human NK 1, HSCT=hematopoietic stem cell transplantation, IRP=immune-risk phenotype, KIR=killer Ig-like receptor, KLRG1=killer cell lectin-like receptor subfamily G, member 1, LGL=large granular lymphocyte, NLPHD=nodular lymphocyte predominance type of Hodgkin's lymphoma, PD-1=programmed death 1, PNH=paroxysmal nocturnal hemoglobinuria, RCC=renal cell carcinoma, TB=tuberculosis, TTV=torquetenovirus

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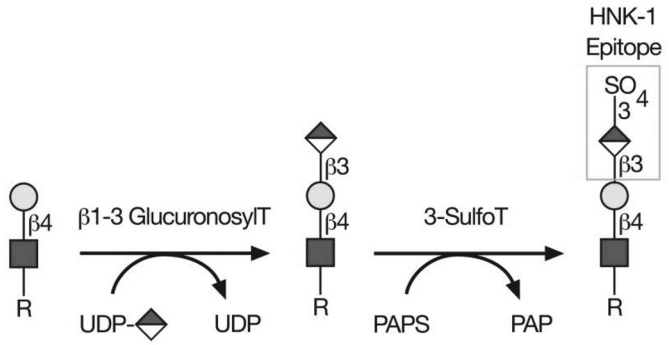

Figure 1. Synthesis of the HNK epitope. Squares represent N-acetylglucosamine, circles represent galactose, and rhombs represent GlcA (modified from ref. [1]). GlucuronosylT, Glucuronosyltransferase; SulfoT, sulfotransferase; UDP, uridine diphosphate; R, radical; PAPS, 3′-phosphoadenosine-5′-phosphosulfate; PAP, adenosine 3′,5′-diphosphate.

$CD8^+CD57^+$ T lymphocytes to differentiate further is highlighted by a distinct cytokine profile late after activation that includes the unexpected release of high levels of IL-5 [27].

Although in vivo, data are still lacking, what remains true is that expression of CD57 on $CD4^+$ and $CD8^+$ T lymphocytes is a general marker of proliferative instability, correlating directly with the number of cell divisions and inversely with telomere length, with a sensitivity greater than the presence of CCR7 or lack of CD28 [15]. CD57 expression correlates strongly with simultaneous expression of granzymes A, B, and perforin so that FACS provides a means to isolate viable cells easily with high cytolytic potential, without the need for lethal fixation/permeabilization techniques [28].

In healthy controls, CD57 antigen is expressed normally only by a minority of peripheral blood $CD8^+$ T lymphocytes. The transcriptional profiles of $CD8^+CD57^+$ and $CD8^+CD57^-$ T lymphocytes differ substantially. $CD8^+CD57^+$ T lymphocytes have high cytotoxic effector potential including perforin, granzymes, and granulysin, regardless of HIV status. At the messenger and protein levels, $CD8^+CD57^+$ T lymphocytes express more adhesion molecules and fewer chemokine receptors (CCR7 and CXCR4) than $CD8^+CD57^-$ T lymphocytes but express CX_3CR1 preferentially. The lower expression level of genes involved in cell-cycle regulation supports the limited proliferation capacities of $CD8^+CD57^+$ T lymphocytes, even in response to TCR and IL-2, IL-7, and IL-15 stimulation. In conclusion, $CD8^+CD57^+$ T lymphocytes from HIV and uninfected subjects maintain effective cytotoxic potentials but are destined to migrate to nonlymphoid tissues without further cycling [29].

As detailed below, these $CD8^+CD57^+$ T lymphocytes are commonly found in individuals with chronic immune activation and increase in frequency with age (from absence in newborns to 15–20% in adults), but the percentage of $CD8^+CD57^+$ cells has been shown to increase in a series of clinical conditions whose common denominator is functional immune deficiency, including HIV and CMV infection, common variable immunodeficiency, hematological cancers, and autoimmune diseases, and especially after HSCT (in which expression can peak up to 50% of all T lymphocytes [30]). These expansions have been characterized first in AIDS patients, where $CD8^+CD57^+$ lymphocytes specific for many epitopes of HIV proteins produce IFN-γ but in the presence of costimulation, are unable to proliferate in response to peptides for which they are specific: In such patients, HIV-specific $CD8^+$ T cells contribute to up to 80% of the total $CD8^+CD57^+$ population. CD57 is also expressed on a small subset of $CD4^+$ lymphocytes populating the GC of lymph nodes, termed GC-T_h cells, but gene-expression profiling studies have shown that these are remotely related to peripheral blood $CD57^+$ T lymphocytes in global gene expression [31]. On the basis of data from ICOS-deficient mice, it has been proposed that circulating $CD57^+CXCR5^+$ T cells are GC-derived and thus, may serve as a surrogate marker for the presence of functional GCs in humans [32]. Similarly to circulating $CD57^+$ T cells, Marinova et al. [33] showed that $CD4^+CD45RO^+CD57^+$ T cells have a high propensity for apoptosis in vivo. Anyway, $CD4^+CD57^+$ T cells derived from peripheral blood do not support Ig production by B cells [34]. Another difference between circulating and GC $CD57^+$ T cells is expression of CD28, occurring only in the second subset [35].

Most importantly, a lectin-binding soluble factor released by $CD8^+CD57^+$ lymphocytes inhibits cytolytic functions of effector cells, including $CD8^+CD57^-$, in HSCT recipients and HIV patients, creating an immunodeficient status [17, 30, 36].

So, $CD57^+$ T lymphocytes percentage estimation in peripheral blood could be a new surrogate marker to evaluate the quality of functional cell-mediated immune competence and immune reconstitution, suggesting the existence of a threshold beyond which the risk for opportunistic infections becomes significant, and prophylactic measures and strict clinical follow-up are required. Even in the case in which oligoclonal expansion [17, 37] of such a cell subset would not be the predisposing condition but rather, the result of antigen selection during a persistent disseminated infection [19, 38], CD57 quantification could correlate with the risk for more infectious complications.

We review below the main conditions associated with increased $CD57^+$ lymphocyte count in peripheral blood.

$CD57^+$ T LYMPHOCYTES IN NORMAL PHYSIOLOGY

Stress

Stress per se can affect the immune system, an interaction that is studied by a branch of immunology called psychoneuroimmunology. Physical and emotional stress can increase $CD57^+$ T lymphocytes in peripheral blood, potentially explaining the increased susceptibility to viral infections (e.g., herpes virus reactivations) seen in stressed individuals.

Physical stress. When eight male runners performed an intensive treadmill-running protocol until volitional exhaustion, mobilized T lymphocyte populations expressing KLRG1 and CD57 appeared to be removed from the bloodstream after 1 h of recovery [39]. The magnitude of change was not age-depen-

dent [40]. These data were confirmed by Campbell et al. [41], who estimated the increase in CD57$^+$ T lymphocytes at +450%.

Psychological stress. Parental psychiatric symptom scores are associated with increased percentages of CD8$^+$CD28$^-$ CD57$^+$ cells in the blood of CMV-seropositive children [42].

Aging

Healthy aging leads to accumulation of memory cells [43, 44], which may fill the "immunological space" and block release of naïve T cells to the periphery, resulting in a shrunken T cell repertoire for new antigens. HCMV pp65-specific CD8$^+$ T cells express CD28 on <10% of cells in the elderly and >75% in the young. The elderly commonly possess oligoclonal expansions of T cells, especially of CD8 cells, which surprisingly, are associated with HCMV seropositivity (as detailed below). This in turn is associated with many of the same phenotypic and functional alterations to T cell immunity that have been suggested as biomarkers of immune system aging. Some authors have tried to summarize risk factors in an IRP (**Table 1**) [43]. In fact, HCMV, not age per se, is the prime driving force behind many or most of the oligoclonal expansions and altered phenotypes and functions of CD8 cells in the elderly [45]. The Swedish Octogenarian (OCTO) and Nonagenarian (NONA) longitudinal studies distinguished an IRP [46], one important component of it being HCMV seropositivity [47–49]. Centenarian donors are an example of the successfully aged HCMV repertoire more similar to that of the young than the old.

CD57$^+$ T LYMPHOCYTES IN INFECTIOUS DISEASES

AIDS

AIDS is mostly a quantitative deficiency of CD4$^+$ T lymphocytes. Actually, before such a cell subset drops down, CD57$^+$ T lymphocyte expansions are commonly detected [50–52], which can also be observed in long-term nonprogressors [53]. The clonal exhaustion hypothesis of CD8$^+$ T lymphocytes was first formulated in AIDS patients, after observation that HIV-specific CD8$^+$ T lymphocytes produce cytokines in response to cognate antigen but are unable to divide and die during a 48-h in vitro culture [16, 54]. Percentages of CD4$^+$ CD57$^+$ CCR7$^-$ T lymphocytes are significantly higher in untreated HIV-1-infected subjects than in HIV-1-seronegative donors, and CD57 expression does not normalize in subjects receiving at least 6 months of effective antiretroviral therapy. HIV-1-specific CD4$^+$ T lymphocytes, producing only IFN-γ, have the highest expression of CD57, whereas few cells producing IL-2 alone express CD57 [55, 56]. During long-term HAART, HIV-1 is able to persist in CD4$^+$ CD57$^+$ T lymphocytes as proviral DNA: Anyway, viral evolution was restricted; and in 80% of the patients with undetectable viremia, no sign of viral replication can be detected [57]. The percentage of CD4$^+$CD57$^+$ T lymphocytes correlates negatively with CD4$^+$ count change during treatment interruption [58].

Changes in clonal dominance (clonal turnover) of HIV-specific CD8$^+$ T lymphocyte are related to the replacement of clonotypes that approach replicative senescence, reflected by CD57 expression [59]. The high prevalence of these dysfunctional lymphocyte subsets could explain the occurrence of opportunistic infections and cancers in HIV patients with normal lymphocyte counts, such as Kaposi's sarcoma [60]. Expansion of suppressive CD8$^+$CD57$^+$ T lymphocytes has been shown in the lungs of HIV-infected subjects with advanced disease [61]. HCV coinfection reduces expression of perforin and CD57 on HIV-specific CD8$^+$ T lymphocytes [62]. A large-scale gene array analysis (3158 genes) found no distinction in the transcriptional profiles of CD8$^+$CD57$^+$ T lymphocytes from HIV-infected and uninfected subjects. In both groups, these cells showed specificity for multiple antigens and produced large amounts of IFN-γ and TNF-α [29]. On the contrary of CD4$^+$CD57$^+$ T lymphocytes, CD8$^+$CD57$^+$ T lymphocytes have a significant decrease during follow-up of salvage antiretroviral therapy with lopinavir/ritonavir [63], and pediatric patients responsive to HAART produce similar percentages of CD8$^+$CD57$^+$ T lymphocytes compared with controls [64]. The functional meaning of CD8$^+$CD57$^+$ T lymphocytes in HIV infection is still under debate: In contrast to maturation of EBV- and CMV-specific memory CD8$^+$ T lymphocytes, HIV-1-specific CD8$^+$ T lymphocytes do not display coordinated down-regulation of CD27 and up-regulation of CD57 and accumulate in an atypical CD27^{high}CD57^{low} subset. Moreover, accumulation of CD27^{high}CD57^{low} HIV-1-specific CD8$^+$ T cells positively correlates with HIV-1 plasma viremia [65].

Accordingly, CD57 is expressed on CD8$^+$CD45RA$^+$CCR7$^-$ CD28$^-$ effector memory T lymphocytes, which retain a long half-life and accumulate in the face of progressive HIV disease [66].

Recently, Petrovas et al. [67] have reported that CD57 is linked to higher apoptosis resistance in CD8$^+$ T lymphocytes during HIV infection, and cells expressing a PD-1^{low}CD57^{high} phenotype exhibit lower levels of cell death. The majority of HIV-specific CD8$^+$ T cells expresses a PD-1^{high}CD57^{low} or PD-1^{high}CD57^{high} phenotype. Contrary to CD57, high expres-

TABLE 1. Marker of the So-Called "IRP"

Alterations with age	non-IRP	IRP
Markers of cells		
CD:CD8 ratio	>1	<1
T cell proliferation	Normal	Reduced
CD28	Increased	Reduced
CD57	Reduced	Increased
CD45RA	Increased	Reduced
CD45RO	Reduced	Normal
KLRG1	Reduced	Increased
Cytokines and growth factor		
IL-2	Increased	Reduced
IL-10	Stable	Stable
IFN-γ	Increased	Reduced
CMV/EBV status		
CMV+cells	Lower frequencies, mostly KLRG1+	Higher frequencies, mostly KLRG1+
EBV+cells	Lower frequencies	Higher frequencies

sion of PD-1 was characterized by translocation of PD-1 into the area of CD95/Fas-capping, an early, necessary step of CD95/Fas-induced apoptosis [67].

HCMV

HCMV infection is associated with the emergence of the largest long-term memory populations with the most "mature" phenotype, CD27/CD28^{low}, CD57^{high}, and often perforin$^+$. The vast majority of resting CD8$^+$ T lymphocytes capable of rapid induction of IFN-γ and TNF-α synthesis in response to HCMV peptides was found in a subset characterized by intermediate-to-high expression of CD57, down-regulation/loss of CD27, and varying degrees of reversal of the classical "memory" CD45RO^{bright}/RA^{dim} phenotype [68]. HCMV seropositivity is associated with marked changes in the phenotype of the overall CD4$^+$ T cell repertoire in healthy, aged donors, including an increase in CD57$^+$ expression and a decrease in CD28 and CD27 expression, a phenotypic profile characteristic of immune senescence. This "memory inflation" of CMV-specific CD4$^+$ T cells contributes to evidence that HCMV infection may be damaging to immune function in elderly individuals [69]. The expression of CD28 was decreased, whereas CD57 expression was increased in pp65(495-503)-loaded HLA-A(*)0201 tetramer-negative CD8$^+$ T cells in the elderly when compared with the young group. However, neither of these changes was found within tetramer-positive cell populations [70]. One of the strongest indirect evidences that these lymphocytes could actually be immunosuppressive is that young and adult nonresponders to anti-influenza vaccination have higher levels of anti-HCMV IgG [71] and higher percentages of CD57$^+$ T lymphocytes together with increased concentrations of TNF-α and IL-6 and decreased levels of cortisol [71]. Similarly, CMV-seropositive patients fail more commonly to control HIV in progression to AIDS [72]. Curiously, in allogeneic peripheral blood HSCT recipients, significant expansion of CD8$^+$CD57$^+$ T lymphocyte subsets is associated with recovery from viremia and no progression to HCMV disease [73]. In common variable immunodeficiency patients, there is an association between a high percentage of circulating CD8$^+$CD57$^+$ T lymphocytes and HCMV infection [74]. Finally, cases of transient monoclonal CD8$^+$CD57$^+$ T lymphocytosis with LGL morphology have been reported after primary HCMV infection [75]. Alterations occur within 8 weeks after primary CMV infection [46], and of interest in congenital CMV infection, CD28 expression is decreased already in fetal CD8$^+$ T lymphocytes [76]. Less differentiated CD27$^+$CD57$^-$ CMV-specific memory T cells are more likely to persist in the recipient post-HSCT compared with more terminally differentiated CD27$^-$CD57$^+$ CMV-specific memory T cells [77].

Measles virus

Natural measles virus infection is recognized to induce immunosuppression, contributing to an increased susceptibility to other infections. Elevated proportions of CD8$^+$CD57$^+$ cells were found in the peripheral blood of children with natural measles early after infection ($P<0.05$), whereas the proportion of other cell surface markers remained stable. No corresponding change in CD8$^+$CD57$^+$ lymphocytes was noted in measles, mumps, and rubella-vaccinated children or in healthy controls, suggesting that the live attenuated vaccine does not induce immunosuppression [78].

Hepatitis B virus

Most CD4$^+$CD28^{null} T cells showed a CD27$^-$CD45RA$^-$ CD45RO$^+$ surface phenotype. The markers CD56, CD57, and KIR were detected on CD4$^+$CD28^{null} T cells, but the majority was positive for CD57 [79].

HCV

IFN-α therapy of HCV infection enhances the differentiation of CD8$^+$ T lymphocytes toward a late differentiation phenotype (CD28$^-$CD57$^+$), which disappears in cases of virus elimination [80]. The same phenomenon occurs in the livers of those with chronic HCV after combined treatment with IFN-α_{2b} and ribavirin [81]. CD57$^+$ HCV-specific CTLs in peripheral blood and livers also express KIRs [82] and the inhibitory molecule PD-1 [83]. Interestingly, PD-1 in vitro blockade by mAb specific to its ligands (PDL-1 and PDL-2) results in restoration of functional competence (proliferation and IFN-γ, IL-2 secretion), even in those individuals who lack HCV-specific CD4$^+$ T lymphocyte help [83]. The proportions of effector-senescent CD8$^+$CD45RO$^+$CD57$^+$ T lymphocytes and of those near to apoptosis are significantly higher in patients with liver cirrhosis [84].

B_{19} virus

CD8$^+$ T lymphocyte responses increase in magnitude over the first year post-B_{19} infection, despite resolution of clinical symptoms and control of viremia, and T cell populations specific for individual epitopes comprise up to 4% of CD8$^+$ T cells. B_{19}-specific T cells develop and maintain an activated CD38$^+$ phenotype, with strong expression of perforin and CD57 and down-regulation of CD28 and CD27. CD57 expression levels increase over time in almost all acutely infected individuals. These cells possess strong effector function and intact proliferative capacity (in line with recent evidences [27]). Individuals tested many years after infection exhibit lower frequencies of B_{19}-specific cytotoxic T lymphocytes (typically 0.05–0.5% of CD8$^+$ T cells), with low levels of CD57 expression [85].

TTV

Our group reported recently that changes in CD8$^+$57$^+$ T lymphocyte expansions after autologous HSCT correlate with changes in TTV viremia [86], suggesting that this lymphocyte subset can also play a role at control of orphan endogenous viruses. We showed recently that the kinetics of TTV viremia are highly predictable and could serve as surrogate markers for functional immune reconstitution [87].

TB

TB patients show an increase in CD8$^+$CD57$^+$ T lymphocytes compared with age-matched healthy donors ($P<0.0001$) [68]. CD8$^+$CD57$^+$ T lymphocytes from TB patients express CD69, perforin, granzyme-A, and a CD28$^-$CD62L$^-$CD161$^-$ phenotype

without recognition for the α-galactosylceramide-CD1d complex. This cell subset also expresses TNF-α and IFN-γ under PMA/ionomycin stimulation. Interestingly, the cytotoxicity against autologous monocytes in the presence of *Mycobacterium tuberculosis* H37Rv culture filtrate is higher in CD57$^-$ cells from TB patients and donors than their CD57$^+$ counterparts, but only CD8$^+$CD57$^+$ T lymphocytes from TB patients exhibit spontaneous cytotoxicity against monocytes in the absence of antigen [88]. Anyway, Jafari et al. [89] showed that compared with a group of control patients with alternative pulmonary pathologies, there was no significant difference in lymphocyte subpopulations in bronchoalveolar lavage fluid.

Trypanosomiasis

There is a correlation between disease severity and the frequency of *Trypanosoma cruzi*-specific, IFN-γ-producing CD4$^+$ T lymphocytes. The high expression of CD27 and CD28 with a relative low expression of CD57 found on CD4$^+$IFN-γ$^+$ T cells suggests that the effector T lymphocyte pool in chronic *T. cruzi* infection includes a high proportion of newly recruited T cells but a low frequency of long-term memory cells. The total CD4$^+$ T cell compartment shows signs of senescence and later stages of differentiation associated with more severe stages of the disease. These findings support the hypothesis that long-term *T. cruzi* infection in humans might exhaust long-lived memory T cells.

Alcoholism

Chronic human alcoholics are often immunodeficient and have a correspondingly increased incidence of infectious diseases [96]. A clinically important example is an up to fourfold increase in pneumonia that occurs in alcoholics across various ethnic and racial backgrounds. There is a large, additional group of infectious diseases that preferentially afflicts alcoholics, including TB. Most alcoholics (with or without liver disease) have stably increased T cell expression of the carbohydrate-rich marker, CD57 (HNK-1, Leu-7) [97, 98].

CD57$^+$ T LYMPHOCYTES IN AUTOIMMUNE DISEASES

Wegener's granulomatosis

Peripheral blood T lymphocytes in Wegener's granulomatosis are characterized by mono/oligoclonal CD4$^+$ T lymphocyte expansions expressing CD57 and CCR5 (CD195) [99].

Pars planitis

CD57$^+$ T lymphocyte subsets are increased (P=0.002). The majority of CD4$^+$CD57$^+$ T lymphocytes includes CCR7$^-$CD27$^-$CD28$^-$CD45RO$^+$, and the most CD8$^+$CD57$^+$ T cells are CCR7$^-$CD27$^-$CD28$^-$CD45RA$^+$. The number of cells positive for intracellular IFN-γ and IL-4 is higher in the CD57$^+$ T cell populations. A greater number of CD8$^+$CD57$^+$ T cells than CD8$^+$CD57$^-$ T cells were positive to perforin (P=0.006) and granzyme-A (P=0.01) [100].

CD57$^+$ T LYMPHOCYTES IN CANCER

One of the most intriguing evidences about the role of CD57$^+$ T lymphocytes in cancer comes from the fact that metastasis-free regional lymph nodes draining different human epithelial tumors present a reduction in almost all immune cells, except CD57$^+$ lymphocytes [101]. CD8$^+$CD28$^-$CD57$^+$ T lymphocyte clones may be the result of persistent stimulation by tumor-associated antigens, combined with a reduced cellular death rate secondary to reduced expression of the apoptosis-related molecule CD95 [20, 102, 103].

Solid cancers

Melanoma. A retrospective analysis in 16 IFN-α-treated melanoma patients with resected regional lymph node metastases showed that the median survival time of patients with >23% CD8^{high}CD57$^+$ lymphocytes prior to treatment with IFN-α was 14.2 months, whereas the median survival time of patients with <23% CD8^{high}CD57$^+$ lymphocytes was not reached at the time of analysis (median follow-up 24.6 months) [104].

Advanced gastric cancers. Akagi and Baba [105] showed that an increased proportion (≥18%) of CD57$^+$ T lymphocyte in the peripheral blood of patients with advanced gastric carcinomas (Stages III and IV) could indicate a shorter overall survival.

RCC. Advanced RCC patients with higher than 30% CD8^{hi}CD57$^+$ lymphocytes in the CD8$^+$ subset had shorter survival compared with patients with <30% CD8^{hi}CD57$^+$ lymphocytes in the CD8$^+$ subset. Treatment with IFN-α_{2b} increased overall survival only in the former subgroup of RCC patients [106].

Hematological malignancies

In 1998, Van den Hove et al. [107] showed that in untreated hemato-oncological patients (n=48) with lymphomas, acute and chronic myeloid, and lymphocytic leukemias; monoclonal gammopathy of undetermined significance; and multiple myeloma, 42% had (nonmalignant) lymphocyte profiles clearly distinct from healthy donors, with a notably similar pattern of increased CD3$^+$ CD57$^+$ and CD8$^+$ CD57$^+$ lymphocytes, suggesting systemic activation of the T cell compartment. Since then, more evidences have cumulated for selected hematological malignancies.

FL. The tumor microenvironment has been shown to play a major role for FL. Gene microarray analyses have shown that two specific patterns exist in the reactive microenvironment of FL: an immunosurveillance pattern (T lymphocytes and macrophages) and an immune-escape pattern (CD57$^+$ T cells), which were associated directly with the clinicobiologic features of these patients (such as more "B" symptoms and bone marrow involvement) [108]. CD57$^+$ cells are observed predominantly outside of the neoplastic follicle in FL on the contrary of the diffuse infiltration seen in reactive follicular hyperplasia [109–111].

Hodgkin lymphoma. Atayar et al. [90] showed that CD4$^+$CD57$^+$ T lymphocyte rosettes occur around neoplastic cells and throughout the nodules in NLPHD [112]. CD4$^+$CD57$^+$ occur in an average of 19% of the small lymphocytes in the nod-

ules of NLPHD compared with 4% in nodular sclerosing Hodgkin's disease, 4.3% in T cell-rich B cell lymphoma, and 2.1% in FL. Moreover, $CD57^+$ small lymphocytes often showed a distinctive pattern in NLPHD, forming a ring of cells around the large luteinizing-hormone cells [113].

Multiple myeloma. A long-lived population of $CD8^+CD57^+CD28^-$ perforin$^+$ T lymphocyte clones has been reported in the peripheral blood of patients with multiple myeloma: Despite being more commonly found in patients with progressive and advanced-stage disease, this population was associated with superior survival [102]. In patients with relapsed/refractory multiple myeloma treated with thalidomide, multivariate analysis showed that inferior survival was associated with low pretreatment bone marrow $CD57^+$ cells ($P<0.001$), and overall, $CD8^+CD57^+$ T lymphocytes account for up to 25% of the marrow T cell population [114]. Such $CD8^+CD57^+$ T lymphocytes have been shown to suppress T cell functions in multiple myeloma [115, 116].

Myelodysplastic syndromes and acute myeloid leukemia. Clonal $CD8^+/CD57^+/CD28^-/CD62L^-/$ $NKG2D^+/CD244^+$ effector T lymphocytes occur in 50% of myelodysplastic syndrome patients ($n=52$) compared with 5% of age-matched normal controls [117–119]. Similarly, Meers et al. [120] showed recently increased surface expression of activation markers ($HLA\text{-}DR^+$, $CD57^+$, $CD28^-$, $CD62L^-$) on T lymphocytes in peripheral blood and bone marrow ($n=131$). T lymphocyte activation was not restricted to any relevant clinical subgroup (French-American-British, International Prognostic Scoring System, cytogenetics) and did not correlate with blood counts or need for treatment. In vitro clonogenic growth of marrow mononuclear cells ($n=18$) was not influenced by T lymphocytes expressing these markers [120]. Accordingly, in acute myeloid leukemia, CD4+ naive and memory T lymphocyte distribution is normal, but the cytotoxic $CD8^+CD57^+$ subset is increased significantly ($P<0.001$) [121].

CLL. Terstappen et al. [122] first reported in 1990 that $CD57^+$ lymphocytes in the lymph nodes of B-CLL patients had abnormal orthogonal light-scattering signals and an abnormal density of $CD57^+$ receptors in comparison with their peripheral blood $CD57^+$ lymphocytes or the $CD57^+$ lymphocytes in the peripheral blood, bone marrow, and tonsils of hematological normal donors. Katrinakis et al. [123] then reported in 1995 that B-CLL patients with neutropenia had higher numbers of peripheral blood $CD8^+CD57^+$ T lymphocytes than the non-neutropenic ones. Finally, in 1997, Serrano et al. [124] showed that oligoclonality was substantially more frequent in the $CD4^+$ and $CD8^+$ T lymphocyte populations of B-CLL patients than in the age-matched controls ($P<0.001$). The frequency of the CD57 marker on $CD4^+$ T cells was increased in the setting of CLL (% CD57=14.8±13.0%) compared with that in normal controls (% CD57=3.3±3.0%; $P<0.001$). An elevated frequency of $CD4^+CD57^+$ T cells was correlated with more advanced disease. Similarly, the most extreme oligoclonal expansions of $CD4^+CD57^+$ T lymphocytes occurred in CLL patients who had progressed beyond Rai stage 0 [124]. Anyway, in 1997, Martín et al. [125] showed that the percentage of $CD3^+CD57^+$ T lymphocytes in low blood lymphocyte-count patients was higher than those found in high blood lymphocyte-count patients. Porakishvili et al. [126] showed in 2001 that up to 50% of blood $CD4^+$ T lymphocytes in B-CLL patients have a cytotoxicity-related $CD28^-CD57^+$ phenotype and high content of granzyme B and perforin, suggesting a mature population. The same phenotype in $CD8^+$ T cells is characteristic of mature cytotoxic T cells. However, in contrast to the $CD8^+$ T cells, the $CD4^+$ T cells were $CD45RO^+$ more frequently than $CD45RA^+$, indicating prior antigen experience. In contrast, this population lacked expression of CD69 or HLA-DR, arguing that they were not activated or that they are an abnormal population of T lymphocytes. Their constitutive cytokine levels showed them to contain mainly IL-4 and not IFN-γ, suggesting a T_h2 phenotype. The role of the $CD4^+$ perforin$^+$ T cell population is at present uncertain. However, this potentially cytotoxic T cell population could contribute to enhancing survival of the B-CLL cells through production of IL-4 and to the immunodeficient state seen frequently in patients with this tumor, independent of drug treatment [126]. Porakishvili et al. [127] also showed in 2004 that these $CD4^+$ $CD57^+$ T lymphocytes are able to kill autologous B-CLL cells ex vivo, through bispecific antibodies and via a perforin-mediated mechanism.

LGL leukemia of T cell type. T cell LGL is characterized by the $CD3^+$ $CD57^+CD56^-$ immunophenotype and the clonal rearrangement of the $\alpha\beta$ or $\gamma\delta$ [128] TCR genes, which suggests that senescent cells have the potential anyway for neoplastic transformation, although the prognosis is usually excellent, with some cases of spontaneous remission. Kaplanski et al. [129] showed in 1992 that hypogammaglobulinemia observed in a patient may be related to a cytotoxic effect exerted on B lymphocytes by a $CD3^+CD8^+$ $CD57^+$ $CD16^-$ LGL proliferation.

PNH. The percentage of $CD8^+CD57^+$ T lymphocytes in PNH is similar to healthy controls, but most patients share at least one clonotype. The presence of T cell clones bearing a set of highly homologous TCR-β molecules in most patients with hemolytic PNH is consistent with an immune process driven by the same (or similar) antigen(s): probably a nonpeptide antigen, as patients sharing clonotypes do not all share identical HLA alleles. These data support the hypothesis that the expansion of the GPI blood-cell population in PNH is a result of selective damage to normal hematopoiesis, mediated by an autoimmune attack against a nonpeptide antigen(s) that could be the GPI anchor itself [130].

$CD57^+$ T LYMPHOCYTES IN ALLOGENEIC TRANSPLANTATION

Sabnani et al. [131] showed that 71% of cardiac transplant patients and 44% of renal transplant patients, without evidence of allograft rejection or a viral syndrome, have monoclonal expansion of $CD8^+CD57^+$ T lymphocytes.

Liver transplantation recipients receiving induction therapy with ATG showed persistently higher levels of $CD8^+CD57^+$ lymphocytes in the late postoperative phase than recipients not treated with ATG, which was not associated with any clinical effect [132]. The same effect was seen in pediatric renal transplant recipients [133].

CONCLUSIONS

Since its first description in 1981 [2], the CD57 glycoepitope has gained much interest in fields as different as the immunology of aging and chronic infectious diseases to immunooncology, with often-relevant clinical implications. We foresee that large screening of CD57$^+$ subpopulations in selected oncological cohorts could confirm their prognostic value, and hopefully, such measurements could be incorporated in predictive scores. Such scores could prove most useful in patients at high risk for opportunistic infections (such as hemato-oncological patients) and could guide decisionmaking, e.g., in discontinuation of antimicrobial prophylaxis or planning retreatment for consolidation chemotherapy [86, 87].

DISCLOSURE

We declare that we have no conflict of interest or funding source related to this manuscript.

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KEY WORDS:
LEU7 · cancer · autoimmunity · immune senescence