

論 文 要 旨

Reduced Tim-3 expression on human T-lymphotropic virus type I (HTLV-I) Tax-specific cytotoxic T lymphocytes in HTLV-I infection

〔 HTLV-I 感染症における HTLV-I Tax 特異的細胞傷害性 T リンパ球上の Tim-3 発現の低下 〕

ナシュワ ハゼイン アブデルバリー リスク

【Introduction and Objectives】

Human T-lymphotropic virus type I (HTLV-I) is a retrovirus that preferentially infects CD4⁺ lymphocytes in vivo. Although HTLV-I infection is life long, less than 1% of infected individuals develop HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a neurologic disease. HTLV-I proviral load and frequency of HTLV-I-specific CD8⁺ cytotoxic T lymphocytes (CTLs) are increased in the peripheral blood of patients with HAM/TSP as compared to asymptomatic carriers. Although increasing evidence supports the hypothesis that such a strong CTL response could certainly contribute to the control of viral replication and disease development, the exact pathogenic role of the CTL responses remains unclear. T-cell immunoglobulin and mucin domain-containing molecule-3 (Tim-3) and programmed cell death-1 (PD-1) are T-cell exhaustion molecules and it remains unclear whether CTL function is impaired in HAM/TSP patients. In this study, we investigated Tim-3 and PD-1 expression in HTLV-I infection. In particular, we studied HTLV-I-specific CTLs and their degranulation activity in HAM/TSP patients and asymptomatic carriers as well as the role of Tim-3 and PD-1 in regulating their function.

【Materials and Methods】

Using the PBMCs of 32 HAM/TSP patients, 31 asymptomatic carriers (ACs) and 11 healthy controls (HCs), by the flow cytometer, we detected:

- Tim-3 or PD-1 expression on CD3+CD4+, CD3+CD8+ and CD8+Tax tetramer+ cells.
- IFN- γ production in Tim-3+ and Tim-3- or in PD-1+ and PD-1- cells in both CD8+ and Tax tetramer+ cells.
- CTL cytolytic activity measured by CD107a degranulation assay in Tim-3+ and Tim-3- or in PD-1+ and PD-1- cells in Tax tetramer+ cells.
- Tim-3 or PD-1 expression on HTLV-I-infected CD4+ or CD8+ cells.

The quantitative PCR of HTLV-I proviral load for infected cases was done.

【Results】

- Low expression of Tim-3 on CD4+ and CD8+ T cells in HTLV-I infected individuals in comparison to

healthy controls.

- Low expression of Tim-3 on HTLV-I Tax-specific CTLs compared with CMV-specific CTLs in HTLV-I infection.
- There is no significant difference in frequency of Tim-3⁺ cells in HTLV-I Tax-specific CTLs in both HAM/TSP patients and asymptomatic carriers, although the mean fluorescence intensity (MFI) is higher in asymptomatic carriers than in HAM/TSP patients.
- There is no significant difference in PD-1 expression (neither frequency nor MFI) between HAM/TSP patients, asymptomatic carriers and healthy controls in either CD4⁺ or CD8⁺ cells.
- Significant higher expression of PD-1 on HTLV-I Tax-specific CTLs compared with CMV-specific CTLs in HAM/TSP patients, and on Tax-specific CTLs in asymptomatic carriers than in HAM/TSP patients.
- Reduced IFN- γ production and cytolytic activity (CD107a expression) in Tim-3⁺, but not PD-1⁺, HTLV-I Tax-specific CTLs.
- No difference in the expression of Tim-3 or cytolytic activity between Tax-specific CTLs of HAM/TSP patients or asymptomatic carriers.
- The frequencies of Tim-3⁺ or PD-1⁺ cells in Tax-specific CTLs did not correlate with HTLV-I proviral loads, duration of illness, disease activity, age of the patients or serum HTLV-1 antibody titer in HAM/TSP patients.
- Low expression of Tim-3 on CD4⁺ and CD8⁺ HTLV-I-infected cells. Low expression of PD-1 on CD8⁺ HTLV-I infected cells.

【Discussion and Conclusions】

The decreased expression of Tim-3 in HTLV-I infection is a marked contrast to other chronic viral infections such as HIV and HCV infection, where Tim-3 expression is increased in T cells, including the virus-specific CTLs. As our and others' results proved that Tim-3 identifies a subset of CTLs with impaired production of cytokines and cytolytic activity. It strongly suggests that the Th1/Tc1 immune response is not negatively regulated by Tim-3 in HTLV-I infection. Rather, immune cells such as HTLV-I-specific CTLs may be resistant to cell death through the Tim-3/galectin-9 pathway. IFN- γ production was higher in CD8⁺ cells and HTLV-I Tax-specific CTLs that expressed PD-1, which also show higher CD107a expression as compared to their PD-1-counterparts in HAM/TSP patients. These results indicate that PD-1⁺ HTLV-I Tax-specific CTLs are capable of producing proinflammatory cytokines and have high cytolytic activity during HTLV-I infection. These results suggest that PD-1 and Tim-3 may have a distinct function in regulating immune responses in HTLV-1 infection. Tim-3 and CD107a expression in HTLV-I Tax-specific CTLs are not significantly different between HAM/TSP patients and asymptomatic carriers. Therefore, we concluded that Tim-3, but not PD-1, expression is reduced in HTLV-I infection and that the expression levels on HTLV-I Tax-specific CTLs are not different between HAM/TSP patients and HTLV-I carries. These results suggest that HTLV-I Tax-specific CTLs preserve their cytolytic activity, thereby controlling viral replication.