In vivo loss of PD-1 accelerates neoplastic and inflammatory diseases induced by HTLV-1 bZIP factor

Sonoda M[1], Yasunaga J[1], Shichijo T[1], Toyoda K[1], Higuchi Y[1], Inoue Y[1], Nosaka K[1], Murata M[3,4], Akari H[3,4], Nakashima K[2], Ohshima K[2], Matsuoka M[1]

[1]Hematology, Rheumatology and Infectious Diseases, Kumamoto University, Kumamoto, Japan
[2]Pathology, Kurume University School of Medicine, Kurume, Japan
[3]Center for Human Evolution Modeling Research, Primate Research Institute, Kyoto University
[4]Laboratory of Infectious Disease Model, Institute for Frontier Life and Medical Sciences, Kyoto University

Background:
Programmed cell death-1 (PD-1) is an inhibitory receptor that suppresses T-cell responses. Anti-PD-1 drugs show antitumor activity by activating host immune responses against tumor cells. In ATL, leukemic cells have a high immunogenicity and often increase the expression of PD-L1, so anti-PD-1 therapy has been expected to be effective. In the clinical trial of an anti-PD-1 antibody nivolumab for ATL conducted in the U.S., however, all three patients who received nivolumab showed rapid progression of the disease. Thus, the exact roles of PD-1 in ATL cells remains unclear.

Methods:
Previously, we have shown that transgenic expression of HBZ in CD4+ T cells induced T-cell lymphomas and systemic inflammation in mice. In this study, we generated HBZ-Tg/PD-1 (Pdcd1) KO mice and compared their phenotypes with those of HBZ-Tg mice. We also analyzed STLV-1 infected Japanese macaques that received administration of anti-PD-1 antibody.

Results:
Up to 24 weeks old, the frequency of dermatitis in HBZ-Tg/Pdcd1 KO mice was higher than HBZ-Tg mice. Histopathological analysis revealed that 63% of HBZ-Tg/Pdcd1 KO mice had lymphomas at 24 weeks of age compared with 33% in HBZ-Tg mice. In addition, flow cytometric analyses showed that the percentages of Foxp3 positive T cells and Ki67 positive T cells were higher in the spleen of HBZ-Tg/Pdcd1 KO mice than that of HBZ-Tg mice. RNA-seq analysis revealed that the pathways involved in inflammatory response and cell proliferation were differentially activated in CD4+ T cells of HBZ-Tg/Pdcd1 KO mice. Additionally, the administration of anti-PD-1 antibody to STLV-1 infected Japanese macaques partly increased the proviral load.

Conclusion:
These results indicate that loss of PD-1 accelerates the development of the inflammation and lymphomagenesis caused by HBZ in vivo, suggesting suppressive roles of PD-1 in the pathogenesis of HTLV-1.

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