produced by stimulation of T cells, indicating that activation domain of HBZ plays an important role in suppression of AP-1 signaling.

The immune deficiency observed in ATL patients is one of the major factors in their poor prognosis. The mechanisms of HTLV-1–associated oncogenesis have been extensively investigated, yet there are only a limited number of reports regarding HTLV-1-related immune deficiency. Our results contribute to the understanding of this phenomenon by identifying a new mechanism of HTLV-1–induced immunodeficiency.

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Authorship

Contribution: K.S., Y.S., J.Y., H.H., M. Mitsuyama, and M. Matsuoka conceived and designed the experiments; K.S., Y.S., and K.O. performed the experiments; K.S., Y.S., J.Y., H.H., K.O., M. Mitsuyama, and M. Matsuoka analyzed the data; A.U. and M. Mitsuyama contributed reagents/materials/analysis tools; and K.S., Y.S., J.Y., M. Mitsuyama, and M. Matsuoka wrote the paper.

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References

1. Matsuoka M, Jeang KT. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. *Nat Rev Cancer.* 2007;7(4):270-280.
2. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. *Blood.* 1977; 50(3):481-492.
3. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci U S A.* 1980; 77(12):7415-7419.
4. Hinuma Y, Nagata K, Hanaoka M, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc Natl Acad Sci U S A.* 1981;78(10): 6476-6480.
5. Gessain A, Barin F, Vernant JC, et al. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet.* 1985; 2(8452):407-410.
6. Osame M, Usuku K, Izumo S, et al. HTLV-I associated myelopathy, a new clinical entity. *Lancet.* 1986;1(8488):1031-1032.
7. Sugimoto M, Nakashima H, Watanabe S, et al. T-lymphocyte alveolitis in HTLV-I-associated myelopathy. *Lancet.* 1987;2(8569):1220.
8. Takatsuki K, Matsuoka M, Yamaguchi K. ATL and HTLV-I-related diseases. In: Takatsuki K, ed. *Adult T-Cell Leukemia.* New York: Oxford University Press; 1994:1-27.
9. Cavrois M, Leclercq I, Gout O, Gessain A, Wain-Hobson S, Wattel E. Persistent oligoclonal expansion of human T-cell leukemia virus type 1-infected circulating cells in patients with tropical spastic paraparesis/HTLV-1-associated myelopathy. *Oncogene.* 1998;17(1):77-82.
10. Etoh K, Tamiya S, Yamaguchi K, et al. Persistent clonal proliferation of human T-lymphotropic virus type I-infected cells in vivo. *Cancer Res.* 1997; 57(21):4862-4867.
11. Nicot C, Harrod RL, Ciminale V, Franchini G. Human T-cell leukemia/lymphoma virus type 1 nonstructural genes and their functions. *Oncogene.* 2005;24(39):6026-6034.
12. Gaudray G, Gachon F, Basbous J, Biard-Piechaczyk M, Devaux C, Mesnard JM. The complementary strand of the human T-cell leukemia virus type 1 RNA genome encodes a bZIP transcription factor that down-regulates viral transcription. *J Virol.* 2002;76(24):12813-12822.
13. Satou Y, Yasunaga J, Yoshida M, Matsuoka M. HTLV-I basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells. *Proc Natl Acad Sci U S A.* 2006;103(3):720-725.
14. Cavanagh MH, Landry S, Audet B, et al. HTLV-I antisense transcripts initiating in the 3′LTR are alternatively spliced and polyadenylated. *Retrovirology.* 2006;3:15.
15. Usui T, Yanagihara K, Tsukasaki K, et al. Characteristic expression of HTLV-1 basic zipper factor (HBZ) transcripts in HTLV-1 provirus-positive cells. *Retrovirology.* 2008;5:34.
16. Yoshida M, Satou Y, Yasunaga J, Fujisawa J, Matsuoka M. Transcriptional control of spliced and unspliced human T-cell leukemia virus type 1 bZIP factor (HBZ) gene. *J Virol.* 2008;82(19): 9359-9368.
17. Satou Y, Yasunaga J, Zhao T, et al. HTLV-1 bZIP factor induces T-cell lymphoma and systemic inflammation in vivo. *PLoS Pathog.* 2011;7(2): e1001274.
18. Zhao T, Yasunaga J, Satou Y, et al. Human T-cell leukemia virus type 1 bZIP factor selectively suppresses the classical pathway of NF-kappaB. *Blood.* 2009;113(12):2755-2764.
19. Basbous J, Arpin C, Gaudray G, Piechaczyk M, Devaux C, Mesnard JM. The HBZ factor of human T-cell leukemia virus type I dimerizes with transcription factors JunB and c-Jun and modulates their transcriptional activity. *J Biol Chem.* 2003;278(44):43620-43627.
20. Milligan GN, Bernstein DI, Bourne N. T lymphocytes are required for protection of the vaginal mucosae and sensory ganglia of immune mice against reinfection with herpes simplex virus type 2. *J Immunol.* 1998;160(12):6093-6100.
21. Iijima N, Linehan MM, Zamora M, et al. Dendritic cells and B cells maximize mucosal Th1 memory response to herpes simplex virus. *J Exp Med.* 2008;205(13):3041-3052.
22. Magee DM, Wing EJ. Cloned L3T4+ T lymphocytes protect mice against *Listeria monocytogenes* by secreting IFN-gamma. *J Immunol.* 1988;141(9):3203-3207.
23. Yang J, Kawamura I, Mitsuyama M. Requirement of the initial production of gamma interferon in the generation of protective immunity of mice against *Listeria monocytogenes*. *Infect Immun.* 1997; 65(1):72-77.
24. Iwamasa T, Utsumi Y, Sakuda H, et al. Two cases of necrotizing myelopathy associated with malignancy caused by herpes simplex virus type 2. *Acta Neuropathol.* 1989;78(3):252-257.
25. Ikehara O, Endo K, Hakamada K. Listeriosis in hematological malignancies: report of two cases. *Jpn J Clin Oncol.* 1989;19(2):159-162.
26. Suzutani T, Machida H, Sakuma T, Azuma M. Effects of various nucleosides on antiviral activity and metabolism of 1-beta-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil against herpes simplex virus types 1 and 2. *Antimicrob Agents Chemother.* 1988;32(10):1547-1551.
27. Hara H, Kawamura I, Nomura T, Tominaga T, Tsuchiya K, Mitsuyama M. Cytolysin-dependent escape of the bacterium from the phagosome is required but not sufficient for induction of the Th1 immune response against *Listeria monocytogenes* infection: distinct role of Listeriolysin O determined by cytolysin gene replacement. *Infect Immun.* 2007;75(8):3791-3801.
28. Fan J, Kodama E, Koh Y, Nakao M, Matsuoka M. Halogenated thymidine analogues restore the expression of silenced genes without demethylation. *Cancer Res.* 2005;65(15):6927-6933.
29. Iwasaki A. Antiviral immune responses in the genital tract: clues for vaccines. *Nat Rev Immunol.* 2010;10(10):699-711.
30. Kaushic C, Ashkar AA, Reid LA, Rosenthal KL. Progesterone increases susceptibility and decreases immune responses to genital herpes infection. *J Virol.* 2003;77(8):4558-4565.
31. Unanue ER. Studies in listeriosis show the strong symbiosis between the innate cellular system and the T-cell response. *Immunol Rev.* 1997;158:11-25.
32. Ladel CH, Flesch IE, Arnoldi J, Kaufmann SH. Studies with MHC-deficient knock-out mice reveal impact of both MHC I- and MHC II-dependent T cell responses on *Listeria monocytogenes* infection. *J Immunol.* 1994;153(7):3116-3122.
33. Bettelli E, Dastrange M, Oukka M. Foxp3 interacts with nuclear factor of activated T cells and NF-kappa B to repress cytokine gene expression and effector functions of T helper cells. *Proc Natl Acad Sci U S A.* 2005;102(14):5138-5143.
34. Nakanishi K. Innate and acquired activation pathways in T cells. *Nat Immunol.* 2001;2(2):140-142.
35. Brown DA, Nelson FB, Reinherz EL, Diamond DJ. The human interferon-gamma gene contains an inducible promoter that can be transactivated by tax I and II. *Eur J Immunol.* 1991;21(8):1879-1885.
36. Hall WW, Fujii M. Deregulation of cell-signaling pathways in HTLV-1 infection. *Oncogene.* 2005; 24(39):5965-5975.
37. Matsumoto J, Ohshima T, Isono O, Shimotohno K. HTLV-1 HBZ suppresses AP-1 activity by impairing

both the DNA-binding ability and the stability of c-Jun protein. *Oncogene.* 2005;24(6):1001-1010.

38. Rouse BT, Sehrawat S. Immunity and immunopathology to viruses: what decides the outcome? *Nat Rev Immunol.* 2010;10(7):514-526.
39. Johnson JM, Nicot C, Fullen J, et al. Free major histocompatibility complex class I heavy chain is preferentially targeted for degradation by human T-cell leukemia/lymphotropic virus type 1 p12(I) protein. *J Virol.* 2001;75(13):6086-6094.
40. Sundstrom S, Ota S, Dimberg LY, Masucci MG, Bergqvist A. Hepatitis C virus core protein induces an anergic state characterized by decreased interleukin-2 production and perturbation of mitogen-activated protein kinase responses. *J Virol.* 2005;79(4):2230-2239.
41. Myskiw C, Arsenio J, van Bruggen R, Deschambault Y, Cao J. Vaccinia virus E3 suppresses expression of diverse cytokines through inhibition of the PKR, NF-kappaB, and IRF3 pathways. *J Virol.* 2009;83(13):6757-6768.
42. Li JC, Au KY, Fang JW, et al. HIV-1 trans-activator protein dysregulates IFN-gamma signaling and contributes to the suppression of autophagy induction. *AIDS.* 2011;25(1):15-25.
43. Li-Weber M, Krammer PH. Regulation of IL4 gene expression by T cells and therapeutic perspectives. *Nat Rev Immunol.* 2003;3(7):534-543.
44. Matsuoka M. HTLV-1 bZIP factor gene: its roles in HTLV-1 pathogenesis. *Mol Aspects Med.* 2010; 31(5):359-366.
45. Belkaid Y, Piccirillo CA, Mendez S, Shevach EM, Sacks DL. CD4+CD25+ regulatory T cells control Leishmania major persistence and immunity. *Nature.* 2002;420(6915):502-507.
46. Kursar M, Bonhagen K, Fensterle J, et al. Regulatory CD4+CD25+ T cells restrict memory CD8+ T cell responses. *J Exp Med.* 2002; 196(12):1585-1592.
47. Billiau A, Matthys P. Interferon-gamma: a historical perspective. *Cytokine Growth Factor Rev.* 2009;20(2):97-113.
48. Ungar BL, Kao TC, Burris JA, Finkelman FD. Cryptosporidium infection in an adult mouse model. Independent roles for IFN-gamma and CD4+ T lymphocytes in protective immunity. *J Immunol.* 1991;147(3):1014-1022.
49. Cenci E, Mencacci A, Del Sero G, et al. IFN-gamma is required for IL-12 responsiveness in mice with *Candida albicans* infection. *J Immunol.* 1998;161(7):3543-3550.
50. Sun JC, Bevan MJ. Defective CD8 T cell memory following acute infection without CD4 T cell help. *Science.* 2003;300(5617):339-342.