is associated with the progression of adult T-cell leukemia. *Cancer Sci.* 98, 240–245

Sagara, Y., Inoue, Y., Sagara, Y., and Kashiwagi, S. (2009). Involvement of molecular mimicry between human T-cell leukemia virus type 1 gp46 and osteoprotegerin in induction of hypercalcemia. *Cancer Sci.* 100, 490–496.

Saitoh, Y., Yamamoto, N., Dewan, M. Z., Sugimoto, H., Martinez Bruyn, V. J., Iwasaki, Y., Matsubara, K., Qi, X., Saitoh, T., Imoto, I., Inazawa, J., Utsunomiya, A., Watanabe, T., Masuda, T., Yamamoto, N., and Yamaoka, S. (2008). Overexpressed NF-kappaB-inducing kinase contributes to the tumorigenesis of adult T-cell leukemia and Hodgkin Reed-Sternberg cells. *Blood* 111, 5118–5129.

Sakashita, A., Hattori, T., Miller, C. W., Suzushima, H., Asou, N., Takatsuki, K., and Koeffler, H. P. (1992). Mutations of the p53 gene in adult T-cell leukemia. *Blood* 79, 477–480.

Sanda, T., Asamitsu, K., Ogura, H., Iida, S., Utsunomiya, A., Ueda, R., and Okamoto, T. (2006). Induction of cell death in adult T-cell leukemia cells by a novel IkappaB kinase inhibitor. *Leukemia* 20, 590–598.

Sasaki, D., Imaizumi, Y., Hasegawa, H., Osaka, A., Tsukasaki, K., Choi, Y. L., Mano, H., Marquez, V. E., Hayashi, T., Yanagihara, K., Moriwaki, Y., Miyazaki, Y., Kamihira, S., and Yamada, Y. (2011). Overexpression of enhancer of zeste homolog 2 with trimethylation of lysine 27 on histone H3 in adult T-cell leukemia/lymphoma as a target for epigenetic therapy. *Haematologica* 96, 712–719.

Sasaki, H., Nishikata, I., Shiraga, T., Akamatsu, E., Fukami, T., Hidaka, T., Kubuki, Y., Okayama, A., Hamada, K., Okabe, H., Murakami, Y., Tsubouchi, H., and Morishita, K. (2005). Overexpression of a cell adhesion molecule, TSLC1, as a possible molecular marker for acute-type adult T-cell leukemia. *Blood* 105, 1204–1213.

Satou, Y., Nosaka, K., Koya, Y., Yasunaga, J. I., Toyokuni, S., and Matsuoka, M. (2004). Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both in vivo and in vitro. *Leukemia* 18, 1357–1363.

Satou, Y., Yasunaga, J., Yoshida, M., and Matsuoka, M. (2006). HTLV-I basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells. *Proc. Natl. Acad. Sci. U.S.A.* 103, 720–705.

Satou, Y., Yasunaga, J., Zhao, T., Yoshida, M., Miyazato, P., Takai, K., Shimizu, K., Ohshima, K., Green, P. L., Ohkura, N., Yamaguchi, T., Ono, M., Sakaguchi, S., and Matsuoka, M. (2011). HTLV-1 bZIP factor induces T-cell lymphoma and systemic inflammation in vivo. *PLoS Pathog.* 7, e1001274. doi:10.1371/journal.ppat.1001274

Schmitt, I., Rosin, O., Rohwer, P., Gossen, M., and Grassmann, R. (1998). Stimulation of cyclin-dependent kinase activity and G1- to S-phase transition in human lymphocytes by the human T-cell leukemia/lymphotropic virus type 1 Tax protein. *J. Virol.* 72, 633–640.

Schuettengruber, B., Chourrout, D., Vervoort, M., Leblanc, B., and Cavalli, G. (2007). Genome regulation by polycomb and trithorax proteins. *Cell* 128, 735–745.

Shembade, N., Pujari, R., Harhaj, N. S., Abbott, D. W., and Harhaj, E. W. (2011). The kinase IKKα inhibits activation of the transcription factor NF-κB by phosphorylating the regulatory molecule TAX1BP1. *Nat. Immunol.* 12, 834–843.

Simonis, N., Rual, J. F., Lemmens, I., Boxus, M., Hirozane-Kishikawa, T., Gatot, J. S., Dricot, A., Hao, T., Vertommen, D., Legros, S., Daakour, S., Klitgord, N., Martin, M., Willaert, J. F., Dequiedt, F., Navratil, V., Cusick, M. E., Burny, A., Van Lint, C., Hill, D. E., Tavernier, J., Kettmann, R., Vidal, M., and Twizere, J. C. (2012). Host-pathogen interactome mapping for HTLV-1 and -2 retroviruses. *Retrovirology* 9, 26.

Sparmann, A., and van Lohuizen, M. (2006). Polycomb silencers control cell fate, development and cancer. *Nat. Rev. Cancer* 6, 846–856.

Spiegel, S., Milstien, S., and Grant, S. (2012). Endogenous modulators and pharmacological inhibitors of histone deacetylases in cancer therapy. *Oncogene* 31, 537–551.

Sun, S. C., and Yamaoka, S. (2005). Activation of NF-kappaB by HTLV-I and implications for cell transformation. *Oncogene* 24, 5952–5964.

Suzuki, T., Kitao, S., Matsushime, H., and Yoshida, M. (1996). Tax protein interacts with cyclin-dependent kinase inhibitor p16INK4A and counteracts its inhibitory activity towards CDK4. *EMBO J.* 15, 1607–1614.

Suzuki, T., Narita, T., Uchida-Toita, M., and Yoshida, M. (1999). Down-regulation of the INK4 family of cyclin-dependent kinase inhibitors by tax protein of HTLV-1 through two distinct mechanisms. *Virology* 259, 384–391.

Tagawa, H., Miura, I., Suzuki, R., Suzuki, H., Hosokawa, Y., and Seto, M. (2002). Molecular cytogenetic analysis of the breakpoint region at 6q21-22 in T-cell lymphoma/leukemia cell lines. *Genes Chromosomes Cancer* 34, 175–185.

Takaori-Kondo, A., Imada, K., Yamamoto, I., Kunitomi, A., Numata, Y., Sawada, H., and Uchiyama, T. (1998). Parathyroid hormone-related protein-induced hypercalcemia in SCID mice engrafted with adult T-cell leukemia cells. *Blood* 91, 4747–4751.

Takemoto, S., Mulloy, J. C., Cereseto, A., Migone, T. S., Patel, B. K., Matsuoka, M., Yamaguchi, K., Takatsuki, K., Kamihira, S., White, J. D., Leonard, W. J., Waldmann, T., and Franchini, G. (1997). Proliferation of adult T cell leukemia/lymphoma cells is associated with the constitutive activation of JAK/STAT proteins. *Proc. Natl. Acad. Sci. U.S.A.* 94, 13897–13902.

Tamiya, S., Etoh, K., Suzushima, H., Takatsuki, K., and Matsuoka, M. (1998). Mutation of CD95 (Fas/Apo-1) gene in adult T-cell leukemia cells. *Blood* 91, 3935–3942.

Tamiya, S., Matsuoka, M., Etoh, K., Watanabe, T., Kamihira, S., Yamaguchi, K., and Takatsuki, K. (1996). Two types of defective human T-lymphotropic virus type I provirus in adult T-cell leukemia. *Blood* 88, 3065–3073.

Taniguchi, A., Nemoto, Y., Yokoyama, A., Kotani, N., Imai, S., Shuin, T., and Daibata, M. (2008). Promoter methylation of the bone morphogenetic protein-6 gene in association with adult T-cell leukemia. *Int. J. Cancer* 123, 1824–1831.

Taniguchi, Y., Nosaka, K., Yasunaga, J., Maeda, M., Mueller, N., Okayama, A., and Matsuoka, M. (2005). Silencing of human T-cell leukemia virus type I gene transcription by epigenetic mechanisms. *Retrovirology* 2, 64.

Tawara, M., Hogerzeil, S. J., Yamada, Y., Takasaki, Y., Soda, H., Hasegawa, H., Murata, K., Ikeda, S., Imaizumi, Y., Sugahara, K., Tsuruda, K., Tsukasaki, K., Tomonaga, M., Hirakata, Y., and Kamihira, S. (2006). Impact of p53 aberration on the progression of adult T-cell leukemia/lymphoma. *Cancer Lett.* 234, 249–255.

Thu, Y. M., and Richmond, A. (2010). NF-kappaB inducing kinase: a key regulator in the immune system and in cancer. *Cytokine Growth Factor Rev.* 21, 213–226.

Tian, Y., Kobayashi, S., Ohno, N., Isobe, M., Tsuda, M., Zaike, Y., Watanabe, N., Tani, K., Tojo, A., and Uchimaru, K. (2011). Leukemic T cells are specifically enriched in a unique CD3(dim) CD7(low) subpopulation of CD4(+) T cells in acute-type adult T-cell leukemia. *Cancer Sci.* 102, 569–577.

Tsuchiya, T., Tamura, G., Sato, K., Endoh, Y., Sakata, K., Jin, Z., Motoyama, T., Usuba, O., Kimura, W., Nishizuka, S., Wilson, K. T., James, S. P., Yin, J., Fleisher, A. S., Zou, T., Silverberg, S. G., Kong, D., and Meltzer, S. J. (2000). Distinct methylation patterns of two APC gene promoters in normal and cancerous gastric epithelia. *Oncogene* 19, 3642–3646.

Tsukasaki, K., Krebs, J., Nagai, K., Tomonaga, M., Koeffler, H. P., Bartram, C. R., and Jauch, A. (2001a). Comparative genomic hybridization analysis in adult T-cell leukemia/lymphoma: correlation with clinical course. *Blood* 97, 3875–3881.

Tsukasaki, K., Miller, C. W., Kubota, T., Takeuchi, S., Fujimoto, T., Ikeda, S., Tomonaga, M., and Koeffler, H. P. (2001b). Tumor necrosis factor alpha polymorphism associated with increased susceptibility to development of adult T-cell leukemia/lymphoma in human T-lymphotropic virus type 1 carriers. *Cancer Res.* 61, 3770–3774.

Tsukasaki, K., Tanosaki, S., DeVos, S., Hofmann, W. K., Wachsman, W., Gombart, A. F., Krebs, J., Jauch, A., Bartram, C. R., Nagai, K., Tomonaga, M., Said, J. W., and Koeffler, H. P. (2004). Identifying progression-associated genes in adult T-cell leukemia/lymphoma by using oligonucleotide microarrays. *Int. J. Cancer* 109, 875–881.

Twizere, J. C., Springael, J. Y., Boxus, M., Burny, A., Dequiedt, F., Dewulf, J. F., Duchateau, J., Portetelle, D., Urbain, P., Van Lint, C., Green, P. L., Mahieux, R., Parmentier, M., Willems, L., and Kettmann, R. (2007). Human T-cell leukemia virus type-1 Tax oncoprotein regulates G-protein signaling. *Blood* 109, 1051–1060.

Uchida, T., Kinoshita, T., Watanabe, T., Nagai, H., Murate, T., Saito, H., and Hotta, T. (1996). The CDKN2 gene alterations in various types of adult T-cell leukaemia. *Br. J. Haematol.* 94, 665–670.

Uota, S., Zahidunnabi Dewan, M., Saitoh, Y., Muto, S., Itai, A., Utsunomiya, A., Watanabe, T., Yamamoto, N., and Yamaoka, S. (2012). An IκB kinase 2 inhibitor

IMD-0354 suppresses the survival of adult T-cell leukemia cells. *Cancer Sci.* 103, 100–106.

Uribesalgo, I., Ballaré, C., and Di Croce, L. (2012). Polycomb regulates NF-κB signaling in cancer through miRNA. *Cancer Cell* 21, 5–7.

Valastyan, S., Reinhardt, F., Benaich, N., Calogrias, D., Szász, A. M., Wang, Z. C., Brock, J. E., Richardson, A. L., and Weinberg, R. A. (2009). A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. *Cell* 137, 1032–1046.

Villiger, P. M., Cronin, M. T., Amenomori, T., Wachsman, W., and Lotz, M. (1991). IL-6 production by human T lymphocytes. Expression in HTLV-1-infected but not in normal T cells. *J. Immunol.* 146, 550–559.

Wäldele, K., Schneider, G., Ruckes, T., and Grassmann, R. (2004). Interleukin-13 overexpression by tax transactivation: a potential autocrine stimulus in human T-cell leukemia virus-infected lymphocytes. *J. Virol.* 78, 6081–6090.

Wano, Y., Hattori, T., Matsuoka, M., Takatsuki, K., Chua, A. O., Gubler, U., and Greene, W. C. (1987). Interleukin 1 gene expression in adult T cell leukemia. *J. Clin. Invest.* 80, 911–916.

Watanabe, M., Nakahata, S., Hamasaki, M., Saito, Y., Kawano, Y., Hidaka, T., Yamashita, K., Umeki, K., Taki, T., Taniwaki, M., Okayama, A., and Morishita, K. (2010). Down-regulation of CDKN1A in adult T-cell leukemia/lymphoma despite overexpression of CDKN1A in human T-lymphotropic virus 1-infected cell lines. *J. Virol.* 84, 6966–6977.

Watanabe, M., Ohsugi, T., Shoda, M., Ishida, T., Aizawa, S., Maruyama-Nagai, M., Utsunomiya, A., Koga, S., Yamada, Y., Kamihira, S., Okayama, A., Kikuchi, H., Uozumi, K., Yamaguchi, K., Higashihara, M., Umezawa, K., Watanabe, T., and Horie, R. (2005). Dual targeting of transformed and untransformed HTLV-1-infected T cells by DHMEQ, a potent and selective inhibitor of NF-kappaB, as a strategy for chemoprevention and therapy of adult T-cell leukemia. *Blood* 106, 2462–2471.

Watanabe, T., Yamaguchi, K., Takatsuki, K., Osame, M., and Yoshida, M. (1990). Constitutive expression of parathyroid hormone-related protein gene in human T cell leukemia virus type 1 (HTLV-1) carriers and adult T cell leukemia patients that can be trans-activated by HTLV-1 tax gene. *J. Exp. Med.* 172, 759–765.

Watters, K. M., Dean, J., Hasegawa, H., Sawa, H., Hall, W., and Sheehy, N. (2010). Cytokine and growth factor expression by HTLV-1 Lck-Tax transgenic cells in SCID mice. *AIDS Res. Hum. Retroviruses* 26, 593–603.

Wu, K., Bottazzi, M. E., de la Fuente, C., Deng, L., Gitlin, S. D., Maddukuri, A., Dadgar, S., Li, H., Vertes, A., Pumfery, A., and Kashanchi, F. (2004). Protein profile of tax-associated complexes. *J. Biol. Chem.* 279, 495–508.

Yamada, Y., Hatta, Y., Murata, K., Sugawara, K., Ikeda, S., Mine, M., Maeda, T., Hirakata, Y., Kamihira, S., Tsukasaki, K., Ogawa, S., Hirai, H., Koeffler, H. P., and Tomonaga, M. (1997). Deletions of p15 and/or p16 genes as a poor-prognosis factor in adult T-cell leukemia. *J. Clin. Oncol.* 15, 1778–1785.

Yamada, Y., Ohmoto, Y., Hata, T., Yamamura, M., Murata, K., Tsukasaki, K., Kohno, T., Chen, Y., Kamihira, S., and Tomonaga, M. (1996). Features of the cytokines secreted by adult T cell leukemia (ATL) cells. *Leuk. Lymphoma* 21, 443–447.

Yamada, Y., Tomonaga, M., Fukuda, H., Hanada, S., Utsunomiya, A., Tara, M., Sano, M., Ikeda, S., Takatsuki, K., Kozuru, M., Araki, K., Kawano, F., Niimi, M., Tobinai, K., Hotta, T., and Shimoyama, M. (2001). A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukaemia-lymphoma: Japan Clinical Oncology Group Study 9303. *Br. J. Haematol.* 113, 375–382.

Yamagishi, M., Nakano, K., Miyake, A., Yamochi, T., Kagami, Y., Tsutsumi, A., Matsuda, Y., Sato-Otsubo, A., Muto, S., Utsunomiya, A., Yamaguchi, K., Uchimaru, K., Ogawa, S., and Watanabe, T. (2012). Polycomb-mediated loss of miR-31 activates NIK-dependent NF-κB pathway in adult T cell leukemia and other cancers. *Cancer Cell* 21, 121–135.

Yamaguchi, K., Kiyokawa, T., Watanabe, T., Ideta, T., Asayama, K., Mochizuki, M., Blank, A., and Takatsuki, K. (1994). Increased serum levels of C-terminal parathyroid hormone-related protein in different diseases associated with HTLV-1 infection. *Leukemia* 8, 1708–1711.

Yamaguchi, K., and Watanabe, T. (2002). Human T lymphotropic virus type-I and adult T-cell leukemia in Japan. *Int. J. Hematol.* 76, 240–245.

Yamamoto, K., Ishida, T., Nakano, K., Yamagishi, M., Yamochi, T., Tanaka, Y., Furukawa, Y., Nakamura, Y., and Watanabe, T. (2011). SMYD3 interacts with HTLV-1 Tax and regulates subcellular localization of Tax. *Cancer Sci.* 102, 260–266.

Yamamoto, M., Ito, T., Shimizu, T., Ishida, T., Semba, K., Watanabe, S., Yamaguchi, N., and Inoue, J. I. (2010). Epigenetic alteration of the NF-kappaB-inducing kinase (NIK) gene is involved in enhanced NIK expression in basal-like breast cancer. *Cancer Sci.* 101, 2391–2397.

Yamazaki, J., Mizukami, T., Takizawa, K., Kuramitsu, M., Momose, H., Masumi, A., Ami, Y., Hasegawa, H., Hall, W. W., Tsujimoto, H., Hamaguchi, I., and Yamaguchi, K. (2009). Identification of cancer stem cells in a Tax-transgenic (Tax-Tg) mouse model of adult T-cell leukemia/lymphoma. *Blood* 114, 2709–2720.

Yang, J., Ikezoe, T., Nishioka, C., Furihata, M., and Yokoyama, A. (2010). AZ960, a novel Jak2 inhibitor, induces growth arrest and apoptosis in adult T-cell leukemia cells. *Mol. Cancer Ther.* 9, 3386–3395.

Yang, Y., Takeuchi, S., Tsukasaki, K., Yamada, Y., Hata, T., Mori, N., Fukushima, A., Seo, H., and Koeffler, H. P., and Taguchi, H. (2005). Methylation analysis of the adenomatous polyposis coli (APC) gene in adult T-cell leukemia/lymphoma. *Leuk. Res.* 29, 47–51.

Yashiki, S., Fujiyoshi, T., Arima, N., Osame, M., Yoshinaga, M., Nagata, Y., Tara, M., Nomura, K., Utsunomiya, A., Hanada, S., Tajima, K., and Sonoda, S. (2001). HLA-A*26, HLAB* 4002, HLA-B*4006, and HLA-B*4801 alleles predispose to adult T cell leukemia: the limited recognition of HTLV type 1 tax peptide anchor motifs and epitopes to generate anti-HTLV type 1 tax CD8(+) cytotoxic T lymphocytes. *AIDS Res. Hum. Retroviruses* 17, 1047–1061.

Yasunaga, J., Lin, F. C., Lu, X., and Jeang, K. T. (2011). Ubiquitin-specific peptidase 20 targets TRAF6 and human T cell leukemia virus type 1 tax to negatively regulate NF-kappaB signaling. *J. Virol.* 85, 6212–6219.

Yasunaga, J., Taniguchi, Y., Nosaka, K., Yoshida, M., Satou, Y., Sakai, T., Mitsuya, H., and Matsuoka, M. (2004). Identification of aberrantly methylated genes in association with adult T-cell leukemia. *Cancer Res.* 64, 6002–6009.

Yeung, M. L., Yasunaga, J., Bennasser, Y., Dusetti, N., Harris, D., Ahmad, N., Matsuoka, M., and Jeang, K. T. (2008). Roles for microRNAs, miR-93 and miR-130b, and tumor protein 53-induced nuclear protein 1 tumor suppressor in cell growth dysregulation by human T-cell lymphotrophic virus 1. *Cancer Res.* 68, 8976–8985.

Yi, B., Williams, P. J., Niewolna, M., Wang, Y., and Yoneda, T. (2002). Tumor-derived platelet-derived growth factor-BB plays a critical role in osteosclerotic bone metastasis in an animal model of human breast cancer. *Cancer Res.* 62, 917–923.

Yoshida, M., Nosaka, K., Yasunaga, J., Nishikata, I., Morishita, K., and Matsuoka, M. (2004). Aberrant expression of the MEL1S gene identified in association with hypomethylation in adult T-cell leukemia cells. *Blood* 103, 2753–2760.

Yoshie, O., Fujisawa, R., Nakayama, T., Harasawa, H., Tago, H., Izawa, D., Hieshima, K., Tatsumi, Y., Matsushima, K., Hasegawa, H., Kanamaru, A., Kamihira, S., and Yamada, Y. (2002). Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. *Blood* 99, 1505–1511.

Zhao, T., Satou, Y., Sugata, K., Miyazato, P., Green, P. L., Imamura, T., and Matsuoka, M. (2011). HTLV-1 bZIP factor enhances TGF-β signaling through p300 coactivator. *Blood* 118, 1865–1876.

Zoncu, R., Efeyan, A., and Sabatini, D. M. (2011). mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev. Mol. Cell Biol.* 12, 21–35.

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 29 June 2012; accepted: 29 August 2012; published online: 17 September 2012.*

*Citation: Yamagishi M and Watanabe T (2012) Molecular hallmarks of adult T cell leukemia. Front. Microbio. 3:334. doi: 10.3389/fmicb.2012.00334*

*This article was submitted to Frontiers in Virology, a specialty of Frontiers in Microbiology.*

frontiers in
MICROBIOLOGY

REVIEW ARTICLE
published: 10 September 2012
doi: 10.3389/fmicb.2012.00322

# Adult T-cell leukemia: a review of epidemiological evidence

***Masako Iwanaga[1]*, Toshiki Watanabe[2] and Kazunari Yamaguchi[3]***

[1] *Graduate School of Public Health, Teikyo University, Tokyo, Japan*
[2] *Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan*
[3] *Department of Safety Research on Blood and Biologics, National Institute of Infectious Diseases, Tokyo, Japan*

***Edited by:***
*Renaud Mahieux, Ecole Normale Superieure de Lyon, France*

***Reviewed by:***
*Mirdad Kazanji, Institut Pasteur, France*
*Ali Bazarbachi, American University of Beirut, Lebanon*

***Correspondence:**
*Masako Iwanaga, Graduate School of Public Health, Teikyo University, 2-11-1 Kaga, Itabashi, Tokyo 173-8605, Japan.*
*e-mail: masakoiwng@gmail.com*

Adult T-cell leukemia (ATL) is an aggressive T-cell malignancy caused by human T-cell leukemia virus type I (HTLV-1) infection and often occurs in HTLV-1-endemic areas, such as southwestern Japan, the Caribbean islands, Central and South America, Intertropical Africa, and Middle East. To date, many epidemiological studies have been conducted to investigate the incidence of ATL among general population or HTLV-1 carriers and to identify a variety of laboratory, molecular, and host-specific markers to be possible predictive factors for developing ATL because HTLV-1 infection alone is not sufficient to develop ATL. This literature review focuses on the epidemiology of ATL and the risk factors for the development of ATL from HTLV-1 carriers, while keeping information on the epidemiology of HTLV-1 to a minimum. The main lines of epidemiological evidence are: (1) ATL occurs mostly in adults, at least 20–30 years after the HTLV-1 infection, (2) age at onset differs across geographic areas: the average age in the Central and South America (around 40 years old) is younger than that in Japan (around 60 years old), (3) ATL occurs in those infected in childhood, but seldom occurs in those infected in adulthood, (4) male carriers have about a three- to fivefold higher risk of developing ATL than female, (5) the estimated lifetime risk of developing ATL in HTLV-1 carriers is 6–7% for men and 2–3% for women in Japan, (6) a low anti-Tax reactivity, a high soluble interleukin-2 receptor level, a high anti-HTLV-1 titer, and high levels of circulating abnormal lymphocytes and white blood cell count are accepted risk factors for the development of ATL, and (7) a higher proviral load (more than 4 copies/100 peripheral blood mononuclear cells) is an independent risk factor for progression of ATL. Nevertheless, the current epidemiological evidence is insufficient to fully understand the oncogenesis of ATL. Further well-designed epidemiological studies are needed.

**Keywords: adult T-cell leukemia, ATL, epidemiology, human T-cell leukemia virus type I, HTLV-1**

## INTRODUCTION

Adult T-cell leukemia (ATL) was first reported as a distinct clinical entity in Japan in 1977 (Takatsuki et al., 1977; Uchiyama et al., 1977). The clustering of patients in the southwestern part of Japan propelled Japanese investigators to the interest that the disease could be virally induced. Subsequently, human T-cell leukemia virus type I (HTLV-1) was discovered as the causative virus for ATL (Poiesz et al., 1980; Yoshida et al., 1982). The discoveries of ATL and HTLV-1 ushered in the development of virology, oncology, molecular biology, epidemiology, and other fields of medicine.

The etiological association of HTLV-1 with ATL was established on the basis of the following findings: (1) all patients with ATL have antibodies against HTLV-1 (Hinuma et al., 1981; Hinuma et al., 1982), (2) geographical areas of high incidence of ATL patients correspond closely with those of high incidence of HTLV-1 carriers (The T- and B-Cell Malignancy Study Group, 1985), (3) HTLV-1 immortalizes human CD4 T cells *in vitro* (Hattori et al., 1981), and (4) monoclonal integration of HTLV-1 proviral DNA was demonstrated in ATL cells (Yamaguchi et al., 1984). Subsequently, the Japanese Lymphoma Study Group proposed the first diagnostic criteria for ATL in 1991, and the disease was classified into four clinical subtypes; acute, lymphoma, chronic, and smoldering (Shimoyama, 1991).

ATL patients have been reported mainly from HTLV-1-endemic areas. The global geographical distribution of HTLV-1 seropositive individuals has been well documented (Proietti et al., 2005). Areas with seroprevalence of more than 2% are recognized as high endemic regions (Gessain, 1996). The main endemic areas are Japan, the Caribbean islands, Central and South America, Central and South Africa, a part of the Middle East and Melanesia, and Aboriginal regions in Australia (IARC, 1996). Moreover, regional clustering of virus positivity and high incidence of ATL has been detected even within the endemic areas. The prevalence of HTLV-1 carriers in Europe, North America, China, and Korea is low (Proietti et al., 2005).

This literature review focuses on the epidemiology of ATL and the risk factors for the development of ATL from HTLV-1 carriers with asymptomatic status, while keeping information on the epidemiology of HTLV-1 to a minimum. A variety of study designs and settings, e.g., case series, nation wide surveys, and regional population-based studies using cancer registries were reported to assess incidence, prevalence, and other epidemiological

information on ATL from many countries, mostly from Japan. However, there have been few prospective cohort studies to assess reliable incidence rate of ATL. Readers should keep in mind that all epidemiological studies have individual limitations in the case accumulation and the population setting.

## INCIDENCE AND PREVALENCE

### JAPAN

In Japan, approximately one million individuals are carriers of HTLV-1 (Tajima, 1990; Satake et al., 2012). Both HTLV-1 and ATL have been shown to be endemic in southwest districts (Kyushu and Shikoku Islands; Tajima, 1990; Satake et al., 2012). Several epidemiological studies have been conducted to estimate annual incidence of ATL in HTLV-1 carriers or general population, but the exact annual incidence of ATL is still unclear. Most of the studies estimated the incidence of ATL just by merging the number of cases of ATL in one population to the number of people in another population such as demographic statistics, blood donors positive for HTLV-1, or an existing group of HTLV-1 carriers. Few prospective studies were conducted (**Table 1**).

Adult T-cell leukemia accounts for 51–59% of non-Hodgkin lymphoma (NHL) in HTLV-1 endemic areas in the Kyushu district, southwest Japan (Arisawa et al., 2000; Ohshima et al., 2002), which was extremely higher than that of nationwide data reporting that ATL accounts for 7.5% of all lymphomas (Lymphoma Study Group of Japanese Pathologists, 2000).

#### *Annual mortality of ATL*

Approximately 1,000 people die of ATL each year in Japan according to Japanese vital statistics data for 1998–2008 (Portal Site of Official Statistics of Japan, 2012; **Figure 1**). This indicates that infection with HTLV-1 was associated with approximately 1,000 deaths from ATL annually, with clustering in people aged over 50 years (Ikeda et al., 2012).

#### *Annual incidence of ATL in nationwide studies*

In the first nationwide hospital-based survey, 657 new cases of ATL were accumulated during 1986–1987, estimating the annual number of ATL in Japan to be approximately 700 cases (Tajima, 1990; Shimoyama, 1991). The new nationwide hospital-based survey was conducted recently, in which a total of 910 new cases of ATL were accumulated during 2006–2007, estimating the annual number of ATL in Japan to be approximately 1,000 cases (Yamada et al., 2011). In the new survey, two new findings were revealed in contrast to the first nationwide study. First, the age at diagnosis increased from a mean age of 52.7 years in the previous survey to 66.0 years in the new survey (**Figure 2**). Second, there were differences in the proportion of subtypes; the acute subtype accounted for the highest percentage (60.2%), followed by the lymphoma subtype (23.7%) in the previous survey, however, the percentage of the lymphoma subtype increased to 34.8%, contrary to the decrease in the acute subtype to be 46.7% in the new study. However, Takezaki et al. (1997) suggested that the annual incidence of ATL based on the nationwide hospital-based survey could be underestimated because approximately 65% of ATL cases might have been missed due to low response of the participating hospitals from endemic areas.

#### *Annual incidence of ATL in HTLV-1 endemic areas*

Results differ according to study methods and the HTLV-1 – positive rate of the study population. A series of cross-sectional survey for residents in Uwajima City (population size; 290, 464, HTLV-1-positive rate; 5.4% in men and 8.3% in women) reported that the annual incidence of ATL was estimated to be approximately 6.1 in adults aged over 30 years per 100,000 populations (Kondo et al., 1985, 1987, 1989). In another cross-sectional studies by the use of the regional cancer registry data in Nagasaki prefecture (an endemic area, the population size; 1.56 million), the age-standardized annual incidence rate of ATL (among 100,000 individuals aged 30 or older) was estimated to be 10.5 for men and 6.0 for women during 1985–1995 (Arisawa et al., 2000) and 8.7 for men and 5.5 for women during 1995–2004 (Arisawa et al., 2009). There was no significant decrease in the overall incidence rate between the two decades, however, age-specific incidence of ATL among those aged over 60 years increased significantly during 1995–2004 compared to the period of 1985–1995 (Arisawa et al., 2009).

#### *Incidence of ATL among HTLV-1 carriers*

In studies used blood donors seropositive for HTLV-1, the annual incidence of ATL was estimated to be approximately 60 per 100,000 HTLV-1 carriers over 20 years old in Japan (Tajima, 1990) or approximately 116 for men and 66 for women per 100,000 HTLV-1 carriers in Saga prefecture (an endemic area, the population size; 880,000; Tokudome et al., 1989). In a study used serological survey for residents in small cluster areas, The crude annual incidence of ATL was estimated to be 137.7 for men and 57.4 for women among 100,000 HTLV-1 carriers aged 30 years or older (Arisawa et al., 2000). Furthermore, in a study performed record linkage between the cancer registry and HTLV-1 carriers in hospital, the crude annual incidence of ATL was estimated to be 61 per 100,000 HTLV-1 carriers (Koga et al., 2010).

#### *Lifetime risk of ATL among HTLV-1 carriers*

For HTLV-1 carriers, the lifetime risk was estimated to be 4.5% for men and 2.6% for women in Saga prefecture (Tokudome et al., 1989), 6.6% for men and 2.1% for women in Nagasaki prefecture (Arisawa et al., 2000), 6.9% for men and 2.95% for women in Uwajima City (Kondo et al., 1989), and 7.29% for men and 3.78% for women in a hospital-based study (Koga et al., 2010).

In summary, in Japan, nearly 1,000 new cases of ATL are diagnosed and nearly 1,000 patients die of ATL each year over a period of 20 years. The annual incidence of ATL among HTLV-1 carriers is approximately 60 per 100,000 with the lifetime risk of 6–7% for men and 2–3% for women. The incidence was 1.35 times higher in men than in women, contrary to the higher HTLV-1-positive rate in women than in men. ATL occurs predominantly in elderly male carriers, and the mean age at diagnosis increased from the early 1950s in 1980 to the late 1960s recently. Most of Japanese epidemiological studies were population-based descriptive types using cancer registries, therefore those have limitations as follows; cases of smoldering ATL were excluded; hematological diagnoses were not performed. These limitations might have introduced an underestimation of the actual risk.

**Table 1 | Epidemiological studies of ATL in literatures.**

| Study design | Reference | Country | Targeted population | Size of population | No. ATL cases | Incidence rate (IR) | Lifetime risk (estimated cumulative risk) |
|---|---|---|---|---|---|---|---|
| Population-based descriptive study | Kondo et al. (1989) | Japan | Inhabitants of Uwajima City (an endemic area in Japan) | Data from the Statistics Bureau in 1981<br>M + F: 290,464 | Data from a survey in 1981–1987<br>M: 46<br>F: 34 | Annual IR:<br>3.9 per 100,000 population<br>6.1 per 100,000 aged over 30<br>6.6 per 100,000 aged over 40 | NA |
| | | | HTLV-1 carriers aged over 30 years | Data from HTLV-1 screening in 1981<br>M: 4,522<br>F: 8,801 | Data from a survey in 1981–1987<br>M: 46<br>F: 34 | Annual IR: (per 100,000 HTLV-1 carriers aged over 30 years)<br>Total: 85.0 M: 145.3<br>F: 55.2 | (0–79 years):<br>M: 6.9%<br>F: 2.95% |
| Population-based descriptive study | Tokudome et al. (1989) | Japan | Entire residents of the Saga Prefecture (an endemic area in Japan) | Data from the Statistics Bureau in 1981<br>M + F: 880,000 | Data from a cancer registry in 1981–1983<br>M: 36<br>F: 33 | Annual IR: (per 100,000 population aged 40–79 years)<br>M: 4.9∼12.6 (depend on age)<br>F: 1.6∼8.1 (depend on age) | NA |
| | | | Estimated HTLV-1 carriers in the Saga Prefecture (an endemic area in Japan) | Data calculated by multiplying HTLV-1 positivity rate among blood donors with the number of the population in Saga<br>M: 14,236<br>F: 19,596 | Data from a cancer registry in 1981–1983<br>M: 36<br>F: 33 | Annual IR: (per 100,000 HTLV-1 carriers aged 40–79)<br>M: 115.9<br>F: 66.4 | (40–79 years):<br>M: 4.5%<br>F: 2.6% |
| Nationwide hospital-based survey | Tajima (1990) | Japan | Whole Japanese population | Data from the Statistics Bureau in 1986<br>Total: 120,720,000<br>Kyushu: 14,460,000 | Data from 192 hospitals 1986–1987<br>Total: 657 | Annual IR: (per 100,000 adults)<br>M: 4.04 (in Kyushu)<br>F: 2.64 (in Kyushu) | NA |
| | | | Estimated HTLV-1 carriers in Japan | Data calculated by multiplying the HTLV-1 seropositivity rate in blood donors in an individual prefecture with the number of the population in this individual prefecture<br>Total: 1,200,000 | Data from 192 hospitals 1986–1987<br>Total: 657 | Annual IR (per 100,000 HTLV-1 carriers over 20 years old)<br>Total: 60 | NA |

*(Continued)*

**Table 1 | Continued**

| Study design | Reference | Country | Targeted population | Size of population | No. ATL cases | Incidence rate (IR) | Lifetime risk (estimated cumulative risk) |
|---|---|---|---|---|---|---|---|
| Population-based descriptive study | Gérard et al. (1995) | French Guiana | Whole French Guiana population | Total 115,000 | Enrolled in the study in 1990–1993<br>Total: 18 | Crude annual IR (per 100,000 entire population) Total: 3.5<br>Crude annual IR in an endemic region (per 100,000 population) Total: 30 | NA |
| Cohort study (Miyazaki Cohort study) | Hisada et al. (1998a)<br><br>Okayama et al. (2004) | Japan | Residents in two HTLV-1 endemic villages in the Miyazaki Prefecture (an endemic area in Japan) | 1,960 of whom 27% were HTLV-1 antibody-positive in 1984 | Data in 1984–2000<br><br>Total: 6 | NA | NA |
| Population-based descriptive study | Levine et al. (1999) | US | Central Brooklyn black community (an endemic area in New York) | Total: 1,184,670 | Data from a survey in 1994<br><br>M: 2<br>F:10 | NA | NA |
| Population-based descriptive study | Arisawa et al. (2000) | Japan | Entire residents of the Nagasaki Prefecture (an endemic area in Japan) | Data from the Statistics Bureau in 1990<br><br>M: 736,729<br>F: 826,230 | Data from a cancer registry in 1985–1995<br><br>M: 567<br>F: 422 | World age-standardized annual IR (cases/100,000 population):<br>M: 10.5<br>F: 6.0 | NA |
| | | | Residents of 4 towns on the K Islands (a cluster regions in Nagasaki) | Data from the Statistics Bureau in 1990<br><br>M: 12,820<br>F: 14,050 | Data from a cancer registry in 1985–1995<br><br>M: 24<br>F: 16 | Crude IR (per 100,000 person-years of residents)<br><br>M: 27.4<br>F: 15.9 | (30–79 years):<br><br>M: 1.7%<br>F: 0.7% |
| | | | HTLV-1 carriers of 4 towns on the K Islands (a cluster regions in Nagasaki) | Data from HTLV-1 screening in 1985–1996<br><br>M + F: 18,485 | Data from a cancer registry in 1985–1995<br><br>M: 24<br>F: 16 | Crude IR (per 100,000 person-years of HTLV-1 carriers)<br>M: 137.7<br>F: 57.4 | (30–79 years):<br><br>M: 6.6%<br>F: 2.1% |

*(Continued)*

**Table 1 | Continued**

| Study design | Reference | Country | Targeted population | Size of population | No. ATL cases | Incidence rate (IR) | Lifetime risk (estimated cumulative risk) |
|---|---|---|---|---|---|---|---|
| Population-based descriptive study (NAACCR) | Yamamoto and Goodman (2008) | US | General population in US | Approximately 61% of the US population | Data from cancer registry in 1997–2002 | Age adjusted to the 2000 US standard population per 100,000 population | NA |
| | | | | | M: 248<br>F: 183 | M: 0.05<br>F: 0.03 | |
| | | | White population in US | NA | M: 187<br>F: 104 | M: 0.05<br>F: 0.02 | NA |
| | | | Black population in US | NA | M: 46<br>F: 69 | M: 0.12<br>F: 0.13 | NA |
| Population-based descriptive study | Arisawa et al. (2009) | Japan | Entire residents of the Nagasaki Prefecture (an endemic area in Japan) | Data from the Statistics Bureau in 1995 | Data from a cancer registry in 1985–2004 | World age-standardized annual IR (per 100,000 population) | (30–99 years): |
| | | | | M: 726,894<br>F: 818,040 | M: 1,022<br>F: 829 | M: 8.7<br>F: 5.5 | M: 0.88%<br>F: 0.57% |
| Hospital-based and Population-based descriptive study | Koga et al. (2010) | Japan | Estimated HTLV-1 carriers in Nagasaki City (an endemic area in Japan) | Data calculated by multiplying the HTLV-1 positivity rate in the University hospital with the number of the population census in Nagasaki City | Data from a cancer registry in 1990–2005 | Annual IR (per 100,000 HTLV-1 carriers) | (30–79 years): |
| | | | | M: 12,755<br>F: 24,228 | M: 188<br>F: 172 | M: 92<br>F: 44 | M: 7.29%<br>F: 3.78% |
| Nationwide hospital-based survey | Yamada et al. (2011) | Japan | Whole Japanese population | Data from the Statistics Bureau in 2006 | Data from 156 hospitals 2006–2007 | Annual IR (per 100,000 population) | NA |
| | | | | Total: 127,053,000<br>Kyushu: 13,407,000 | Total: 910<br>Kyusyu: 544 | Total: 0.91<br>Kyushyu: 5.11 | |
| | | | Estimated HTLV-1 carriers in Japan | Data calculated by multiplying the HTLV-1 seropositivity rate in blood donors in an individual prefecture by the number of the population in this individual prefecture | Data from 156 hospitals 2006–2007 | Annual IR (per 100,000 HTLV-1 carriers over 20 years old) | M:8.73% |
| | | | | Total: 1,078,722 | Total: 910 | Total: 106 | F:5.14% |

*NA, not available.*

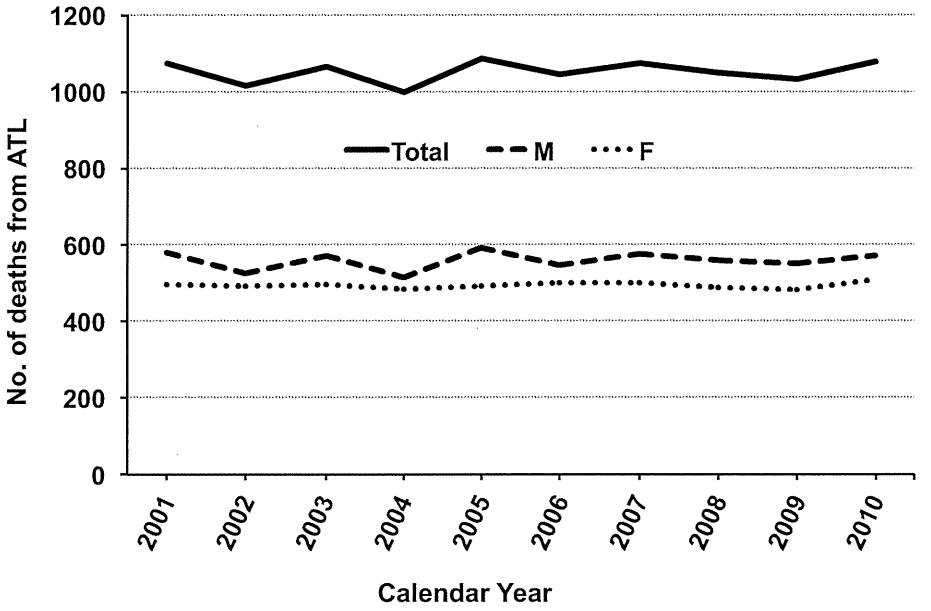


**FIGURE 1 | Annual number of deaths from adult T-cell leukemia (ATL) during 2001–2010 in Japan.** The raw data were obtained from vital statistics in the Portal Site of Official Statistics of Japan (e-Stat; accessed April 8, 2012). Abbreviations: M, male; F, female.

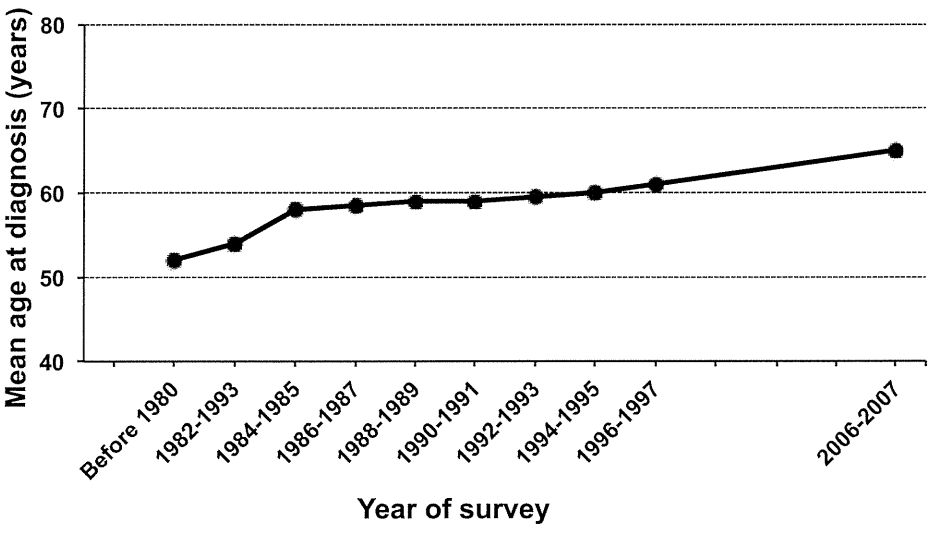


**FIGURE 2 | Chronological changes in the mean age at diagnosis of adult T-cell leukemia (ATL) in Japan.** The figure was modified from Figure 2 in Yamada et al. (2011).

## EAST ASIA (EXCLUDING JAPAN)

Although there were several reports of blood donor screening for HTLV-1, no epidemiological study of ATL has been published from East Asian countries other than Japan because of the lower prevalence of HTLV-1 (less than 0.1%). Nevertheless, several case series of ATL were available. The first case of ATL was reported in Taiwan in 1985 (Chen et al., 1985), in Korea in 1987 (Lee et al., 1987), and in China in 1995 (Zhuo et al., 1995). In Hong Kong, since the first case of ATL was reported in 1994 (Liang, 1994), all patients with T-cell lymphoma have been routinely screened for HTLV-1 antibody. In a registration study of lymphoma between 1993 and 2002 in Hong Kong, six cases of ATL were diagnosed among 5,911 lymphomas, in which ATL contributed to 0.1% of all cases of lymphoma and 1.3% of T-cell lymphoma (Au and Lo, 2005). Recently, 17 cases of ATL were reported from Taiwan (Lee et al., 2010), of those approximately 40% of the patients co-infected with HBV and HCV, which may be a characteristic of the Taiwanese ATL.

### MIDDLE EAST

The prevalence of HTLV-1 infection among healthy subjects is reported to be very low, less than 0.1%, in Lebanon, Saudi Arabia, Egypt, and Kuwait (Proietti et al., 2005). However, there are some areas with a very high rate of HTLV-1 infection.

Northeast province of Iran (Mashhad, Sabzevar, and Neyshabour) and Urmia are known to be an endemic area for HTLV-1, where the prevalence of HTLV-1 infection was reported to be 0.34–0.77% in blood donors (Abbaszadegan et al., 2003; Khameneh et al., 2008), 1.7–12% in cross-sectional studies (Meytes et al., 1990; Safai et al., 1996; Hedayati-Moghaddam et al., 2011; Azarpazhooh et al., 2012), and 2–3% in community-based population (Rafatpanah et al., 2011).

Romania is also suggested to be an endemic area for HTLV-1 because antibodies to HTLV-1 were found in 0.64% of blood donors (Paun et al., 1994), which was an extremely higher seroprevalence rate than in Europe and the USA. In Israel, HTLV-1 seropositive were discovered only in 0.0018% out of 276,000 blood donations, but a very high rate of infection (over 20%) has been identified among a segregated community of Jews originated from the city of Mashhad in Iran (Miller et al., 1998).

Although, there are several clinical studies for ATL patients in the Middle East (Kchour et al., 2007, 2009), epidemiological studies regarding incidence and prevalence of ATL were not available in literature from the Middle East. There were several case reports of ATL, most of which were Mashhad origins or Romanian origins (Sidi et al., 1990; Veelken et al., 1996; Shtalrid et al., 2005; Bitar et al., 2009).

### UNITED STATES

HTLV-1 and ATL are extremely rare in North America. Several ATL cases have been reported sporadically (Catovsky et al., 1982). Most of the cases were migrants from endemic areas. A population-based survey reported that the annual incidence in African Americans in central Brooklyn (population size; 1,184,670) was estimated to be approximately 3.2 per 100,000 person-years (Levine et al., 1999). An interesting finding in their study was that the male-to-female ratio of 1:3 was different from the male dominance reported in Japan. Recent cancer registry systems for hematological malignancies allow a precise evaluation of epidemiological features of ATL in the USA. In a recent report from the North American Association of Central Cancer Registries (NAACCR; Yamamoto and Goodman, 2008), a total of 431 cases (248 men and 183 women) of ATL (ICD-O-3 code; 9,827) were registered between 1997–2002, showing that the age adjusted incidence rate was 0.05 for men and 0.03 for women per 100,000 population. The study also reported a racial difference in the incidence rate, showing that African Americans had the highest rates of ATL (0.12 for men and 0.13 for women per 100,000 population). A possible explanation for this observation might be the higher number of migrants from endemic areas of the Caribbean and parts of Sub-Saharan Africa rather than a racial difference in susceptibility.

### THE CARIBBEAN

In the early 1980s, eight patients were diagnosed with ATL in the USA, and all of them were Blacks from the Caribbean (Blattner et al., 1982). Since then, Central/South America and the Caribbean are known as areas of high prevalence of HTLV-1. Although there is no concrete epidemiological report regarding the incidence or prevalence of ATL from Central and South America, several case series have been published. A regional registration study of Jamaica reported a total of 126 cases of ATL (acute 46.8%, lymphoma 27%, chronic 20.6%, and smoldering 5.6%) between January 1985 and July 1995 (Hanchard, 1996). The mean age was 43 years old (17–85 years old), which is similar to that reported in Brazil (43 years; Pombo de Oliveira et al., 1995) but younger than that in Japan (50–60 years; Yamaguchi et al., 1987). There is definite evidence that the age at diagnosis in Central/South America and the Caribbean is younger than that in Japan. This difference in the age at diagnosis might be due to different environmental backgrounds.

### CENTRAL AND SOUTH AMERICA

In Central and South America, HTLV-I has been shown to be endemic mainly in populations of African ancestry and in some populations of Japanese origin.

Brazil has the highest HTLV-1 seroprevalence rate in healthy subjects (approximately 1%), especially in Rio de Janeiro and Salvador (1.8%) on the northeast coast of the country where the population is largely of African descent. ATL accounts for approximately 30% of patients with T-cell malignancies in Brazil (Pombo de Oliveira et al., 1995; Farias de Carvalho et al., 1997). A Brazilian ATLL Study Group identified 195 cases of ATL in the national registry of T-cell malignancies between 1994 and 1998 (Pombo de Oliveira et al., 1999), but no epidemiological indicators were available. In Argentina, HTLV-1 infection is known to be highly prevalent among Native Americans living in the Andes, and ATL accounts for approximately 14.7% of patients with lymphoid malignancies (Marin et al., 2002).

Chile is a non-tropical country but small case series of ATL patients have been reported frequently (Cabrera et al., 1994, 1999, 2003). The characteristics of Chilean ATL were reported that the most of patients were of Caucasian origin, and age at diagnosis (50 years old) was younger than Japanese patients but older than those from other Latin American countries. According to the recent pathological study in Chile, ATL accounts for 0.5% of patients with of NHL (Cabrera et al., 2012).

French Guiana (population 115,000), an overseas French administrative district located on the northeast coast of the South American continent between Brazil and Surinam, is also known to be an area of high endemicity for HTLV-I (Plancoulaine et al., 1998; Talarmin et al., 1999, Pouliquen et al., 2004). Although the population consists of various ethnic groups, a high seroprevalence of HTLV-I (8%) and a high incidence of cases of ATL were found among the Noirs-Marrons, an isolated population descended from Surinam slaves (Gérard et al., 1995; Tuppin et al., 1995; Plancoulaine et al., 1998). An epidemiological study was performed in French Guiana to determine the prevalence and incidence of ATL (Gérard et al., 1995). Only 18 patients with ATL (8 acute forms, 8 lymphoma types, and 2 smoldering cases) were enrolled during 1990–1993 and the annual crude incidence rate was estimated to be around 3.5 per 100,000 populations. However, in a small remote ethnic group of African origin (around 6200 inhabitants), the annual crude incidence rate was the highest to be around 30 per 100,000 populations.

**Table 2 | Risk factors for the development of ATL with regard to the HTLV-1 carrier status.**

| | Reference |
|---|---|
| **Host susceptibility** | |
| Vertical infection with HTLV-1 as infant | Murphy et al. (1989) |
| Attained at an age of >50 years | Many references |
| Male sex | Many references |
| HLA-A*26, HLA-B*4002, HLA-B*4006, and HLA-B*4801 (Japanese ATL) | Yashiki et al. (2001) |
| Co-infected with *Strongyloides stercoralis* | |
| **Laboratory markers** | |
| A high level of sil-2R, more than 500 U/ml | Arisaw et al. (2002) |
| A high level of anti-HTLV-1, titer more than × 1,024 | Arisaw et al. (2002) |
| A high level of circulating abnormal lymphocytes, more than 0.6% | Hisada et al. (1998a) |
| A low level of of anti-Tax reactivity | Hisada et al. (1998b) |
| A high level of white blood cell count, more than 9,000/μL | Imaizumi et al. (2005) |
| **Viral markers** | |
| A higher HTLV-1 proviral load level, more than 4 copies per 100 PBMCs | Iwanaga et al. (2010) |

*ATL, adult T-cell leukemia; HTLV-1, human T-cell leukemia virus type 1; HLA, human leukocyte antigen; PBMC, peripheral blood mononuclear cell; sIL-2R, soluble interleukin-2 receptor.*

### AFRICA AND EUROPE

In Africa, a high HTLV-I seroprevalence rate (>2% in the adult population) has been reported in sub-Saharan African countries, especially in Gabon (Hunsmann et al., 1984; Delaporte et al., 1988; Gessain, 1996; Etenna et al., 2008; Gonçalves et al., 2010). Although there are many reports regarding the HTLV-I seroprevalence rates in African countries, only a few epidemiological studies of ATL were available. In a case-control study including NHL and control that performed in Gabon, only four cases of the 26 patients with NHL fitted the criteria of ATL (Delaporte et al., 1993), but further information on epidemiological feature of ATL was not available.

In Europe, HTLV-1 is endemic in Southern Italy (Manzari et al., 1985). Several case series of ATL were reported from Europe (Manzari et al., 1985; Gessain et al., 1990). Most of ATL patients were African origin from high-HTLV-1-endemic areas (West Indies, Nigeria, and other African areas); however, some patients had no background regarding endemic areas (Manzari et al., 1985).

## RISK FACTORS FOR ATL IN HTLV-1 CARRIERS

Although a variety of genetic abnormalities due to HTLV-1 infection have been reported to explain the characteristics of ATL oncogenesis, HTLV-1 infection alone is not sufficient to develop ATL from HTLV-1 carrier status. Risk factors for developing ATL in HTLV-1 carriers have been investigated in many epidemiological and clinical studies (**Table 2**).

### HOST SUSCEPTIBILITY

Age is a well-known risk factor for the development of ATL. ATL occurs mostly in adults, at least 20–30 years after HTLV-1 infection. However, the age at onset differs across geographic areas, which may be affected by racial or environmental characteristics. In Japan in the early 1980s, an average age at diagnosis of ATL was reported to be individuals in their early 1950s (The T- and B-Cell Malignancy Study Group, 1981, 1985), but the age at diagnosis increased yearly, reaching 65 years in the latest nationwide survey for ATL (Yamada et al., 2011). However, the average age at diagnosis of ATL in Jamaican and Brazilian series was reported to be individuals in the 1940s (43 years in Jamaica and 44 years in Brazil; Hanchard, 1996; Pombo de Oliveira et al., 1999), which is younger than that in Japan (Yamaguchi et al., 1987).

The age at the time of HTLV-1 infection is also a very important risk factor for the development of ATL. Individuals infected in childhood (vertical transmission) may be at higher risk for developing ATL (Murphy et al., 1989). ATL seldom develops in individuals infected in adulthood, although no epidemiological study has proven this fact. There was one case report describing that a female HTLV-1 carrier known as conclusively transmitted horizontally by her partner developed ATL (Sakuma et al., 1988). To clarify whether or not ATL develops among individuals infected in adulthood, a large prospective follow-up study is required.

Male sex is considered a risk factor for ATL. In most studies from Japan, the incidence of ATL is two- and threefold higher in male carriers than in female carriers, which is contrary to the higher rate of HTLV-1 positivity in women than in men. However, a population-based survey in central Brooklyn reported that the annual incidence of ATL was higher in women than in men (male-to-female ratio of 1:3; Levine et al., 1999). Modeling data from Jamaican series also showed a higher cumulative lifetime risk of ATL in women than in men (4.0% for men and 4.2% for women; Murphy et al., 1989). The reason for the sex-related differences in the incidence rate of ATL between Japan and other regions is unknown.

It seems unlikely that there are apparent ethnical differences in susceptibility to infection by HTLV-1 and developing ATL. A higher incidence of ATL was found individual of African origin than in others (Manzari et al., 1985; Gessain et al., 1990; Yamamoto and Goodman, 2008), however, most of patients of African origin came from HTLV-1 endemic areas.

Earlier epidemiologic studies have found that ATL patients are more likely to have a family history of lymphoid malignancy (Ichimaru et al., 1979; The T- and B-Cell Malignancy Study Group, 1981). Since then, several host genetic background factors influencing the onset of ATL have been investigated. Human leukocyte antigen (HLA) is a candidate for the genetic factors controlling the immune response against the viral antigen. Specific HLA antigen alleles have been reported to be associated with an increased risk of developing ATL (Uno et al., 1988). The allele frequencies of HLA-A*26, HLA-B*4002, HLA-B*4006, and HLA-B*4801 were significantly higher in ATL patients than in asymptomatic HTLV-1 carriers in southern Japan, and ATL patients possessing these alleles developed ATL 12.6 years earlier than patients with other alleles (Yashiki et al., 2001). Ethnic differences in HLA alleles related to ATL were also investigated in another study (Sonoda et al., 2011).

HTLV-1 carriers with abnormal immune system may be at high-risk of developing ATL. Several studies reported that HTLV-1 carriers co-infected with *Strongyloides stercoralis* are considered

a high-risk group for developing ATL because of the clonal proliferation of HTLV-1-infected lymphocytes and high proviral load (Nakada et al., 1987; Yamaguchi et al., 1988; Plumelle et al., 1997; Gabet et al., 2000). Satoh et al. (2002) suggested that *S. stercoralis* infection induces polyclonal expansion of HTLV-1-infected cells by activating the interleukin 2/interleukin 2 receptor (IL-2/IL-2R) system in dually infected carriers, which may be a precipitating factor for ATL. The immunosuppressive state has been reported to potentially contribute to ATL development in HTLV-1 carriers. There were several case reports of ATL developed in HTLV-1 carriers undergoing immunosuppressive treatment after living-donor liver transplantation (Kawano et al., 2006; Yoshizumi et al., 2012) and kidney transplantation (Hoshida et al., 2001).

## LABORATORY MARKERS

Several laboratory abnormalities were found to be markers for the development of ATL. Kamihira et al. (1994) measured prospectively soluble IL-2R (sIL-2R) levels and lactate dehydrogenase (LDH) levels in HTLV-1 carriers, reporting that the increasing level of sIL-2R may be a more sensitive indicator of ATL than LDH. A nested case-control study also showed that high levels of sIL-2R (more than 500 U/mL) and HTLV-1 antibody titers (more than 1,024) were independently associated with an increased risk of developing ATL (Arisaw et al., 2002). Imaizumi et al. (2005) analyzed the outcomes of 50 HTLV-1 carriers with monoclonal proliferation of HTLV-1-infected T cells in a 20-year follow-up study, reporting that a high white blood cell count more than 9,000/μL was a potential prognostic factor for developing ATL, even after adjustment for age, sex, and relative lymphocyte counts.

A series of the Miyazaki Cohort Study (population size; 1,960 people, of whom 27% were HTLV-1 antibody-positive) reported that an HTLV-1 carrier with a high anti-HTLV-1 titer (odds ratio; 1.6), a high number of circulating abnormal lymphocytes, and a low anti-Tax reactivity were associated with a greater risk of developing ATL (Mueller et al., 1996; Hisada et al., 1998a,b). Recently, an international ATL Cohort Consortium study by merging eight cohorts from Japan, Jamaica, the United States, and Brazil examined serologic markers of HTLV-I pathogenesis and host immunity in 53 ATL cases and 150 matched asymptomatic HTLV-I carriers (Birmann et al., 2011). The study confirmed that above-median sIL-2R and anti-Tax seropositivity were independently associated with an increased ATL risk, and found that above-median total immunoglobulin E levels predicted a lower ATL risk.

Aberrant expression of cell-surface antigens is usually used for clinical routine diagnosis on ATL. ATL cells phenotypically express CD4, CCR4, and CD25. However, data of cell-surface antigens rarely used for a prognostic marker of ATL from HTLV-I carriers. Two studies reported that expression of CD3, CD7, and CD26 on HTLV-1-infected cells were diminished in acute and chronic ATL and those were slightly down-regulated in smoldering ATL (Tsuji et al., 2004; Tian et al., 2011). These results suggest that the down-regulation of those cell-surface antigens could be possible predict markers for the early phase leukemogenesis of ATL from HTLV-1 carriers. A resent study serially evaluated cell-surface antigens on HTLV-1-infected cells in HTLV-1 carriers, smoldering ATL, and chronic ATL, by taking into consideration the pattern of Southern blot hybridization and proviral load (Kamihira et al., 2012). The report suggests that the decreasing expression of CD26 and the decreasing ratio of CD26/CD25 are novel biomarkers for prediction of clonal bands and discrimination of carriers and smoldering ATL.

## PROVIRUS-INTEGRATION STATUS

Among HTLV-1 carriers, there exist a group of cases having the monoclonal integration of HTLV-1 proviral DNA in mononuclear cells without signs of malignant proliferation or clinical signs and symptoms related to leukemia (Ikeda et al., 1993). Such carriers have been suggested to be a high-risk group of developing ATL, but their prognosis varied from being stable carriers for long to developing ATL (Ikeda et al., 1993; Imaizumi et al., 2005). There are only a few epidemiological studies to investigate the significance of the provirus-integration status on non-malignant infected cells from asymptomatic HTLV-1 carriers.

Nakada et al. (1987) reported that patients with *S. stercoralis* infection and co-infected with HTLV-1 had a high frequency (35%) of patients presenting a monoclonal integration of HTLV-1 proviral DNA in their blood lymphocytes. Carvalho and Da Fonseca Porto (2004) also The author also found a correlation between monoclonal integration of proviral DNA and abnormal lymphocytes in peripheral blood, with a trend for greater severity of the parasitic infection. Although several studies reported that HTLV-1 carriers co-infected with *S. stercoralis* are considered a high-risk group for developing ATL (Nakada et al., 1987; Yamaguchi et al., 1988; Plumelle et al., 1997; Gabet et al., 2000), no study investigated the clinical significance of the monoclonal integration of HTLV-1 proviral DNA in their blood lymphocytes in HTLV-1 carriers with *S. stercoralis*.

## PROVIRAL LOAD

In the area of viral oncogenesis, there are accumulated data indicating a relationship between an increased viral load and viral-associated malignancies. HTLV-1 proviral DNA load in the peripheral blood mononuclear cells (PBMCs) are also evaluated in some epidemiological and clinical studies to support the hypothesis that increased HTLV-1 proviral load level is an important predictor of developing ATL.

A cross-sectional study (Manns et al., 1999) and a series of the Miyazaki cohort study (Tachibana et al., 1992; Hisada et al., 1998a,b; Okayama et al., 2004) reported that HTLV-1 proviral load level was higher in HTLV-1 carriers who developed ATL than in asymptomatic HTLV-1 carriers. However, the proviral load was measured only in a small number of subjects in the above literature.

Several large-scale prospective studies support results from the previous small studies that an increased HTLV-1 proviral load is an important predictor of developing ATL. In Japan in 2002, a nationwide prospective cohort study for asymptomatic HTLV-1 carriers, the Joint Study on Predisposing Factors of ATL Development (JSPFAD), was initiated (Yamaguchi et al., 2007) to investigate viral- and host-specific determinants of the development of ATL in more detail. In the cohort of 1,218 asymptomatic HTLV-1 carriers (426 men and 792 women), 14 subjects progressed to overt ATL during a follow-up of 1981.2 person-years (Iwanaga et al., 2010). All of the 14 subjects were among those with the highest group of baseline proviral load (range, 4.17–28.58 copies/100

PBMCs). Multivariate Cox analyses indicated that a higher proviral load (more than 4 copies/100 PBMCs) is an independent risk factor for progression of ATL, even after adjusting for sex, age, family history of ATL, and other possible risk factors. The result indicated that HTLV-1 carriers with higher HTLV-1 proviral load levels belong to the high-risk group of carriers who develop ATL and in whom any measures to prevent the development of ATL should be instituted.

Nevertheless, the association between HTLV-1 proviral load and disease development remains unclear because a higher proviral load is also an important predictor in patients with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Further viral markers are needed to determine the function of a higher HTLV-1 proviral load to direct the way to developing ATL or developing HAM/TSP from HTLV-1 carriers.

## CONCLUDING REMARKS

Although many prior studies found important epidemiological evidence on ATL and risk factors for the development of ATL in HTLV-1 carriers, limited data are available on the valid annual incidence of ATL from longitudinal prospective studies. Existing predisposing factors are still insufficient to explain the characteristics of ATL oncogenesis. Unknown risk factors may be involved in the acquisition of malignant characteristics of HTLV-1 infected cells. Further well-designed epidemiological studies are needed to fully understand the oncogenesis of ATL.

Even though the incidence of ATL is relatively low among HTLV-1 carriers and a novel promising agent, mogamulizumab (humanized anti-CCR4 monoclonal antibody), is released (Ishida et al., 2003, 2012), preventing new HTLV-1 infections and the development of ATL are major public health concerns in HTLV-1 endemic countries in the world. In Japan, there are approximately one million of HTLV-1 carriers, 1,000 new ATL cases, and 1,000 new deaths from ATL every year. However, only recently has the Japanese government for the first time begun to implement a nationwide comprehensive package of measures covering the prevention of mother-to-child HTLV-1 transmission and the development of medical researches on HTLV-1 and ATL (http://www.kantei.go.jp/foreign/kan/actions/201009/13htlv_e.html). The challenge in the next few years will be to reduce the number of HTLV-1 carriers, to develop an easy method that allows identification of high-risk carriers, and to implement earlier therapeutic interventions for carriers with high-risk markers.

## ACKNOWLEDGMENTS

A part of this review was supported by grants (201123050A, H23-gan rinsho-ippan-021, H23-gan rinsho-ippan-022) from the Ministry of Health, Labor, and Welfare in Japan.

## REFERENCES

Abbaszadegan, M. R., Gholamin, M., Tabatabaee, A., Farid, R., Houshmand, M., and Abbaszadegan, M. (2003). Prevalence of human T-lymphotropic virus type 1 among blood donors from Mashhad, Iran. *J. Clin. Microbiol.* 41, 2593–2595.

Arisaw, K., Katamine, S., Kamihira, S., Kurokawa, K., Sawada, T., Soda, M., Doi, H., Saito, H., and Shirahama, S. (2002). A nested case-control study of risk factors for adult T-cell leukemia/lymphoma among human T-cell lymphotropic virus type-I carriers in Japan. *Cancer Causes Control* 13, 657–663.

Arisawa, K., Soda, M., Endo, S., Kurokawa, K., Katamine, S., Shimokawa, I., Koba, T., Takahashi, T., Saito, H., Doi, H., and Shirahama, S. (2000). Evaluation of adult T-cell leukemia/lymphoma incidence and its impact on non-Hodgkin lymphoma incidence in southwestern Japan. *Int. J. Cancer* 85, 319–324.

Arisawa, K., Soda, M., Ono, M., Uemura, H., Hiyoshi, M., and Suyama, A. (2009). Trends of incidence rate of adult T-cell leukemia/lymphoma in an HTLV-1 endemic area in Japan. *Int. J. Cancer* 125, 737–738.

Au, W. Y., and Lo, J. Y. (2005). HTLV-1-related lymphoma in Hong Kong Chinese. *Am. J. Hematol.* 78, 80–81.

Azarpazhooh, M. R., Hasanpour, K., Ghanbari, M., Rezaee, S. A., Mashkani, B., Hedayati-Moghaddam, M. R., Valizadeh, N., Farid Hosseini, R., Foroghipoor, M., Soltanifar, A., Sahebari, M., Azadmanesh, K., Hassanshahi, G., and Rafatpanah, H. (2012). Human T-lymphotropic virus type 1 prevalence in Northeastern Iran, Sabzevar: an epidemiologic-based study and phylogenetic analysis. *AIDS Res. Hum. Retroviruses* 28, 895–901.

Birmann, B. M., Okayama, A., Kim, N., Arisawa, K., Breen, E. C., Carneiro-Proietti, A. B. F., Falk, K. I., Hanchard, B., Inoue, M., Martínez-Maza, O., Murphy, E. L., Pfeiffer, R. M., Sawada, T., Stuver, S. O., Tsugane, S., Li, H., Suppan, C. A., Mueller, N. E., and Hisada, M. (2011). Altered host immunity, human T lymphotropic virus type I replication, and risk of adult T-cell leukemia/lymphoma: a prospective analysis from the ATL Cohort Consortium. *Retrovirology* 8, A81.

Bitar, N., Hajj, H. E., Houmani, Z., Sabbah, A., Otrock, Z. K., Mahfouz, R., Zaatari, G., and Bazarbachi, A. (2009). Adult T-cell leukemia/lymphoma in the Middle East: first report of two cases from Lebanon. *Transfusion* 49, 1859–1864.

Blattner, W. A., Kalyanaraman, V. S., Robert-Guroff, M., Lister, T. A., Galton, D. A., Sarin, P. S., Crawford, M. H., Catovsky, D., Greaves, M., and Gallo, R. C. (1982). The human type-C retrovirus, HTLV, in Blacks from the Caribbean region, and relationship to adult T-cell leukemia/lymphoma. *Int. J. Cancer* 30, 257–264.

Cabrera, M. E., Labra, S., Catovsky, D., Ford, A. M., Colman, S. M., Greaves, M. F., and Matutes, E. (1994). HTLV-I positive adult T-cell leukaemia/lymphoma (ATLL) in Chile. *Leukemia* 8, 1763–1767.

Cabrera, M. E., Labra, S., Meneses, P., Matutes, E., Cartier, L., Ford, A. M., and Greaves, M. F. (1999). Adult T cell leukemia lymphoma in Chile. A clinical pathologic and molecular study of 26 patients. *Rev. Med. Chil.* 127, 935–944.

Cabrera, M. E., Marinov, N., Guerra, C., Morilla, R., and Matutes, E. (2003). Chronic lymphoproliferative syndromes in Chile. A prospective study in 132 patients. *Rev. Med. Chil.* 131, 291–298.

Cabrera, M. E., Martinez, V., Nathwani, B. N., Muller-Hermelink, H. K., Diebold, J., MacLennan, K. A., Armitage, J., and Weisenburger, D. D. (2012). Non-Hodgkin lymphoma in Chile: a review of 207 consecutive adult cases by a panel of five expert hematopathologists. *Leuk. Lymphoma* 53, 1311–1317.

Carvalho, E. M., and Da Fonseca Porto, A. (2004). Epidemiological and clinical interaction between HTLV-1 and Strongyloides stercoralis. *Parasite Immunol.* 26, 487–497.

Catovsky, D., Greaves, M. F., Rose, M., Galton, D. A., Goolden, A. W., McCluskey, D. R., White, J. M., Lampert, I., Bourikas, G., Ireland, R., Brownell, A. I., Bridges, J. M., Blattner, W. A., and Gallo, R. C. (1982). Adult T-cell lymphoma-leukaemia in Blacks from the West Indies. *Lancet* 1, 639–643.

Chen, P. M., Chiu, C. F., Chiou, T. J., Tzeng, C. H., and Chiang, B. N. (1985). Adult T-cell leukemia. First case reported in Taiwan. *Nippon Ketsueki Gakkai Zasshi* 8, 1035–1041.

Delaporte, E., Dupont, A., Peeters, M., Josse, R., Merlin, M., Schrijvers, D., Hamono, B., Bedjabaga, L., Cheringou, H., Boyer, F., Brun-Vézinet, F., and Larouzé, B. (1988). Epidemiology of HTLV-I in Gabon (Western Equatorial Africa). *Int. J. Cancer* 42, 687–689.

Delaporte, E., Klotz, F., Peeters, M., Martin-Prevel, Y., Bedjabaga, L., Larouzé, B., Nguembi-Mbina, C., Walter, P., and Piot, P. (1993). Non-Hodgkin lymphoma in Gabon and its relation to HTLV-I. *Int. J. Cancer* 53, 48–50.

Etenna, S. L., Caron, M., Besson, G., Makuwa, M., Gessain, A., Mahé, A., and Kazanji, M. (2008). New insights into prevalence, genetic diversity, and proviral load of human T-cell leukemia virus types 1 and 2 in pregnant women in Gabon in equatorial central Africa. *J. Clin. Microbiol.* 46, 3607–3614.

Farias de Carvalho, S. M., Pombo de Oliveira, M. S., Thuler, L. C., Rios, M., Coelho, R. C., Rubim, L. C., Silva, E. M., Reis, A. M., and Catovsky, D. (1997). HTLV-I and HTLV-II infections in hematologic disorder patients, cancer patients, and healthy individuals from Rio de Janeiro, Brazil. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 15, 238–242.

Gabet, A. S., Mortreux, F., Talarmin, A., Plumelle, Y., Leclercq, I., Leroy, A., Gessain, A., Clity, E., Joubert, M., and Wattel, E. (2000). High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with strongyloidiasis. *Oncogene* 19, 4954–4960.

Gérard, Y., Lepere, J. F., Pradinaud, R., Joly, F., Lepelletier, L., Joubert, M., Sainte Marie, D., Mahieu, R., Vidal, A. U., Larregain-Fournier, D., Valensi, F., Moynet, D., de Thé, G., Guillemain, B., Moreau, J. P., and Gessain, A. (1995). Clustering and clinical diversity of adult T-cell leukemia/lymphoma associated with HTLV-I in a remote black population of French Guiana. *Int. J. Cancer* 60, 773–776.

Gessain, A. (1996). "Epidemiology of HTLV-I and associated diseases," in *Human T-Cell Lymphotropic Virus Type 1*, eds P. Höllsberg and D. A. Hafler (Chichester: John Wiley & Sons Ltd.), 33–64.

Gessain, A., Gout, O., Saal, F., Daniel, M. T., Rio, B., Flandrin, G., Sigaux, F., Lyon-Caen, O., Periès, J., and de-Thé, G. (1990). Epidemiology and immunovirology of human T-cell leukemia/lymphoma virus type I-associated adult T-cell leukemia and chronic myelopathies as seen in France. *Cancer Res.* 50, 5692S–5696S.

Gonçalves, D. U., Proietti, F. A., Ribas, J. G., Araújo, M. G., Pinheiro, S. R., Guedes, A. C., and Carneiro-Proietti, A. B. (2010). Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. *Clin. Microbiol. Rev.* 23, 577–589.

Hanchard, B. (1996). Adult T-cell leukemia/lymphoma in Jamaica: 1986–1995. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 13, S20–S25.

Hattori, T., Uchiyama, T., Toibana, T., Takatsuki, K., and Uchino, H. (1981). Surface phenotype of Japanese adult T-cell leukemia cells characterized by monoclonal antibodies. *Blood* 58, 645–647.

Hedayati-Moghaddam, M. R., Fathi-moghadam, F., Eftekharzadeh Mashhadi, I., Soghandi, L., and Bidkhori, H. R. (2011). Epidemiology of HTLV-1 in Neyshabour, Northeast of Iran. *Iran. Red Crescent Med. J.* 13, 424–427.

Hinuma, Y., Komoda, H., Chosa, T., Kondo, T., Kohakura, M., Takenaka, T., Kikuchi, M., Ichimaru, M., Yunoki, K., Sato, I., Matsuo, R., Takiuchi, Y., Uchino, H., and Hanaoka, M. (1982). Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nation-wide sero-epidemiologic study. *Int. J. Cancer* 29, 631–635.

Hinuma, Y., Nagata, K., Hanaoka, M., Nakai, M., Matsumoto, T., Kinoshita, D., Shirakawa, S., and Miyoshi, I. (1981). 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.* 78, 6476–6480.

Hisada, M., Okayama, A., Tachibana, N., Stuver, S. O., Spiegelman, D. L., Tsubouchi, H., and Mueller, N. E. (1998a). Predictors of level of circulating abnormal lymphocytes among human T-lymphotropic virus type I carriers in Japan. *Int. J. Cancer* 77, 188–192.

Hisada, M., Okayama, A., Shioiri, S, Spiegelman, D. L., Stuver, S. O., and Mueller, N. E. (1998b). Risk factors for adult T-cell leukemia among carriers of human T-lymphotropic virus type I. *Blood* 92, 3557–3561.

Hoshida, Y., Li, T., Dong, Z., Tomita, Y., Yamauchi, A., Hanai, J., and Aozasa, K. (2001). Lymphoproliferative disorders in renal transplant patients in Japan. *Int. J. Cancer* 91, 869–875.

Hunsmann, G., Bayer, H., Schneider, J., Schmitz, H., Kern, P., Dietrich, M., Büttner, D. W., Goudeau, A. M., Kulkarni, G., and Fleming, A. F. (1984). Antibodies to ATLV/HTLV-1 in Africa. *Med. Microbiol. Immunol.* 173, 167–170.

IARC. (1996). Human immunodeficiency viruses and human T-cell lymphotropic viruses. *IARC Monogr. Eval. Carcinog. Risks Hum.* 67, 1–424.

Ichimaru, M., Kinoshita, K., Kamihata, S., Ikeda, S., Yamada, Y., and Amagasaki, T. (1979). T-cell malignant lymphoma in Nagasaki district and its problems. *Jpn. J. Clin. Oncol.* 9, S337–S346.

Ikeda, N., Inoue, M., Iso, H., Ikeda, S., Satoh, T., Noda, M., Mizoue, T., Imano, H., Saito, E., Katanoda, K., Sobue, T., Tsugane, S., Naghavi, M., Ezzati, M., and Shibuya, K. (2012). Adult mortality attributable to preventable risk factors for non-communicable diseases and injuries in Japan: a comparative risk assessment. *PLoS Med.* 9, e1001160. doi:10.1371/journal.pmed.1001160

Ikeda, S., Momita, S., Kinoshita, K., Kamihira, S., Moriuchi, Y., Tsukasaki, K., Ito, M., Kanda, T., Moriuchi, R., and Nakamura, T. (1993). Clinical course of human T-lymphotropic virus type I carriers with molecularly detectable monoclonal proliferation of T lymphocytes: defining a low- and high-risk population. *Blood* 82, 2017.

Imaizumi, Y., Iwanaga, M., Tsukasaki, K., Hata, T., Tomonaga, M., and Ikeda, S. (2005). Natural course of HTLV-1 carriers with monoclonal proliferation of T lymphocytes ("pre-ATL") in a 20-year follow-up study. *Blood* 105, 903–904.

Ishida, T., Joh, T., Uike, N., Yamamoto, K., Utsunomiya, A., Yoshida, S., Saburi, Y., Miyamoto, T., Takemoto, S., Suzushima, H., Tsukasaki, K., Nosaka, K., Fujiwara, H., Ishitsuka, K., Inagaki, H., Ogura, M., Akinaga, S., Tomonaga, M., Tobinai, K., and Ueda, R. (2012). Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J. Clin. Oncol.* 30, 837–842.

Ishida, T., Utsunomiya, A., Iida, S., Inagaki, H., Takatsuka, Y., Kusumoto, S., Takeuchi, G., Shimizu, S., Ito, M., Komatsu, H., Wakita, A., Eimoto, T., Matsushima, K., and Ueda, R. (2003). Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. *Clin. Cancer Res.* 9, 3625–3634.

Iwanaga, M., Watanabe, T., Utsunomiya, A., Okayama, A., Uchimaru, K., Koh, K. R., Ogata, M., Kikuchi, H., Sagara, Y., Uozumi, K., Mochizuki, M., Tsukasaki, K., Saburi, Y., Yamamura, M., Tanaka, J., Moriuchi, Y., Hino, S., Kamihira, S., Yamaguchi, K., and Joint Study on Predisposing Factors of ATL Development investigators. (2010). Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan. *Blood* 116, 1211–1219.

Kamihira, S., Atogami, S., Sohda, H., Momita, S., Yamada, Y., and Tomonaga, M. (1994). Significance of soluble interleukin-2 receptor levels for evaluation of the progression of adult T-cell leukemia. *Cancer* 73, 2753–2758.

Kamihira, S., Iwanaga, M., Doi, Y., Sasaki, D., Mori, S., Tsurda, K., Nagai, K., Uno, N., Hasegawa, H., Yanagihara, K., Morinaga, Y., Tsukasaki, K., and Taniguchi, H. (2012). Heterogeneity in clonal nature in the smoldering subtype of adult T-cell leukemia: continuity from carrier status to smoldering ATL. *Int. J. Hematol.* 95, 399–408.

Kawano, N., Shimoda, K., Ishikawa, F., Taketomi, A., Yoshizumi, T., Shimoda, S., Yoshida, S., Uozumi, K., Suzuki, S., Maehara, Y., and Harada, M. (2006). Adult T-cell leukemia development from a human T-cell leukemia virus type I carrier after a living-donor liver transplantation. *Transplantation* 82, 840–843.

Kchour, G., Makhoul, N. J., Mahmoudi, M., Kooshyar, M. M., Shirdel, A., Rastin, M., Rafatpanah, H., Tarhini, M., Zalloua, P. A., Hermine, O., Farid, R., and Bazarbachi, A. (2007). Zidovudine and interferon-alpha treatment induces a high response rate and reduces HTLV-1 proviral load and VEGF plasma levels in patients with adult T-cell leukemia from North East Iran. *Leuk. Lymphoma* 48, 330–336.

Kchour, G., Tarhini, M., Kooshyar, M. M., El Hajj, H., Wattel, E., Mahmoudi, M., Hatoum, H., Rahimi, H., Maleki, M., Rafatpanah, H., Rezaee, S. A., Yazdi, M. T., Shirdel, A., de Thé, H., Hermine, O., Farid, R., and Bazarbachi, A. (2009). Phase 2 study of the efficacy and safety of the combination of arsenic trioxide, interferon alpha, and zidovudine in newly diagnosed chronic adult T-cell leukemia/lymphoma (ATL). *Blood* 113, 6528–6532

Khameneh, Z. R., Baradaran, M., and Sepehrvand, N. (2008). Survey of the seroprovalence of HTLVI/II in hemodialysis patients and blood donors in Urmia. *Saudi J. Kidney Dis. Transpl.* 19, 838–841.

Koga, Y., Iwanaga, M., Soda, M., Inokuchi, N., Sasaki, D., Hasegawa, H., Yanagihara, K., Yamaguchi, K., Kamihira, S., and Yamada, Y. (2010). Trends in HTLV-1 prevalence and the incidence of adult Tcell leukemia/lymphoma (ATLL) in Nagasaki, Japan. *J. Med. Virol.* 82, 668–674.

Kondo, T., Kono, H., Miyamoto, N., Yoshida, R., Toki, H., Matsumoto, I., Hara, M., Inoue, H., Inatsuki, A., Funatsu, T., Yamano, N., Bando, F., Iwao, E., Miyoshi, I., Hinuma, Y., and Hanaoka, M. (1989). Age- and sex-specific cumulative rate and risk of ATLL for HTLV-I carriers. *Int. J. Cancer* 43, 1061–1104.

Kondo, T., Kono, H., Nonaka, H., Miyamoto, N., Yoshida, R., Bando, F., Inoue, H., Miyoshi, I., Hinuma, Y., and Hanaoka, M. (1987). Risk of adult T-cell leukaemia/lymphoma in HTLV-I carriers. *Lancet* 2, 159.

Kondo, T., Nonaka, H., Miyamoto, N., Yoshida, R., Matsue, Y., Ohguchi, Y., Inouye, H., Komoda, H., Hinuma, Y., and Hanaoka, M. (1985). Incidence of adult T-cell leukemia-lymphoma and its familial clustering. *Int. J. Cancer* 35, 749–751.

Lee, C. W., Chang, M. C., Chang, Y. F., Hsieh, R. K., Lin, J., and Chen, K. S. (2010). Adult T-cell leukemia/lymphoma in Taiwan: an analysis of 17 patients and review of the literature. *Asia Pac. J. Clin. Oncol.* 6, 161–164.

Lee, M., Kim, B. K., Lee, H. B., Park, K. S., Suh, C., Lee, I. H., Bang, Y. I., Kim, S. T., Kim, N. K., Cha, C. Y., Moon, S. B., Cho, H. I., Lee, S. Y., and Takatsuki, K. (1987). Adult T-cell leukemia – the first case in Republic of Korea. *J. Kor. Med. Assoc.* 30, 1146–1152.

Levine, P. H., Dosik, H., Joseph, E. M., Felton, S., Bertoni, M. A., Cervantes, J., Moulana, V., Miotti, A. B., Goberdhan, L. J., Lee, S. L., Daouad, A., DaCosta, M., Jaffe, E. S., Axiotis, C. A., Cleghorn, F. R., Kahn, A., and Welles, S. L. (1999). A study of adult T-cell leukemia/lymphoma incidence in central Brooklyn. *Int. J. Cancer* 80, 662–666.

Liang, R. (1994). HTLV-I associated adult T-cell leukaemia/lymphoma in Hong Kong. *Am. J. Hematol.* 45, 100–101.

Lymphoma Study Group of Japanese Pathologists. (2000). The World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. *Pathol. Int.* 50, 696–702.

Manns, A., Miley, W. J., Wilks, R. J., Morgan, O. S., Hanchard, B., Wharfe, G., Cranston, B., Maloney, E., Welles, S. L., Blattner, W. A., and Waters, D. (1999). Quantitative proviral DNA and antibody levels in the natural history of HTLV-1 infection. *J. Infect. Dis.* 180, 1487–1493.

Manzari, V., Gradilone, A., Barillari, G., Zani, M., Collalti, E., Pandolfi, F., De Rossi, G., Liso, V., Babbo, P., and Robert-Guroff, M. (1985). HTLV-I is endemic in southern Italy: detection of the first infectious cluster in a white population. *Int. J. Cancer* 36, 557–559.

Marin, O., Hasui, K., Remondegui, C., Sato, E., Aye, M. M., Takenouchi, N., Izumo, S., and Tajima, K. (2002). Adult T-cell leukemia/lymphoma in Jujuy, north-west Argentina. *Pathol. Int.* 52, 348–357.

Meytes, D., Schochat, B., Lee, H., Nadel, G., Sidi, Y., Cerney, M., Swanson, P., Shaklai, M., Kilim, Y., Elgat, M., Chin, E., Danon, Y., and Rosenblatt, J. D. (1990). Serological and molecular survey for HTLV-I infection in a high-risk Middle Eastern group. *Lancet* 336, 1533–1535.

Miller, M., Achiron, A., Shaklai, M., Stark, P., Maayan, S., Hannig, H., Hunsmann, G., Bodemer, W., and Shohat, B. (1998). Ethnic cluster of HTLVI infection in Israel among the Mashhadi Jewish population. *J. Med. Virol.* 56, 269–274.

Mueller, N., Okayama, A., Stuver, S., and Tachibana, N. (1996). Findings from the Miyazaki Cohort Study. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 13, S2–S7.

Murphy, E. L., Hanchard, B., Figueroa, J. P., Gibbs, W. N., Lofters, W. S., Campbell, M., Goedert, J. J., and Blattner, W. A. (1989). Modelling the risk of adult T-cell leukemia/lymphoma in persons infected with human T-lymphotropic virus type I. *Int. J. Cancer* 43, 250–253.

Nakada, K., Yamaguchi, K., Furugen, S., Nakasone, T., Nakasone, K., Oshiro, Y., Kohakura, M., Hinuma, Y., Seiki, M., Yoshida, M., Matutes, E., Catovsky, D., Ishii, T., and Takatsuki, K. (1987). Monoclonal integration of HTLV-I proviral DNA in patients with strongyloidiasis. *Int. J. Cancer* 40, 145–148.

Ohshima, K., Suzumiya, J., and Kikuchi, M. (2002). The World Health Organization classification of malignant lymphoma: incidence and clinical prognosis in HTLV-1-endemic area of Fukuoka. *Pathol. Int.* 52, 1–12.

Okayama, A., Stuver, S., Matsuoka, M., Ishizaki, J., Tanaka, G., Kubuki, Y., Mueller, N., Hsieh, C. C., Tachibana, N., and Tsubouchi, H. (2004). Role of HTLV-1 proviral DNA load and clonality in the development of adult T-cell leukemia/lymphoma in asymptomatic carriers. *Int. J. Cancer* 110, 621–625.

Paun, L., Ispas, O., Del Mistro, A., and Chieco-Bianchi, L. (1994). HTLV-I in Romania. *Eur. J. Haematol.* 52, 117–118.

Plancoulaine, S., Buigues, R. P., Murphy, E. L., van Beveren, M., Pouliquen, J. F., Joubert, M., Rémy, F., Tuppin, P., Tortevoye, P., de Thé, G., Moreau, J. P., and Gessain, A. (1998). Demographic and familial characteristics of HTLV-1 infection among an isolated, highly endemic population of African origin in French Guiana. *Int. J. Cancer* 76, 331–336.

Plumelle, Y., Gonin, C., Edouard, A., Bucher, B. J., Thomas, L., Brebion, A., and Panelatti, G. (1997). Effect of strongyloides stercoralis infection and eosinophilia on age at onset and prognosis of adult T-cell leukemia. *Am. J. Clin. Pathol.* 107, 81–87.

Poiesz, B. J., Ruscetti, F. W., Gazdar, A. F., Bunn, P. A., Minna, J. D., and Gallo, R. C. (1980). 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.* 77, 7415–7419.

Pombo de Oliveira, M. S., Loureiro, P., Bittencourt, A., Chiattone, C., Borducchi, D., De Carvalho, S. M., Barbosa, H. S., Rios, M., Sill, A., Cleghorn, F., and Blattner, W. (1999). Geographic diversity of adult t-cell leukemia/lymphoma in Brazil. The Brazilian ATLL Study Group. *Int. J. Cancer* 83, 291–298.

Pombo de Oliveira, M. S., Matutes, E., Schulz, T., Carvalho, S. M., Noronha, H., Reaves, J. D., Loureiro, P., MacHado, C., and Catovsky, D. (1995). T-cell malignancies in Brazil: clinico-pathological and molecular studies of HTLV-I positive and negative cases. *Int. J. Cancer* 60, 823–827.

Portal Site of Official Statistics of Japan. (2012). *Portal Site of Official Statistics of Japan (e-Stat), Developed by Statistics Bureau, Ministry of Internal Affairs and Communications with the collaboration of Ministries and Agencies, and Managed by Incorporated Administrative Agency National Statistics Center.* Available at: http://www.e-stat.go.jp/SG1/estat/GL08020101.do?_toGL08020101_&tstatCode=000001028897&requestSender=dsearch [In Japanese, accessed April 8, 2012]

Pouliquen, J. F., Hardy, L., Lavergne, A., Kafiludine, E., and Kazanji, M. (2004). High seroprevalence of human T-cell lymphotropic virus type 1 in blood donors in Guyana and molecular and phylogenetic analysis of new strains in the Guyana shelf (Guyana, Suriname, and French Guiana). *J. Clin. Microbiol.* 42, 2020–2026.

Proietti, F. A., Carneiro-Proietti, A. B., Catalan-Soares, B. C., and Murphy, E. L. (2005). Global epidemiology of HTLV-I infection and associated diseases. *Oncogene* 24, 6058–6068.

Rafatpanah, H., Hedayati-Moghaddam, M. R., Fathimoghadam, F., Bidkhori, H. R., Shamsian, S. K., Ahmadi, S., Sohgandi, L., Azarpazhooh, M. R., Rezaee, S. A., Farid, R., and Bazarbachi, A. (2011). High prevalence of HTLV-I infection in Mashhad, Northeast Iran: a population-based seroepidemiology survey. *J. Clin. Virol.* 52, 172–176.

Safai, B., Huang, J. L., Boeri, E., Farid, R., Raafat, J., Schutzer, P., Ahkami, R., and Franchini, G. (1996). Prevalence of HTLV type I infection in Iran: a serological and genetic study. *AIDS Res. Hum. Retroviruses* 12, 1185–1190.

Sakuma, T., Satoh, T., Satodate, R., Madarame, T., Onodera, I., Suzuki, Z., and Itoh, C. (1988). Adult T-cell leukemia by probable horizontal transmission from husband to wife. *Jpn. J. Clin. Oncol.* 18, 75–79.

Satake, M., Yamaguchi, K., and Tadokoro, K. (2012). Current prevalence of HTLV-1 in Japan as determined by screening of blood donors. *J. Med. Virol.* 84, 327–335.

Satoh, M., Toma, H., Sugahara, K., Etoh, K., Shiroma, Y., Kiyuna, S., Takara, M., Matsuoka, M., Yamaguchi, K., Nakada, K., Fujita, K., Kojima, S., Hori, E., Tanaka, Y., Kamihira, S., Sato, Y., and Watanabe, T. (2002). Involvement of IL-2/IL-2R system activation by parasite antigen in polyclonal expansion of CD4(+)25(+) HTLV-1-infected T-cells in human carriers of both HTLV-1 and S. stercoralis. *Oncogene* 21, 2466–2475.

Shimoyama, M. (1991). Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: a report from the Lymphoma Study Group (1984–87). *Br. J. Haematol.* 79, 428–437.

Shtalrid, M., Shvidel, L., Korenfeld, R., Duek, A., Landau, Z., and Berrebi, A. (2005). HTLV-1 associated adult T-cell leukemia/lymphoma in Israel: report of two patients of Romanian origin. *Haematologica* 90, ECR13.

Sidi, Y., Meytes, D., Shohat, B., Fenig, E., Weisbort, Y., Lee, H., Pinkhas, J., and Rosenblatt, J. D. (1990). Adult T-cell lymphoma in Israeli patients of Iranian origin. *Cancer* 65, 590–593.

Sonoda, S., Li, H. C., and Tajima, K. (2011). Ethnoepidemiology of HTLV-1 related diseases: ethnic determinants of HTLV-1

susceptibility and its worldwide dispersal. *Cancer Sci.* 102, 295–301.

Tachibana, N., Okayama, A., Ishihara, S., Shioiri, S., Murai, K., Tsuda, K., Goya, N., Matsuo, Y., Essex, M., Stuver, S., and Mueller, N. (1992). High HTLV-I proviral DNA level associated with abnormal lymphocytes in peripheral blood from asymptomatic carriers. *Int. J. Cancer* 51, 593–595.

Tajima, K. (1990). The 4th nationwide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. The T- and B-cell Malignancy Study Group. *Int. J. Cancer* 45, 237–243.

Takatsuki, K., Uchiyama, J., Sagawa, K., and Yodoi, J. (1977). "Adult T-cell leukemia in Japan," in *Topics in Hematology*, eds S. Seno, F. Takaku, and S. Irino (Amsterdam: Excerpta Medica), 73–77.

Takezaki, T., Hirose, K., Hamajima, N., Kuroishi, T., and Tajima, K. (1997). Estimation of adult T-cell leukemia incidence in Kyushu District from vital statistics Japan between 1983 and 1982: comparison with a nationwide survey. *Jpn. J. Clin. Oncol.* 27, 140–145.

Talarmin, A., Vion, B., Ureta-Vidal, A, Du Fou, G., Marty, C., and Kazanji, M. (1999). First seroepidemiological study and phylogenetic characterization of human T-cell lymphotropic virus type I and II infection among Amerindians in French Guiana. *J. Gen. Virol.* 80, 3083–3088.

The T- and B-Cell Malignancy Study Group. (1981). Statistical analysis of immunologic, clinical and histopathologic data on lymphoid malignancies in Japan. *Jpn. J. Clin. Oncol.* 11, 15–38.

The T- and B-Cell Malignancy Study Group. (1985). Statistical analyses of clinico-pathological, virological and epidemiological data on lymphoid malignancies with special reference to adult T-cell leukemia/lymphoma: a report of the second nationwide study of Japan. *Jpn. J. Clin. Oncol.* 15, 517–535.

Tian, Y., Kobayashi, S., Ohno, N., Isobe, M., Tsuda, M., Zaike, Y., Watanabe, N., Tani, K., Tojo, A., and Uchimaru, K. (2011). Leukemic T cells are specifically enriched in a unique CD3(dim) CD7(low) subpopulation of CD4(+) T cells in acute-type adult T-cell leukemia. *Cancer Sci.* 102, 569–577.

Tokudome, S., Tokunaga, O., Shimamoto, Y., Miyamoto, Y., Sumida, I., Kikuchi, M., Takeshita, M., Ikeda, T., Fujiwara, K., Yoshihara, M., Yanagawa, T., and Nishizumi, M. (1989). Incidence of adult T-cell leukemia/lymphoma among human T-lymphotropic virus type I carriers in Saga, Japan. *Cancer Res.* 49, 226–228.

Tsuji, T., Sugahara, K., Tsuruda, K., Uemura, A., Harasawa, H., Hasegawa, H., Hamaguchi, Y., Tomonaga, M., Yamada, Y., and Kamihira, S. (2004). Clinical and oncologic implications in epigenetic down-regulation of CD26/dipeptidyl peptidase IV in adult T-cell leukemia cells. *Int. J. Hematol.* 80, 254–260.

Tuppin, P., Lepère, J. F., Carles, G., Ureta-Vidal, A., Gérard, Y., Peneau, C., Tortevoye, P., de Thé, G., Moreau, J. P., and Gessain, A. (1995). Risk factors for maternal HTLV-I infection in French Guiana: high HTLV-I prevalence in the Noir Marron population. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 8, 420–425.

Uchiyama, T., Yodoi, J., Sagawa, K., Takatsuki, K., and Uchino, H. (1977). Adult T-cell leukemia: clinical and hematologic features of 16 cases. *Blood* 50, 481–492.

Uno, H., Kawano, K., Matsuoka, H., and Tsuda, K. (1988). HLA and adult T-cell leukaemia: HLA-linked genes controlling susceptibility to human T-cell leukaemia vims type I. *Clin. Exp. Immunol.* 71, 211–215.

Veelken, H., Kohler, G., Schneider, J., Dierbach, H., Mertelsmann, R., Schaefer, H. E., and Lubbert, M. (1996). HTLV-I-associated adult T cell leukemia/lymphoma in two patients from Bucharest, Romania. *Leukemia* 10, 1366–1369.

Yamada, Y., Atogami, S., Hasegawa, H., Kamihira, S., Soda, M., Satake, M., and Yamaguchi, K. (2011). Nationwide survey of adult T-cell leukemia/lymphoma (ATL) in Japan. *Rinsho Ketsueki* 52, 1765–1771.

Yamaguchi, K., Kiyokawa, T., Nakada, K., Yul, L. S., Asou, N., Ishii, T., Sanada, I., Seiki, M., Yoshida, M., and Matutes, E. (1988). Polyclonal integration of HTLV-I proviral DNA in lymphocytes from HTLV-I seropositive individuals: an intermediate state between the healthy carrier state and smouldering ATL. *Br. J. Haematol.* 68, 169–174.

Yamaguchi, K., Matutes, E., Catovsky, D., Galton, D. A., Nakada, K., and Takatsuki, K. (1987). Strongyloides stercoralis as candidate co-factor for HTLV-I-induced leukaemogenesis. *Lancet* 2, 94–95.

Yamaguchi, K., Seiki, M., Yoshida, M., Nishimura, H., Kawano, F., and Takatsuki, K. (1984). The detection of human T cell leukemia virus proviral DNA and its application for classification and diagnosis of T cell malignancy. *Blood* 63, 1235–1240.

Yamaguchi, K., Uozumi, K., Taguchi, H., Kikuch, H, Okayama, A., Kamihira, S., Hino, S., Nosaka, K., and Watanabe, T. (2007). Nationwide Cohort Study of HTLV-1 Carriers in Japan: Joint Study on Predisposing Factors of ATL Development (JSPFAD) [Abstract O-23]. *AIDS Res. Hum. Retroviruses* 23, 581–600.

Yamamoto, J. F., and Goodman, M. T. (2008). Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997–2002. *Cancer Causes Control* 19, 379–390.

Yashiki, S., Fujiyoshi, T., Arima, N., Osame, M., Yoshinaga, M., Nagata, Y., Tara, M., Nomura, K., Utsunomiya, A., Hanada, S., Tajima, K., and Sonoda, S. (2001). HLA-A*26, HLA-B*4002, HLAB*4006, and HLA-B* 4801 alleles predispose to adult T cell leukemia: the limited recognition of HTLV type 1 tax peptide anchor motifs and epitopes to generate anti-HTLV type 1 tax CD8(+) cytotoxic T lymphocytes. *AIDS Res. Hum. Retroviruses* 17, 1047–1061.

Yoshida, M., Miyoshi, I., and Hinuma, Y. (1982). Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. *Proc. Natl. Acad. Sci. U.S.A.* 79, 2031–2035.

Yoshizumi, T., Shirabe, K., Ikegami, T., Kayashima, H., Yamashita, N., Morita, K., Masuda, T., Hashimoto, N., Taketomi, A., Soejima, Y., and Maehara, Y. (2012). Impact of human T cell leukemia virus type 1 in living donor liver transplantation. *Am. J. Transplant.* 12, 1479–1485.

Zhuo, J., Yang, T., Zeng, Y., and Lu, L. (1995). Epidemiology of anti-human T-cell leukemia virus type I antibody and characteristics of adult T-cell leukemia in China. *Chin. Med. J.* 108, 902–906.

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 02 May 2012; accepted: 20 August 2012; published online: 10 September 2012.*

*Citation: Iwanaga M, Watanabe T and Yamaguchi K (2012) Adult T-cell leukemia: a review of epidemiological evidence. Front. Microbio. 3:322. doi: 10.3389/fmicb.2012.00322*

*This article was submitted to Frontiers in Virology, a specialty of Frontiers in Microbiology.*

# 【成人T細胞白血病（ATL）におけるmicroRNAの発現異常】

## Abnormal expression of miRNA in Adult T Cell Leukemia

山岸　誠・渡邉　俊樹

Makoto Yamagishi　Toshiki Watanabe

Key words
expression profile, genome-wide analysis, epigenetics, signal transduction, JSPFAD

要　約

T細胞白血病（ATL）は，母乳を介したHTLV-1感染の後，約50年以上の臨床的潜伏期間の後に発症する。感染T細胞はウイルス遺伝子産物により不死化し，遺伝子異常の蓄積を介して腫瘍化して発症する。しかし，不死化と腫瘍化に関わる遺伝子の実体と分子機構は未だに不明である。がん研究の領域でmicroRNA（miRNA）発現異常の意義が広く認められている。HTLV-1/ATLの領域でも幾つかの先行研究の報告があったが，情報は不十分であった。筆者らはHTLV-1感染者コホート共同研究組織JSPFADの全面的協力を得て，世界で初めてATL細胞のDNA，mRNA，miRNAの大規模な統合解析を完了した。その結果，miRNA-31（miR-31）がすべてのATL患者検体で著明な減少を示すことを見いだした。miR-31の減少は新たに同定した標的遺伝子NIKの過剰発現とそれに伴うNF-κBシグナルの恒常的活性化を誘発すること，miR-31を再導入するとNF-κB経路が不活化され細胞死が誘導される事を示した。miR-31の発現欠失の原因が，ゲノムの欠損及びPolycombファミリー依存的なエピジェネティックな異常であることも明らかにした。またATLだけでなく乳がん細胞やB細胞における免疫応答反応でも同機構が保存されていることがわかった。従ってPolycombファミリー，miR-31，NIKのバランスが細胞の運命に重要であることが示された。Polycombファミリーの異常は種々のがん細胞で注目されており，重要な分子標的となる。miRNAを介したPolycombとNF-κBのクロストークは新たな概念であり，本研究の成果によりエピジェネティックな異常がNF-κBの恒常的活性化を介してアポトーシス抵抗性の獲得に寄与することが明らかとなった。

## はじめに

成人T細胞白血病（Adult T cell Leukemia, ATL）はヒトT細胞白血病ウイルスI型（Human T cell Leukemia Virus type 1, HTLV-1）の感染によって引き起こされる重篤なT細胞性白血病/リンパ腫である。50～60年という長い潜伏期間にHTLV-1感染末梢血T細胞に複数の遺伝子異常が蓄積しがん化が引き起こされる。現在世界には2000万人以上の感染者がいるとされるが，日本は特に多く，約120万人の感染者が存在し毎年約1000人を超えるATLが発症している。白血病やウイルスの発見当時から，この分野における日本人研究者の貢献度は多大であるが，ウイルスによる細胞の不死化や腫瘍化，治療抵抗性などの分子メカニズムは未だに不明な点が多く残されており，有効な治療法は未だに存在しない。ウイルスの根絶と白血病の予防，新規治療法開発を目指した分子レベルの病態解明が必須である[1]。

ATL細胞及びHTLV-1感染細胞の生物学的な特徴として，恒常的なNF-κBシグナル経路の活性化があり，これによって細胞の異常な増殖及び生存が確保されている[2]。HTLV-1感染細胞ではウイルスタンパク質であるTaxがNF-κBの定型的（canonical）及び非定型的（noncanonical）経路を劇的に活性化するが，Taxの発現が認められないATL腫瘍細胞におけるNF-κBの活性化メカニズムは不明な点が多かった。その後，遺伝子発現解析によってNF-κB inducing kinase（NIK）のmRNAの過剰発現が恒常的なNF-κBの活性化に寄与していることが明らかになっているが[3]，NIKの異常発現機構については不明であった。NF-κBシグナルの異常な活

東京大学大学院新領域創成科学研究科 メディカルゲノム専攻 病態医療科学分野
Laboratory of Tumor Cell Biology, Department of Medical Genome Sciences, Graduate School of Frontier Sciences, The University of Tokyo
〒108-8639　東京都港区白金台4-6-1　TEL：03-5449-5298

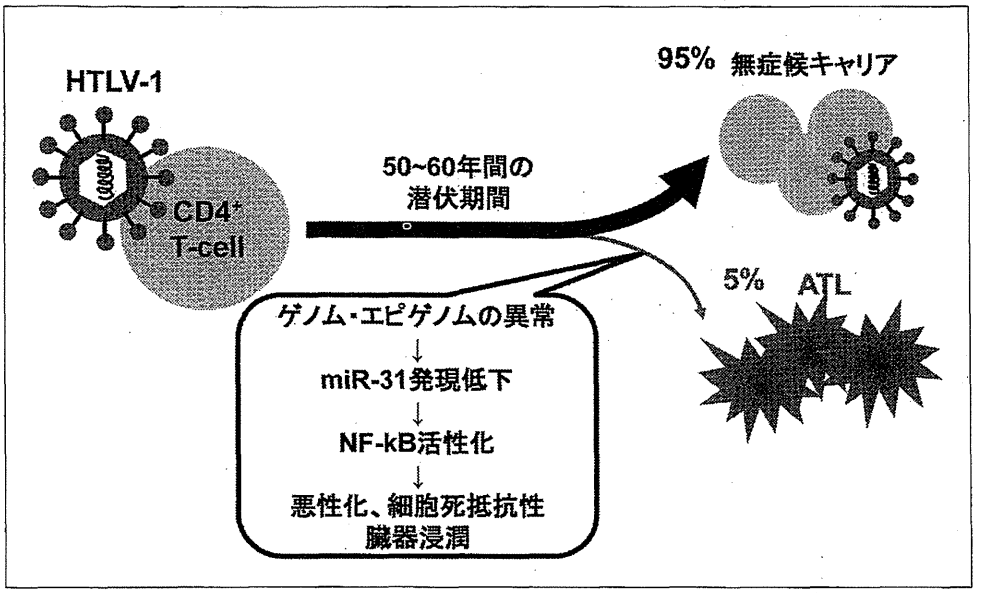


図1
HTLV-1感染から腫瘍化へのモデル図
ATLはHTLV-1感染者（キャリア）の約5%で発症する。白血病細胞はウイルス遺伝子の発現が低く，様々な遺伝子異常の蓄積によってシグナル伝達系の攪乱が起こっている。miR-31はATL全例で低下しており，腫瘍細胞の悪性化に寄与する。

性化とそれに伴う腫瘍細胞の生存能の獲得と悪性化は，ATLだけでなく多くの固形癌や悪性リンパ腫，白血病で共通して見られるがん細胞の特徴的な分子病態の1つである。その中でもNIKの高発現による異常活性化は重要な位置を占めているが，正常を逸脱するその機構は不明であり，がん研究全体の課題であった。

我々は，ATLのmiRNA，mRNA発現解析及びゲノム異常の解析を統合してATLの分子病態の全貌を明らかにすることを目指して来た。その結果明らかとなったATLの分子異常は臨床的特徴をよく反映しており，分子マーカーや治療標的として様々な情報を提示した。さらに，明らかとなった新たな分子メカニズムはがん研究および新規治療法開発の基盤となる新たな概念を提唱した。

## 1. ATL臨床検体を用いた大規模統合解析からみるATLの分子病態

従来のATL研究の多くは，細胞株か，少数の患者由来細胞から得られた情報を基盤としたものが主であり，限界があることは周知のことであった。従って，実際の個体内のATL細胞における分子異常の実体を正確に理解することがATL/HTLV研究において重要な課題とされていた。未だに有効な治療法が無いATLに対して最も基本となるATL細胞そのものの分子病態に関わる根本的な情報を得るために，筆者らはまず，全国的な共同研究組織JSPFAD（http://htlv1.org/）の全面的な協力を得て，その検体バンクを利用してATLの臨床検体を用いたmiRNAおよびmRNAの大規模解析に着手した。Agilent Technologies社のmiRNAマイクロアレイを用いてATL40例，正常CD4+T細胞22例について解析を行った結果，非常に厳しい検定をクリアした61個のmiRNAの発現異常を同定した。他のがん細胞の報告と同様に，ATL細胞では正常T細胞に比べて異常を示すmiRNAのほとんどが「発現低下」と言う異常を示すことが明らかになった。また，ATLのmiRNA発現プロファイルはユニークであり，miRNAの発現をもって正常T細胞と区別ができることもわかった。この61個のmiRNAのなかで最も著明な発現低下を示したmiR-31は，正常T細胞では比較的発現量が高く，一方でATL細胞は非常に発現が低い，もしくは検出限界以下にまで低下している事が確認された。miR-31は乳がん細胞の転移能を始めとする様々な細胞機能に関わる重要なmiRNAで[4]，発現の欠損が細胞の運命に重要な意味を包含すると推察された。

## 2. miR-31の発現減少とその生物学的意義

miRNAの主な生物学的機能は，標的遺伝子の3' UTRに結合することによって遺伝子発現を負に制御することである。外来の合成siRNAと異なり，miRNAの配列認識は揺らぎが特徴的であり，1つのmiRNAが複数個の遺伝子を制御することができる（Pleiotropic function）。細胞の運命に重大な影響を与える標的の遺伝子の探索には，物理的な抑制効果と同時に標的側の機能や挙動も重要な指標となり，従って多角的な実験的検証が必須になる。筆者らは，ATL全例で発現が欠損していたmiR-31のT細胞における生物学的意義を明らかにする為に，以下の検討を行った。

①miR-31の標的遺伝子の予測を4つのアルゴリズムによって予測，②ATL細胞のmRNA大規模解析データとの擦り合わせによる検証，③変異を導入したレポーターアッセイ，④miR-31の増減に対する標的候補遺伝子の定量，⑤miR-31と標的遺伝子の関係の保存性。以上の検討の結果，NF-κB Inducing Kinase（NIK）がmiR-31の新規標的遺伝子であることを初めて明らかにした。NIKはNF-κBの非定型的経路の活性化に必須のリン酸化酵素であり，NIKの発現レベルがNF-κBシグナルの恒常的活性化に直接的に寄与することが複数のがんに関して報告されている。ATLではNIKのmRNA量が増加していることがわかっていたが[9]，過剰発現の原因は明らかにされていなかった。ATL患者から樹立された細胞株にmiR-31を過剰発現させると，NIK mRNA及びタンパク質レベルが低下し，NF-κBの活性化が抑制されることが示された。これらの細胞では細胞増殖レベルの低下，抗アポトーシス遺伝子の発現低下，アポトーシス感受性の増加，が認められた。さらにmiR-31を発現するレンチウイルスベクターは，ATL患者から直接取り出したATL細胞にアポトーシスを誘導することが示された（後述）。以上より，miR-31の発現低下はATL細胞の生存にとって重要であり，その分子メカニズムはNIKの過剰発現の誘導であることが示された。NF-κBシグナルは非常に複雑な制御機構を備えているが，本研究によりmiR-31が新たなNF-κB抑制因子として同定されたことになる。

## 3. ゲノム及びエピゲノムの異常とmiR-31の発現制御

細胞内の成熟miRNAのダイナミズムは，転写制御と，転写後の成熟過程の制御によって規定される。ATL全例で発現欠損があるmiR-31は，転移性乳がんや前立腺がんなどでも発現が減少しており，がん細胞における一般性と重要性が示唆されたが，細胞内のmiR-31レベルがどのように制御されるかについては不明であった。hsa-miR-31は，多くのがん細胞でゲノムの欠失が頻発する9p21.3のCDKN2A/B領域に隣接しており，ATLにおいてもゲノムの不安定性が予測された。ATL168症例の大規模なDNAコピー数解析の結果，12.5%の症例においてmiR-31ゲノムの，ホモもしくはヘテロの欠損があることがわかった。一方で，同時に行ったmiRNA発現解析では，ゲノムの欠損が無い症例でも正常T細胞に比べてmiR-31レベルが著しく減少していることが示された。一方，発現解析データとアルゴリズムからmiR-31の転写構造を予測すると，miR-31はLOC554202遺伝子のイントロン領域にコードされ，独立した転写が起こっていることが明らかになった。また興味深い事に，YY1という転写因子の認識配列がmiR-31の転写開始点上流に集簇していることも明らかになった。YY1は，Polycombファミリーに属するDNA結合タンパク質で，ヒストンH3K27のメチル化酵素であるEZH2を始めとするPolycomb Repressive Complex 2（PRC2）のリクルーターとしての機能が注目されている[9]。そこでYY1のノックダウン実験を行ったところ，miR-31領域へのYY1の蓄積が低下し，それに付随してEZH2のリクルートが減少することが示された。

我々の解析で示された，最も基本的な問題は，ATL細胞を始めとする高悪性度の腫瘍においてなぜmiR-31の発現が激減するのか?である。この問題の答を求めるため種々の解析を行った。まず，ATLのmRNA発現解析の結果から，Polycombファミリーのヒストン H3K27のトリメチル化を誘導するEZH2及びSUZ12遺伝子の発現が正常T細胞に比べて高発現していることが明らかになった。ATL細胞株においてこれらのPolycombファミリー遺伝子をノックダウンすると，miR-31ゲノム領域へのPRC2のリクルートレベルが低下し，その結果H3K27及びH3K9のメチル化のレベルが低下した。さらに，ヒストンの脱アセチル化を介して転写抑制に働くHDAC1の結合レベルも低下し，その結果miR-31の発現が回復することが示された。以上の実験データからPolycombファミリーの発現異常がmiR-31の発現低下を誘導するという新たな分子メカニズムが明らかとなった。この事実は以下のデータからもサポートされる。

①ATL患者由来のATL細胞をChIPアッセイによって直接解析した結果，hsa-miR-31領域に異常な抑制的メチル化ヒストンが検出され，またEZH2のノックダウンが直接細胞死を誘導した（後述）。

②同様の分子メカニズムが好転移性乳がん細胞やB細胞株においても保存されていた。

以上より，細胞内における成熟miR-31の発現レベルはゲノムの安定性と，YY1-PRC2によるエピジェネティックな制御の両側面により規定されることが示された。

## 4. Polycombファミリーによる miR-31制御を介したNF-κB経路への影響

miR-31はNIKの他にRhoA，Radixin，Integrin α5，FoxP3，FIH，E2F2など様々な遺伝子を負に制御し，細胞

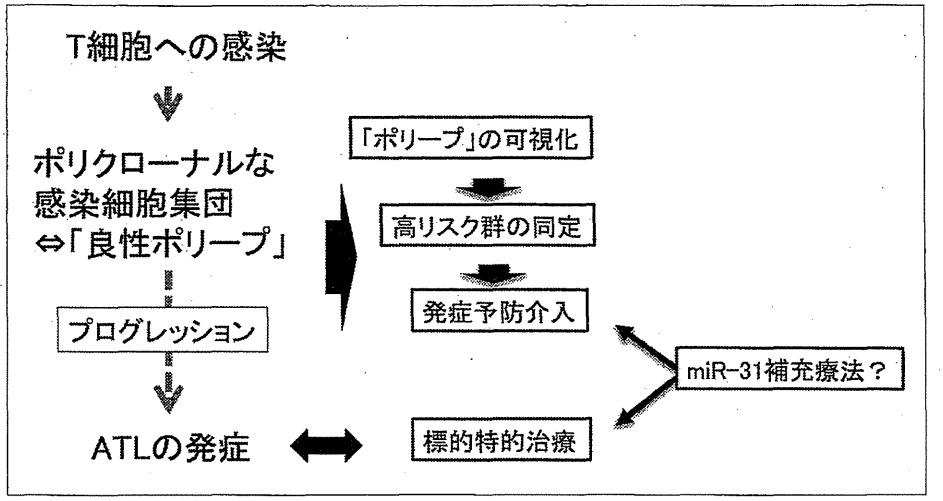


図2
HTLV-1による腫瘍化機構と治療戦略の可能性

ATL未発症キャリアの末梢血中の感染細胞はクローンとして増殖した感染細胞集団からなることが明らかになって来た。つまり，大腸がんにおける「ポリープ」の様な前癌病変であると捉えることができる。「miR-31補充療法」は，発現レベルの低下していない正常細胞には影響せず，発現低下を示す感染細胞集団とATL細胞を特異的に排除する治療法となる可能性がある。

の運命に強く影響すると言われている。一方でmiR-31を制御するPolycombファミリーは多くの悪性リンパ腫，白血病，固形癌等の細胞の増殖，生存，転移能に重要な因子であることが報告されているが，どの標的遺伝子が細胞の表現型に直接影響するかは不明な点が多かった。筆者らは，本研究で明らかとなった，①miR-31によるNIKを介したNF-κB経路の制御と，②PolycombファミリーによるmiR-31の発現制御を合わせ，Polycombによるエピジェネティックな制御がNIK依存的なNF-κB経路の制御に関わる，という仮説を立てた。これまでPolycombファミリーとNF-κB経路の関係は全く注目されていなかった。

上述した様に，ATL細胞株においてEZH2もしくはSUZ12をノックダウンすると，miR-31の発現が誘導され，このときNIKのレベルが低下することによって下流のシグナルが停止し，NF-κB活性レベルが低下した。さらにこれらの細胞では細胞増殖及び細胞死抵抗性が低下した。Polycomb，miR-31，NIKは各経路の上流に位置する因子で，細胞に対するアウトプットは様々な形に拡散すると考えられるが，以下の実験事実により，上記の分子機構は非常に重要であると考えられる。①Polycombファミリーのノックダウンによって低下したNF-κB活性レベルは，miR-31の阻害剤を共存させることによって回復することから，PolycombによるNF-κBの制御はmiR-31を介していることが示唆される。②Polycombのノックダウンによって誘導されるATL細胞の強制的なApoptosisは3'UTRを持たないNIKによってレスキューされる。つまりPolycombファミリーによって獲得する異常な生存能の一部はNIKの機能によって具現化される。③miR-31の過剰発現やPolycombのノックダウンは，B細胞におけるBAFFやCD40Lからの非定型的NF-κB経路の活性化を阻害することから，がん細胞シグナルだけでなく，正常細胞のシグナルの調整にも重要である。④miR-31の発現及びPolycombのノックダウンによりATL細胞のMDC（CCR4リガンド）に対する走化性が低下した。従って，NIK以外のmiR-31の標的遺伝子群による表現型はPolycombファミリーによって規定されている。

## 5. 新規治療法の開発へ

Polycombの過剰発現，miR-31の発現欠損，NIKの過剰発現とNF-κBの恒常的活性化は，いずれもATLの臨床検体から明らかになった。筆者らは本研究の総括として，上記のATL細胞の分子レベルの特徴が細胞の生存にどのように影響するかを検討した。miR-31の強制発現，EZH2もしくはNIKのノックダウンを行うレンチウイルスベクターを作製し，患者由来ATL細胞に直接導入することによって*ex vivo*での評価を行った。その結果，ある程度の個人差は認められるが，いずれのレンチウイルスも複数のATL末梢血検体のATL細胞に強烈なアポトーシスを誘導することが示された。同様の処理は健常者由来の末梢血単核球もしくはT細胞に対してはほとんど影響が無く，分子レベルのバランス異常がATL腫瘍細胞の生存に必須となっていることが示された。これらの結果は，miR-31がATL細胞特異的な細胞障害性を持つことを示している。従って，miR-31のATL細胞特異的な導入法を開発することにより，「miR-31補充療法」などの発症予防法やATLの新規治療法開発につながる可能性を示す結果と考えられる（図2）。

## おわりに

本研究では，ATLにおける新たな分子標的とNF-κB

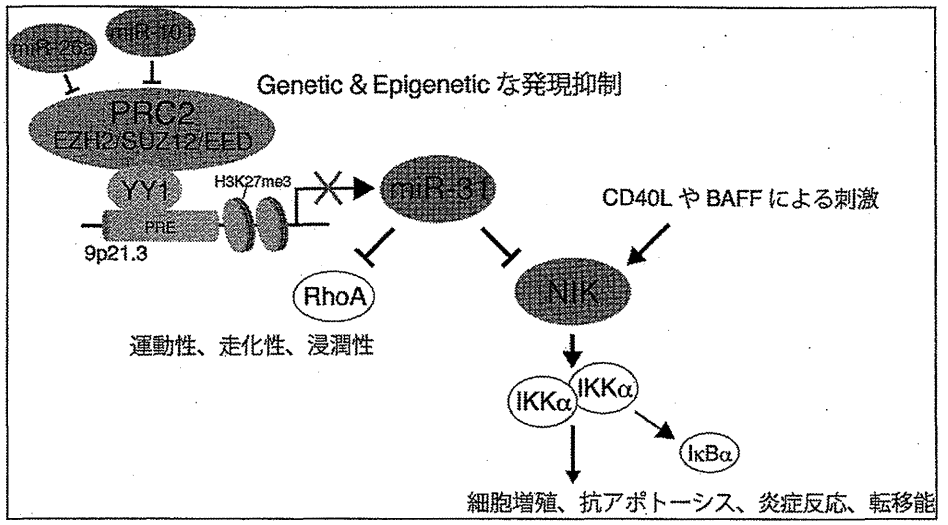


図3
Polycomb-miR-31-NF-kB のリンケージ

Polycomb 依存的な miR-31 の発現低下は NIK などの標的遺伝子を介して細胞の表現型に影響する。この分子間の関係は様々な細胞で保存されており、各因子の存在量のバランスによって均衡が保たれている。バランスを崩した細胞は悪性化をたどると考えられる。

の活性化機序を解明することに成功した。これに加えて，Polycomb によるエピジェネティックな制御，miRNA による細胞運命の決定，NF-κB シグナル経路による免疫細胞及び腫瘍細胞の分子基盤，という3つのコンテクストに新たな生物学的リンクを見いだした（図3）。また，本研究で得られた知見は以下の点で重要であると考えられる。

まず，NIK の新たな制御機構を明らかにしたこと。NIK は ATL 以外に多発性骨髄腫，悪性リンパ腫，乳がんなどの NF-κB 異常活性化の原因因子である。また免疫担当細胞を始めとする種々の細胞の正常機能に NIK は必須であり，NIK を巡る基礎研究は注目をあつめている。NF-κB 経路の複雑な制御システムに miR-31 が組み込まれていること，さらに Polycomb 依存的なエピジェネティックな制御が miRNA を介して NF-κB 制御に寄与するという発見は，今後のシグナル伝達研究に対して大きく貢献すると考えられる。

2つ目は，Polycomb ファミリーは，miRNA の発現を制御することによって，より多くの遺伝子発現を転写及び翻訳の段階で影響力を持つ可能性が示されたことである。また Polycomb ファミリー自身も複数の miRNA によって制御されることが分かっている。現に，ATL においては EZH2 を抑制する miRNA 群が減少を示していた。

3つ目は，Polycomb ファミリーによる標的領域の認識機構の一端を明らかにしたこと。PRC2 の標的領域の認識は YY1 だけでは説明できないことは複数の研究によって示されているが，miR-31 のように YY1 結合配列の蓄積という特殊なケースが細胞に対する影響力が大きい可能性がある。

4つ目は，シグナルのクロストークと細胞の正常機能について。本研究で得られた知見はそれぞれの鍵分子の異常な挙動を指標にして明らかとなったが，各分子は元来，細胞の恒常性や正常機能に重要であると考えられる。がん研究から得られたこの様な知見がより基礎及び臨床的な理解へと貢献することを期待したいる。

最後に，前項でも触れた様に，ATL に対する分子標的薬として，miR-31 の応用可能性が示されたと言える。今後の研究により実用化が可能になれば，ATL のみならず同様の病態を示すがんの新たな治療法開発の先例となる可能性がある。

なお，本研究成果は Cancer Cell 誌，同刊のプレビューにて解説が掲載されている[6]。

## 文　献


1) Iwanaga, M., Watanabe, T., Utsunomiya, A. *et al.*: Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan. Blood, 116, 1211–1219 (2010).
2) Watanabe, M., Ohsugi, T., Shoda, M. *et al.*: Dual targeting of transformed and untransformed HTLV-1-infected T cells by DHMEQ, a potent and selective inhibitor of NF-kappaB, as a strategy for chemoprevention and therapy of adult T-cell leukemia. Blood, 106, 2462–2471 (2005).
3) Saitoh, Y., Yamamoto, N., Dewan, M.Z. *et al.*: Overexpressed NF-kappaB-inducing kinase contributes to the tumorigenesis of adult T-cell leukemia and Hodgkin Reed-Sternberg cells. Blood, 111, 5118–5129 (2008).
4) Valastyan, S., Reinhardt, F., Benaich, N. *et al.*: A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. Cell, 137, 1032-1046 (2009).
5) Simon, J.A. and Kingston, R.E.: Mechanisms of polycomb gene silencing: knowns and unknowns. Nat. Rev. Mol. Cell. Biol., 10, 697-708 (2009).
6) Uribesalgo I., Ballare C., and Croce LD.: Polycomb Regulates NF-κB Signaling in Cancer through miRNA. Cancer Cell, 21, 5-7 (2012).