Meeting Report on the 13th International Conference on Human Retrovirology: Human T-Cell Leukemia Virus Research

30 Years after Adult T-Cell Leukemia

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Introduction

Thirty years ago, in 1977, a new clinical entity called adult T-cell leukemia (ATL) was described in Japan by Takatsuki and colleagues. Subsequently, Poiesz, Ruscetti, Gallo, and coworkers; and Yoshida, Miyoshi, Hinuma, and colleagues isolated a human retrovirus named human T-cell leukemia virus type-1 (HTLV-1). The history of the discovery of ATL and the isolation of HTLV-1 has been recently reviewed elsewhere (1–3).

From May 22 to 25, 2007, 350 researchers gathered in Hakone, Japan, at the 13th International Conference on Human Retrovirology organized by Toshiki Watanabe (University of Tokyo, Tokyo, Japan) to discuss the latest findings on HTLV-1 pathogenesis. The meeting opened with a keynote presentation by Kuan-Teh Jeang (National Institute of Allergy and Infectious Diseases [NIAID], Bethesda, MD) reviewing cell proliferative changes, genetic damaging events, and checkpoint inactivation in the development of ATL (4). Over the next 4 days, >320 papers were presented. Conference highlights are summarized below.

Epidemiology of HTLV

HTLV infects 10 to 20 million individuals worldwide. Masahiro Satake (Tokyo Red Cross Blood Center, Tokyo, Japan) reported on HTLV-1 positivity rate (0.37%) in Japanese first-time blood donors. HTLV-1 seropositivity in donors was 1.18% in their 30s in 1995 and 1.28% in their 40s in 2005, showing an 8% increase in 10 years. The same trend was found in the donors who were an additional 10 years older. Satake interpreted these figures to reveal the rate of horizontal infection in Japan. How individuals become susceptible to HTLV infection was commented upon by Sabine Plancoulaine [Institut National de la Sante et de la Recherche Medicale (INSERM), Paris, France] using a genome-wide linkage analysis mapping the susceptibility locus in children of African origin for HTLV-1 infection through breast feeding. She found significant linkage between HTLV-1 susceptibility and two chromosomal loci at 2p25 and 6q27.

HTLV-1 infection is also associated with an inflammatory pathology termed HTLV-associated myelopathy (HAM) or tropical spastic paraparesis (TSP). The association of neurologic abnormalities and HTLV-1 infection was discussed by Edward Murphy (University of California San Francisco, San Francisco, CA). In his study (HTLV Outcome Study), Murphy followed 151 HTLV-1–positive and 387 HTLV-2–positive former blood donors for 10 years (5). Compared with uninfected controls, HTLV-positive subjects had significantly more motor and coordination abnormalities. Murphy concluded that HTLV-1 and HTLV-2 infections are associated with a spectrum of neurologic defects beyond those described previously for classic HAM.

Tax, Transcription, Cellular Proliferation, and Transformation

The HTLV-1 Tax oncoprotein induces cellular proliferation, survival, and genetic damage. Nuclear factor-κB (NF-κB) has been described as an important cellular target activated by Tax through both the canonical and noncanonical pathways. Masahiro Fujii (Niigata University, Niigata, Japan) suggested in new findings a specificity of noncanonical NF-κB activation in HTLV-1 pathogenesis. He found that noncanonical activation of NF-κB, as measured by p52 processing from its p100 precursor, is restricted to HTLV-1, but not HTLV-2. Tax. Interestingly, HTLV-1, but not HTLV-2, is oncogenic. Fujii further reported that noncanonical NF-κB activation depends on the PDZ binding motif (PBM) of Tax1 (located in carboxyl-terminal amino acids 350–353).

Following-up on the role of Tax PBM, complete genome sequences from two recently isolated African HTLVs, HTLV-3 (Sara Calattini and Renaud Mahieux, Pasteur, Paris, France) and HTLV-4 (William Switzer, Centers for Disease Control and Prevention, Atlanta, GA), were presented. The data revealed that HTLV-3 Tax retains a PBM that is absent from HTLV-4 Tax. This observation predicts different pathogenic outcomes from HTLV-3 and HTLV-4 infections.

Two presentations addressed Tax and genetic instability. Susan Marriott (Baylor College of Medicine, Houston, TX) reported that Tax represses double-strand DNA repair, which is partly governed by a protein complex containing DNA-protein kinase (DNA-PK). John Semmes (Eastern Virginia University, Norfolk, VA) showed that Tax binds DNA-PK directly and sequesters this factor into nuclear speckles, thus repressing double-strand DNA repair.
Tax can affect host cell metabolism through transcriptional activation of cellular genes. Jennifer Nyborg (Colorado State University, Fort Collins, CO) found that Tax promotes cyclic AMP–responsive element binding protein (CREB) phosphorylation, increasing the availability of modified CREB for promoter transactivation. Paul Laybourn (Colorado State University) identified a new function of Tax abrogation of H1-mediated repression of p300 coactivator activity. Laybourn also found that Tax decreased histone mRNA levels, arguing that such reduction may contribute to dysregulated expression of many cellular genes. Additional insight into Tax activation of promoters was provided by Nicholas Polakowski and Isabelle Lemasson (East Carolina University, Greenville, NC) who used a chromatin immunoprecipitation assay/microarray (ChIP-on-chip) approach to describe direct recruitment of Tax to many cellular promoters.

What are some of these promoters? Cynthia Pise-Masison’s [National Cancer Institute (NCI), Bethesda, MD) microarray analyses revealed increased expression in ATL leukemic cells of genes linked to cell cycle progression (e.g., CDC2, CCNI1), apoptosis repression (e.g., survivin), and tyrosine kinases (e.g., Lyn). Separately, Ralph Grassmann (University of Erlangen-Nuremberg, Erlangen, Germany) and Kuan-Teh Jeang (NIADD) showed altered microRNA (miRNA) expression in HTLV-1–transformed cells, suggesting that Tax also affects/occupies promoters that transcribe oncogenic miRNAs.

Many questions pertaining to in vivo tax and virus expression are currently unanswered. Charles Bangham (Imperial College, London, United Kingdom) used deuterated glucose for labeling patients’ lymphocytes to check the in vivo effect of taxHTLV expression on lymphocyte population dynamics. He saw increased patients’ lymphocytes to check the...
is an important possibility because ATL is characterized by even more profound immunosuppression than is seen in other leukemias.

Hiroki Yano (Nagoya City University, Nagoya, Japan) tested the ability of ATL cells (identified by a receptor frequently coexpressed on ATL cells, CCR4) to inhibit the proliferation of autologous CD4+ non-ATL cells. In five ATL cases studied, evidence was obtained of a degree of suppression in one case, and suggestive evidence was obtained in one further case. Frederic Toulza (Imperial College, London, United Kingdom) used a simple phenotypic definition of Treg cells, CD4+ FoxP3+, and reported that the percentage of CD4+ FoxP3+ cells in the circulation was negatively correlated with the rate of lysis of autologous naturally immune response.

Therapeutic Approaches to HTLV-1 Infection

Several speakers reviewed various ATL treatment options. Deidre O’Mahony (NCI) presented a phase 1 trial of Splizumab, a monoclonal antibody that binds to CD2 on human T-cells and natural killer cells, in CD2-positive lymphoid malignancies, including aggressive ATL with early encouraging response rates and relatively low toxicities. Lee Ratner (Washington University, St. Louis, MO) reported mixed clinical and virological findings from etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) infusional chemotherapy followed by zidovudine and interferon-α. Low levels of viral RNA were seen at the initiation of therapy, but viral RNA levels increased >10-fold in most relapsed cases during therapy. Juan Carlos Ramos (University of Miami, Miami, FL) found that the expression of IRF-4/MUM-1 and c-Rel in the absence of Tax in primary ATL cells was associated with resistance to zidovudine and interferon-α treatment.

Impressive treatment efficacy was seen from reduced-intensity stem cell transplantation (RIST) as reported by Ryuji Tanosaki (National Cancer Center Hospital, Tokyo, Japan). Among 18 patients who received RIST, 14 patients achieved complete remission. Three-year overall survival and event-free survival were 67 ± 12% and 55 ± 12%, respectively. Further explaining why stem cell transplantation is effective for ATL, Nanae Harashima (Tokyo Medical and Dental University) reported that Tax-specific CTL response was recovered [by stimulating peripheral blood mononuclear cells (PBMC) in vitro with HTLV-1–infected cells] after stem cell transplantation, suggesting a role for CTL in eliminating Tax-expressing cells and preventing relapse of ATL.

Development of Mouse Models for HTLV-1 and ATL

To date, oncogenic potential of Tax in transgenic mice has been intensively studied. However, all extant lymphoid and nonlymphoid tumors in mice have lacked the CD4 surface marker. By contrast, CD4 is present on almost all patient ATL cells. Hideki Hasegawa (National Institute of Infectious Diseases, Tokyo, Japan) had published recently that transgenic mice expressing Tax driven by a lymphocyte-specific protein tyrosine kinase Lck-proximal promoter, targeting immature thymocytes, developed CD4+ CD8- double-negative pre-T-cell leukemia/lymphoma (8). In new findings using the distal lck promoter, Takeo Ohsugi and Toru Urano (Kumamoto University, Kumamoto, Japan) now reported a tax transgenic mouse, which developed CD4+ T-cell leukemia (9).

It is popular to use nonobese diabetic severe combined immunodeficient (NOD-SCID) common γ-chain null (NOG) mice for transplantation with human cells. Paola Miyazato (Kyoto University) showed that spread of HTLV-1 infection in human PBMCs transplanted into NOG mice could be blocked by azidothymidine and tenofovir but only in early stages of infection. She discussed that Tax mRNA expression in the infected human cells in NOG mice increased after in vitro culture, similar to that seen in human cases. In a related approach, Praban Banerjee (State University of New York, Syracuse, NY) explanted HTLV-1–infected human CD34+ hematopoietic progenitor cells into NOD-SCID mice. He observed HTLV-1–infected human T cells, B cells, and monocytes/macrophages in transplanted mice. Some of the mice showed proliferation of HTLV-1–infected CD4+ T cell in lymphoid tissues as well as HTLV-1–infected CD34+ cells persisting in the bone marrow and thymus. Banerjee also reported that reconstitution of NOD-SCID mice with HTLV-1 Tax-transduced human CD34+ cells produced proliferating CD4+ T cells.

Future Perspectives

In the 30 years since the description of ATL, much has been learnt about HTLV-1 pathogenesis. Going forward, several important questions remain to be addressed for oncological research on ATL. Will the next years bring clarifying insights into roles contributed by human miRNAs to ATL initiation and progression? Would we learn...
why Tax is dispensable for ATL maintenance and why ATL does not use the “oncogene addiction” model of transformation? Will findings of virus-induced senescence, checkpoint inactivation, and cellular genetic damage meld into a coherent chronology of transformation events? In addition to these questions, equally important topics challenge immunologic and clinical HTLV-1 research. Indeed, one can look with anticipation to many intriguing answers that await revelation over the next 30 years.

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References

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