The First Human Retroviruses: The Human T Lymphotropic Viruses (HTLVs)

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Human retroviruses

**Delta retroviruses**
- Human T lymphotropic virus, type I (HTLV-I)
- Human T lymphotropic virus, type II (HTLV-II)
- Simian T lymphotropic viruses (STLVs)
- Bovine leukemia virus (BLV)

**Lentiviruses**
- Human immunodeficiency virus, type 1 (HIV-1)
- Human immunodeficiency virus, type 2 (HIV-2)

Endemic areas of HTLV-I infection
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HTLV-I: associated clinical disorders

Lymphoproliferative disorders
• Adult T cell leukaemia/lymphoma (ATLL)

Inflammatory disorders
• HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP)
• Arthopathy
• Uveitis
• Alveolitis

HAM/TSP
• Onset usually in 3rd to 4th decade of life, more common in females
• Insidious onset with initial symptoms of stiffness, weakness of lower extremities and frequency and urgency of urination
• Physical findings include weakness of the legs with spasticity, hyperreflexia and extensor plantar responses
• Associated with high HTLV-I proviral loads and certain HLA backgrounds

Adult T cell leukemia/lymphoma (ATLL) clinical/epidemiological features
• Spectrum of T cell malignancies: ranging from indolent (smouldering, chronic) to aggressive (acute, lymphomatous) forms
• Majority of cases are associated with infection at or around the time of birth, suggesting that infection of cells of the developing immune system may be important
• Prolonged incubation period of 20-50 years supporting multiple events in the transformation process
• Aggressive forms of ATLL have poor responses to therapeutic intervention; In addition patients are functionally immunocompromised and susceptible to a range of opportunistic infections e.g., Pneumocystis jiroveci which are associated with impaired T cell responses
Adult T cell leukemia/lymphoma (ATLL) pathological and immunological features

- **Acute leukemia** - high grade leukemia with typical “flower cells” in peripheral blood; Extensive visceral and cutaneous infiltrates; Leukemic cells express increased levels of the IL-2R and a range of other activation markers
- **Lymphomatous form** - extensive infiltration in mesentery, liver, spleen and skin; On occasions pan-organ infiltration is evident (lungs, kidneys, meninges)
- Histologically, these are large diffuse T cell lymphomas with numerous cytological abnormalities, generally CD4+; However, other phenotypes (CD4-CD8- double negative, CD8+ single positive and CD4+ CD8+ double positive) also occur
Cutaneous infiltrates in ATLL

HTLV-I Tax: cellular proliferation and transformation

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HTLV-I Tax and NF-kB activation

- MEKK3
- PKCα
- Rel
- p50
- IκB
- Canonical NF-kB pathway
- Phosphorylation and ubiquitination of IκB
- IκB degradation
- 26S proteasome
- NF-kB activation in patients with ATLL

- NF-κB activation in patients with ATLL

- NF-κB activation in patients with ATLL

Development of ATLL

- HTLV-I infected cell
- IL-2
- IL-2R
- IL-2 dependent growth
- Healthy HTLV-I carrier
- (Smoldering ATL)
- Overt ATL

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Established HTLV-I Tax-transgenic mouse models

<table>
<thead>
<tr>
<th>Promoter</th>
<th>Phenotype</th>
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<tr>
<td>Virus</td>
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<td>LTR RFLP</td>
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<td>LTR</td>
<td>Polyarthritis</td>
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<td>LTR HAM</td>
<td>Fibrosarcoma of the tail</td>
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Generation of Tax transgenic (Tg) mice

- Tg mice were generated with Tax expression under the control of lck proximal promoter which restricts expression to developing thymocytes

Background and pathological findings of three established Tax transgenic mice lineages

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<thead>
<tr>
<th>Founder</th>
<th>P1</th>
<th>P2</th>
<th>Gender</th>
<th>Age (months)</th>
<th>Lymphoma involvement</th>
<th>Leukemia</th>
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<td>2</td>
<td>Lymphoma</td>
<td>ND</td>
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### Estimation of Tax DNA copy number

![Genetic marker graph]

### Tax integration sites-genome walking analysis

- 3′-Flanking sequence:
  - TTTGGAGCATAGGTA TT
  - GCTGCAGGTCGAGGAATTC
  - AACAGGCATCTACTGAGTGGACCCAACGCATGAGAA

- Transgene sequences:
  - Chr.4:
    - A1 A2 A3 A4 A5 B1 B3 B2 C7 C6 C5 C4 C3 C2 C1 D1 D3 E1 E2

### Gross pathological findings

- **Mesenteric lymphoma**
- **Splenomegaly**
- **Control animal**
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Histological findings

- Lymph node
- Bone marrow
- Liver

Histological findings

- Skin

Peripheral blood: leukemic cells

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Histological findings

Pneumocystis jiroveci pneumonia

NFκB activation in Tax Tg mice

Transfer of Tg Tax ATLL disorder to SCID mice

Splenic lymphoma cells

i.p. or s.c.

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SCID mice peripheral blood

SCID mice histology

Lymph node

Liver

Lung

Kidney

Flow cytometry analysis

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Cell surface
CD3ε
CD3ε + PI

Permeabilization

Data analysis
Distribution of ratio values
Data were pre-processed using RMA (2270)
VSN (2465)
Li & Wong (1000)
A total of 839 probe sets out of 45,000 exhibiting greater than two fold difference were selected

Conclusions
• Tax transgenic mice under the control of the lck promoter develop aggressive T cell leukemias and lymphomas, the latter being clinically and histologically identical to that observed in ATLL
• Disease development was associated with NFκκκκB activation and characteristically Tax expression at all stages of disease
• The findings suggest that the expression of Tax alone is sufficient for the development of T cell leukemia/lymphoma and does not require the involvement of other viral gene products
• Leukemia/lymphoma could be readily transferred to SCID mice with the rapid development of fulminant disease
• It is expected that the SCID mouse model will allow the development and evaluation of novel therapeutics for the treatment of this disorder

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HTLV-II infection in American Indian populations

HTLV-II infection in IDUs

HTLV-II phylogenetic tree

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HTLV Tax heterogeneity

- **Tax I**: FQTKAYHPSFLLSHGQYSSPSHSLFEYINIPSLLPNEK
- **Tax IIa**: F_ Y_ Q_ N_ D_ V_ I_ KE
- **Tax IIb**: F_ Y_ Q_ N_ D_ V_ I_ KG
- **Tax IIc**: F_ Y_ Q_ N_ D_ V_ I_ KE

HTLV-II molecular epidemiology

- **HTLV-IIa**: Predominant infection in urban areas of North America (blood donors, IVDA's)
- **HTLV-IIb**: Predominant infection in most Native Indian groups in North, Central and South America; Predominant infection in urban areas of Italy and Spain
- **HTLV-IIc**: Found exclusively in urban areas and Native Indian groups in Brazil

Human T lymphotropic virus type II:
onscogenic properties of Tax

- **In vitro**: Tax transformation of PBMCs and established cell lines
- **In vivo**: Development of Tax transgenic animal models
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