VIRUSES AND LYMPHOMAS

Molecular aspects of HTLV-I infection and adult T-cell leukaemia/lymphoma

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Human T-cell lymphotropic virus-I (HTLV-I) is the cause of adult T-cell leukaemia/lymphoma. Various viral proteins, especially, but not exclusively, Tax have been implicated in oncogenesis, mostly through in vitro studies. Tax transactivates a large and apparently ever expanding list of human genes through transcriptional factors. Elucidating not only the pathways but also the timing of action of HTLV proteins is important for understanding the pathogenesis and development of new treatments.

Human T-cell lymphotropic virus-I (HTLV-I) infection is aetiologically linked to adult T-cell leukaemia/lymphoma (ATLL). HTLV, the first human retrovirus to be identified, was originally isolated from the cells of a patient in North America with a cutaneous T-cell lymphoma[1] and from the cells of a patient with the still newly described condition, adult T-cell leukaemia.[2] Serology for ''adult T-cell leukaemia virus'' (ATLV) showed the presence of antibodies to ATLV, not only in the majority of other patients with ATLL, but also in the blood of family members without disease.[3] Subsequent serological studies in Japan and elsewhere showed that infection with HTLV-I, as it was finally named, was endemic in some countries and rare in others with considerable intra-regional variation. Data from the cancer registries of Nagasaki Prefecture, Japan, have suggested that the lifetime risk of developing ATLL among HTLV-I seropositive persons is 2.1% for females and 6.6% for males.[4] Family studies have found a very high likelihood of HTLV-I infection in the mothers of patients with ATLL compared with the mothers of asymptomatic carriers or the mothers of patients with the HTLV-I-associated inflammatory disease, HTLV-I-associated myelopathy (HAM). Conversely ATLL following proven acquisition of HTLV-I in adult life, for example through blood transfusion, is rarely reported. In Japan the median age at presentation of ATLL is 57.5 years[5] and although occurring in a somewhat younger population in Europe, ATLL in children is rare. In summary, this brief epidemiological review suggests that ATLL occurs in a minority of HTLV-I infected subjects, usually after decades of infection, and that infection in infancy may be important.

A characteristic of ATLL is the presence of HTLV-I DNA in each and every malignant cell. Thus the HTLV-I viral load in the peripheral blood mononuclear cells (PBMCs) of patients with leukaemic ATLL approaches or, when more than one viral DNA copy is present in the malignant clone, exceeds 100%. The clonal nature of these cells can be demonstrated by T-cell receptor gene analysis and also by demonstrating a single integration site of the HTLV-I provirus. Thus, HTLV-I was present in the cell from which the malignancy developed rather than infecting malignant cells later. Thus ATLL is closely linked to the presence of an integrated HTLV-I genome. However, the nature of the oncogenic role of HTLV-I remains poorly understood. ATLL cells when analysed ex vivo, do not seem to be expressing viral proteins or RNA, and defective viral genomes are reported in some cases. What then is the evidence for the role of HTLV-I in the pathogenesis of ATLL and when does this occur?

HTLV-I is a small virus of 9060 bp. The structural genes, *gag*, *pol* and *env*, are flanked by the 5′ and 3′ long terminal repeats, and sandwiched between *env* and the 3′ long terminal repeat (LTR) is the *pX* region which encodes a small number of regulatory and accessory proteins. These are *tax*, the transactivating gene of the X region, *rex*, the regulatory gene, $p12^{I}$, $p30^{II}$ and $p13^{II}$. In addition the virus encodes from the minus DNA strand of this region an intriguing anti-sense RNA from which is translated the HTLV-I bZIP protein (HBZ). The group antigen or *gag* genes encode the matrix p19, capsid p24 and nucleocapsid p15 proteins. Polymerase encodes the three essential enzymes of a retrovirus, reverse transcriptase, integrase and proteinase. *Env* encodes the two envelope proteins surface (SU) and transmembrane (TM). The LTRs contain regulatory elements that are essential for viral replication, including the viral promoter which is transactivated by the Tax protein.

EFFECT OF HTLV-I TAX ON TRANSCRIPTION FACTORS

In addition to activation of the viral genome, the Tax protein transactivates a host of cellular genes through various transcription factors: nuclear factor-κB (NF-κB), activator protein-1 (AP1), c-AMP response element binding proteins/activating transcription factors (CREB/ATF), serum-response factor (SRF) and nuclear factor of activated T-cells (NFAT). These include but are not restricted to cytokines, early response genes, growth factors and cellular oncogenes.

The effect of Tax through NF-κB seems to be by two mechanisms: direct activation by binding to NF-κB and an indirect effect by interference with the normal regulation/inhibition of NF-κB. NF-κB

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is found in the cytoplasm of inactive cells along with its inhibitor. Expression of Tax protein in a cell results in the migration of NF-κB from the cytoplasm to the nucleus where it activates genes responsible for cell proliferation. Tax expression is also associated with the concentration of the inhibitor of κB kinase (IKK) in the vicinity of the Golgi apparatus. IKKs phosphorylate IκB (inhibitor of NF-κB) which results in the ubiquitination of IκB and hence its eventual proteasomal degradation.[6] Among other functions, NF-κB is responsible for the activation of the interleukin-2 (IL-2) receptor gene.

AP1 is a group of transcription factor complexes composed of members of the Fos and Jun families, the activation of which has been shown to contribute to Tax-driven cell growth in the absence of NFκB activity, although the Tax mutant used was still able to activate CREB/ATF.[7] However, AP1 does not appear to be essential for T-cell transformation[8] or for the inhibition of apoptosis of immortalised T-cells.[9]

NFAT proteins are a family of transcription factors regulated by calcineurin, a calcium-dependent phosphatase. In the phosphorylated state they are found in the cytoplasm but during T-cell activation they are rapidly dephosphorylated and migrate to the nucleus where they contribute to *IL2* gene activation. Tax has been shown to induce NFAT-containing, DNA-binding, protein complexes which activate the *IL2* promoter, an effect that was not found following activation of the NF-*K*B/rel or CREB/ATF transcription factor pathways.[10] Cyclosporine, an agent used to prevent transplant rejection and in the treatment of inflammatory conditions, blocks T-cell activation by inhibiting calcineurin, thereby blocking the effects of NFAT. The activation of both IL-2 and IL-2 receptor genes by Tax lead to the hypothesis of an oncogenic IL-2/IL-2R loop. While this loop theory is no longer considered to be a cause of ATLL, the activation of these genes remains potentially important, both because Tax induced activated T-cells may be subject to further mitogenic ''hits'' and because the IL-2 receptor alpha chain (CD25) has been used to deliver targeted therapy in ATLL.[11–13] The clinical presentation and diagnostic features of ATLL are described elsewhere.[13a]

The CREB/ATF family is important in viral transcription as well as in Tax induced transcription of cellular genes. The affect of Tax appears to be to bypass the normal requirement for phosphorylation for CREB to bind to a transcriptional activator, CBP. Tax bound to CBP forms the bridge between CREB and CBP, resulting in histone acetylation, opening of the nucleosome and activating transcription.[14]

One of the physiological functions of SRF is to respond to mitogenic signals, activate ''immediate early genes'' and thereby stimulate the cell to enter the next cycle round. Tax alters the binding of SRF to DNA, one of the effects of which is to increase binding to the *FOS* promoter.[15]

The consequence of these interactions is the potential for a multiplicity of host cell genes to be up-regulated through Tax expression. The list of genes demonstrably affected in vitro is ever increasing. Some are listed in table 1.

EFFECT OF TAX ON THE CELL CYCLE

Akagi *et al* found changes in cell cycle regulatory proteins in HTLV-I-immortalised cell lines and Tax-immortalised cell lines, with preferential expression of cyclin D2 compared to cyclin D3, reduced p18Ink4 compared to uninfected cells and high levels of p21Waf1/Cip1/Sdi1. Cyclin G2 is required for G1 cell cycle progression, whereas p18Ink4 is a cyclin-dependent kinase inhibitor (CKI). p21 is however, among other functions, a cyclin-dependent kinase interacting protein (CIP) that potently inhibits G_1 cyclin-dependent kinases (CDK)[38] and has been associated with G_1 arrest induced by irradiation.[39] Tax appears to up-regulate cyclin D2 via a CRE,[40] but may also have an indirect effect on cyclins through up-regulation of IL-2 and IL-2R which in turn leads to induction of the cyclin D2 (CCND2) promoter.[41] In vitro studies using retroviral vectors to express Tax in a hamster fibroblast cell line, BHK-21, have shown an association between Tax expression and a significant shift of cells from G_0/G_1 to S and G_2/M phases of the cell cycle,[42] while Schmitt *et al*, using a tetracycline-repressible model, demonstrated reversible effects of Tax on cell cycling—with progression to S phase when Tax was expressed and arrest in G1 phase when Tax expression was blocked.[43]

EFFECT OF TAX ON TUMOUR SUPPRESSOR PROTEINS

Evidence points to an effect of Tax on three key tumour suppressors: p53, Rb and human homologue of Drosophila discs large (DLG). The role of p53 is to activate DNA repair proteins, hold the cell at a cycle check point (G_1/S) to allow the repair and finally, if the damage cannot be repaired, to initiate programmed cell death. Although it is clear that p53 is inactivated by Tax,[44] whether this is through the p300/CBP or NF-kB/RelA pathways is uncertain.[45] Treatment responses to zidovudine can be predicted by p53: wild-type p53 is associated with induction of remission while malignancies with a mutated p53 did not respond.[46] The tumour suppressor protein, Rb, linked initially to retinoblastomas, also controls cell cycle according to its degree of phosphorylation. Hypophosphorylated Rb suppresses cell proliferation, while Tax promotes the hyperphosphorylated state.[47] Kehn *et al* have reported that Tax binding may also result in targeting Rb for proteasomal degradation.[48] A third tumour suppression protein bound by Tax is DLG.[49] Whether this results in proteasomal degradation, as is the case with EBV's E6, has not been reported.

APOPTOSIS

Programmed cell death is important in regulating cell growth and preventing malignancy. Various effects of Tax on apoptosis have been reported. Tax induced apoptosis of serum-deprived fibrocytes, an effect that could be blocked by the product of the proto-oncogene BCL2,[50] while in an oestrogen receptor-inducible system apoptosis of T-cells was seen as an early (up to 3 days) effect of Tax. In this system antibody stimulation of the T-cell receptor(TCR)/CD3 complex was required for induction of apoptosis.[51] The Fas (CD95)/FasL pathway was at least partially implicated in Tax-induced apoptosis, but failure to completely block the effect with blocking antibodies and blocking of apoptosis with peptide specific inhibition of the IL-1β-converting enzyme (ICE) pointed to the role of ICE or ICE-like proteases[52 53] as mediators of the tax apoptotic effect. These proteases have been implicated in apoptosis in a variety of cells. HTLV-I infected cells are resistant to a variety of physical, chemical and biological inducers of apoptosis,[54] but expression of transfected Tax sensitised cells to apoptosis after radiation and chemical induction of DNA damage.[55]

Conversely, intracellular and extracellular Tax was shown to inhibit anti-APO-1 induced cell death in T-cells, and the extracellular effect could be blocked by anti-Tax antibodies.[56] Tax has been shown to repress transcription of the Bax gene, the product of which accelerates apoptosis,[57] and through NF-*K*B and CREB to transactivate BCL2 with inhibition of apoptosis.[58]

Arsenic trioxide in synergy with interferon-α induces the degradation of Tax. This was associated with up-regulation of I*K*B-α, which in turn resulted in a decrease in RelA DNA binding NF-*K*B complexes due to cytoplasmic retention of RelA (see section on NF-*K*B with cell cycle arrest and apoptosis).[59]

Table 1 Host cell genes up-regulated by HTLV-I Tax

Regulated through AP-1	NFAT	NF-κB	CREB
AP-1 proteins	IL-2[10]	IL-2Rα (CD25)[26]	ETR101[37]
FOS[16]	IL13[23]	IL-15R[27]	
FOSL1(FRA-1)[17]	TNFSF6 (Fas ligand)[24]	IL-8[28]	
JUN[18]	IRF4 (interferon regulatory factor 4)[25]	TERT[29] (telomerase)	
JUND		MYC[30]	
TGFB1 (TGF-β)[19]		TNF (TNF-α)[31]	
NR4A1 (TR3/nur77)[20]		LTA (TNF-β)[32]	
TIMP-1[21]		PTHR1 (PTHr-P)[33 34]	
IL-8[22]		TNFRSF4 (OX40/OX40L)[35]	
		GM-CSF[36]	

TAX AND GENOMIC INSTABILITY

In addition to effects on tumour suppressor genes which will reduce DNA repair, Tax down-regulates DNA-polymerase β, affecting base excision repair,[60] and suppresses nucleotide excision repair.[61] More recently the interaction between Tax and the telomerase reverse transcriptase gene (TERT) has been studied. TERT is the major, catalytic subunit of telomerase. A lack of telomerase activity is associated with telomere shortening and eventual senescence, and a feature of immortalised cells is expression of TERT with maintenance or extension of telomere length. However, Tax inhibits TERT expression[62] by competing with MYC for a binding site in the TERT promoter. Mortreux *et al* reported that the negative effect of Tax on TERT involves recruitment of the phosphorylated form of an abundant chromatin protein, DEK, to the TERT promoter.[63]

Malignancies are often associated with changes in chromosome number. Whether this aneuploidy is causative of malignancy is uncertain, but ATLL cells are nearly always aneuploid.[64] Mitotic arrest deficiency proteins (MAD) are important in ensuring correct segregation of the chromosomes during mitosis. Tax has been shown to bind directly to MAD1L1 (MAD1) and repress its function,[65] and defective mitotic spindle assembly checkpoint function has been shown in ATLL-derived cell lines.[66]

Many immortalised HTLV-I infected cell lines have been generated and studied for insight into the transformation process. Often these originated from PBMCs from patients with ATLL and are still referred to as ATLL cell lines. However, genetic studies have revealed that many were not derived from the malignant clone but were the result of in vitro transformation of a non-malignant PBMC from the patient that may have been infected during culture. Other cell lines were deliberately derived from co-culture experiments. Some transformed lines are IL-2 independent, while others require this T-cell growth factor. Tax alone has been shown to be sufficient to transform primary lymphocytes.[67]

OTHER REGULATORY PROTEINS

The first open reading frame (ORF) of pX encodes a 12 kilodalton protein. $P12^{I}$ is known to be important in HTLV-I infectivity[68 69] and can activate resting lymphocytes which would make them susceptible to infection with HTLV-I.[70] $P12^{I}$ binds to the cytoplasmic domain of the IL-2 receptor β chain with a resultant increase in transcription through increased signal transducers and activators of transcription 5 (STAT5) DNA binding. In the presence of low concentrations of IL-2, HTLV-I $p12^{I}$ is associated with increased cell proliferation[71] and $p12^{I}$ increases IL-2 production in lymphocytes.[72] $P12^{I}$ induces NFAT transcription, an effect that can be blocked by cyclosporine.[73] However, as is so often the case with HTLV-I proteins, apparently conflicting actions are found. While T-cell activation is essential for infection it also leads to viral protein expression and potentially to immune recognition and destruction of the infected cell. $P12^{I}$ has also been shown to down-regulate NFAT following TCR binding to MHC-presented antigen and decrease TCR signalling.[74]

ORF II encodes $p13^{II}$ and $p30^{II}$. $P13^{II}$ localises to the mitochondria and plays a role in maintaining high viral loads,[75] but has been associated with decreased cell proliferation and reduced tumour growth in in-vitro systems[76] and increased sensitivity of Jurkat cells to FasL mediated apoptosis.[77] $P30^{II}$ (sometimes known as Tof) localises to the nucleus and has transcriptional activity[78] through binding CREB binding protein/p300.[79] Viral mutants that lack $p30^{II}$ persist at low viral load and reversion to wild type has been reported.[80] Like $p12^{I}$, a role in immune evasion has been reported with $p30^{II}$ binding to Tax/Rex mRNA and retaining it in the nucleus.[81] Further studies suggest that $p30^{II}$ binds to Rex/CRM1 complexes in the nucleoplasm, preventing them from transporting Tax-induced gene transcripts to the cytoplasm.[82] P30 has now been shown to impact on the cell cycle at the G2–M phase through differential phosphorylation of several regulatory proteins—cell division cycle 25C, checkpoint kinase1 and polo-like kinase 1.[83]

On the negative (complementary or antisense) strand of HTLV-I pX is encoded HBZ.[84] This leucine zipper protein inhibits CREB-2 binding to the viral promoter, thus countering the action of Tax. Furthermore, HBZ modulates the effect of Tax on cellular genes by decreasing the binding of the BZip transcription factors, JUNB and JUN, to AP1 sites[85] and by sequestering JUNB in nuclear bodies.[86] While the HBZ protein suppresses the activity of Tax, the mRNA of HBZ has been shown through mutation experiments to contribute to the proliferation of T cells.[87]

Many ATLL cells (and infected lymphocytes from carriers and patients with HAM) contain defective provirus with large 5′ deletions.[88] It was thought that Tax was constantly found in the 3′ remnant, but deletions encroaching into the 3′ end of Tax, including the NF-*K*B binding site have been reported. In these large deletions the second exon of *tax*, *rex* and *p30* are deleted but HBZ remains intact.[89] Non-function Tax has also been reported in 2 out of 6 ATLL patients due to nonsense mutation or frameshift.[90]

In summary, in vitro studies clearly demonstrate the ability of Tax, through multiple cellular mechanisms, to cause T-cell transformation. Other viral proteins can also be implicated to a lesser extent while the HBZ protein suppresses Tax. There remains however a significant gap between these findings and the in vivo experience. The lack of HTLV mRNA and protein expression at the time of clinical presentation with ATLL may not be important in understanding pathogenesis if the implication is that HTLV-I causes ATLL by changes in the cell early in the malignant process, following which subsequent ''hits'' result in malignant transformation and viral expression

Take-home messages

- HTLV-I Tax transforms lymphocytes in vitro.
- In vitro studies have identified multiple mechanisms which may contribute to the development of adult T-cell leukaemia/lymphoma.
- There are many paradoxes, however, and malignant transformation of HTLV-I infected cells in vivo is either rare or rapidly eliminated.
- Molecular studies may predict treatment response.

becomes irrelevant. While an attractive hypothesis, does this explain the very typical ATLL phenotype? Second, and perhaps more difficult to explain is the finding that many ATLL cells contain provirus in which *tax*, *rex* and $p30^{II}$ are defective. The recent generation of a mouse model that closely resembles ATLL[91] may lead to the unravelling of these conundrums. Equally importantly, the model allows for the first time in vivo testing of therapeutic strategies for this rapidly progressive and therapy resistant disease.[85]

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