

# Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation

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**Abstract** | It has been 30 years since a 'new' leukaemia termed adult T-cell leukaemia (ATL) was described in Japan, and more than 25 years since the isolation of the retrovirus, human T-cell leukaemia virus type 1 (HTLV-1), that causes this disease. We discuss HTLV-1 infectivity and how the HTLV-1 Tax oncoprotein initiates transformation by creating a cellular environment favouring aneuploidy and clastogenic DNA damage. We also explore the contribution of a newly discovered protein and RNA on the HTLV-1 minus strand, HTLV-1 basic leucine zipper factor (HBZ), to the maintenance of virus-induced leukaemia.

## Deltaretrovirus

A genus of the retroviridae family, whose members include HTLV-1 and bovine leukaemia virus, amongst others.

## Provirus

Usually represents the integrated DNA form of retroviruses.

## Helper T cells

A subset of lymphocytes that activate the immune system. Helper cells enhance the functions of B cells, cytotoxic T cells and macrophages.

## Regulatory T cells (T<sub>Reg</sub> cells)

Also known as suppressor T cells. These cells function in establishing immune tolerance.

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doi:10.1038/nrc2111

In the mid-to-late 1970s, a geographical clustering of leukaemias in southwestern Japan led to the description of a unique clinical entity termed adult T-cell leukaemia (ATL)<sup>1</sup>. A few years later, in 1980 and 1981, investigators from the USA and Japan separately isolated human T-cell leukaemia virus type 1 (HTLV-1) as the exclusive causal agent of ATL (reviewed in REFS 2,3). This landmark achievement established HTLV-1, a member of the Deltaretrovirus family, as the first retrovirus directly associated with a human malignancy. HTLV-1 and its relative, simian T-cell leukaemia virus type 1 (STLV-1), induce T-lymphocytic neoplasia and infection. Another relative, bovine leukaemia virus (BLV), causes B-cell neoplastic diseases. However, human T-cell leukaemia virus type 2 (HTLV-2) does not cause any neoplasia. These leukaemia viruses differ from earlier described transforming animal retroviruses in that they do not harbour viral homologues of cellular proto-oncogenes. Instead, the primary transforming entities for HTLV-1, STLV-1 and BLV map to respective viral reading frames that encode imperfectly conserved Tax proteins (FIG. 1). Tax is a nuclear phosphoprotein that has pleiotropic activities in cell-cycle progression and cyclic AMP (cAMP) and nuclear factor  $\kappa$ B (NF $\kappa$ B) signalling pathways (reviewed in REF. 4) (TABLE 1).

## Natural history and clinical features of ATL

HTLVs and STLVs are anciently related primate T-cell leukaemia viruses (PTLVs) that share molecular and virological features. It is speculated that HTLV-1 was repeatedly transmitted in separate independent events from simians to humans beginning 50,000  $\pm$  10,000

years ago; this course has resulted in the formation of several viral subtypes around the world<sup>5</sup>. Newer HTLVs, HTLV-3 and 4, have been identified recently from bush meat hunters in central Africa<sup>6,7</sup>.

At present, an estimated 10–20 million people worldwide are infected with HTLV-1 (REF. 8). HTLV-1 is endemic in southwestern Japan, Africa, the Caribbean Islands and South America. HTLV-1 infection is rare in North Americans and Europeans but is frequent in inhabitants of Melanesia, Papua New Guinea and the Solomon Islands, as well as among Australian aborigines. ATL develops only in HTLV-1-infected individuals, and all ATL cells contain integrated HTLV-1 provirus, supporting the causal aetiology of the virus for leukaemogenesis. Nevertheless, only a small minority of HTLV-1-infected individuals progress to ATL. Indeed, the cumulative risks of developing ATL among virus carriers are estimated to be approximately 6.6% for males and 2.1% for females<sup>9</sup>.

ATL has four subtypes: acute, lymphoma-type, chronic and smouldering. The first two types show aggressive clinical courses, whereas the second two types progress more indolently. HTLV-1 infection also induces inflammatory manifestations (which will not be discussed here), including HTLV-1-associated myelopathy and tropical spastic paraparesis (HAM and TSP), uveitis, arthropathy and infective dermatitis (reviewed in REF. 10). Current data support the view that the viral Tax protein is instrumental for oncogenesis, and is also the main *in vivo* target of the host's cytotoxic T lymphocytes (CTLs) (FIG. 2). Therefore, it is not uncommon that in the late stages of *in vivo* leukaemogenesis, ATL cells that lack Tax expression are selected to emerge<sup>11</sup>.

**At a glance**

- Human T-cell leukaemia virus type 1 (HTLV-1), a retrovirus that infects 20 million people worldwide, was the first retrovirus to be shown to be causal for a human cancer, adult T-cell leukaemia (ATL).
- The infectivity of HTLV-1 is tightly cell-associated, and is mediated through a virological synapse. Cell-free virus is largely non-infectious.
- HTLV-1 does not use viral capture of a cellular proto-oncogene for oncogenesis. Its viral oncoprotein, Tax, is needed to initiate but not maintain cellular transformation.
- Tax transforms cells through various mechanisms, including the creation of chromosomal instability, the amplification of centrosomes, the abrogation of DNA repair, the activation of cyclin-dependant kinases and nuclear factor  $\kappa$ B (NF $\kappa$ B) and Akt signalling, and the silencing of p53 and spindle-assembly checkpoints.
- The maintenance of ATL transformation seems to require the function of a novel antisense protein and RNA, termed HTLV-1 basic leucine zipper factor (HBZ).

**Parenteral**

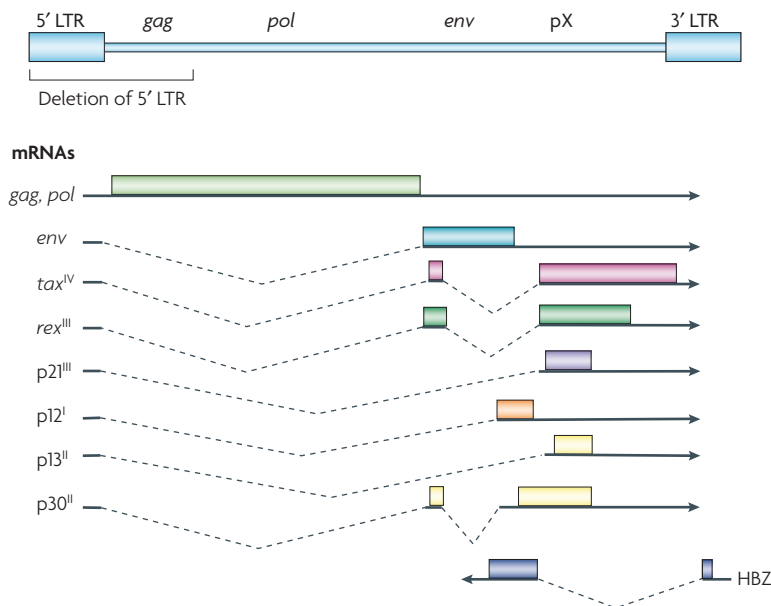
A route to introduce material into the body by injection or infusion.

**Gag complex**

Gag is a retroviral structural protein that wraps the retroviral RNA genome.

Much clinical knowledge about ATL has come from experience in Japan. Japan has approximately 1.2 million individuals infected with HTLV-1, and 800–1,000 new ATL cases each year. The average Japanese ATL patient is 60 years old, which is consistent with a long latent period after virus infection before the onset of ATL. Familial clustering of ATL cases has been reported<sup>12</sup>, indicating that genetic background influences ATL development. HTLV-1 proviral load (reflecting the number of infected

**Transcriptional silencing by DNA methylation of 5' LTR      Genetic changes in the tax gene**



**Figure 1 | The HTLV-1 proviral genome.** The gag, pol, and env structural genes are flanked by 5' and 3' long terminal repeats (LTRs). Of note, the 5' LTR is frequently deleted and methylated, whereas the 3' LTR invariably remains intact in all cases of adult T-cell leukemia (ATL)<sup>135</sup>. In the 3' portion of the genome is a pX region that encodes the Tax, Rex, p21, p12, p13 and p30 proteins in its various reading frames. Because the Tax oncoprotein is the primary viral antigen targeted by the host's cytotoxic T-lymphocyte response, ATL cells with mutations in the tax gene frequently emerge as disease progressors. The HTLV-1 basic leucine zipper factor (HBZ) minus strand RNA and protein synthesized in an antisense fashion from the 3' LTR are shown in blue. Superscript Roman numerals indicate the respective open reading frame used for the translation of the indicated protein. HTLV-1, human T-cell leukaemia virus type 1.

cells) can differ by more than 1,000-fold between different carriers. However, within each infected person the viral burden (before the onset of leukaemogenesis) is relatively stable, indicating that the amount of viral dissemination is determined by individual host factors such as major histocompatibility antigens and gene polymorphisms<sup>13</sup>. Indeed, immunosuppression in HTLV-1-infected individuals triggers ATL onset, suggesting that host immune competence has a crucial role in controlling the proliferation of HTLV-1-infected cells and keeping ATL development at bay.

Clinical features of ATL include leukaemic cells with multi-lobulated nuclei called 'flower cells' (FIG. 2), which infiltrate various tissues (skin lesions are very common), abnormally high blood calcium and opportunistic infections. The immunological phenotype of ATL cells is CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>-</sup> and CD25<sup>+</sup>, indicating that the cells derive from activated helper T-cells. In one study, it was reported that 10 of 17 ATL cases (59%) expressed forkhead box P3 (FOXP3) (FOXP3 expression was identified to be characteristic of CD4<sup>+</sup> and CD25<sup>+</sup> regulatory T cells (T<sub>Reg</sub> cells)) transcripts<sup>14</sup>, and that ATL cells can suppress the proliferation of bystander CD4<sup>+</sup> T lymphocytes<sup>15</sup>, suggesting that some cases of ATL originate from virus-infected T<sub>Reg</sub> cells. If so, severe immunodeficiency and complicated opportunistic infections in ATL patients could arise in part from the immunosuppressive properties of ATL T<sub>Reg</sub> cells. Separately, there is also evidence that HTLV-1 can infect human haematopoietic progenitor cells and immature human thymocytes<sup>16</sup> to perturb normal thymopoiesis<sup>17</sup>. Therefore, another view of leukaemogenesis, which is consistent with recent results from Tax transgenic mice in which Tax expression was restricted to thymocytes and T lymphocytes by the lymphocyte-specific protein tyrosine kinase (LCK) promoter<sup>18</sup>, is that HTLV-1 infection of immature human thymocytes selects over time (after additional secondary mutations) for the outgrowth of malignant clones.

**HTLV-1 infectivity and transmission**

**Cell-cell transmission.** HTLV-1 is transmitted primarily in three ways: mother–infant (mainly through breastfeeding), sexual contact and parenteral transmission. For all three routes, infected cells must be passed from the infected individual because HTLV-1 transmits by cell–cell contact. When an infected cell contacts an uninfected cell, a microtubule-organizing center (MTOC) is polarized at the cell–cell junction, and a virological synapse forms at the interface<sup>19</sup>. Thereafter, the HTLV-1 Gag complex and viral genomic RNAs accumulate at the synapse and egress into the uninfected cell (FIG. 3). The engagement of intercellular adhesion molecule 1 (ICAM1) increases the polarization of the MTOC at the point of contact, indicating that the interaction of ICAM1 and lymphocyte function-associated antigen 1 (LFA1) is important for HTLV-1 infection<sup>20</sup>. In addition to cell–cell contact, synapse formation is also triggered by the HTLV-1 Tax protein, which can be found around the MTOC and in the contact region; Tax has been shown to promote MTOC formation and ICAM1

Table 1 | Cellular activities modulated by Tax

Activated by Tax	Consequences
Cell-cycle phase activators (CDK2 and CDK4; cyclin D2; cyclin D3; WAF1; E2F1)	Accelerated G1–S progression and DNA hyper-replication
Growth receptors and proliferative factors (IL2 and IL15; IL2R $\alpha$ and IL15R $\alpha$ ; telomerase; PCNA)	Increased cellular proliferation and decreased NER DNA repair
Transcription factors (CREB; AP1; SRF)	Increased cellular proliferation
Survival factors (Akt; NF $\kappa$ B)	Suppression of apoptosis and/or senescence; aneuploidy
Centrosome amplification (RANBP1; TAX1BP2)	Aneuploidy
Inactivated by Tax	
Cell-cycle phase inhibitors (p15, p16 and p18; RB; DLG1)	Increased cell-cycle phase transition
DNA repair factors (DNA polymerase $\beta$ ; MMR)	Increased ambient DNA breaks and microsatellite instability
DNA damage response (p53; CHK1; CHK2; telomerase; KU80)	Suppression of apoptosis and/or senescence; abrogation of tumorigenesis barrier
Chromosome instability checkpoint (MAD1; CHK1)	Aneuploidy

AP1, activator protein 1; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; CREB, cyclic AMP responsive element binding protein; DLG1, discs large homologue 1; IL, interleukin; IL15R $\alpha$ , interleukin 15 receptor  $\alpha$ ; IL2R $\alpha$ , interleukin 2 receptor  $\alpha$ ; MAD1, mitotic arrest deficiency protein 1; MMR, mismatch repair; NER, nuclear excision repair; NF $\kappa$ B, nuclear factor  $\kappa$ B; PCNA, proliferating cell nuclear antigen; RANBP1, Ran-binding protein 1; RB, retinoblastoma; SRF, serum response factor (also known as MCM1); TAX1BP2, Tax-binding protein 2.

engagement<sup>21</sup>. LFA3, selectin L (SELL) and vascular cell adhesion molecule 1 (VCAM1) are also upregulated by Tax<sup>22–24</sup>. As LFA1 is expressed on T lymphocytes, this mechanism is consistent with preferential infection of T lymphocytes by HTLV-1 *in vivo*.

HTLV-1 integrates randomly into the host genome<sup>25</sup>. Sequential analyses of integration sites verify that the proliferation of HTLV-1-infected cells is clonal<sup>26</sup> and persistent<sup>27,28</sup>. Recently, the administration of reverse transcriptase inhibitors (RTIs) to patients with HAM or TSP revealed that proviral loads do not change despite treatment with RTIs, confirming that *de novo* spread does not contribute significantly to *in vivo* provirus burden<sup>29</sup>. Moreover, RTI treatment immediately after infection by HTLV-1 *in vivo* does not change subsequent proviral load<sup>30</sup>. In addition, although the HTLV-1 RT is error-prone, variations in proviral sequences are small compared with similar changes seen with HIV-1 infection<sup>31</sup>. Taken together, the findings support clonal proliferation as the dominant contributor to increasing the number of HTLV-1-infected cells, rather than the *de novo* infection of cells, which occurs to amplify HIV-1 proviral genomes.

**Accessory genes.** HTLV-1 can infect various cells. Accordingly, the HTLV-1 receptor has been reported to be the glucose transporter 1 protein (GLUT1)<sup>32</sup>. Recently, surface heparin proteoglycan has also been suggested to serve as a receptor for HTLV-1 (REF. 33). Both GLUT1 and heparin proteoglycan are ubiquitously expressed on

the surface of many cell types. Hence, it has been found that CD4<sup>+</sup> and CD8<sup>+</sup> T cells can be infected by virus; however, most *in vivo* infection is detected in the memory subpopulation of CD4<sup>+</sup> T cells<sup>34</sup>. The explanation for this finding is unclear, but it suggests that although HTLV-1 might be capable of infecting many cell types, infection selectively increases the abundance of only a particular cellular subset(s), perhaps because of the action of virus-encoded accessory gene products in those cells.

Animal experiments conducted using HTLV-1 infectious clones with mutated accessory genes provide evidence that the accessory *p12*, *p30*, *rex*, *p13* and HTLV-1 basic leucine zipper factor (*HBZ*) (FIG. 1) genes contribute to establishing persistent viral infection *in vivo*<sup>35–38</sup>. One thought is that there is a direct effect of accessory gene products on replication of the virus and the proliferation of infected cells. For example, the p12 protein, which is present in the endoplasmic reticulum and the golgi<sup>39</sup>, has been shown to interact with calreticulin and calnexin. p12 increases cytoplasmic calcium, leading to the activation of the nuclear factor of activated T-cells (NFAT) transcription factor, thereby influencing the proliferation and differentiation of T lymphocytes. By facilitating host cell proliferation and survival, p12 assists in establishing a persistent viral infection. In addition, p12 also suppresses the expression of class I major histocompatibility complex (MHC) molecules<sup>40</sup>, which might help infected cells escape host immune surveillance, and promotes LFA1 expression<sup>41</sup>, which could increase cell–cell contact between infected cells. The p30 accessory protein can bind *tax* and *rex* mRNAs and retain both transcripts in the nucleus<sup>42</sup>, thereby preventing their translation in the cytoplasm. By suppressing Tax protein synthesis, p30 attenuates HTLV-1 transcription and possibly regulates a switch between productive versus latent viral infection *in vivo*. p30 can also interact with CREB binding protein (CBP) and p300, and modulate transcription from the HTLV-1 long terminal repeat (LTR) and of CREB-, CBP- and p300-dependent cellular genes<sup>43</sup>. The role of the HTLV-1 p13 protein, which has been reported to be localized in mitochondria, is currently unclear. The influence of the HBZ protein and RNA on cellular metabolism is expanded on below.

**Requirements for Tax in ATL**

The HTLV-1 Tax protein is required for the virus to transform cells<sup>44</sup>; however, *tax* transcripts are detected in only ~40% of all ATLs. Analyses of HTLV-1 proviruses and *tax* transcripts in ATL cells revealed three ways in which cells can silence Tax expression: the accumulation of nonsense mutations, insertions and deletions in *tax*<sup>45,46</sup>; silencing viral transcription by DNA methylation of the provirus<sup>46–48</sup>; and the deletion of the proviral 5’LTR<sup>49</sup> (FIG. 1). Genetic changes in *tax* are seen in ~10% of ATLs, DNA methylation in another 15% of ATLs, and 5’LTR deletions are found in a further 27% of ATL cases. The last change is especially prevalent in aggressive forms of ATL.

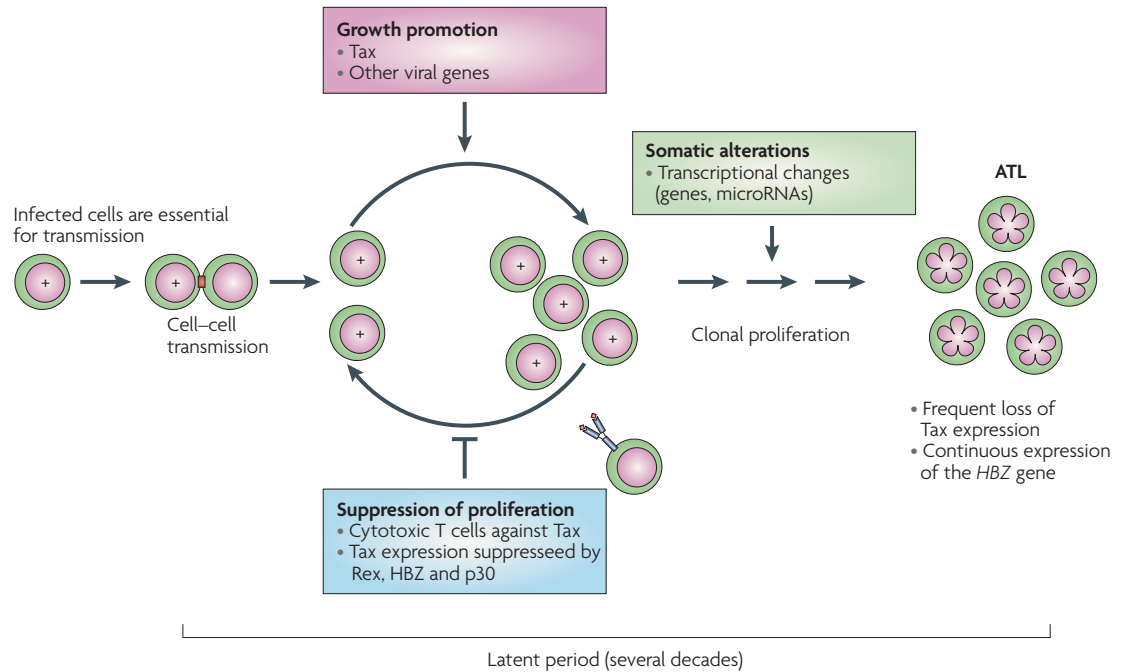
Why do ATL cells silence Tax expression when this protein is required by HTLV-1 to initiate leukaemogenesis? The currently accepted view is that Tax is needed

**Long terminal repeat**

A repeated sequence, several hundred base pairs long, found at the 5’ and the 3’ ends of the retroviral genome.

**Memory T-cell subpopulation**

A specialized population of T lymphocytes that recognizes foreign antigens. Memory T cells mount a faster and stronger T-cell response against antigens that they have been previously exposed to.



**Figure 2 | The natural history of HTLV-1 infection.** Cell-cell transmission of human T-cell leukaemia virus type 1 (HTLV-1), early expression of Tax and subsequent cytotoxic T lymphocyte (CTL) selection against Tax are shown. HTLV-1 basic leucine zipper factor (HBZ) is continuously and durably expressed in infected cells. A T cell with '+' in the nucleus represents an infected cell with integrated provirus. An uninfected T cell (empty nucleus) is poised to become infected through a virological synapse (small red rectangle) created by cell-cell contact with an infected cell. The clonal expansion of infected cells is promoted through the actions of Tax and HTLV-1 accessory proteins, and selected against by host CTLs. After a prolonged asymptomatic period of 20–40 years, aneuploid adult T-cell leukaemia (ATL) cells ('flower cells', with flower-shaped nuclei) emerge in approximately 5% of infected individuals. Most HTLV-1-infected individuals remain life-long asymptomatic carriers.

early after infection to initiate transformation, but is not required later to maintain the transformed phenotype of ATL cells. As Tax is the main target of the host's CTLs, cells that shut down Tax expression (using one of the three genetic or epigenetic means described above) have an advantage in evading immunosurveillance and are preferentially selected for *in vivo* during disease progression<sup>46</sup>. The HTLV-1 paradigm, wherein Tax is not needed to maintain transformation, differs from other cancer virus systems such as human papillomavirus (HPV), in which the continuous expression of viral oncoprotein(s) is required to sustain virus-induced cancers<sup>50</sup>.

**Cellular functions of Tax**

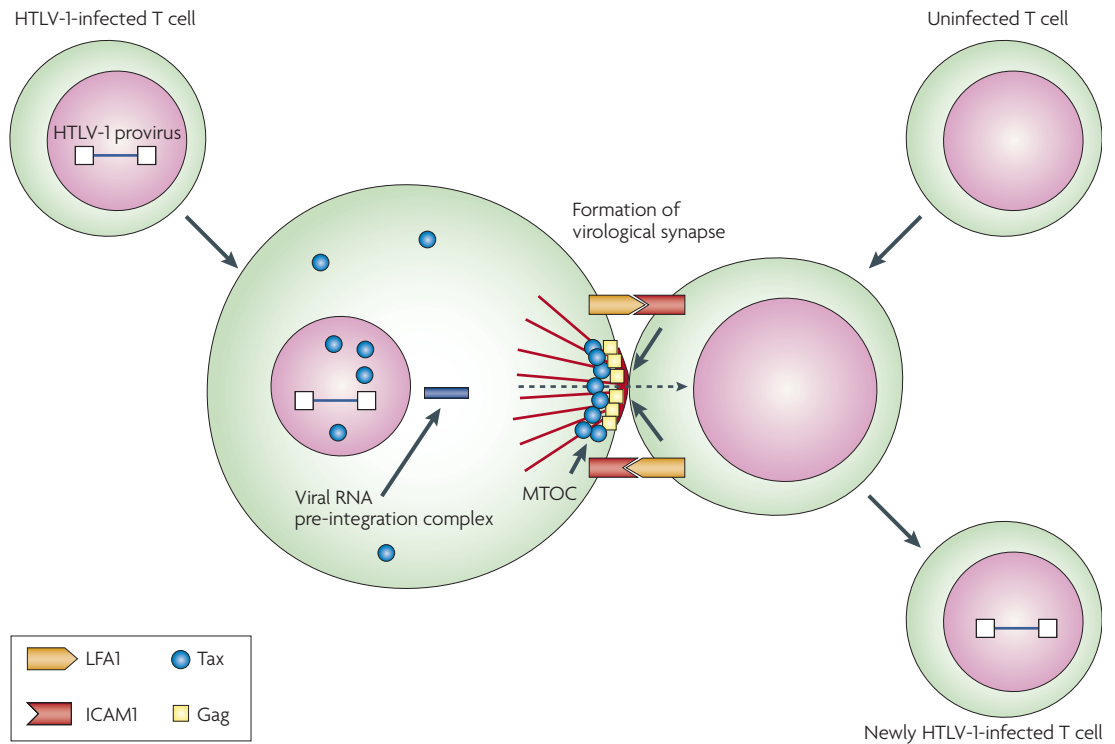
*Cell survival.* An ultimate outcome of the HTLV-1 infection of T cells is the emergence of ATL. To reach the end point of converting a normal T cell to a leukaemic cell, the virus must overcome several barriers. Therefore, HTLV-1 must quell the tendency of virus-infected cells to undergo apoptosis and/or senescence<sup>51,52</sup>, defeat cellular checkpoints that censor genetic damage, and trigger proliferative factors that guide cell-cycle progression and cell division<sup>53</sup>.

The virus uses Tax to engage two cellular pathways for quelling apoptosis (FIG. 4). First, Akt, a serine/threonine kinase that influences cell survival and proliferation, is activated. Akt is regulated by phosphatidylinositol

3-kinase (PI3K) through site-specific phosphorylation, primarily on Ser473 (REF. 54). Activated Akt signals through downstream transcription factors such as activator protein 1 (AP1), which is highly expressed in many invasive human cancers<sup>55</sup>, including ATL<sup>56</sup>. Tax promotes Akt phosphorylation by directly binding PI3K<sup>57</sup> (FIG. 4). Through a Tax-PI3K-Akt chain of events, the survival and proliferation of virus-infected cells are increased. When Tax-expressing cells are treated with PI3K inhibitors to prevent Akt phosphorylation, cell death ensues<sup>58</sup>; this outcome is consistent with the importance of Akt signalling for HTLV-1 transformation.

NFκB is a second major survival pathway engaged by HTLV-1 (FIG. 4). Many human cancers have activated NFκB<sup>59</sup>, and although NFκB is tightly regulated in normal T cells, this pathway is constitutively active in HTLV-1 cells. An important advance in our mechanistic understanding of ATL came from experiments that showed that Tax activation of NFκB occurs predominantly in the cytoplasm. Cytoplasmic Tax was shown to bind IKKγ (also known as NEMO). This binding triggers the phosphorylation of IKKα and IKKβ, which form a complex with IKKγ. Subsequently the IKKα-IKKβ-IKKγ complex phosphorylates IκBα, leading to its proteasome-mediated degradation, which frees IκBα-sequestered cytoplasmic NFκB to migrate into the nucleus where it activates the transcription

Human papillomavirus  
A small DNA virus that causes cervical cancer.



**Figure 3 | Cell-cell transmission of HTLV-1 occurs through a virological synapse.** Unlike many other viruses, cell-free human T-cell leukaemia virus type 1 (HTLV-1) virions are largely non-infectious. This figure illustrates the cell-cell contact required to create a virological synapse through which the viral genome is transmitted from one cell to another. The roles played by lymphocyte function-associated antigen 1 (LFA1), and intercellular adhesion molecule 1 (ICAM1) in forming cell-cell contact are shown. Tax contributes to the formation of a microtubule organizing centre (MTOC).

of NFκB-responsive genes<sup>60</sup>. Tax can also stimulate a second NFκB pathway through the IKKα-dependent processing of the NFκB p100 precursor protein to its active p52 form. This alternative pathway is activated by Tax binding to IKKγ and p100 in an IKKα–IKKγ–p100 complex that lacks IKKβ<sup>61</sup>. However, the above two Tax–NFκB pathways may not fully explain ATL biology, because some leukaemic cells that no longer express Tax continue to show constitutive NFκB activation<sup>62,63</sup>. How these ATL cells sustain NFκB activation is not fully understood, but this finding is consistent with the requirement for Tax in the initiation but not the maintenance of transformation.

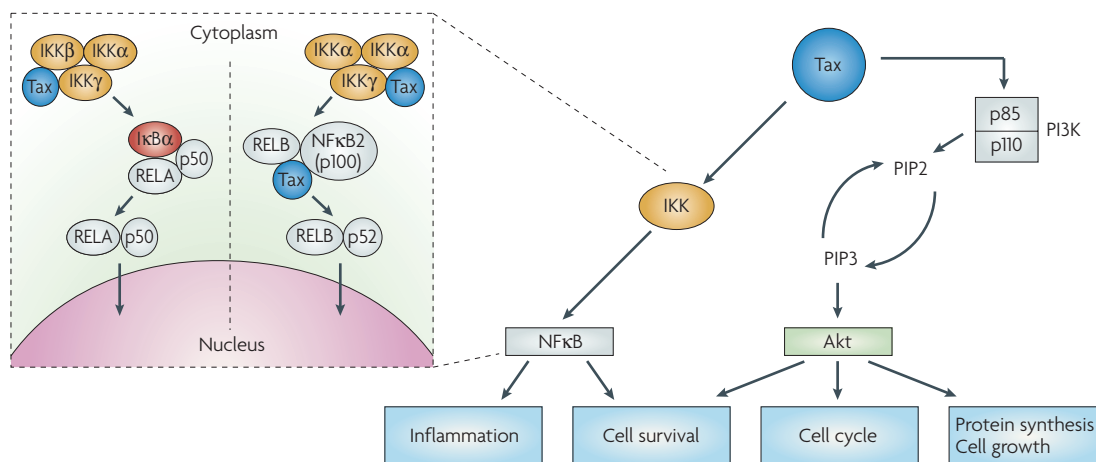
**Cell-cycle progression.** Cancers have increased DNA replication and cellular proliferation. Tax provides significant mitogenic activity, especially at the G1–S-phase transition<sup>64,65</sup>, by provoking several cellular activities (TABLE 1). First, levels of G1 D cyclins are increased<sup>66–68</sup>. Increased cyclin D2 (encoded by *CCND2*) expression occurs through direct activation of the *CCND2* promoter by Tax and increased interleukin 2 (IL2) receptor signalling<sup>67</sup>, which is consistent with findings of increased IL2 secretion from HTLV-1-infected T lymphocytes. Second, Tax activates cyclin-dependent kinases (CDKs) (for example, *CDK4* and *CDK6*) through direct protein binding<sup>69,70</sup>, leading to the hyper-phosphorylation of retinoblastoma (RB) protein (and perhaps the proteasomal

degradation of RB<sup>71</sup>). The phosphorylation and/or degradation of RB frees the E2F1 transcription factor<sup>65,68</sup>, accelerating cell-cycle transition from G1 to S. There is also some evidence that Tax can stimulate the transcription of the *E2F1* gene<sup>72</sup>. Finally, Tax transcriptionally represses CDK inhibitors (CKIs) such as *INK4C*<sup>66</sup>, *INK4D*<sup>68</sup> and *KIP1* (REF. 68). This occurs through the direct binding of Tax to E-box binding factors, which otherwise activate transcription from the promoters for *INK4C* and *INK4D*<sup>73,74</sup>, and through Tax binding to and inactivating *INK4A* and *INK4B*<sup>75,76</sup>. Intriguingly, Tax increases the levels of *WAF1* in cells. *WAF1* was originally thought to be purely a cell-cycle inhibitor. However, later studies showed that in context-specific settings *WAF1* can also promote the organization of an active *WAF1*–cyclin D2–CDK4 complex that phosphorylates RB and promotes, rather than inhibits, the G1–S transition<sup>77</sup>. The cell-cycle promoting activity of *WAF1* is activated in the context of HTLV-1 infection and Tax expression.

Different cancer viruses often conserve mechanisms of cellular transformation. A few years ago, it was discovered that HTLV-1 and HPV shared the ability to target cellular proteins with PDZ protein–protein interaction domains. Both Tax and E6 proteins from highly oncogenic HPVs were found to have PDZ-binding motifs (PBMs) in their C termini<sup>78</sup>. Why would Tax and E6 proteins contain PBMs? The answer came from the discovery that a PDZ substrate bound by both Tax and E6 is *DLG1*, the

**PDZ domains**

PDZ is an abbreviation using the first letters of three proteins — post synaptic density protein 95 (PSD95), *Drosophila* discs large 1 tumour suppressor (DLG1) and zona occludens 1 (ZO1). These three proteins were the first to be described as sharing a domain that specifies protein–protein association and the association of transmembrane proteins to the cytoskeleton of the cell.



**Figure 4 | The HTLV-1 oncoprotein Tax activates two survival pathways, NFκB and Akt, to promote cell survival and proliferation.** Tax activates nuclear factor κB (NFκB) in two ways (see inset). The first is through a canonical pathway involving an IKKα–IKKβ–IKKγ complex that results in the nuclear migration of a RELA–p50 NFκB complex. The second is a non-canonical pathway that uses an IKKα–IKK γ–NFκB2 (p100) complex, which results in the nuclear translocation of a transcriptionally active RELB–p52 NFκB complex. RELA, RELB, p100, p52 and p50 are all members of the NFκB protein family. Details of how Tax activates these two NFκB routes are reviewed elsewhere<sup>148</sup>. Tax also activates Akt signalling through direct contact with phosphatidylinositol 3-kinase (PI3K). HTLV-1, human T-cell leukaemia virus type 1.

human homologue of the *Drosophila melanogaster* discs large tumour-suppressor protein<sup>79</sup>. DLG1 signals downstream of Wnt and frizzled<sup>80</sup>, and binds the C terminus of the adenomatous polyposis complex (APC) tumour suppressor, thereby regulating cellular proliferation and cell-cycle phase transition<sup>81</sup>. Although its physiological function remains to be fully clarified, evidence indicates that DLG1 enforces G0/G1 cell-cycle arrest<sup>82</sup>. To override the regulatory function of DLG1, HPV E6 promotes the proteasome degradation of DLG1, whereas Tax inactivates DLG1 by inducing its hyperphosphorylation and subcellular mis-localization<sup>83</sup>. Mechanistically, how Tax exerts its effect on DLG1 remains unclear; however, the need to inactivate DLG1 in order for Tax to transform cells was recently established using mouse cells<sup>84</sup>. It is noteworthy that PBMs are absent from E6 proteins from HPVs that are poorly-oncogenic<sup>85</sup> and from the non-transforming HTLV-2 Tax protein<sup>83</sup>; these natural examples lend support to the idea that Tax and E6 binding to PDZ domains has a role in transforming cells.

**Multipolar mitosis and aneuploidy.** Structurally damaged DNA and chromosomal numerical abnormalities (that is, aneuploidy and/or polyploidy) are common in cancers. Because most human cancers are aneuploid, aneuploidy has been proposed to be a cause of transformation<sup>86</sup>. Like many cancers ATL has chromosomal instability<sup>87</sup>, with cells that are usually aneuploid.

Aneuploidy can arise from multipolar mitoses (FIG. 5), which happen when more than two spindle poles (supernumerary centrosomes) emerge in one cell. Normally, a single centrosome is duplicated once in interphase. Mistaken centrosome replication is linked to oncogenesis<sup>88</sup>, with supernumerary centrosomes being common in many human cancers, including prostate, breast, lung and colon<sup>89–91</sup>. Given the link between centrosome

abnormalities and transformation, it is not surprising that human cancer viruses, such as HPV<sup>92</sup> and hepatitis B virus (HBV)<sup>93</sup>, use their oncoproteins to deregulate centrosomal replication. Three recent studies have now shown that HTLV-1 also causes multipolar mitosis<sup>94–96</sup> in two ways. First, Tax creates over-duplication by targeting the cellular TAX1BP2 protein, which normally blocks centriole replication. Second, during mitosis, Tax engages RANBP1 and fragments spindle poles, provoking multipolar segregation. These mechanisms explain long-standing observations of aneuploidy and frequent multipolar spindles in ATL cells<sup>97</sup>.

Cells have a mitotic spindle assembly checkpoint<sup>98</sup> (SAC) that maintains the correct number of chromosomes by monitoring the fidelity of chromosomal segregation. SAC proteins, which include MAD1 and MAD2 (FIG. 5), function at kinetochores to check for proper microtubule attachment and orderly mitotic chromosome partitioning<sup>98</sup>. The importance of SAC function and aneuploidy to oncogenesis is attested by findings that mice with heterozygous loss of *Mad1* (REF. 99) or *Mad2* (REF. 100) show increased tumorigenesis. Normally, nascent aneuploid cells would be expected to be censored by an intact SAC. The emergence of aneuploid ATL cells implies that these cells lack intact SAC function, a notion that has been experimentally verified in several ATL cell lines<sup>87</sup>. Mechanistically, the loss of SAC function in ATL arises from Tax binding to MAD1 (REFS 101,102). Intriguingly, results from two acute myeloid leukaemia (AML) studies support a role for reduced MAD1 function in cancer progression, as monosomy for the chromosome that contains *MAD1* was correlated with a poor 5-year survival rate<sup>103,104</sup>. That leukaemias with only one copy of *MAD1* are more aggressive cancers is consistent with SAC inactivation by HTLV-1 Tax in ATL progression. Tax has also been shown to bind to and activate

**Wnt**

A protein family of highly conserved secreted signalling molecules that regulate cell–cell interactions during embryogenesis. Wnt protein functions have also been implicated in cancer development.

**Frizzled**

Frizzled proteins are seven-transmembrane molecules that act as receptors for Wnt proteins.

**Hepatitis B virus**

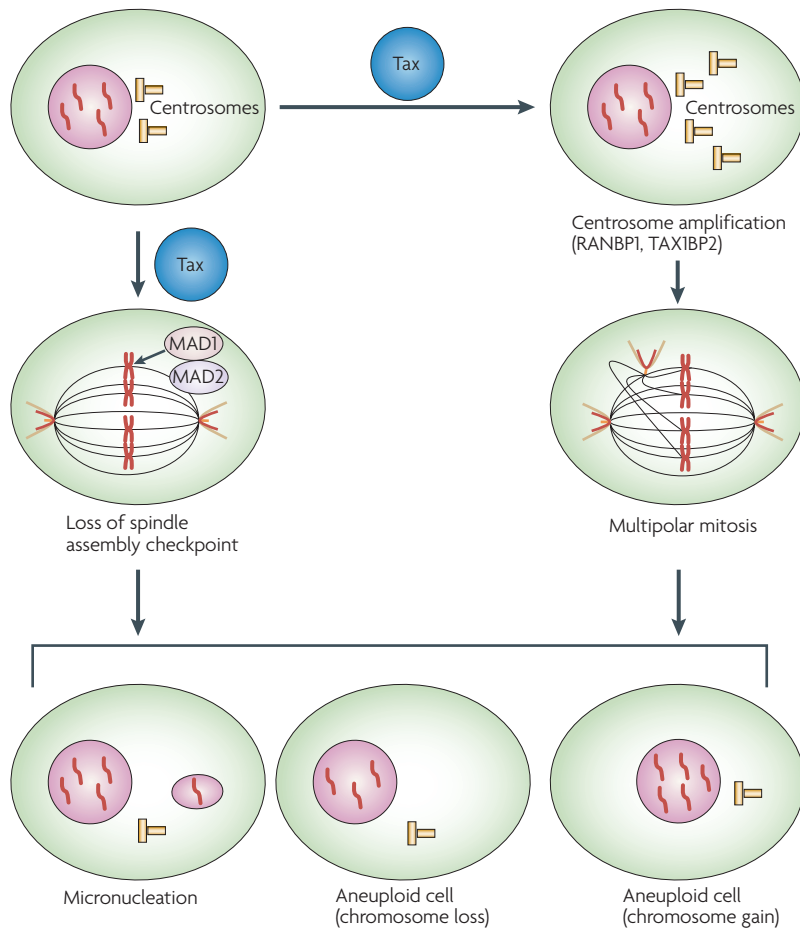
A virus that has been associated with hepatocellular cancers.

**Epstein–Barr virus**

A herpes virus that has been linked to Burkitt lymphoma and nasopharyngeal carcinoma.

**Clastogenic**

A term denoting a breakage in a chromosome.



**Figure 5 | Aneuploidy and multipolar mitosis in HTLV-1-infected cells.** Tax causes multipolar mitosis through the amplification of centrosomes during interphase by affecting the centrosome-associated protein TAX1BP2, and during mitosis by affecting RANBP1. To allow the emergence of aneuploid cells, Tax attenuates the cell's spindle assembly checkpoint (SAC) by binding to the MAD1 protein. The result is that mis-segregated chromosomes are captured in a small effete nuclear sack to create a micronucleus that is separate from the cell's main nucleus, or cells have a loss or gain of chromosome copies (bottom row). HTLV-1, human T-cell leukaemia virus type 1.

**Base excision repair**  
A cellular mechanism to repair bases in DNA that are mutated, for example by deamination or alkylation. Base excision repair removes and repairs the mutated base alone.

**Nucleotide excision repair**  
This type of DNA repair is used by cells after UV irradiation. Nucleotide excision repair enzymes recognize bulky distortions in DNA and excise a short single-stranded DNA stretch that includes the bulky lesion. Defects in NER lead to diseases such as Xeroderma pigmentosum and Cockayne syndrome.

the anaphase-promoting complex/cyclosome (APC/C), which functions downstream of the SAC. By interaction with the APC/C, Tax is thought to promote premature mitotic exit and contribute to aneuploidy<sup>105</sup>. Indeed, other human cancer viruses such as Epstein–Barr virus (EBV) also target the SAC in their cellular transformation mechanism<sup>106</sup>.

**DNA structural damage.** ATL cells also have clastogenic DNA damage<sup>107</sup>. Although other oncoproteins can induce direct DNA damage through increased reactive oxygen species<sup>108</sup>, such activity has yet to be demonstrated for Tax. On the other hand, HTLV-1 abrogates cellular checkpoints and DNA repair functions that monitor and censor ambient DNA structural damage (FIG. 6). Several cellular processes including CHK1- (REF. 109) and CHK2-mediated<sup>110</sup> checkpoints at G1 or G2/M; the expression of the DNA polymerase  $\beta$  enzyme used for base excision repair (BER)<sup>111,112</sup>; nucleotide excision repair (NER)<sup>113</sup>

and mismatch repair (MMR)<sup>114</sup>, are attenuated in HTLV-1-infected cells. In addition, chromosome end-to-end fusions, which are common in cancers, and shortened telomeres are also seen in ATL cells<sup>115</sup>. This could be explained by the observation that Tax suppresses the expression of human telomerase reverse transcriptase (TERT)<sup>116</sup> early in cellular transformation and targets the DNA-end-binding and protective activity of the KU80 protein<sup>117,118</sup>, which reduces the capacity of the cell to protect new double strand breaks (DSBs) as well as extant chromosome ends<sup>119–121</sup>. Interestingly, late in ATL when Tax expression is lost, cells display heightened TERT activity<sup>122,123</sup>. How HTLV-1 cells move from low (early) to high (late) TERT activity is not currently understood, but could be due to the expression of viral factors such as HBZ (see below).

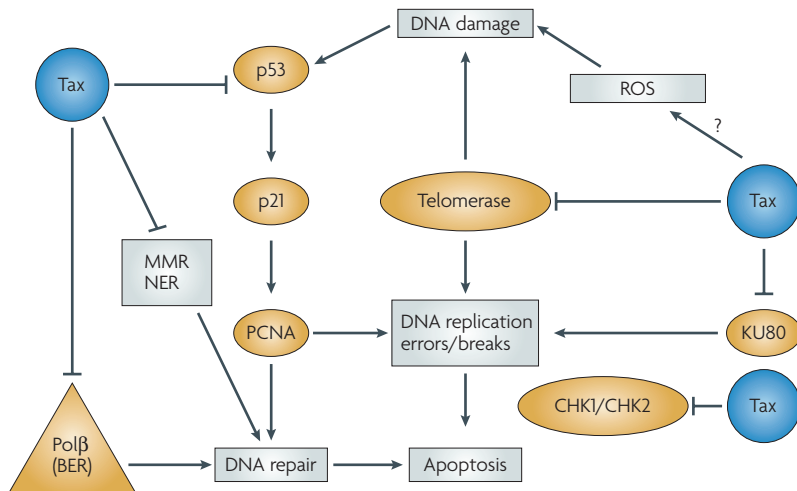
Structurally damaged DNA is prevalent in cancer cells because roughly 50% of human cancers have checkpoint-disabling mutations in TP53. Among leukaemias, ATL cells are notable for a dearth of TP53 mutations. However, the p53 checkpoint is ineffective in ATL owing to Tax-mediated inactivation (reviewed in REF. 124). Tax-inactivation of p53 has been attributed to signalling by the NF $\kappa$ B–RELA complex<sup>125</sup> and oncoprotein interference with the CREB–CBP or p300 pathway<sup>126</sup>, or Tax might inactivate p53 through another as yet uncharacterized pathway<sup>127</sup>. Although mechanistic details remain to be fully clarified, the Tax-mediated loss of p53 function might partly explain the existence of structural DNA damage in ATL cells.

**HBZ RNA and protein, and other factors in ATL**

A recent remarkable finding in HTLV-1 biology is the characterization of a viral gene, HBZ, encoded by the minus strand of the provirus<sup>128,129</sup>. HBZ was found to inhibit the Tax-mediated transactivation of viral transcription from the 5'LTR by heterodimerizing with JUN and CREB2 (REF. 130) (FIG. 7). However, HBZ also interacts with JUND to activate the transcription of JUND-dependent promoters of cellular genes without increasing transcription from the HTLV-1 LTR<sup>131,132</sup>.

As noted, the 5'LTR is frequently deleted and/or methylated in ATLS (FIG. 1). Interestingly, the proviral 3'LTR remains intact and unmethylated at all stages of ATL development, suggesting that the 3' LTR has a crucial role in leukaemia maintenance. Alternatively-spliced transcripts for HBZ have been identified by rapid amplification of 5' complementary DNA ends (5' RACE)<sup>133</sup>, and in all ATL cells studied to date, HBZ transcripts are detected whereas tax mRNAs (see above) are present in only ~40% of cases<sup>134</sup>. Intriguingly, when HBZ mRNAs were reduced using short hairpin RNAs, the proliferation of ATL cells was slowed. Conversely, overexpression of HBZ in a human T-cell line accelerated cellular division. These results link HBZ function to ATL proliferation<sup>135</sup>.

Based on DNA microarray experiments, HBZ was found to upregulate the transcription of E2F1 and many cellular E2F1 target genes<sup>135</sup> (FIG. 7). Of particular interest is the finding that HBZ RNA, rather than HBZ protein, promotes T-cell proliferation and upregulates

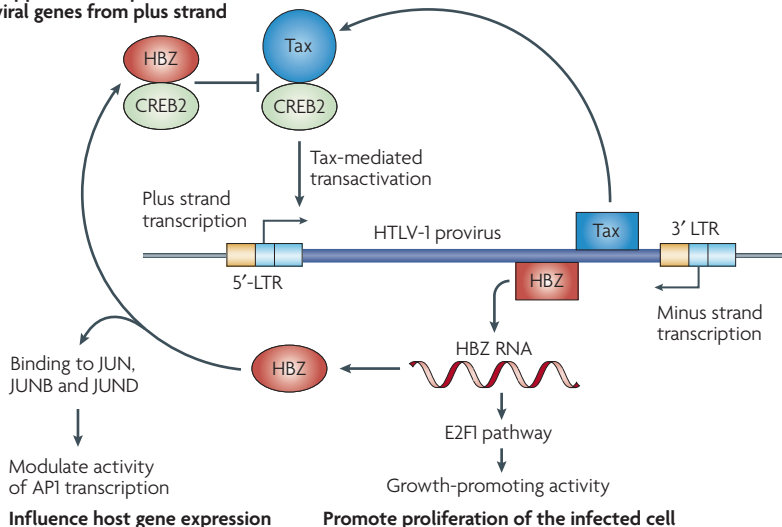


**Figure 6 | Tax affects many cellular factors that contribute to clastogenic DNA damage in HTLV-1-infected cells.** The activities perturbed by Tax include the loss of the p53 checkpoint, decreased cellular DNA repair functions (nucleotide excision repair (NER), base excision repair (BER) or mismatch repair (MMR)), and the attenuation of telomerase, checkpoint kinase 1 (CHK1) and CHK2 activities. Tax also targets the double strand break (DSB)-end protecting protein, KU80. HTLV-1, human T-cell leukaemia virus type 1; ROS, reactive oxygen species; PCNA, proliferating cell nuclear antigen; Polβ, DNA polymerase β.

**Mismatch repair**  
A repair system that removes the erroneous insertion, deletion and mis-incorporation of bases during DNA replication, usually on the newly synthesized strand.

*E2F1* transcription<sup>135</sup>. Mutational analyses suggest that the secondary structure of the *HBZ* RNA is important for its proliferative function, raising the possibility of a structure-driven interaction with an as yet uncharacterized cellular factor(s). Current results support the notion that the *HBZ* protein suppresses the Tax-mediated transactivation of viral transcription from the 5'LTR, and *HBZ* RNA promotes ATL cellular proliferation.

**Suppress transcription of viral genes from plus strand**



**Figure 7 | Schematic illustration of the expression and the activities of the HBZ RNA and protein in HTLV-1-infected cells.** The effect of HTLV-1 basic leucine zipper factor (HBZ) on CREB2 and activating protein 1 (AP1) are shown. The effect of *HBZ* RNA on the *E2F1* transcription factor and downstream *E2F1*-responsive genes are also shown. Current evidence suggests that the *HBZ* protein might antagonize the positive transcriptional effect of Tax on the HTLV-1 (human T-cell leukaemia virus type 1) long terminal repeat (LTR). CREB, cyclic AMP responsive element binding protein.

This unprecedented bimodal protein- and RNA-based function could be a previously undiscovered way for a virus to regulate self-replication and proliferation of the infected host cell (FIG. 7).

A gene encoded by the proviral minus strand has been identified in HTLV-1, STLV-1 and HTLV-3 (REF. 136), but not in HTLV-2 or STLV-2. Although it remains unknown whether HTLV-3 induces cancer, this suggests that members of the *Deltaretrovirus* family that induce T-cell neoplasia encode genes in their complementary strand that are linked with oncogenesis. Interestingly, it was reported that HTLV-1 without its *HBZ* gene can immortalize T lymphocytes<sup>137</sup>. However, when an HTLV-1 with a mutation in the leucine zipper domain of *HBZ* was inoculated into rabbits, proviral load was reduced, supporting a necessary role for *HBZ* in the proliferation of infected cells *in vivo*<sup>137</sup>. Although current results are intriguing, further studies are needed to more clearly elucidate the role of *HBZ* in leukaemogenesis.

*HBZ* RNA might only be a part of the RNA story for ATL transformation. Emerging evidence indicates that some cellular microRNAs (miRNAs) function as tumour suppressors<sup>138</sup>. For example, a proposed mechanism for B-cell chronic lymphocytic leukaemia (B-CLL) arises from the deletion of human miR-15a and miR-16-1, which normally suppress *BCL2* expression. Such deletion of miRNAs can increase *BCL2* expression and its resulting cellular transformation. Ongoing studies suggest a distinct miRNA signature in ATL cells different from normal T cells (Yeung, M.L. and K.T.J., unpublished observations). When ATL cell lines were compared with Jurkat cells (an immortalized but non-ATL T-cell line), a small number (<10) of human miRNAs were observed to be consistently upregulated, whereas a larger number (>50 miRNAs) were downregulated (Yeung, M.L. and K.T.J., unpublished data). How miRNA changes contribute to initiating or maintaining ATL is currently being investigated.

**Future perspectives on clinical treatment**

More than 25 years have passed since ATL was recognized as a distinct clinical entity and HTLV-1 was isolated. Ensuing advances in HTLV-1 virology, immunology and clinical understanding have been remarkable. However, the prognosis for ATL patients, even those treated intensively with chemotherapy, remains poor. Currently, the mean survival time of aggressive ATL is less than 1 year, with extant chemotherapy improving survival only slightly<sup>139</sup>. Prominent treatment impediments include the resistance of ATL cells to anticancer drugs and immunodeficiency in ATL patients, with its complication in opportunistic infections.

A better molecular understanding of ATL might improve therapeutics. For example, as the survival of ATL cells requires activated NFκB<sup>140</sup>, the chemical blockade of NFκB can induce apoptosis and might be envisioned as a treatment for ATL<sup>141,142</sup>. Similarly, the disruption of PI3K–Akt signalling has been effective against highly invasive breast cancer cells<sup>143</sup>, and given the recent

evidence linking PI3K–Akt and the proliferation of Tax-expressing cells, PI3K inhibitors<sup>144</sup> might merit consideration for treating ATL.

Encouraging advances in treating ATL are also coming from stem cell transplantation regimens<sup>145,146</sup>. Allogeneic stem cell transplantation is effective in some ATL cases, with remarkable reductions in proviral load to undetectable levels. An explanation for this finding suggests that the transplantation protocols potentiate anti-HTLV-1 immune responses. In support of this interpretation, CTLs directed to Tax are seen in patients after transplantation<sup>147</sup>. Even in

cases of relapsed ATL in patients who received stem cell transplantation, the relapsed leukaemia frequently regresses after the discontinuation of immunosuppressive agents. These findings indicate that stimulating anti-HTLV-1 immune responses could be useful therapeutically and therefore anti-Tax immunization might be a candidate therapy for ATL.

At this juncture, ATL therapy remains unsatisfactory. One can hope that future insight into the immunology and molecular mechanisms of ATL and the role of HTLV-1 in its development and progression will improve the clinical treatment of this leukaemia.

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**Acknowledgements**

We thank L.-M. Huang for critical reading of this manuscript, and A. Pearl-Jacobovitz and J.-M. Peloponese for help with manuscript preparation. We apologize to investigators whose contributions could not be included owing to space limitations.

**Competing interests statement**

The authors declare no competing financial interests.

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The following terms in this article are linked online to:

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**FURTHER INFORMATION**

Kuan-Teh Jeang's laboratory homepage: <http://www3.niaid.nih.gov/labs/aboutlabs/1mm/MolecularVirologySection/>

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