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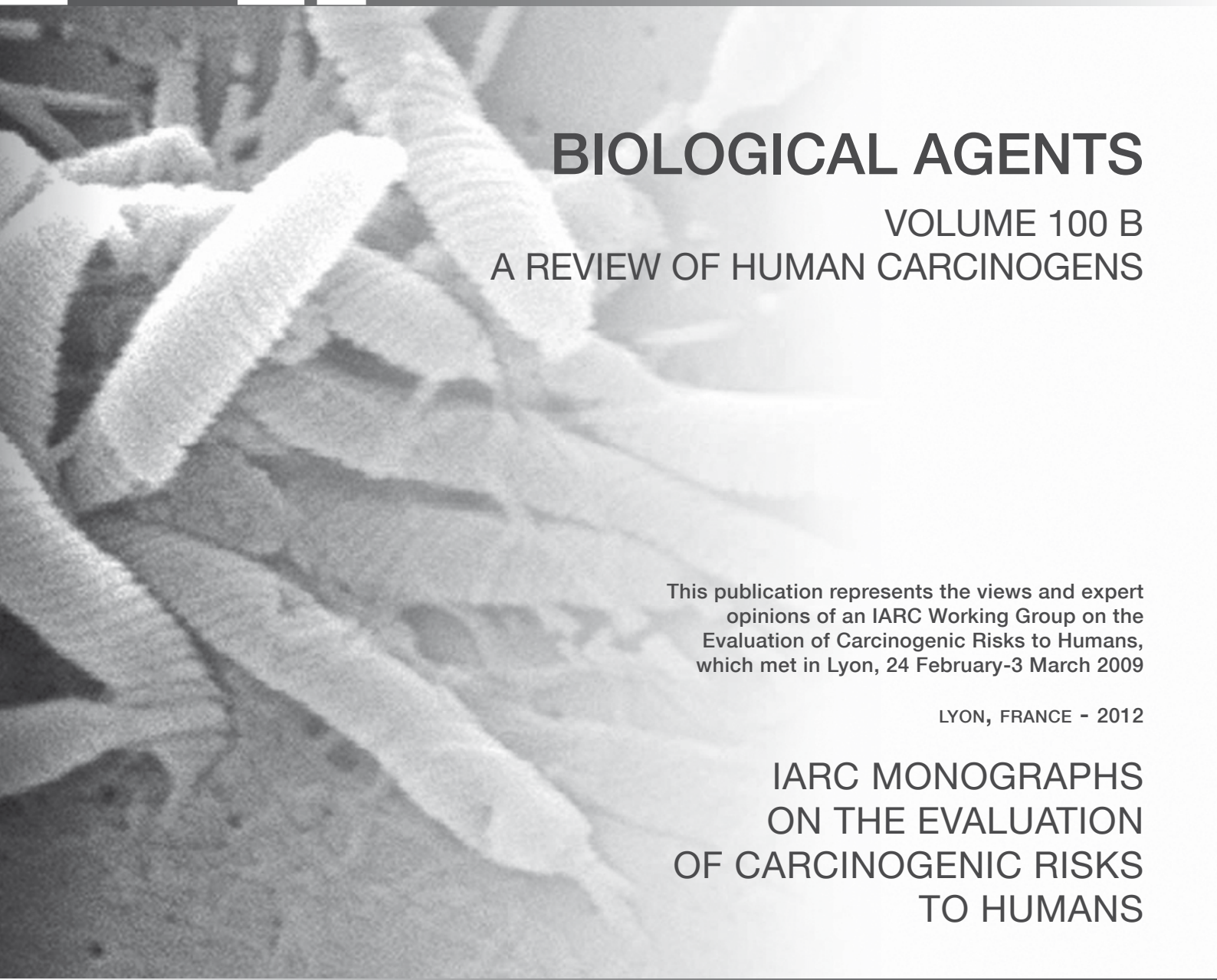

BIOLOGICAL AGENTS

VOLUME 100 B
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 24 February-3 March 2009

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OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1

Human T-cell lymphotropic virus Type 1 was considered by a previous IARC Working Group in 1996 (IARC, 1996). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Taxonomy, structure, and biology

1.1.1 Taxonomy

Retroviruses can be classified according to the morphology of their virion core or according to sequence homologies that become evident after phylogenetic analyses. Human T-lymphotropic virus type 1 (HTLV-1) is a member of the delta-type retrovirus group, other members of which include HTLV types 2, 3 and 4, bovine leukaemia virus (BLV), and simian T-cell leukaemia virus (STLV) types 1, 2 and 3 (Matsuoka & Jeang, 2007). STLV-1 is found in Old World monkeys and great apes. HTLV-1 and STLV-1 are thought to originate from common ancestors (Vandamme *et al.*, 1998). Together with the STLVs, HTLVs form the primate T–cell lymphotropic viruses (PTLV) group. The PTLVs belong to the complex retrovirus family since, in addition to the structural *gag*, *pol* and *env* genes, their genome also contains regulatory and accessory genes. Among these retroviruses, HTLV-1 and STLV-1 induce T-cell neoplasms (Tsujimoto *et al.*, 1987; Gallo, 2002), BLV causes a B-cell neoplastic disease in cattle and in sheep, and HTLV-3 and HTLV-4 have not been clearly associated with any haematological disease (Mahieux & Gessain, 2009). A recent report demonstrated that HTLV-2 infection is linked with higher lymphocyte and platelet counts, although it has not been yet associated with oncogenesis (Bartman *et al.*, 2008).

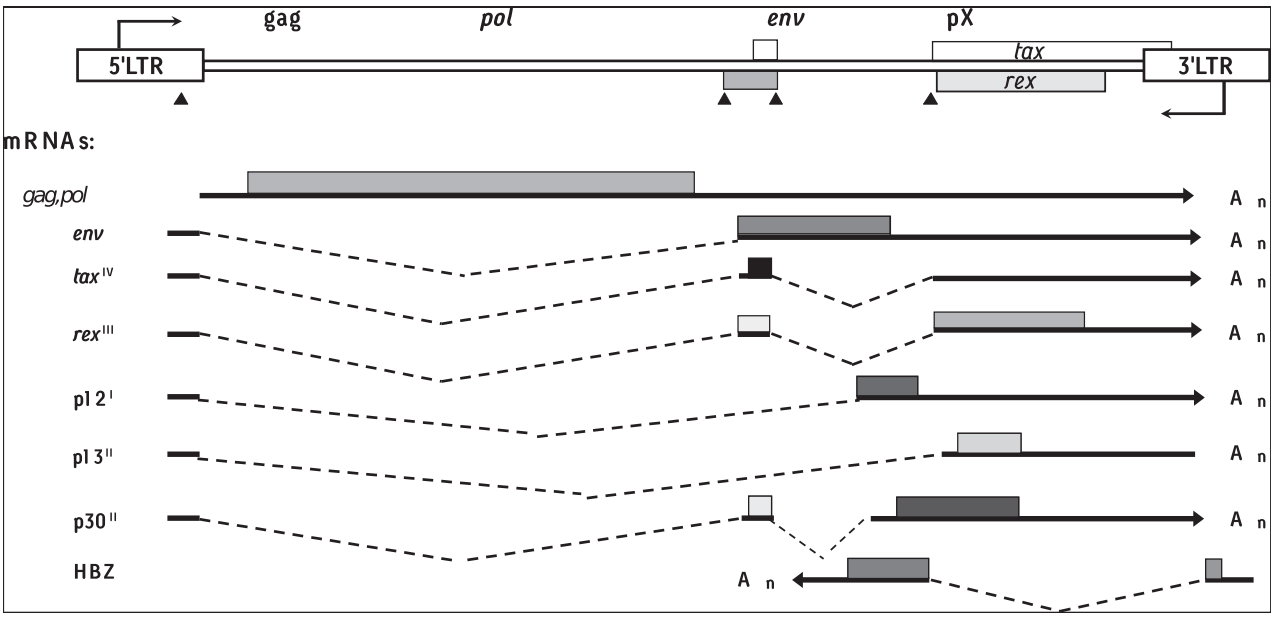
1.1.2 Structure of the virion

The structure of retroviruses is reviewed in the *Monograph* on HIV-1 in this volume. HTLVs are enveloped viruses with a diameter of approximately 80–100 nm. The HTLV virions contain two covalently bound genomic RNA strands, which are complexed with the viral enzymes reverse transcriptase (RT; with associated RNAse H activity), integrase and protease, and the capsid proteins. The outer part of the virions consists of a membrane-associated matrix protein and a lipid layer intersected by the envelope proteins (IARC, 1996).

1.1.3 Structure of the viral genome

As stated above, HTLV-1 is a complex retrovirus that contains regulatory genes (*tax* and *rex*) and accessory genes (*p12, p13, p30* and *HBZ*), in

Fig. 1.1 Scheme of the HTLV-1 genome: alternatively spliced mRNAs and putative proteins encoded by each mRNA are shown



Prepared by the Working Group

addition to structural genes (*gag, pol* and *env*) (see Fig. 1.1). The Gag precursor protein (53 kD) is translated from unspliced genomic RNA. This protein is cleaved into p19 (matrix), p24 (capsid), and p15 (nucleocapsid) by the viral protease. The protease–polymerase products are generated by two frameshifts, which produce protease, reverse transcriptase, and integrase. The Env precursor protein is translated from a single-spliced mRNA, and is cleaved by a cellular protease into the extracellular protein, gp46, and the transmembrane protein, gp21 (Seiki *et al.*, 1983; Sakalian & Hunter, 1998; Matsuoka & Jeang, 2007; Verdonck *et al.*, 2007).

1.1.4 Host range

HTLV-1 naturally infects humans. However, several publications have clearly demonstrated that HTLV-1 can experimentally be inoculated to different animals, including rabbits, rats, mice, and New World monkeys (Lairmore *et al.*, 2005).

1.1.5 Target cells

HTLV-1 can infect different cell types (T cells, B cells, dendritic cells, fibroblasts, etc.) in tissue culture. However, it can transform only T cells both *in vitro* and *in vivo*. HTLV-1 induces the clonal proliferation of T lymphocytes, mainly CD4-positive T cells, and to a lesser extent, CD8-positive T cells (Etoh *et al.*, 1997; Cavrois *et al.*, 1998; Yasunaga *et al.*, 2001). Proliferation is thought to be mediated by one or several viral genes, such as *tax, rex, p12, p13, p30*, or *HBZ*.

HTLV-1 infection of dendritic cells has been recently shown to play a major role in HTLV-1 cell-to-cell transmission (Jones *et al.*, 2008). In experimentally infected squirrel monkeys (*S. Sciureus*), HTLV-1 was mainly detected in the lymphoid organs, which were therefore suggested

to be a major reservoir of the virus (Kazanji *et al.*, 2000).

1.1.6 Life cycle, replication, and regulation of gene expression

The glucose transporter 1 (GLUT1), neuropilin 1, and heparan sulfate proteoglycan form the HTLV-1 receptor complex (Manel *et al.*, 2003; Ghez *et al.*, 2006). These proteins are ubiquitously expressed in cultured cells, therefore allowing HTLV-1 to infect a variety of cell types *in vitro*.

The life cycle of HTLV-1 is similar to that of other retroviruses. A characteristic of HTLV-1 is that it is mainly spread through cell-to-cell contact, although the exact mechanism is still a matter of debate (Igakura *et al.*, 2003). After reverse transcription and integration into the genome, HTLV-1 propagates through clonal expansion of infected cells (Etoh *et al.*, 1997; Cavrois *et al.*, 1998). The limited use of the viral reverse transcriptase explains the remarkable genetic stability of HTLV-1. This is why the administration of reverse transcriptase inhibitors *in vivo* does not influence provirus load (Miyazato *et al.*, 2006; Taylor *et al.*, 2006). Consequently, the HTLV-1 provirus sequence variability is very low (Gessain *et al.*, 1992; Van Dooren *et al.*, 2004). This striking genetic stability is used as a molecular tool to follow the migration of infected populations in the recent or distant past to gain new insights into the origin, evolution, and modes of transmission of such retroviruses and their hosts. The few nucleotide substitutions observed among virus strains are indeed specific to the geographic origin of the patients rather than being linked to the pathology.

Three modes of transmission are known for HTLV-1, and for each of these routes, cell-to-cell contact is required. The transmission is discussed in Section 1.2.

(a) Regulation of gene expression

Viral gene expression initiates from the 5′Long Terminal Repeat (LTR), and is highly dependent on the Tax protein. The details on the regulation of the viral LTR are described in Section 4. However, Tax is a major target of cytotoxic T cells *in vivo* (Koenig *et al.*, 1993), and Tax-expressing cells are, therefore, rapidly eliminated by cytotoxic T cells (Hanon *et al.*, 2000; Asquith *et al.*, 2007; Asquith & Bangham, 2008). Despite a strong cytotoxic T-cell response, proliferation of HTLV-1-infected cells *in vivo* is likely to depend on viral gene expression (Asquith *et al.*, 2007). Epigenetic changes to the 5′LTR may control viral gene expression *in vivo*, enabling escape from cytotoxic T cells. A recent report demonstrated that the administration of valproate, a histone deacetylase inhibitor, to tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM) patients decreased the provirus load *in vivo* without, however, improving the clinical symptoms (Lezin *et al.*, 2007). The mechanism by which the infected cells are eliminated is unknown, but these results indicate that increasing viral expression may represent a potential approach to decreasing the proviral load.

1.2 Epidemiology of infection

In 1977, Takatsuki *et al.* described regions in Japan with high frequencies of T-cell-associated lymphoproliferative disorders and proposed that these diseases shared a viral etiology (Takatsuki *et al.*, 1977). This led to the discovery of HTLV-1 just a few years later, and it became the first human retrovirus to be implicated as a causative agent for human malignancy (Poiesz *et al.*, 1980; Hinuma *et al.*, 1981). Its discovery paved the way to a greater understanding of retroviruses, notably HIV, and their effects on humans. It is now apparent that HTLVs have been infecting humans for thousands of years. An estimated

15–20 million persons worldwide are infected with HTLV-1 (Gessain & de Thé, 1996) [The Working Group noted that the accuracy of this estimate is unknown], and a vaccine is not yet available.

All HTLV types have simian counterparts, and the viral strains found are predominantly related to geography rather than pathology (Slattery *et al.*, 1999). These are all believed to have originated from Africa, the only continent where all PTLVs have been found. From there, PTLV migrated to Asia, where it evolved into STLV-1. This Asian STLV-1 virus type diffused through India, Japan, and Indonesia before returning to Africa, where phylogenetic analyses and anthropological studies place PTLV-1 spread among non-human primates at approximately 27300 years ago (95% confidence interval [CI]: 19100–35500) (Van Dooren *et al.*, 2001).

Interspersed patterns of STLV-1 and HTLV-1 strains suggest frequent interspecies transmissions between humans and primates in Africa. Evidence of these frequent crossings are distinguished by the four major geographic subtypes: cosmopolitan HTLV-1 subtype A, Central African subtype B, Melanesian subtype C, and subtype D, also found in Central Africa (Cassar *et al.*, 2007). The slave trade and an increase in human immigration and mobility facilitated the expansion of HTLV-1 into the New World, Japan, the Middle East, and North Africa (Verdonck *et al.*, 2007). The majority of infected individuals from these regions are infected with cosmopolitan subtype A (HTLV-1A) (Proietti *et al.*, 2005).

1.2.1 Prevalence, geographic distribution

Even though the global geographic distribution of HTLV-1 has been well defined in the literature, fine-scale variations in HTLV-1 prevalence are less well understood. HTLV-1 is often found in micro-epidemic regions surrounded by regions with low prevalence (Fig. 1.2). For example, regions of Kyushu and Okinawa, Japan, have rates as high as 20%; whereas, neighbouring the People's Republic of China and the Republic of Korea have rates of less than 0.1% (Proietti *et al.*, 2005). In general, regions of high endemicity include south-western Japan, parts of subSaharan Africa, the Caribbean Islands, and South America (IARC, 1996). Infection has also been detected in Melanesia, the Solomon Islands, and among Australian Aborigines; there is only low prevalence in Europe and North America.

There is a characteristic age- and gender-dependence of HTLV-1 seroprevalence in many populations. HTLV-1 prevalence increases with age and is higher in women (Beilke & Murphy, 2006). Published studies from several countries including Jamaica, Japan, Brazil, and the United States of America (Beilke & Murphy, 2006) have demonstrated similar trends, in addition to a significant increase of seropositivity in low socioeconomic strata, and in those with a history of blood transfusions. HTLV-1 is most prevalent in populations that have a low geographic mobility, and correspondingly higher rates of vertical and sexual transmission.

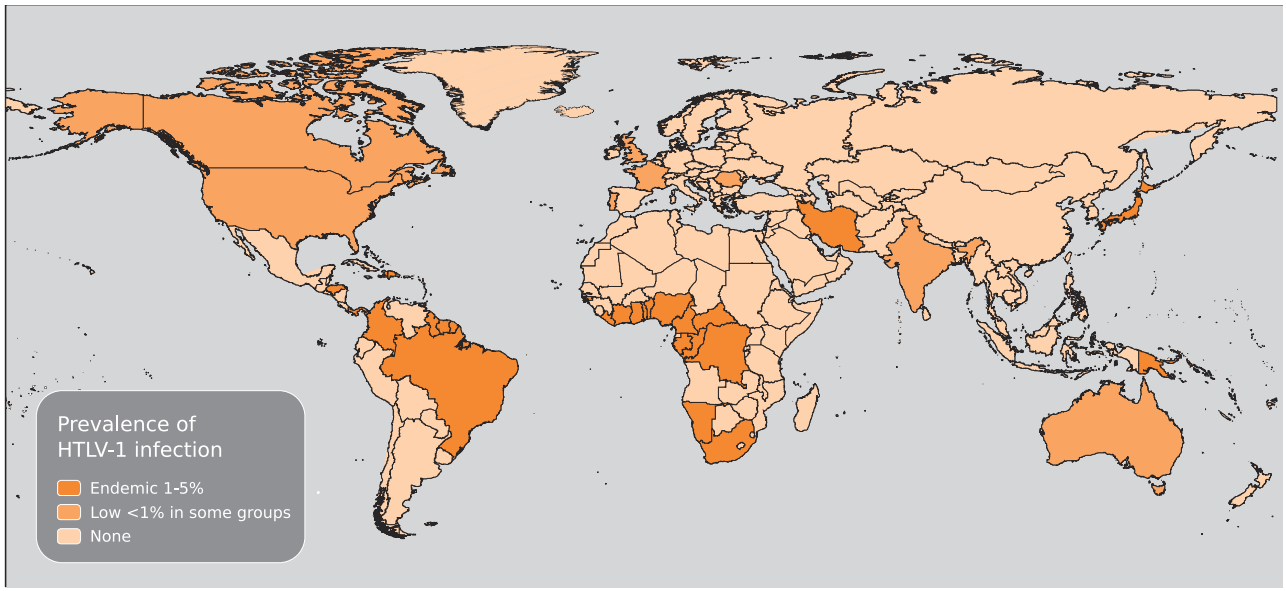
1.2.2 Transmission, and risk factors for infection

There are three main modes of transmission in HTLV-1 infection: vertical transmission, sexual transmission, and parenteral transmission. Each has its respective risk factors: prolonged breastfeeding; unprotected sex with an infected partner, multiple lifetime sexual partners, infection with sexually transmitted diseases (STDs); blood transfusion before institution of HTLV-antibody screening of donors, and injection drug use.

(a) Vertical transmission

The highest rates of HTLV-1 transmission are due to breastfeeding, and in southern Japan, the overall infection rate of breastfed children by HTLV-1-carrier mothers is estimated at 10–30%

Fig. 1.2 Global geographic distribution of HTLV-1 infection: It should be noted that HTLV-1 endemic areas do not correspond exactly to the country boundarie shown in the map, for example, Brazil, Japan and Iran, where HTLV-1 is limited to residents of certain areas of each country



Adapted from and reprinted by permission from Macmillan Publishers Ltd: Oncogene, Proietti *et al.* (2005). http://www.nature.com/onc/index.html

(Tajima & Hinuma, 1992). There may be a higher rate of transmission of mother-to-female compared to mother-to-male infants for HTLV in French Guyana (Ureta-Vidal *et al.*, 1999). In Japan, there does not appear to be gender differences in HTLV-1 before the age of 20 years (Hino, 1990). In a longitudinal study of Japanese children born to carrier mothers, those who did not seroconvert by the age of 3 years remained seronegative until the age of 18 years (Kusuhara *et al.*, 1987). In-utero infectivity is much lower, probably because of limited trafficking of HTLV-1-infected lymphocytes across the placenta. The risk of infection in children has been shown to correspond to the proviral load in the mother's breast milk, and to the duration of breastfeeding (Wiktor *et al.*, 1997). In Japan, the avoidance of breastfeeding by an HTLV-1-infected mother reduced the transmission from 20% to 3%, and efforts to eliminate breastfeeding or to at least reduce its duration to less than 12 months by seropositive mothers, significantly reduced HTLV-1 transmission to children. In a subset of children with HTLV-1 positive cord blood, none had seroconverted (Hino *et al.*, 1996).

(b) Sexual transmission

The second main type of transmission is sexual. One prospective study of heterosexual discordant couples (one partner seropositive, one partner seronegative) suggested higher male- to-female transmission (Stuver *et al.*, 1993), but another did not (Roucoux *et al.*, 2005). In Latin America, gender differences in sexual practices and the seroprevalence of STDs between populations might partially explain these discrepancies (Plancoulaine *et al.*, 1998; Sanchez-Palacios *et al.*, 2003). HTLV-1 carriers infect their spouses at low rates (1–2 per 100 person–years); however, within long-term sexual relationships, HTLV-1 proviral load and lower rates of condom use were shown

to increase transmission efficiency (Kaplan *et al.*, 1996; Iga *et al.*, 2002; Roucoux *et al.*, 2005).

(c) Parenteral transmission

HTLV-1 transmission is also known to occur by the transfusion of cellular blood components, requiring testing of blood products by blood banks in high prevalence regions. The "residual risk" of transfusion-transmitted HTLV-1 infection after serological testing has been estimated as 1 in 641000 blood units transfused in the USA (95%CI: 256000–2000000) (Schreiber *et al.*, 1996). Transmission through this route has been reduced by improvements in the sensitivity of serological assays for HTLV-1 and leukoreduction of blood products, so the current residual risk is probably less than 1 per million blood units transfused. Although nucleic-acid testing of blood products has been introduced for HIV, hepatitis C and hepatitis B viruses (HCV, HBV), it has not yet been developed for HTLV-1, because HTLV-1 would require a cell-based rather than a plasma-based assay (Murphy *et al.*, 1999). HTLV-1 is also transmitted via needle-sharing associated with injection drug use. However, compared to HTLV-2, the prevalence of HTLV-1 is relatively low among injection drug users and their sexual partners in the USA, Italy, Spain, Brazil, and Argentina (Gotuzzo, 2000), perhaps because injection drug use is less common among HTLV-1- as opposed to HTLV-2-risk groups (Roucoux & Murphy, 2004). However, increasing human mobility and cultural interaction create the opportunity for increased HTLV-1 transmission by this route.

1.2.3 Persistence, latency and natural history of infection

The lifetime risk of developing adult T-cell leukaemia/lymphoma (ATLL) has been estimated at 2–4% among HTLV-1 carriers, and the latency period from primary infection until ATLL onset is about 60 years in Japan, and 40 years in Jamaica (Tajima, 1988; Murphy *et al.*, 1989; Takatsuki *et al.*, 1994; Hanchard, 1996; Yasunaga & Matsuoka, 2007). The incubation period for HTLV-associated myelopathy is thought to be shorter: 10–20 years after sexual transmission but as little as 6 months after transfusion-transmitted HTLV-1 infection (Gout *et al.*, 1990). Several viral and immunological markers have been proposed as markers for predicting which infected subjects will progress from latency to disease (see Section 2.1), but prospective validation of these markers is lacking. HTLV-1 may also be associated with increased overall mortality (Arisawa *et al.*, 2003; Orland *et al.*, 2004).

Compared to HIV, the HTLV-1's genome is very stable, with proviral integration predominating over production of viral RNA particles (Mortreux *et al.*, 2003). Occasionally, abnormal, multilobulated lymphocytes "flower cells" can be observed in the peripheral blood (Hisada *et al.*, 1998; Sacher *et al.*, 1999). Aside from detection in the peripheral blood, infected cells have also been detected in the cerebrospinal fluid, an indication of HTLV-1 ability to cross the blood–brain barrier (Mortreux *et al.*, 2003). In an assessment of the patterns of HTLV-1 proviral DNA and antibody titre levels among transfusion recipients, in early infection, proviral loads are initially elevated with corresponding low antibody titres, and as proviral load begins to decrease, antibody titres increase, and later remain stable within each of the cases (Manns *et al.*, 1999). Proviral load may also be related to the route of infection, with transfusion-transmitted HTLV associated with a higher proviral load (Murphy *et al.*, 2004).

Platelet and lymphocyte counts may be chronically elevated in HTLV-1 (Glynn *et al.*, 2000). Both higher platelet counts and lower eosinophils counts were found to be significantly associated with HTLV-1 status among blood donors from the USA (Bartman *et al.*, 2008). HTLV-1 participants also had a small increase in absolute lymphocyte count compared with controls, which was not statistically significant.

HTLV-1 preferentially targets CD4-positive T cells, and infection is transmitted through direct cell-to-cell contact. Recent reports also support a role for dendritic cells in HTLV-1 transmission (Jones *et al.*, 2008). Once inside the cell, the HTLV-1 provirus integrates itself into the host genome. A study. demonstrated a significant rate of viral integration within genes (as opposed to non-coding regions of the genome), which suggests an HTLV-1 preference to insert in growth-related genes over random integration (Hanai *et al.*, 2004). Because of clonal expansion, T cells with identical integration sites are considered to have originated from the same infected cell. More sensitive assays with the ability to amplify regions of the host genome adjacent to the integration site, such as inverse polymerase chain reaction (PCR), may be used to identify clones of infected T lymphocytes in asymptomatic carriers (Okayama *et al.*, 2004; Tanaka *et al.*, 2005).

In contrast to HIV, which produces a large amount of cell-free virions in plasma, HTLV-1 increases its copy number through the proliferation of infected cells, and infection is maintained through this expansion. Early expression of viral tax protein and HTLV-1 accessory proteins induce and maintain initial replication (Manns *et al.*, 1999). An increased proviral load derives from this persistent clonal expansion of virus-infected cells (Wattel *et al.*, 1995). After initial infection, individuals are asymptomatic with proviral loads ranging from 10^2–10^5 per million peripheral blood mononuclear cells (Wattel *et al.*, 1992; Etoh *et al.*, 1999; Mortreux *et al.*, 2003). The proviral load remains relatively stable within a single infected individual over several years (Mortreux *et al.*, 2003; Kwaan *et al.*, 2006).

2. Cancer in Humans

2.1 T-cell malignancies

2.1.1 HTLV-1 infection and ATLL

As described in the previous *IARC Monograph* (IARC, 1996), ATLL occurs almost exclusively in areas where HTLV-1 infection is endemic, such as Japan, the Caribbean, and West Africa. In other areas, cases are usually found among immigrants from endemic populations. Evidence of HTLV-1 infection was initially found in at least 90% of ATLL cases and subsequently, HTLV-1 infection became part of the diagnostic criteria for ATLL. In ATLL, the virus is monoclonally integrated into the tumour cells. The previous IARC Working Group concluded that HTLV-1 infection was a necessary cause of ATLL (IARC, 1996). The current *Monograph* will focus primarily on recent evidence on predictors or risk of ATLL in HTLV-1 carriers. To date, no other malignancies have been convincingly liked to HTLV-1.

Since 1996, several case series have been published on ATLL occurring in diverse HTLV-1-endemic and –non-endemic populations. These include reports from Japan (Tsukasaki *et al.*, 1999); Brazil (Farias de Carvalho *et al.*, 1997; Barbosa *et al.*, 1999; Pombo De Oliveira *et al.*, 1999); Argentina (Marin *et al.*, 2002); Chile (Cabrera *et al.*, 2003); the Commonwealth of Dominica (Adedayo & Shehu, 2004); and Hong Kong Special Administrative Region (Chan & Liang, 1996; Au & Lo, 2005; see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.1.pdf). One report from the Hong Kong Special Administrative Region estimated an HTLV-1 prevalence of only 4×10^{-5} but identified six cases of apparent ATLL by systematically screening all non-Hodgkin lymphoma cases for HTLV-1 antibody (Au & Lo, 2005).

To date, there are a total of six cohort analyses based in Japan that document the incidence

of ATLL among HTLV-1 carriers, and confirm that male carriers have about a 3–5 fold higher risk of developing ATLL than female carriers (Tokudome *et al.* 1991; Iwata *et al.*, 1994; Arisawa *et al.*, 2000, 2003, 2006; Hisada *et al.*, 2001). It is worth noting that because HTLV-1-seropositivity is part of the diagnosis of ATLL, relative risks for ATLL can not be calculated (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.2.pdf). These cohort studies confirm the causal relationship between HTLV-1 infection and the incidence of ATLL, and also underline the higher risk among infected men. However, the reason for the apparently higher disease penetrance in HTLV-1-infected men than HTLV-1-infected women seen in Japan, and whether it exists elsewhere, is unknown. Modelling data from the Carribean have not identified such male excesses (Murphy *et al.*, 1989; see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.3.pdf).

There are four case–control analyses nested within prospective HTLV-1 cohorts in Japan that have compared incident ATLL cases with matched HTLV-1 carriers. These have focused on viral or serological predictors of either ATLL or the prevalence of circulating abnormal lymphocytes that resemble ATLL cells (Hisada *et al.*, 1998a, b; Arisawa *et al.*, 2002; Okayama *et al.*, 2004; see Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.4.pdf). Pre-diagnosis predictors of ATLL included a higher proviral load, higher antibody titres, and a higher prevalence of soluble interleukin-2 receptor-α (sIL2-R). The predictors for higher levels of abnormal lymphocytes were a higher proviral load and male gender. However, these studies are based on a small number of incident cases, and have not been repeated in other HTLV-1-infected populations.

2.1.2 Host susceptibility

As noted above, there is consistent evidence from cohorts in Japan that male carriers have a higher risk compared to female carriers for this malignancy.

It has long been proposed that the risk of ATLL is strongly related to very early HTLV-1 infection. Testing this hypothesis would be difficult, requiring prospective follow-up of large birth cohorts. However, in a recent update of an ongoing study in the Caribbean of mothers of ATLL- and of HTLV-1-associated TSP/HAM patients, 35/36 mothers (97.2%) of ATLL cases were seropositive versus 5/15 mothers (33%) of TSP/HAM patients (P<0.001; Bartholomew *et al.*, 1998). The cells of the sole seronegative mother of an ATLL case were also negative on PCR. However, the father and one older sister of this ATLL case were both HTLV-1 seropositive. All patients in the study were breastfed, and none of the patients or their mothers had a history of a blood transfusion. These findings support the proposal that early and/or mother-to-child infection with HTLV-1 plays an important role in the genesis of ATLL.

Finally, much of the notion of the epidemiology of ATLL is based on epidemiological studies conducted in Japan. It is important to note that geographically defined social environments may alter the natural history of this infection. Specifically, the peak incidence of ATLL occurs earlier and at a reduced frequency among HTLV-1 carriers in the Caribbean in comparison to Japan. Several studies compared viral and immune markers between HTLV-1 carriers and uninfected controls, and between Jamaican and Japanese HTLV-1 carriers as an approach to determine why the penetrance of ATLL may differ between populations.

Hisada *et al.* (2004) analysed viral markers between a matched set of Jamaican (n = 51) and Japanese carriers (n = 51) (Hisada *et al.*, 2004). They found that the anti-HTLV-1 titres were

higher among the Jamaicans (P=0.03), as was the prevalence of antibodies against the tax protein (anti-tax) (P=0.002). There was no significant difference in proviral load between the Jamaican and Japanese carriers.

Birmann *et al.* (2009) further added a matched HTLV-1 seronegative subject to each carrier within each population reported in Hisada *et al.* (2004) to evaluate a set of serum immune markers (Birmann *et al.*, 2009). HTLV-1 infection was associated with activated T-cell immunity among the Jamaican subjects as indicated by a higher prevalence of a low EBV nuclear antigens (EBNA-1:EBNA-2) ratio, higher serum levels of sIL2R, and of soluble CD30. The results among the Japanese subjects indicated diminished T-cell immunity among the carriers, as indicated by lower C-reactive protein levels. [The Working Group noted that the observed population differences in non-carriers between the two populations and the impact of HTLV-1 infection within the population in immune profiles may begin to explain the divergent natural history of HTLV-1 infection in the two sentinel populations, and highlight the importance of social environments. Factors that may contribute to these findings include differences in age-specific infection rates, co-existing infections and nutritional status.] See Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.5.pdf.

2.2 Other malignancies

2.2.1 Cutaneous T-cell lymphoma

One study reported that 60 patients with mycosis fungoides had detectable tax-related proteins in peripheral blood mononuclear cell samples; of these, they reported that 83% also had antibodies to HTLV-1 tax proteins (Pancake *et al.*, 1996). However, several large studies on patients with cutaneous T-cell malignancies, including many cases of mycosis fungoides in the USA, Republic of Korea, Japan, Spain, Europe, Mali, and Taiwan (China) could not replicate these results, and did not confirm an association with HTLV-1 (Wood *et al.*, 1996, 1997; Bazarbachi *et al.*, 1997; Kikuchi *et al.*, 1997a, b; Chang *et al.*, 1998; Fouchard *et al.*, 1998; Kim *et al.*, 1998; see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.6.pdf). Overall, there is no consistent evidence that HTLV-1 is associated with cutaneous T-cell malignancies, with the exception of ATLL presenting in the skin.

2.2.2 B- and T-cell lymphomas

Since the previous *IARC Monograph* (IARC, 1996), several case series have examined HTLV-1 infection in B- and T-cell lymphomas (Farias de Carvalho *et al.*, 1997; Marin *et al.*, 2002; Cabrera *et al.*, 2003; Suefuji *et al.*, 2003; Adedayo & Shehu, 2004). With the exception of some T-cell lymphomas which may, in retrospect, have been cases of ATLL (Marin *et al.*, 2002), there was no evidence that HTLV-1 infection played a role in these lymphomas (see Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.7.pdf).

The majority of primary gastric lymphomas are of B-cell origin, and only rarely of T-cell phenotype (Isaacson *et al.*, 2008). However, a study reported that 18/58 lymphoma-type ATLL patients had gastric involvement of ATLL cells; and of these, three had primary gastric lymphoma (Sakata *et al.*, 2001). Another report described 67 cases of surgically resected primary gastric lymphoma, of which five were found to have T-cell lymphoma: two were HTLV-1 positive and three were HTLV-1 negative (Shimada-Hiratsuka *et al.*, 1997). A final report described 14 T-cell lymphomas in 233 cases of primary gastric lymphoma (Nakamura & Tsuneyoshi, 1998). [The Working Group remarked that although further research may be useful, it is not clear if gastric lymphoma represents a separate

entity, or simply ATLL involving the stomach or adjacent lymphoid tissue.] See Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.8.pdf

Except for a few cases of ATLL, two studies were unable to find HTLV-1 in post-transplant lymphoproliferative disorders. Gentile *et al.* (1998) reported three patients who developed T-cell lymphoproliferative disorders after renal transplantation, but none had evidence of HTLV-1 infection. The second study reported on 24 cases of post-transplant lymphoid proliferation in Japan: 12 B-cell, ten T-cell, and two natural killer phenotype. A total of 5/10 T-cell tumours were classified as ATLL (Hoshida *et al.*, 2001). See Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.9.pdf.

In one study, 12 cases of leukaemia of large granular lymphocytes with and tested for IgG antibodies to proteins related to HTLV-1 were reported (Starkebaum *et al.*, 1987). Sera from 6/12 cases reacted with the HTLV-1 proteins, while none of the 'control' serum (from healthy persons and patients with other disorders) reacted. By analogy, an initial report of HTLV-2 and large granular lymphocytes (Loughran *et al.*, 1992) was not confirmed in a controlled study (Loughran *et al.*, 1994). A set of 27 specimens from cases of splenic lymphoma on Kyushu Island, Japan – an HTLV-1-endemic area – were tested for anti-HTLV-1 antibody, and all were negative (Kumagawa *et al.*, 2001).

2.2.3 Non-lymphomatous tumours

DNA from HTLV-1 and human foamy virus has been detected in recent studies of thymoma, and in 2002, a study reported that 11/12 samples from thymoma patients (91.6%) from Italy tested positive for the *tax* gene of HTLV-1/2 and 9/12 samples (75%) positive for the *tax* and *pol* genes of HTLV-1 (Manca *et al.*, 2002). However, a later study did not find any evidence for HTLV-1 or human foamy virus in 21 thymoma patients from the USA (Li *et al.*, 2004).

Whether or not HTLV-1 is linked to an increased risk of solid malignancies has been studied with generally negative results. However, there is intriguing evidence for a possible protective effect of HTLV-1 on gastric carcinoma. In a prospective cohort study, 4136 adults living in four towns in the Nagasaki Prefecture in south-western Japan were followed for 6 years (Arisawa *et al.*, 2003). A total of 1063 were seropositive for anti-HTLV-1 antibodies at baseline, including 439 (22.9%) men and 624 (26.2%) women. There were a total of 290 deaths in the cohort, with increased all-cause mortality for HTLV-1 both when ATLL was counted among the deaths (RR, 1.5; 95%CI: 1.2–1.9), and when ATLL deaths were excluded (RR, 1.3; 95%CI: 1.0–1.7). HTLV-1 was not associated with an increased risk of all-site cancer mortality after excluding cases of ATLL (RR, 1.1; 95%CI: 0.77–1.7). Other interesting findings from the study included a decreased incidence of gastric cancer (RR, 0.42; 95%CI: 0.17–0.99). These negative results for HTLV-1 and solid tumours are in contrast to previous cross-sectional studies, which reported a higher HTLV-1 seroprevalence among 394 non-transfused patients with non-ATLL malignancy than in age- and sex-matched healthy controls (Asou *et al.*, 1986), and a higher prevalence of all malignant neoplasms among siblings of ATLL patients compared to siblings of HTLV-1 seronegative non-Hodgkin lymphoma cases (Kozuru *et al.*, 1996).

In a recent retrospective cohort study in the Nagasaki Prefecture, Japan, 497 HTLV-1-positive and 497 HTLV-1-negative persons who did not have gastric cancer at baseline were followed with serial endoscopy of the stomach (Matsumoto *et al.*, 2008). *Helicobacter pylori* antibodies were found in 61.7% of HTLV-1-positive cases compared to 71.6% of the HTLV-1-negative cases. There were 14 cases (2.8%) of gastric cancer in the HTLV-1-positive subjects compared to 35

cases (7%) in the age- and sex-matched HTLV-1-seronegatives (OR, 0.38; 95%CI: 0.21–0.70). [The Working Group noted that these data suggest that HTLV-1 infection may reduce the inflammation usually associated with *H. pylori* infection, and thereby reduce the risk of gastric carcinoma.]

[The Working Group noted that further investigation is warranted on the subject of persistent *H. pylori* infection among HTLV-1 seropositives to determine whether HTLV-1 infection may reduce the inflammatory response to *H. pylori* and reduce the risk of gastric carcinoma, as mentioned above (Arisawa *et al.*, 2003; Matsumoto *et al.*, 2008).]

Finally, one study of 85 cases of oesophageal squamous cell carcinoma in the Islamic Republic of Iran found no increase in HTLV-1 antibody prevalence compared to non-cancer controls (Mirsadraee *et al.*, 2007).

See Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.10.pdf.

2.3 Cofactors

In addition to the roles of being of masculine gender and infected at a younger age (described above), undernutrition and repeated exposure to filariasis in childhood were proposed as potential risk factors for ATLL (Tajima & Hinuma, 1984).

Since then, there is some evidence that co-infection with *Strongyloides stercoralis* is detrimental to HTLV-1 carriers. Among 38 ATLL cases, those who were positive for *S. stercoralis* were younger at diagnosis then those uninfected (Plumelle *et al.*, 1997).

Gabet *et al.* (2000) reported that among HTLV-1 carriers from West Guyana and Martinique, those who were co-infected with *S. stercoralis* had a substantially higher HTLV-1 proviral load, and substantially more oligoclonal expansion of HTLV-1-infected lymphocytes than carriers who were negative for *S. stercoralis*. These observations were substantiated in a Japanese population of HTLV-1 carriers (Satoh *et al.*, 2002). [The Working Group noted that, together, these papers suggest that co-infection with *S. stercoralis* may increase the risk of ATLL in HTLV-1 carriers, and presents a potential for risk reduction with parasite treatment and control.]

One case series reported three cases of ATLL among eight HTLV-1 carriers within 2 years after immunosuppression with tacrolimus for liver transplantation (Kawano *et al.*, 2006). In another study, five cases of ATLL were reported following immunosuppression for kidney transplantation (Hoshida *et al.*, 2001).

See Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-07-Table2.11.pdf.

3. Cancer in Experimental Animals

In this volume, the Working Group decided not to include a separate section on "Cancer in Experimental Animals" in the *Monographs* on viruses but rather to include description of such studies under Section 4 (below). The reasoning for this decision is explained in the General Remarks.

4. Other Relevant Data

4.1 Mechanism of HTLV-1-linked carcinogenesis

4.1.1 Transforming capacity of HTLV-1

In vivo, HTLV-1 infection has been reported not only in T lymphocytes, but also in B lymphocytes, myeloid cells, monocytes, and dendritic cells (Koyanagi *et al.*, 1993; Manel *et al.*, 2005; Jones *et al.*, 2008). However, HTLV-1 immortalizes only T lymphocytes *in vitro* through the action of the Tax viral protein.

4.1.2 Biochemical and biological properties of HTLV-1 proteins

HTLV-1 belongs to the complex retroviruses family. The pX region, which is localized between the *env* gene and the 3′LTR, encodes regulatory genes (*tax* and *rex*), and accessory genes (*p12*, *p13*, *p30* and *HBZ*) (Matsuoka & Jeang, 2007). These proteins not only control viral gene transcription, but also modulate the proliferation of infected cells. Indeed, the fact that HTLV-1 induces the proliferation of infected cells facilitates its transmission through cell-to-cell contact rather than through the release of viral particles (see also Section 1 and Fig.1.1).

(a) Rex

The Rex protein binds to Rex-responsive elements (RxRE), a highly stable stem-loop structure in the R/U3 region of the 3′LTR (Hanly *et al.*, 1989). Rex regulates viral gene expression at the post-transcriptional level, by increasing the level of unspliced RNA in the nucleus, and by enhancing the nuclear export and the expression of the unspliced *gag/pol* and single-spliced *env* transcripts (Inoue *et al.*, 1991).

(b) p12

The open reading frame I of the pX region of HTLV-1 encodes the protein p12, which is located in the endoplasmic reticulum and the Golgi. In quiescent primary lymphocytes and *in vivo*, p12 is important for establishing HTLV-1 infection and optimal viral infectivity. The p12 protein therefore facilitates host-cell activation, and the establishment of persistent infection (Collins *et al.*, 1998; Albrecht *et al.*, 2000; Nicot *et al.*, 2005).

(c) p13

The protein p13 contains a mitochondrial-targeting signal, and exists in the nucleus and mitochondria. Mutation of the *p13* gene impairs viral proliferation *in vivo*, indicating that p13 is critical for viral replication (Hiraragi *et al.*, 2006). In addition, p13 expression is associated with a suppressed cell proliferation *in vitro* (Silic-Benussi *et al.*, 2004).

(d) p30

The protein p30 is a nuclear and nucleolar protein (Koralnik *et al.*, 1993) that binds to and retains the *tax/rex* mRNA within the nucleus. Therefore, p30 is a post-transcriptional negative regulator of viral replication and viral gene expression (Nicot *et al.*, 2004).

(e) Tax

Tax, a 40-kD phosphoprotein, encoded from a spliced mRNA, is found mainly in the nucleus but also in the cytoplasm (Meertens *et al.*, 2004). Tax interacts with several host factors (Boxus *et al.*, 2008), which results in *trans*-activation of some genes, *trans*-repression of others, modulation of the cell cycle, and dysregulation of apoptosis (Matsuoka & Jeang, 2007).

The transduction of a pX-containing sequence into primary human T Lymphocytes by use of a defective simian herpesvirus is sufficient to immortalize these cells (Grassmann *et al.*, 1989). However, since this vector could express not only *tax* but also the genes *p12, p13, p30* and *HBZ*, it was difficult to conclude whether Tax was the only responsible viral protein for cell transformation. Subsequently, immortalization (IL-2-dependent growth) of human CD4-positive T cells was demonstrated *in vitro* by the use of a retroviral vector expressing only the *tax* gene (Akagi *et al.*, 1995). In addition, the transforming ability of Tax was demonstrated in the Rat-1 fibroblast cell line *in vitro* in a soft-agar assay, and *in vivo* in nude mice (Tanaka *et al.*, 1990). These findings clearly showed that Tax is oncogenic. In addition, several studies with animals transgenic for Tax have clearly demonstrated that Tax expression leads to the induction of tumours, confirming that Tax is oncogenic *in vivo* (see Section 4.1.6).

Transcription pathways activated by Tax include those of NF-κB, CREB, SRF and AP-1 (Azran *et al.*, 2004). To turn on the NF-κB pathway, Tax binds to IKKγ, and activates the IKK complex, leading to phosphorylation of IκB (Jin *et al.*, 1999). For survival, the Akt/PI3K pathway is also implicated in addition to the NF-κB pathway. Tax also activates this pathway by binding to the p85α subunit of PI3K, leading to activation of AP-1 (Peloponese & Jeang, 2006).

The transcription factor p53 is a crucial element in the cellular defence against tumour development. Mutations in the *TP53* gene are frequently found in human cancers (IARC *p53* database available online at http://www.p53.iarc.fr). Mutations in *TP53* occur in less than 30% of adult T-cell leukaemia (ATLL) cells, depending on the clinical stage, which indicates that other mechanisms are involved. The precise mechanism that leads Tax to inhibit the function of p53 is still a matter of debate: some authors suggested that competition with the transcription co-activators CBP/p300 plays a major role (Mulloy *et al.*, 1998; Suzuki *et al.*, 1999), whereas others reported that activation of the NF-κB pathway was needed (Pise-Masison & Brady, 2005).

Tax activates the transcription of viral genes through three imperfect 21 base-pair repeat elements, the Tax-responsive element (TRE) (Fujisawa *et al.*, 1986). The neighbouring GC-rich sequences of TRE are required for the binding of Tax (Paca-Uccaralertkun *et al.*, 1994). The TRE contains sequences that are similar to that of the cyclic adenosine monophosphate (cAMP)-responsive element (CRE). CRE-binding protein/activating transcription factor (CREB/ATF) family members bind to TRE in a Tax-dependent manner (Franklin *et al.*, 1993). Tax can interact with transcriptional co-activators, CREB-binding protein (CBP) and p300, that acetylate histones in the promoter region. In addition, CREB co-activators – termed transducers of regulated CREB activity (TORCs) – activate Tax-mediated viral gene transcription through the LTR. Tax interacts with TORCs (Siu *et al.*, 2006). Thus, co-activators, TORCs, and CBP/p300 are necessary for the Tax-mediated activation of viral gene transcription.

Tax also inhibits transforming growth factor β (TGF-β)-mediated signals. It is likely that the inhibition of TGF-β-signalling enables HTLV-1-infected cells to escape TGF-β-mediated growth inhibition (Mori *et al.*, 2001; Lee *et al.*, 2002).

The Tax sequence contains several important domains that are involved in CREB and NF-κB activation. Recently, the *C*-terminal sequence of Tax was shown to contain a PDZ-binding motif. This PDZ-binding motif, which is absent from HTLV-2 Tax, seems critical for the ability of HTLV-1 Tax to transform cells *in vitro* (Rousset *et al.*, 1998; Endo *et al.*, 2002). It should be noted that Tax is not expressed in 60% of ATLL cases, due to deletions, epigenetic changes of the 5′LTR, and genetic changes in the Tax sequence (Matsuoka, 2005, 2010; Giam & Jeang, 2007).

(f) HBZ

The HTLV-1 bZIP factor (HBZ) is transcribed from the complementary strand of the proviral genome (Larocca *et al.*, 1989; Gaudray *et al.*, 2002). Viral transcription from the 5′LTR is highly dependent upon Tax expression and this is due to the presence of three TREs, as indicated above. Conversely, the transcription from the 3′LTR is dependent on Sp1 (Yoshida *et al.*, 2008). Therefore, *HBZ* gene transcription is relatively constant, and is correlated with proviral load (Usui *et al.*, 2008). Interestingly, and in contrast to the finding that the *tax* gene has not been frequently detected in ATLL cells, the HBZ mRNA could be detected in all ATLL cases. Even if defective proviruses are commonly detected in ATLL cells, the *HBZ* gene always remains intact (Miyazaki *et al.*, 2007). Importantly, *HBZ* expression is associated with the proliferation of ATLL cells since the knock-down of *HBZ* in ATLL cells decreases the growth of the leukaemic cells (Satou *et al.*, 2006), which further indicates that

HBZ is critical and essential for the growth of these cells. Several transcription factors bind HBZ, including c-Jun, JunD, JunB, RelA/p65, p300, and CREB (Basbous *et al.*, 2003; Hivin *et al.*, 2007; Clerc *et al.*, 2008).

4.1.3 Biological properties of HTLV-1 proteins relevant to carcinogenesis

(a) Immortalization

HTLV-1 can transform CD4-positive T lymphocytes *in vitro*. Among all the viral proteins, only Tax has the ability to immortalize CD4-positive T cells *in vitro* (see above).

(b) Genetic instability

Cytogenetic abnormalities that are specific to ATLL have not been found, but trisomies, deletions, and structural rearrangements are frequently reported in two of the four ATLL subtypes (acute leukaemia and lymphoma ATLL) (Kamada *et al.*, 1992). This is therefore indicative of chromosomal instability in ATLL cells where the altered functions of several centrosome-associated proteins seem also to be involved in the Tax-driven aneuploidy (Afonso *et al.*, 2007). As an example, the functions of HsMAD1 (also known as TXBP181) functions are impaired in Tax-expressing cells. HsMAD1 acts at the G2/M-checkpoint and has been found on the centrosome during metaphase. It is tempting to speculate that the loss of HsMAD1 function could be linked to the loss or modification of the centrosomal activity (Jin *et al.*, 1998).

Tax has also been reported to interact with the anaphase-promoting complex/cyclosome (APC/C). This interaction leads to a premature mitotic exit, and may contribute to aneuploidy (Liu *et al.*, 2005).

Recently, another partner of Tax, the centrosome-associated TAX1BP2 protein (also known as TXBP121) was also implicated in the Tax-dependent initiation of aneuploidy (Ching *et al.*, 2006). By the use of in-situ fluorescence microscopy the authors demonstrated that Tax binds to and co-localizes with endogenous TAX1BP2, forming peri-nuclear dots. In the absence of Tax, overexpression of TAX1BP2 leads to a reduction in the number of cells that contain supernumerary centrosomes. In contrast, depletion of endogenous TAX1BP2 induces centrosome amplification. Therefore, Tax and TAX1BP2 have opposite effects. Besides, a Tax mutant that does not interact with TAX1BP2 can no longer induce centrosome duplication. This suggests that Tax targets TAX1BP2 to cause aneuploidy. In addition, during mitosis, Tax binds to Ran and RanBP1, which fragments spindle poles, and induces multipolar segregation (Peloponese *et al.*, 2005).

(c) DNA-damage responses

Tax has been reported to suppress the expression of DNA polymerase β (Jeang *et al.*, 1990), which is implicated in DNA repair. This suppression is associated with impaired DNA repair in HTLV-1-infected cells. In addition, it has been reported that Tax inhibits ATM-mediated DNA-damage response, resulting in premature DNA replication in the presence of genomic lesions (Chandhasin *et al.*, 2008).

(d) Cell proliferation and differentiation

As mentioned above, the HTLV-1 provirus can be detected not only in CD4-positive T cells, but also in CD8-positive T cells as well as in dentric cells *in vivo*. Among CD4-positive T cells, the HTLV-1 provirus was detected in memory/effector T cells. After infection followed by a couple of cycles during which HTLV-1 uses its reverse transcriptase, the virus is amplified via clonal proliferation of the infected cells (Takemoto *et al.*, 1994; Wattel *et al.*, 1995). The same infected clones survive *in vivo*, indicating that clonal proliferation is persistent (Etoh *et al.*, 1997; Cavrois *et al.*, 1998). A prospective study has shown that this clonal proliferation is associated with the onset of ATLL in some cases (Okayama

et al., 2004), although oligoclonal proliferation without ATLL occurs in most asymptomatic HTLV-1 carriers. Of note, the proviral load ranges from less than 0.1% up to 30% (of total peripheral blood mononuclear cells) in asymptomatic carriers. It is likely that a high proviral load is associated with a higher risk of developing ATLL (Tachibana *et al.*, 1992).

4.1.4 Role of HTLV-1 in malignant conversion

(a) Requirement of HTLV-1 expression for cell growth

Viral gene expression differs between in-vitro-transformed cell lines and primary ATLL cells in a manner that is similar to the relation between EBV-transformed cells and Burkitt lymphoma cells. Tax expression is usually high in transformed cells *in vitro* but TAX gene transcription is detected in only about 40% of ATLL cells cultured *ex vivo* (Matsuoka & Jeang, 2007). Analyses of the HTLV-1 provirus identified three mechanisms that inactivate Tax expression: 1) genetic changes in the TAX gene sequence that lead to a premature stop codon or to insertions/deletions; 2) DNA methylation of the provirus; and, 3) deletion of the proviral 5′LTR (Matsuoka & Jeang, 2007). Deletion or DNA methylation of the 5′LTR silenced transcription of the viral genes, including TAX, REX, P12, P13, and P30. The 3′LTR, on the other hand, was intact and unmethylated in all ATLL cases examined, and *HBZ* was shown to be expressed in all ATLL cases tested, and to induce lymphocyte proliferation (Satou *et al.*, 2006). Interestingly, there is a correlation between the proviral load and *HBZ* mRNA levels (Li *et al.*, 2009).

(b) Persistence of the HTLV-1 genome

HTLV-1 induces ATLL in a subset of carriers after a long latency period. As an example, the cumulative lifetime risk of developing ATLL was estimated to be 6.6% for men and 2.1% for women among Japanese HTLV-1 carriers (Arisawa *et al.*, 2000). ATLL cells retain the HTLV-1 provirus in the genome, but as stated above, defective proviruses are frequently detected, which are classified into two types. A type-1 defective provirus was found in 43% of all defective viruses; it lacks internal sequences such as *gag*, *pol* and *env* but retains both LTRs. A type-2 defective provirus lacks the 5′LTR and internal sequences. It is frequently observed in acute and lymphoma-type ATLLs whereas it is quite rare in chronic ATLL, indicating that this defective provirus is likely to be associated with disease progression (Tamiya *et al.*, 1996). Detailed analyses show that the type-2 defective provirus can be generated before and after integration. A defective provirus formed after integration suggests that the deletion of the 5′LTR may block Tax expression, enabling ATLL cells to escape the host immune system. The frequency of type-2 defective proviruses is low in carriers, indicating that these defective proviruses were selected during leukaemogenesis. Another possibility is that infected cells with the type-2 defective provirus tend to transform into ATLL cells. ATLL cells with the type-2 defective provirus frequently cannot produce Tax as a result of the deletion of the promoter or the deletion of the second exon. However, all cases with the type-2 defective provirus maintain an intact *HBZ* gene sequence (Miyazaki *et al.*, 2007).

As a mechanism of retroviral oncogenesis, the integrated LTR activates the transcription of cellular oncogenes, flanking integration sites. However, there are no common integration sites of HTLV-1 provirus in ATLL cells (Doi *et al.*, 2005).

(c) Alterations of oncogenes and tumour-suppressor genes

Several ways by which tumour-suppressor genes can be inactivated have been demonstrated in cancer cells. Mutations of the *TP53* gene occur in up to 40% of all ATLL patients (Sakashita *et al.*, 1992; Yasunaga & Matsuoka,

2003). Deletion or mutation of the *p16*^{INK4A} gene has also been reported. Such genetic changes in the *p53* and *p16*^{INK4A} gene sequence and/or function are detected in the more aggressive disease states, indicating that somatic DNA changes in these two genes are associated with the progression of ATLL (Yasunaga & Matsuoka, 2003).

Cytogenetic analysis of ATLL cells showed a common breakpoint cluster region in chromosome 10p11.2. Further analyses have shown that the transcription factor 8 (TCF8) is frequently disrupted by several mechanisms, including epigenetic silencing. Suppressed expression of TCF8 is associated with resistance to TGF-β. Mice carrying a mutation in *TCF8* frequently developed thymic T-cell lymphoma, indicating that *TCF8* is a tumour-suppressor gene (Hidaka *et al.*, 2008).

There have been a few reports of cellular oncogenes in ATLL cells. By screening cDNA expression-libraries derived from leukaemic cells of ATLL patients for the potential to transform NIH3T3 mouse fibroblasts, a novel transforming gene, *Tgat*, was identified. Expression of Tgat in NIH3T3 cells resulted in cell transformation, indicated by anchorage-independent growth in semisolid medium, and tumorigenicity in nude mice (Yoshizuka *et al.*, 2004).

4.1.5 Interaction between HTLV-1 and environmental agents

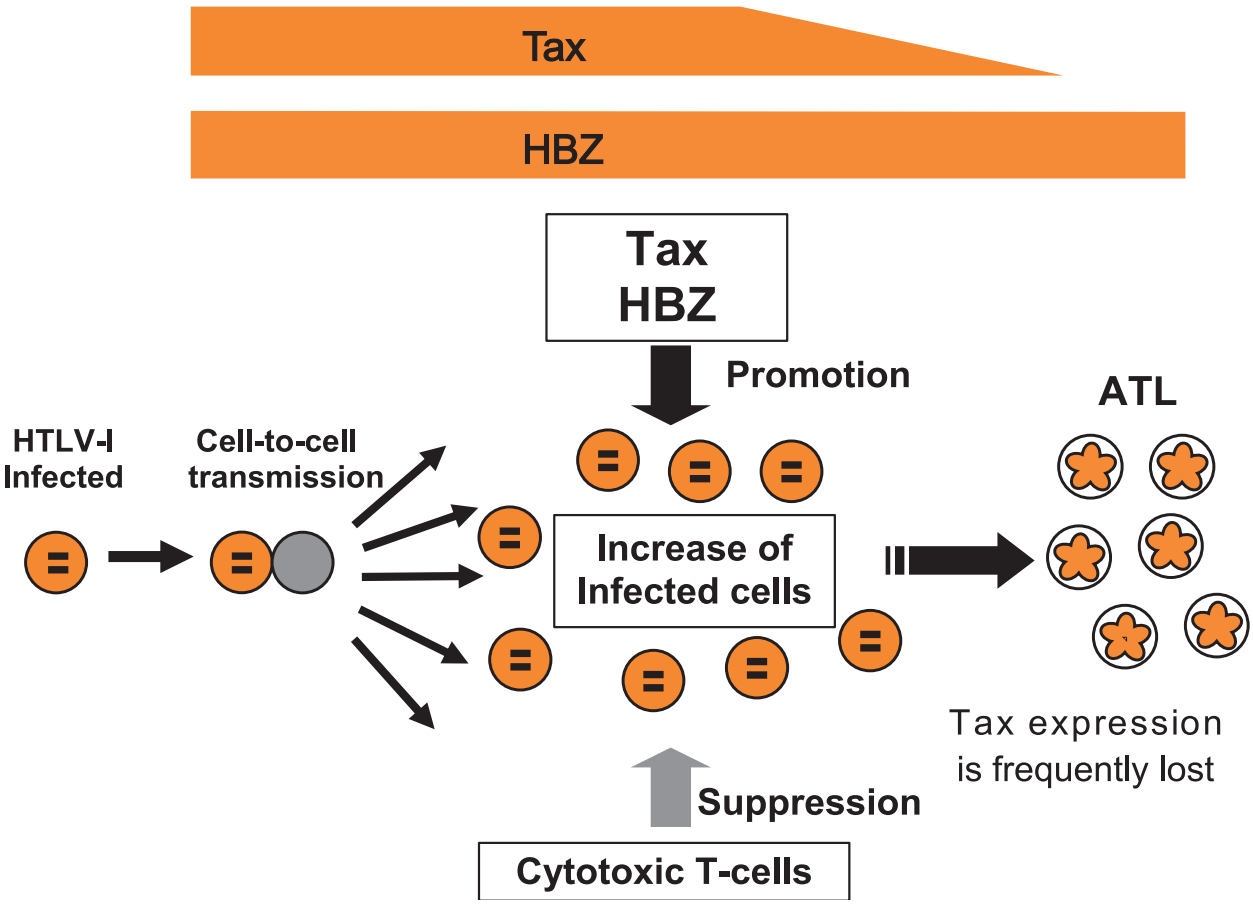
The frequency of opportunistic infections is fairly high among ATLL patients, indicating that T-cell-mediated immunity is severely impaired in such patients. The presence of the parasite *S. stercoralis* is commonly seen in immunosuppressed patients. In a study in the Japanese districts of Kyushu and Okinawa, where strongyloidiasis is endemic, 36 patients were identified as seropositive for HTLV-1. Fourteen of these patients (39%) had HTLV-1 DNA monoclonally integrated in their blood lymphocytes. It has been suggested that the parasitic infestation with *S. stercoralis* may act as a cofactor for HTLV-1-induced leukaemogenesis (Nakada *et al.*, 1987).

4.1.6 Animal models for HTLV-1-associated cancers

Animals, including rabbits, rats, and monkeys can be experimentally infected with HTLV-1 (Lairmore *et al.*, 2005). In rabbits and rats, HTLV-1 infection is persistent, and induces host immune response. However, HTLV-1 does not lead to definite diseases in these two species. A large number of Old World monkeys are naturally infected with STLV-1. This virus is almost identical at the nucleotide level with HTLV-1, and several cases of ATLL have been described in monkeys (Tsujimoto *et al.*, 1987; Akari *et al.*, 1998). Experimental infection with HTLV-1 of squirrel monkeys (*S. Sciureus*) led to a substantial decrease in the proliferation rate of the CD4-positive T-cell population in those infected animals that were affected by a pathology similar to ATLL in humans (Debacq *et al.*, 2005). Co-infection of rhesus macaques (*Macaca mulatta*) with HTLV-1 and simian immunodeficiency virus 1 (SIV-1) increased the number of multilobulated lymphocytes in the circulation. The study showed that SIV-1 may have the potential to upregulate HTLV-1 and disease expression (Traina-Dorge *et al.*, 2007). So far, non-human primates represent the only suitable animal model to study human ATLL.

Several groups have shown that HTLV-1 can infect immunocompetent mice, although in most of these studies, no viral mRNA production or HTLV-1 antibody response were detected. In addition, these mice did not show progression to ATLL (Lairmore *et al.*, 2005). Several transgenic animal models have been established to study HTLV-1; the Tax protein has been shown to be oncogenic in several of these models. The type of tumour depends on the promoter used in each study: transgenic mice expressing Tax using the granzyme B promoter developed tumours of

Fig. 4.1 Natural history of HTLV-1 infection leading to onset of ATL



After infection, HTLV-1 is transmitted mostly through cell-to-cell contacts. Tax and HBZ viral proteins promote oligoclonal proliferation of HTLV-1-infected cells. Tax expression is suppressed by cytotoxic T-lymphocytes *in vivo*. A fraction of carriers develop ATL after a long period. At the leukaemic stage, about 60% of ATL cases do not express Tax. ATLL, adult-T-cell leukaemia
Prepared by the Working Group

natural killer cells (Grossman *et al.*, 1995), and transgenic mice with Tax expression via the lck promoter developed a disease that resembles ATLL (Hasegawa *et al.*, 2006). The major difference between most of these animal tumours and ATLL is the fact that, as stated above, a subset of human ATLL cells do not express Tax. *HBZ*-transgenic mice have also been shown to display increased T-cell proliferation (Satou *et al.*, 2006).

4.2 HTLV-1, host immune system, and genetic susceptibility

The host immune system influences the condition of viral infection, and the diseases induced by it. Large interindividual variations in proviral load are commonly observed between HTLV-1 carriers, but the amount of provirus is relatively constant in HTLV-1-infected individuals over time (Kwaan *et al.*, 2006), suggesting that host factors, including the immune system,

determine the provirus load. In spite of eliciting a strong immune response, HTLV-1 infection persists *in vivo,* mainly in CD4-positive T cells, and part of the CD8-positive T cells are infected by HTLV-1 (Yasunaga *et al.*, 2001). An *in vivo* study of HTLV-1-infected cells used diuterium-labelled glucose to investigate lymphocyte kinetics, and showed that CD4+CD45RO+ and CD8+CD45RO+ T-lymphocyte proliferation was elevated in HTLV-1-infected subjects (Asquith *et al.*, 2007). This was associated with viral gene expression, and indicates that active proliferation induced by viral infection induces the host immune response, and that the proviral load is determined by a balance between Cytotoxic T Lymphocytes activity and viral gene expression. The host immune system probably prevents the development of ATLL *in vivo* as suggested by a study where 3/8 HTLV-1-positive carriers, who were immunosuppressed during the course of a liver transplantation, developed ATLL (Kawano *et al.*, 2006).

4.3 Synthesis

There is strong mechanistic evidence supporting the role of HTLV-1 in human carcinogenesis. The viral protein Tax has the ability to immortalize and to transform human T cells. At the leukaemic stage, the expression of Tax is often not maintained, but the viral protein HBZ continues to be expressed, and supports the sustained growth of the leukaemic cells (see Fig. 4.1).

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of HTLV-1. HTLV-1 causes adult T-cell leukaemia/lymphoma.

HTLV-1 is *carcinogenic to humans (Group 1).*

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