Human T-Cell Lymphotropic Virus Type 1

CAS No.: none assigned

Known to be a human carcinogen

Also known as HTLV-1

Carcinogenicity

Human T-cell lymphotropic virus type 1 (HTLV-1) is *known to be a human carcinogen* based on sufficient evidence from studies in humans. This conclusion is based on evidence from epidemiological and molecular studies, which show that HTLV-1 causes adult T-cell leukemia/lymphoma (ATLL), and on supporting mechanistic data. Infection with HTLV-1 has been shown to precede development of the cancer, and the HTLV-1 DNA is integrated into the genome of the infected cells, at the same location in the host-cell DNA in all of the cancer cells in a given individual (Yoshida *et al.* 1984). In addition, over 90% of ATLL patients are infected with HTLV-1, and cancer-causing (oncogenic) viral proteins are produced in the host cells (IARC 2012).

Cancer Studies in Humans

Epidemiological and molecular studies demonstrate a credible association between HTLV-1 infection and ATLL, which is a rare and aggressive T-cell cancer found most commonly in areas where HTLV-1 is endemic, such as Japan, the Caribbean, and the Middle East. Infection with HTLV-1 is one of the diagnostic criteria for ATLL. The original link between HTLV-1 infection and ATLL came from case reports and case-series studies that found consistent evidence of HTLV-1 infection in ATLL cases; over 550 HTLV-1-associated cases of ATLL were reported in case-series studies published between 1985 and 2005 (IARC 1996, 2012). In addition, eight cohort studies were identified, including six studies in Japan (IARC 2012), one study in the United States (Biswas *et al.* 2010), and one study in Israel (Stienlauf *et al.* 2013). The findings of these studies suggest a greater risk of disease and mortality in male than in female HTLV-1 carriers in Japan, but this might not be true for other populations. In four nested case-control studies in HTLV-1 cohorts (Hisada *et al.* 1998a,b, Arisawa *et al.* 2002, Okayama *et al.* 2004), the risk of developing ATLL was greater with higher proviral load (the percentage of circulating CD4 T cells with integrated viral DNA) or higher anti-HTLV-1 antibody levels. Prospective studies and detection of a monoclonal insertion site of HTLV-1 DNA in tumors indicate that infection precedes diagnosis of ATLL.

Studies on Mechanisms of Carcinogenesis

Studies of human cells demonstrate that a key HTLV-1 protein, Tax, can immortalize T cells (enabling them to proliferate indefinitely) both *in vitro* and in immunodeficient mice in the absence of other viral products (IARC 2012). Tax causes cancer by affecting several oncogenic pathways. It interacts with host-cell proteins (specifically, the NF-κB family of DNA transcription factors), leading to increased production of interleukin 2 (IL-2), its receptor, and interleukin 6 (IL-6) (Currer *et al.* 2012). IL-2 is involved in T-cell proliferation, growth, and survival, and IL-6 is involved in inflammation responses and regulation of metabolic, regenerative, and neural processes. Tax also inhibits DNA repair and triggers genetic instability in host cells (Currer *et al.* 2012). Tax is highly immunogenic (able to provoke an immune response) and is normally held in check by the host's immune system. However, in individuals with a weakened immune response, Tax can initiate and promote cancer. Once cancer has been induced, production of Tax may be reduced or eliminated as a result of changes in the *Tax* gene; however, another HTLV-1 viral protein, HTLV-1 bZIP factor (HBZ), and oncogenic mutations in the host cell's DNA, such as mutations of the $p16^{INK4A}$ and *p53* tumor-suppressor genes, play a role in the continued proliferation of the cancer cells (NTP 2016).

Biological Properties

HTLV-1 is an enveloped single-stranded RNA (ssRNA) delta-type retrovirus (an RNA virus that can make a DNA copy of its genome) of the subfamily Oncovirinae; it was originally found in cells from a patient diagnosed with T-cell lymphoma (IARC 1996, 2012, Jacobson and Massoud 2013). It can integrate into the DNA of CD4 T lymphocytes (helper T cells, which are white blood cells involved in immune function). The three main viral genes are *gag*, which encodes matrix and capsid proteins, *env*, which encodes the envelope proteins, and *pol*, which encodes the enzymes reverse transcriptase (which enables HTLV-1 to make a DNA copy of its genome), integrase (which enables integration of the DNA copy into the host genome), and protease (which breaks down proteins). Single-protein genes encode the regulatory proteins Tax and Rex and the accessory proteins p12, p13, p30, and HBZ. Viral gene expression is controlled by promoters and enhancers in the two long terminal repeat regions (regions at the boundaries of the proviral DNA that contain sequences regulating protein production).

The HTLV-1 virus particle is immunogenic, so active viral production will elicit a cytotoxic T-cell anti-HTLV-1 immune response (Cook *et al.* 2013, Carpentier *et al.* 2015), which is thought to be responsible for controlling viral load. During the latent phase (when the virus is not replicating), Tax promotes host-cell proliferation. However, Tax itself is immunogenic; for a latent infection to be maintained, production of Tax is suppressed, and host-cell proliferation is maintained by HBZ, which is less immunogenic than Tax, allowing proliferation of latently infected cells.

Detection

HTLV-1 is rarely detected free in bodily fluids, but is found in peripheral mononuclear blood cells in breast milk, blood, semen, and cerebrospinal fluid (IARC 1996, Carpentier *et al.* 2015, Schafer *et al.* 2015). Detection is most commonly through measurement of anti-HTLV-1 antibodies, but can also involve measurement of viral RNA or DNA in peripheral mononuclear blood cells (allowing measurement of proviral load) or *in vitro* culture of the virus. Initial anti-HTLV-1 antibody screening tests are performed by several different methods, and specimens with positive results are further tested in a confirmatory laboratory-based Western blot immunoassay, polymerase chain reaction amplification, immunofluorescence assay, or recombinant immunoblot assay (methods for quantitative measurement of antigens) (IARC 1996, Sabino *et al.* 1999). Recombinant immunoblot assays are the most accurate, yielding fewer indeterminate results. The percentage of cells infected with HTLV-1 is determined primarily by the cytotoxic T-cell response against HTLV-1-infected cells and varies widely among infected individuals (Cook *et al.* 2013).

Exposure

Studies measuring antibodies to HTLV-1 have shown that a significant number of people in the United States are exposed to HTLV-1. The number of HTLV-1-infected persons in the United States has been estimated to range from 90,000 to 100,000 persons, based on available U.S. studies, which looked primarily at blood donors and injection drug users and took age, sex, and estimates of worldwide prevalence rates into consideration (Gessain and Cassar 2012). A detailed study of HTLV-1 prevalence in the United States conducted from 2000 to 2009 reported a seroprevalence of 0.0051% (5.1 cases

per 100,000) among blood donors in the United States (Chang *et al.* 2014, Cook and Taylor 2014). Previous studies reported U.S. HTLV-1 seroprevalence ranging from 0.009% to 0.025% (Williams *et al.* 1988, Murphy *et al.* 1999, Poiesz *et al.* 2001). However, data from blood-donor studies most likely underestimate the prevalence in the general population, because the donors might be healthier as a group.

Transmission

Transmission of HTLV-1 requires cell-to-cell contact, as the virus is unstable outside of cells. The three main transmission modes are from mother to child, sexual, and via blood transfusion or organ transplantation (IARC 2012). Since the U.S. blood supply has been screened for HTLV-1 since 1988, the estimated risk of infection via blood transfusion is less than one in two million per transfused unit (American Red Cross 2016). Although solid organs for transplantation are no longer screened for HTLV-1 in the United States (see Regulations and Guidelines), only one U.S. case of HTLV-1-related disease transmission from an infected organ donor (HTLV-1-associated myelopathy) has been identified since organ screening was discontinued in 2009 (Ramanan *et al.* 2014).

HTLV-1 infects T cells, mainly CD4 T cells and, to a lesser extent, CD8 T cells (cytotoxic T cells, which kill damaged or infected cells). Cells involved in blood-cell formation can be infected as well (IARC 1996, 2012, Jacobson and Massoud 2013, Carpentier *et al.* 2015, Schafer *et al.* 2015). HTLV-1 transmission via breastfeeding depends on the proviral load of the mother's breast milk and on breastfeeding duration. Mother-to-child transmission occurs during the perinatal period in less than 5% of cases (Hlela and Bittencourt 2014). Risk factors for sexual transmission include unprotected sex with an infected partner, multiple lifetime sexual partners, and infection with sexually transmitted diseases (IARC 2012). HTLV-1 transmission is efficient via transfusion of cellular blood components and needle-sharing by injection drug users. Although the U.S. Food and Drug Administration prescribes procedures for donor screening and tissue testing to ensure that tissues intended for human transplantation are free of HTLV-1, some vascularized human organs are excluded from testing (see Regulations and Guidelines).

Diseases (Non-Cancer), Prevention, and Treatment

Most HTLV-1-infected individuals are lifelong symptomless carriers (Cook *et al.* 2013); only 2% to 5% of infected people develop diseases related to the virus (Hlela and Bittencourt 2014). In addition to ATLL, HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP, a chronic and progressive inflammatory disease of the central nervous system) is the most common clinical manifestation of HTLV-1 (Fuzii *et al.* 2014). Other diseases associated with HTLV-1 include HTLV-1 uveitis (eye inflammation) (Kamoi and Mochizuki 2012) and infective dermatitis (Hlela and Bittencourt 2014).

Prevention involves reducing transmission of HTLV-1 via breastfeeding, sexual transmission, and blood transfusion (McKendall 2014). Prenatal screening for HTLV-1 and counseling of seropositive mothers to avoid breastfeeding reduces mother-to-child transmission (Hino 2011, IARC 2012). Following practices that prevent sexually transmitted infections, such as using condoms and not having multiple or anonymous sexual partners, can reduce sexual transmission of HTLV-1 (Yoshimitsu *et al.* 2013). Counseling and education of injection drug users (e.g., implementation of harm-reduction practices) may be effective in reducing HTLV-1 infection among this population (Goncalves *et al.* 2010). Screening of the U.S. blood supply for HTLV-1, which began in 1988 (American Red Cross 2016), has reduced the risk of transfusion-related transmission (McKendall 2014). There is no vaccine against HTLV-1 (ACS 2015, CDC 2015, FDA 2015), but vaccine development efforts are ongoing (Kuo *et al.* 2011).

Regulations

Department of Transportation (DOT)

Infectious substances are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Food and Drug Administration (FDA, an HHS agency)

21 CFR 606, 610, 630, 640, and 660 prescribe procedures, including recordkeeping, donor screening and notification, blood and blood component testing, and product labeling to guard against the spread of HTLV-1 through donation of blood, serum, or plasma (except testing for source plasma). (The risk of HTLV-1, a highly cell-associated pathogen, is sufficiently mitigated by plasma-derivative manufacturing steps, including validated viral inactivation and removal procedures. These manufacturing procedures therefore obviate the need to test individual donations of source plasma for HTLV-1.)

21 CFR 1271 prescribes procedures, including donor screening and tissue testing, to ensure that tissues intended for human transplant or other human cells, tissues, and cellular and tissue-based products (HCT/Ps) are free of HTLV-1. (However, certain HCT/Ps, such as vascularized human organs for transplantation, are excluded. These are listed in 21 CFR 1271.3(d)(1).)

Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been developed for employers to develop and adhere to exposure control plans for bloodborne pathogens.

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

Guidelines

American Society of Transplantation (AST)

The AST has issued guidance for the diagnosis and prevention of HTLV-1 infection from solid (vascular) organ transplantation. AST guidelines advise that HTLV-1 screening may be considered by individual organ procurement organizations with higher HTLV-1 prevalence populations (e.g., a high proportion of immigrants from countries where HTLV-1 is endemic). Their guidelines do not preclude solid organ transplantation from HTLV-1-positive donors, but advise that these donors be used only in extreme circumstances (e.g., life-threatening situations, with informed consent) and that recipients of confirmed or suspected HTLV-1-infected organs be monitored periodically.

Food and Drug Administration (FDA, an HHS agency)

The FDA has issued numerous guidance documents prescribing procedures (e.g., use of standardized labels, abbreviated donor screening questionnaires) for reducing the risk of virus transmission by blood and blood products.

Health Resources and Services Administration (HRSA, an HHS agency)

The Organ Procurement and Transplantation Network (OPTN) prescribes voluntary procedures for HTLV-1 screening, confirmation in potential donors, and reporting of potential HTLV-1 infection to reduce the risk of HTLV-1 transmission through solid organ transplantation. Prior to 2009, the OPTN recommended screening of organs for HLTV-1, but that recommendation was removed effective November 23, 2009, because of the low prevalence of HTLV-1 infection in the United States, the loss of potentially usable organs because of a high rate of false-positive test results, and the lack of an FDA-licensed test for HTLV-1 with a rapid turnaround for analysis of single samples.

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