Oncogenic Viruses

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Advanced article

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Infectious agents account for appropriately 25% of cancers worldwide and viruses in particular have been useful in elucidating many of the cellular pathways that can be deregulated in cancer. Therefore, the more that is known about how viral proteins disrupt the normal cell the more we will learn about important regulatory pathways that when altered or abrogated, lead to a transformed cell.

Since the isolation of *Epstein–Barr virus* (EBV) from Burkitt lymphoma (BL) cells some 35 years ago there have been a number of other viruses, which are associated with the aetiology of human cancers. Although there have been some false alarms along the way, the viruses described in this article have been shown to be the aetiological agents of various cancers. One of the problems with confirming that a virus is the aetiological agent of a particular cancer is that infection with the viruses themselves are common in populations throughout the world, allowing for some geographical variations, yet only a small fraction will present with cancer in their lifetime.

Human cancers are caused by both deoxyribonucleic acid (DNA)- and ribonucleic acid (RNA)-containing viruses and the article describes the viruses and the associated cancers and present information on the mechanisms of oncogenesis.

DNA Viruses

There are three DNA virus families, which contain among their number cancer causing viruses. They are the *Herpesviridae* (human herpesvirus 8, HHV8; EBV), *Papovaviridae* (certain human papillomavirus types) and the *Hepadnaviridae* (hepatitis B virus, HBV).

Herpesviridae

Human herpesvirus 8/Kaposi sarcoma-associated herpesvirus (KSHV)

Genomic organization

Human herpesvirus 8 (HHV8) was first discovered in Kaposi's lesions in 1994 when part of the genome was isolated by the polymerase chain reaction (PCR; Chang *et al*., 1994). The whole genome was subsequently isolated from cell lines, which were derived from body cavity-based primary effusion lymphomas also caused by this virus. Primary effusion lymphoma (PEL) cell lines infected with HHV8 have been established and are the only cell culture system at present that will maintain the virus *in vitro*, although the virus can be transmitted to 293 cells (human embryonic kidney cell line transformed by adenovirus 5), but without significant amplification. The genome of HHV8 has been sequenced and is approximately 165 kb in length with variable length terminal repeats (TR) at the ends and in between a single long unique region (LUR) of approximately 140.5 kb, which contains all the coding sequence for the over 80 proteins coded for by the virus. The genomic organization places the virus among the gammaherpes viruses, a group which includes EBV and herpesvirus saimiri. This genomic organization of HHV8 is the same whether isolated from PEL cells or from Kaposi's sarcoma tumours, indicating that the virus is truly involved in the development of two different tumours. **See also**: Herpesviruses (Human); Polymerase Chain Reaction (PCR)

Integration

Some of the DNA tumour viruses integrate their genome into that of the host cell chromosomes but it is unclear at present if this process is essential for the tumourigenesis or for the various transformed phenotypes seen *in vitro*. So far the genome of HHV8 does not appear to integrate into the chromosomes of tumour cells and the virus can be rescued and transmitted to 293 cells although replication is very low and detection by PCR is necessary. The genome is circularized in lytic infection and replication is thought to occur by the rolling circle model.

Activation of cell growth

HHV8 has 81 open reading frames (ORFs) and they have been named according to their homology to those of herpesvirus saimiri. Although HHV8 does not appear to have genes homologous to those in EBV associated with transformation of cells in culture, the virus does code for a number of genes with homologies to mammalian genes. Many of these cellular genes function in cell growth regulation and cell cycle control and so the activity of the viral counterparts may deregulate normal cell growth control. Preliminary studies on the function of these genes suggest that their function is consistent with this idea. The pirated genes include a viral cyclin D, viral interleukin 6 (IL-6),

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homologues of complement-binding proteins, three macrophage inflammatory proteins, Bcl-2, interferon regulatory factor, IL-8 receptor-like G protein-coupled receptor and finally an adhesive molecule related to neural cell adhesion molecule (NCAM). **See also**: G Protein-coupled Receptors; Interleukins

The virus life cycle, like other gammaherpesvirses has two phases, a latent and a lytic stage. In the former, the DNA is maintained in cells and only replicates in synchrony with the replication cycle of the cell and little or no infectious virus is produced. In the lytic phase, the viral DNA is amplified with the production of late mRNA (messenger RNA) and viral particle production. In latency, there are only five proteins expressed, the latency-associated nuclear antigen 1 (LANA-1/orf73), a viral homologue of a D-type cyclin (v-cyc/orf72), a homologue of the cellular inhibitor of the FADD-like IL-1β-converting enzyme (FLICE) apoptosis complex (v-FLIP/orf13) and a group of short membrane-associated proteins called kaposins (orfK12).

Activation of the viral lytic cycle is mediated by transcription factors with an important component being the product of the orf50, called replication and transcription activator (RTA). RTA acts by binding to cellular transcription factors at the promoters of several viral and cellular genes and activating transcription.

Viral cyclin D (v-cyclin D)

Cyclin D is a family of cyclins which act to allow progression from G1 into the S phase of the cell cycle and are therefore at a pivotal point in cell cycle regulation. Cyclin D regulates progression through G1 and into S by binding to cyclin-dependent kinases (cdk), which phosphorylate the retinoblastoma (Rb) protein, resulting in the inactivation of Rb and release of transcription factors, whose activity is necessary for the synthesis of many of the proteins and enzymes needed for DNA synthesis. Cyclin D binds to cdk4 and 6. Inhibition of the kinase activity by cyclin-dependent kinase inhibitors such as p16, p21 and p27 results in inhibition of Rb phosphorylation resulting in cell cycle arrest. The v-cyclin D binds to cdk6 and phophorylates Rb in a similar fashion to the cellular cyclkin/cdk6 complex. However, unlike the cellular complex, v-cyclin D/cdk is not inhibited by the cyclin-dependent kinase inhibitors (Swanton *et al*., 1997). Most tumours require inhibition of the Rb checkpoint control in G1 for successful proliferation and so the virus may help to achieve this by producing a cyclin, which is not regulated by the normal cell regulating proteins such as the cyclin-dependent kinases. Therefore normal messages, which would cause cell cycle arrest, may not function efficiently in HHV8 infected cells. **See also**: Cell Cycle; Cell Cycle: Regulation by Cyclins; Tumour Suppressor Genes

LANA-1

LANA-1 is required for viral persistence and binds to the cell's chromatin and to the terminal repeat regions of the HHV8 genome. It is involved in viral genome replication and segregation as well binding to p53 and Rb. The result of the interaction with p53 and Rb is the inhibition of p53-dependent promoters and the activation of E2f activated promoters. This will stimulate cell cycle progression along with the functions of the v-cyc.

vIL-6

The cellular form of the cytokine IL-6 has been shown to stimulate the growth of cells from human malignancies especially of B-cell origin. The viral IL-6 (vIL-6) is 25% homologous to cellular IL-6 and the viral form has been shown to act on signalling pathways involving jak kinase/signal transducer and activator of transcription (Jak/STAT) receptor/transcription factors. Although the cellular IL-6 requires the two subunits of the IL-6 receptor (IL-6Rα and p130), the vIL-6 requires only one, giving it a wider spectrum of cells to affect since p130 is more widely expressed than IL-6Rα.

vGCR

Orf74 codes for a G protein-coupled receptor (vGCR) which is a homologue of the IL-8 receptor, but unlike the cellular receptor, which is only activated in the presence of IL-8, vGCR is constitutively activated, due to a mutation. It is produced early in the lytic cycle and can transform murine cells and induces vascular endothelial growth factor (VEGF)-dependent angiogenesis, indicating that it may be an important component in the formation of Kaposi's sarcoma.

Viral Bcl-2

This is a homologue of the cellular Bcl-2 protein which is involved in rescuing cells from apoptosis and is a member of a larger set of cellular proteins which can either prevent or stimulate apoptosis. This viral protein is expressed during lytic infection and may function to inhibit apoptosis induced by the lytic phase and so allow more time for replication of the virus. The role in any oncogenic pathway is unclear at present. **See also**: Apoptosis: Molecular Mechanisms

Other potential oncoproteins expressed by HHV8

There are other proteins coded for by HHV8, which are compatible with an involvement in stimulating cell growth, an essential property of an oncoprotein. The G protein-coupled receptor has homology with the IL-8 receptor and is constitutively active in infected cells, but since it is not expressed in latently infected cells its role is not clear although overexpression in NIH3T3 cells causes transformation. **See also**: Oncogenes

Significance for human cancers

HHV8 is associated with malignant transformation of two cell types, endothelial cells and B lymphocytes. Kaposi's sarcoma which is found endemic in African and Mediterranean countries and recently observed in human immunodeficiency virus (HIV) infected males is caused by the same virus. The virus is found in the majority of lesions by PCR technology and serological studies have found $>80\%$ of

patients with Kaposi's sarcoma are antibody positive for HHV8, whereas the level of positivity in the UK and the USA in blood donors is 1–5%. **See also**: B Lymphocytes; Human Immunodeficiency Viruses (HIV)

HHV8 has also been linked to rare lymphoproliferative diseases or body cavity-based primary effusion lymphomas (BCBL/PEL) and to other rare B-cell lymphomas such as Castleman disease and immunoblastic lymphadenopathy. One problem early on was that many of the BCBL/PEL cells also contained the genome of EBV, so it was difficult to differentiate aetiology. Now that EBV negative tumours have been observed the evidence of guilt has shifted to HHV8.

Epstein–Barr virus

This was the first human cancer to be associated with a viral infection. EBV has traditionally been associated with at least two types of cancer, BL and nasopharyngeal carcinoma. Recently, with the appearance of HIV and in other immunosuppressive situations, EBV has been linked with several human malignancies. Unlike herpes simplex virus, EBV has very limited host range and infects and replicates in B- and epithelial cells. However, replication in the former is low and only under certain circumstance is lytic infection observed. The receptor for EBV, CD21 (immunoglobulin superfamily member), is found on B cells and related receptor has been observed on epithelial cells. **See also**: *Epstein-Barr Virus*

Genomic organization

EBV is a double-stranded DNA virus of approximately 184 kb in length encoding more than 70 genes and is a gammaherpes virus. Like HHV8 the genome has terminal repeats at the ends of the genome separated by a unique region coding for the viral proteins. The genome circularizes after infection of the target B cells via the terminal repeat sequences.

Integration

Although, integration has been observed in some cells that have been grown out from tumour tissue, this process is probably not a factor in tumourigenesis *in vivo*.

Activation of cell growth

There are nine EBV proteins that have lymphocyte immortalization functions *in vitro*, the Epstein–Barr nuclear antigen (EBNA) family (EBNA-1, -2, -3A, -3B, -3C and EBNA-LP) and the latent membrane proteins 1, 2A and 2B (LMP-1, 2A and 2B). After infection EBV exhibits both a latency and lytic phase of persistent in the infected host. There are three classes of latency depending on viral gene expression and in the simplest form cells from BL express only the EBNA-1 protein, whereas Hodgkin's disease cells and nasopharyngeal cancer cells express EBNA-1 and all three LMP proteins. EBNA-1 functions to maintain the viral genome as an episome, whereas the other EBNA proteins regulate viral transcription. Although these EBNA factors activate transcription through binding to certain transcription factors, such as PU.1 and core binding factor-1 (CBF-1), it is not clear by which mechanism this activity causes immortalization of B cells. LMP-1 has six hydrophobic transmembrane domains and its expression mimics changes in the B-cell associated with activation. LMP-1 mimics constitutively activated tumour necrosis factor receptor (TNFR) family members (Mosialos *et al.*, 1995), which include TNFR, CD40 receptor and the CD30 receptor resulting in the activation of NFκB, an important transcription factor in B cells. LMP-2A and -2B proteins have 12 transmembrane domains and they appear to act together to increase signal transduction in cells through src and syk pathways.

Significance for human cancer

EBV is associated with a number of different cancers and some of these have only been observed recently since the advent of immunosuppressive therapies or infection with HIV resulting in acquired immunodeficiency syndrome (AIDS). EBV has been known for some time to be associated with BL and nasopharygeal carcinoma (NPC). Both these cancers have geographically restricted distributions with BL found in young children in the central part of Africa, 10 degrees north and south of the equator, whereas NPC is found predominantly in the southern coastal region of the People's Republic of China. **See also**: Acquired Immune Deficiency Syndrome (AIDS); *Epstein-Barr Virus* and Cancer; Non-Hodgkin Lymphomas

Posttransplant lymphoproliferative disease is a well-recognized risk of immunosuppressive therapy or infection with HIV and the development of AIDS. Individuals who are seronegative for EBV before transplant show the highest risk for the development of posttransplant lymphomas. The majority of cases are associated with EBV and the cancers can be poly- or monclonal. They include, poly- and monomorphic diffuse large cell immunoblastic lymphomas, small noncleaved cell lymphomas and diffuse large cell lymphomas. In AIDs, primary central nervous system small noncleaved cell lymphomas are associated with EBV as are non-Hodgkin lymphomas. Hodgkin disease (HD) has been associated with EBV infection for a number of years without real conclusive proof of an aetiological role. However, recent evidence suggests that EBV DNA and RNA are found in the Reed–Sternberg cells (presence of these cells is pathognomonic of HD). So EBV is now associated with a number of lymphoproliferative diseases, which are mainly of B-cell origin. **See also**: *Epstein-Barr Virus* and Cancer; Hodgkin Disease

Papoviridae

Certain members of the subfamily papillomavirinae have been shown to cause lower genital tract cancers and the most common of these is cervical cancer. Human papillomaviruses (HPV) replicate in stratified epithelial cells only and so are the aetiological agents of squamous cell

carcinomas (SCC) at various sites. **See also**: Papillomaviruses

Genomic organization

This genus has a small circular genome of approximately 8 kb. mRNA is transcribed off one strand of the DNA and there are five early genes coding for proteins, which are involved in DNA replication (E1 and E2) and cell cycle disruption (E6, E7 and E5), and three late genes, two of which code for the major and minor capsid proteins (L1 and L2, respectively) and one of unknown function (E4).

Integration

During the malignant phase of the disease when the lesion is confined to the epithelium, the viral DNA in most cells is in an episomal form and amplification of the genome and viral particle production occurs in the upper parts of the epithelium. However, in some cells, especially in carcinoma *in situ*, the viral genome is integrated and integration increases in invasive cancer cells, with over 70% of cancers showing either integration only or a mixture of integration and episomal forms in all cells. In the rest of malignant disease, there is evidence of only episomal copies. Although, integration is not specific to any chromosomal site and there is no obvious region of the viral genome for integration, all of the malignant cells investigated continue to express of E6 and E7 proteins, suggesting that they are essential for maintenance of the malignant phenotype. Integration often takes place in the region of the E1 and E2 ORFs and it is thought that this may relieve the transcriptional inhibition of the E2 protein allowing increased expression of E6 and E7, an observation seen *in vitro*. The importance of E6 and E7 to cellular phenotype is exemplified in Hela cells which contain integrated HPV-18 sequences and express E6 and E7. Even though Hela cells have been in culture for more than 50 years, when E6 or E7 expression is inhibited using RNAi (RNA interference), the cells senesce. It is not clear if the episomal copies observed in a minority of cancers have mutations in the genome, which may exhibit the properties of integrated viral DNA, for example, do they have mutations in E2 that may derepress its activity?

Activation of cell growth

Papillomaviruses code for proteins that activate cell growth and like most of the tumour viruses, these proteins affect either the signal transduction pathways or cell cycle control. The oncogenic HPVs code for three such proteins E6, E7 and E5. **See also**: Checkpoints in the Cell Cycle

E6

E6 binds to the E6 associated protein (E6AP) and p53 in a trimeric complex (Huibregtse *et al*., 1991). The result of this binding is the premature degradation of p53 through the ubiquitin pathway. E6AP is, in fact, an ubiquitin protein ligase called UBE3A. Since one of the functions of p53 is to control the passage of cells through the G1 phase of the cell cycle, any abrogation of this activity could lead to uncontrolled cell cycle progression. E6 has also been shown to bind to a protein called E6 binding protein (E6BP), which has sequence identity to ERC-55, a calcium-binding protein of unknown function and to the membrane-associated guanylate kinase homologues (MAGUKs), which are large proteins with multiple protein–protein interaction domains, including PDZ (*P*ost synaptic density protein, *Drosoplila* disc large tumour suppressor and *Z*onula occludens-1 protein) domains, which are thought to mediate the formation of multiple-protein complexes. It also binds to PDZ containing tumour suppressor human homologue of the *Drosophila* discs large protein, Dlg and degrades it like through interaction with E6AP (Gardiol *et al*., 1999). The degradation of E6 targeted proteins is a major function of this viral protein, resulting in co-operation with E7 to immortalize primary human cells.

E7

E7 binds to the retinoblastoma family of proteins, Rb, p107 and p130. Most of the studies have been on the activity of E7 and Rb. Normally late in G1 Rb is phosphorylated and this releases transcription factors such as E2F, which are necessary for the transcription of genes, whose products are important for DNA synthesis. E7 can cause this same release of factors in the absence of phosphorylation of Rb and so can drive cells into S phase in an uncontrolled manner. E7 has also been shown to bind the AP-1 family of transcription factors and modulate their activity. Rb has also been shown to bind a histone deacetylase activity (Brehm *et al*., 1998), which may explain the ability of this protein to repress transcription. E7 can release this repression but it can only do it using two domains of the E7 protein, the Rb domain and the zinc-finger domain. Therefore, it appears that E7 can bind or compete with the deacetylase enzyme for binding to Rb.

E5

This protein is highly hydrophobic and is found in the membranes of infected cells. It binds to the smallest subunit of the vacuolar adenosine triphosphatase (ATPase), the protein complex responsible for the acidification of the lumen of endosomes. E5 inhibits acidification (Straight *et al*., 1995), although how this is achieved is unknown. A consequence of this inhibition is that internalized epidermal growth factor receptors are not destroyed and continue to signal and produce hyperstimulated cells.

The activities of E6, E7 and E5 are consistent with pushing cells into S phase for viral replication and in the process other factors may in a minority of cases cause the cells to progress to a malignant state.

E1 and E2

Both these proteins are involved in the replication of the viral genome and they bind to specific sequences in the origin region. E1 has ATPase and helicase activity whereas E2 has been shown to be a repression of transcription from

Table 1 HPVs associated with malignant and benign genital disease

HPVs types causing genital cancer: 16, 18, 31–35, 51, 52, 56, 58, 59, 61, 66, 67–70, 73
HPVs causing benign genital disease: 6, 11, 42–44, 53–55

the major early promoter at p97, which controls transcription of E6 and E7 genes. The repressive activity of E2 is removed when the HPV-16 genome is integrated, leading to upregulation of E6 and E7 which may be important in malignant conversion.

Significance to human cancer

Certain HPVs cause epithelial cancers, especially of the genital tract and HPV DNA is found in >99.7% of cervical cancer cells. Cervical cancer is the most common and in fact worldwide it is the leading cancer-related cause of death in women. **Table 1** indicates the genital types causing cancer and others involved in benign genital infections.

Like all cancers of viral aetiology, in normal immunocompetent individuals the progression from infection to cancer is a long process. The highest incidence of HPV-16 infection is in the age group 18–30 years of age; however, the highest incidence of cancer is in the individuals >40 years of age. Although upwards of 80% of young people may be infected with the HPV over time, only a small number (1 in 10 000) will develop malignant disease. HPV has also been shown to be associated with SCC in immunosuppressed patients, although the types involved are different than the genital ones and are not well defined. In the rare autorecessive disease, epidermodyplasia verruciformis, patients are partially immunosuppressed resulting in a high incidence of SCC and the viruses most commonly isolated are HPV-5 and -8.

Vaccine

There is a vaccine against some of the HPV types which is licensed in Europe and the USA. The vaccine is composed of the L1 protein which is the major capsid protein of the virus. The vaccine produced by Merck contains the L1 from HP-6, -11, -16 and -18, whereas that produced by Glaxo Smith Kline contains only the L1 from HPV-16 and -18. Protection against disease is very high when individuals are vaccinated before they meet the natural infection and so at present it is recommended that it will be given to girls between the ages of 11 and 13 (Wheeler, 2007).

Hepadnaviridae

Hepatitis B (HBV) is the member of this family, which is one of the aetiological agents of hepatitis and hepatocellular carcinoma (HCC). Other viral cause of liver cancer is discussed later. **See also**: *Hepatitis B Virus*

Genomic organization

HBV is a double-stranded DNA virus; however, in the virion the double strand is incomplete and is completed only on infection of liver cells. The replication of this DNA virus is unusual because it uses an RNA intermediate and the viral polymerase has a reverse transcriptase activity to synthesis new DNA genomes from the RNA template. The genome is approximately 3 kb in size and it has 4 ORFs, which are coded off the same strand. The largest ORF codes for the viral polymerase, which has an RNA- and DNA-dependent activity. The second largest ORF codes for the surface proteins, which are important for diagnosis of infection, whereas the third ORF codes for the core protein, which encapsidates the viral genome and the fourth ORF codes for a protein called the X-protein, because initially no function was attributable to this protein. However, now the X-protein is known to have transcriptional activation function.

Integration

Integration of the viral genome occurs late in the chronic phase of the disease, but it is unclear if integration is really necessary for malignant conversion. Integration also occurs in HCC caused by woodchuck and ground squirrels hepatitis viruses and it occurs near to the myc family of genes. However, in woodchucks integration usually results in upregulation of N-myc, whereas in ground squirrels there is an upregulation of c-myc (Transy *et al*., 1992). Therefore, induction of HCC in these two closely related species does not appear to occur through the same activated cellular genes. No single gene appears to be upregulated in HCC caused by HBV, although there is evidence that integration can occur in the telomerase gene (hTERT) promoter or in the introns of the gene, resulting in increased expression of hTERT (Horikawa and Barrett, 2003)

Activation of cell growth

HBV, unlike the other viruses discussed so far does not code for an obvious oncoprotein. Apart from the structural proteins and the polymerase HBV codes for the X-protein, which has been shown to be an activator of cellular genes. However, the role of this protein in the tumourigenic process is unclear especially since the virus causing HCC in ducks and other fowl do not appear to code for such a protein. There is evidence that the X-protein is necessary for viral replication *in vivo*, and as such would be important in the persistence of the virus. HCC results from long-term persistence of the virus and it may be due to the constant destruction of infected cells by the immune response and the subsequent proliferation of new liver cells infected with the virus. The continued proliferation may result in the outgrowth of altered cells, which are prone to malignant conversion.

Significance for human cancer

HBV is the cause of HCC and there is a higher incidence in parts of the world where HBV infection is contracted early in life (neonatally) and persistence is common (80–90%). In Western countries such as the USA and northern Europe, persistence occurs in $<10\%$ of infected individuals and infection usually occurs in adulthood. There is now a successful vaccine consisting of the surface antigen (HBsAg) of the virus, which protects against infection of HBV. Since the vaccine protects against infection and subsequent complications, results from the use in Taiwan have shown a fall in the incidence of HCC caused by HBV (Chang *et al*., 1997). **See also**: Hepatitis: Clinical Features and Treatment; Vaccination of Humans

RNA Viruses

There are two families of RNA with a member which causes cancer. One, hepatitis C virus (HCV) belongs to the *Flaviviridae* family and is in the genus *Hepacavirus*, whereas the other is part of the *Retroviridae* and is called human T-cell lymphotropic virus (HLTV) types I and II and belongs to the genus *Oncovirinae*.

Hepacivirus

Genomic organization

HCV is a positive sense single-stranded RNA virus with a genome of approximately 10 kb. The genome codes for 10 proteins including three structural proteins, an RNA-dependent RNA polymerase and various proteases. There are certain hypervariable regions of genome which have necessitated the division into six genotypes and there is some variation in the worldwide distribution of the types. For instance types 1, 2 and 3 have a worldwide distribution with types 1a and 1b predominating in North America whereas type 4 predominates in Africa. **See also**: *Hepatitis C Virus*

Integration

Integration does not occur with these viruses as it is strictly an RNA virus and has no capacity to code for DNA.

Activation of cell growth

Although, HCV does not code for a classical oncoprotein or even any proteins that are obviously involved in cell proliferation, there is now evidence that the core protein (encapsidates the genomic RNA) is able to alter host cell regulation and has been reported to activate cellular proto-oncogenes and repress p53 transcription (Ray *et al*., 1997). However, the mechanism of malignant conversion is unclear and the role of the immune response has been difficult to determine. HCC does not develop for a number of years after initial infection and so long-term immune activation may have a role as it is thought to do with HBV.

Significance for human cancer

HCV infection leads to persistent infection in 50–80% of individuals and is a much higher rate than seen for HBV. HCV is increasingly the cause of HCC and this will presumably continue since there is now an effective vaccine HBV. Approximately 10–20% of persistent carriers will develop cirrhosis of the liver and of these, 1.5% will go to develop HCC. Like infection with HBV, complications from persistence of HCV take years or even two to three decades to appear. At present no other cancer has been associated with HCV infection.

Retroviridae

Although retroviruses are a cause of cancer in animals, only one retrovirus, so far, is the cause of cancer in humans. This virus is called HTLV and there are two types, I and II, but the former appears to be the one associated with malignancies and other pathogenic processes. **See also**: Retroviral Replication

Genomic organization

This is a single-stranded RNA virus, which like all retroviruses carries two copies of the genome in the virion. It has the familiar retrovirus genome of 9 kb and is organized with terminal repeats at either end. The genome codes for viral structural proteins (Gag-core protein and env-envelop proteins) and the organization of these are similar to that of other retroviruses. In addition, located at the 3′ end of the genome are at least four ORFs coding for regulatory proteins.

Integration

As part of their natural history, retroviruses integrate into the host cell chromosome, since they code for an RNA-dependent DNA polymerase which will produce a double-stranded complementary DNA molecule, which will integrate into the host's DNA via the terminal repeats of the 5′ and 3′ ends of the genome. This keeps all the coding capacity of the genome intact and so progeny RNA is produced from the integrated sequences.

Activation of cell growth

HTLV-I codes for a number of proteins from the 3′ end of the genome, often called the pX region. Two of the best-characterized proteins are Tax and Rex. Tax can transactivate the HTLV-I promoter through binding to the transcription factor c-AMP response element binding (CREB) and the coactivator CREB-binding protein (CBP) mediating the interaction of the latter with the basal transcription machinery (Kwok *et al*., 1996). In fact, Tax will activate a number of different cellular promoters through CREB binding and also NFκB transcription factors resulting in the expression of a number of cellular genes including IL-2, TGF-β (transforming growth factor β), GM-CSF (granulocyte macrophage colony stimulating factor), IL-2α

receptor and c-myc. IL-2 is an important growth factor for T cells.

Rex is a nuclear protein and regulates the balance between spliced and nonspliced mRNA and so favours the transcription and translation of the gag, polymerase genes before the cell regulatory genes. Rex appears to affect cellular processes and is thought to act with Tax to increase expression of IL-2α receptor, by an as yet unknown mechanism.

Significance for human cancers

HTLV-I causes adult T-cell leukaemia/lymphoma (ATL), which is more common in Japan, West and Central Africa and in the Caribbean population of African decent. Infection precedes cancer by several years even decades and there is a very tight association between sero-positivity and the development of cancer. However, the lifetime risk of a carrier is estimated to be 2–4% and most have acquired the infection as children. The virus is also the cause of non-malignant disease such as tropical spastic paresis or HTLV-I-associated myelopathy, a chronic progression demyelinating disease. **See also**: Leukaemias and Lymphomas

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