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Current topics

Retroviruses

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Retroviruses have assumed tremendous importance since the discovery of the viruses which cause adult T cell leukaemia[1] and acquired immune deficiency syndrome (AIDS).[2 3] The groundwork which led to the relatively recent isolation of these human viruses was laid over many years in studies of animal retroviruses, particularly those inducing leukaemia in chicken, mice, cats, and cattle. The act of faith in pursuing retroviruses as causes of human disease on the assumption that what occurs in animals is likely to have a counterpart in man has, therefore, been entirely justified.

There are three subfamilies of retroviruses: oncoviruses, lentiviruses, and spumaviruses, the latter of which are not pathogenic. The oncoviruses and lentiviruses, however, are of great medical and veterinary importance. The oncoviruses as their name implies cause tumours, particularly leukaemias and other diseases of the haemopoietic and lymphoid systems in man, cattle, cats, mice, and chickens. The lentiviruses include human immunodeficiency virus (HIV), which is the cause of AIDS, maedi-visna virus of sheep, equine infectious anaemia virus, and feline AIDS virus.

Biology of retroviruses

Retroviruses are so called after the enzyme reverse transcriptase, which they possess and which endows them with their most important biological characteristic, the capacity to set up permanent, life long infections in their host. The basis of retroviral persistence is the incorporation of the viral genes into cellular chromosomal DNA. In infected cells a DNA copy of the viral RNA genome is synthesised by reverse transcriptase. This DNA is then integrated into cellular DNA as a provirus which subsequently behaves like a cellular gene. Under appropriate conditions the proviral genes are expressed and progeny virus is made without harming the infected cell. Expression of retroviral genes may be suppressed, however, by extracellular diffusible factors so that the provirus is maintained in a latent state.

A consistent feature of retroviral infections is that individuals with permanent infections may be apparently healthy for many months or years before developing a serious disease. During this extended latent period they are infectious and unwittingly may spread virus to others.

Oncoviruses

There are two main groups of oncogenic retroviruses. One comprises the leukaemia viruses of the cat, mouse, and chicken, the members of the other are the human T lymphotropic viruses (HTLV), their simian counterparts, and bovine leukaemia virus (BLV). The biology of the two groups is different in several important aspects.

Feline leukaemia virus (FeLV) is an example of the first group. The virus is transmitted congenitally across the placenta or by contact through infected saliva or milk from persistently infected animals. Some cats, especially when exposed congenitally or at an early age become permanently infected, and around 90% develop a serious and often fatal disease within three to four years. The most common related diseases are lymphoid and myeloid leukaemias, pure red cell aplasia, immunodeficiency, or infertility. These cats have large quantities of infectious virus in the blood. They are immunotolerant to the virus so antiviral antibodies are not found in the serum. Most cats, however, recover from contact exposure, develop virus neutralising antibodies, and are immune to reinfection. In an endemic household about 30–40% of cats would be viraemic and the remainder would be immune.

HTLV or BLV infections are rather different. While individuals may become permanently infected, the virus is not found free in the blood but is maintained in a latent state in lymphocytes, T cells for HTLV, and B cells for BLV. One of the major

advances in retrovirus research was the discovery that latent virus becomes reactivated rapidly when infected lymphocytes are established for even a short period in cell culture and is detectable as infectious particles.[1] Individuals with permanent HTLV or BLV infections also make antibodies to viral proteins, unlike cats, mice, or chickens infected with their respective retroviruses. This feature is extremely important in diagnosis as antibodies are much easier to detect than latent virus. The same applies to the AIDS virus HIV.

Surprisingly, the methods of transmission of HTLV or BLV have been difficult to determine. Transmission is very efficient by the transfer of even minute volumes of blood. Undoubtedly, many people have contracted HTLV through blood transfusions, and cows have become infected through needles and syringes used for multiple inoculations in herds. Natural transmission may occur by biting anthropods and some cases arise by congenital transmission—and in HTLV infections, through mother's milk.

HTLV causes acute T cell leukaemia in adults.[4] HTLV and acute T cell leukaemia are found in several areas of the world, notably Kyushu, Shikoku, and Hokkaido islands (but not Honshu) in Japan and in the Caribbean basin. In Kyushu up to 37% of adults are seropositive. Cases of acute T cell leukaemia associated with HTLV-I have been diagnosed in Britain in immigrants from Caribbean islands but the virus does not seem to have spread outside their immediate families.[5] The virus is also endemic in tropical Africa.[6] The basis of the distribution of the virus has yet to be explained satisfactorily. Unlike cats infected with FeLV, only about 1 in 2000 of people infected with HTLV (or cattle infected with BLV) develop leukaemia.

The AIDS lentivirus

AIDS is currently the most important public health concern in many countries. The syndrome was first recognised in 1981 and the causative virus, now called HIV, was isolated over the following three years in France[2] and the United States of America.[3] This new disease most likely spread from Africa where the virus is now common in many areas and may have been derived from closely related simian viruses. Today transmission of HIV is by sexual contact, particularly among male homosexuals, and by intravenous drug abuse through shared needles and syringes; infected mothers can also transmit the virus congenitally to their children. Great efforts are now made to eliminate contaminated blood products which have also transmitted HIV in the past, particularly to haemophiliacs. More than one million people carry the virus in the United States of America and 25 000 people have AIDS or related conditions. The estimated number of deaths in Britain is 377. The proportion of infected individuals who will develop AIDS is not yet known but could be 100%. It has been estimated that by 1991 there will be a cumulative total of more than 270 000 cases of, and 179 000 deaths from, AIDS in the United States of America. Total cases of paediatric AIDS will have increased from 300 to 3000 by that time.

Mechanisms of retroviral disease

The mechanisms by which retroviruses cause disease are rapidly being defined. FeLV and avian leucosis virus—for example, induce many cases of leukaemia by activating the cellular oncogene *myc*.[7] Consequent continuous expression of the *myc* protein seems to be an important step in the selection of leukaemic cells by maintaining infected cells in continuous growth over long periods. The way in which HTLV and BLV are pathogenic is less clear: a viral gene which acts as an activator of transcription in infected lymphocytes may be important in generating cells that eventually become leukaemic.[8]

HIV infection is rather different as AIDS is caused by destruction of cells. Initially a very small proportion of lymphocytes carry the virus. Infection is restricted to T lymphocytes with the CD4 antigen. As the infection progresses, however, more T4 lymphocytes are recruited into the pathogenic process, possibly by cell fusion with infected cells. Eventually so many T4 cells are lost that the function of the immune system is irreparably damaged. A considerable proportion of patients with AIDS have neurological complications, of which dementia is the most severe.

Treatment, control, and prevention

One of the major challenges in medicine today is to devise methods for the treatment, control, and prevention of retroviral infections. Treatment is made difficult because the viral genome is integrated within host cells and can only be eliminated by the eradication of infected cells. Some progress has been made, particularly in testing drugs which interfere with the virus specific enzyme reverse transcriptase. Azidothymidine (AZT) has proved to be palliative in AIDS, but as the drug cannot eliminate virus, only halt further establishment of provirus in new cells, the treatment is incomplete. The therapeutic potential of other drugs such as ribavirin is being assessed.

Control measures are designed to interfere with the transmission cycle of virus. FeLV has been

widely controlled by the isolation or elimination of carrier cats detected by showing the presence of virus in the blood.[9] This veterinary solution is obviously not suitable for HTLV or HIV. Strenuous efforts are now being made by health authorities to minimise the transmission of HIV by testing blood products for virus and by attempting to modify sexual habits and intravenous drug abuse through large scale propaganda.

Prevention by vaccination is more likely to be the method which will eventually control retroviral infections in man and animals. The first retroviral vaccine was launched in 1985 against FeLV infection and is reputed to protect 80% of cats against challenge.[10] Products designed to protect all vaccinates are being developed and are either novel adjuvants which present viral antigen more efficiently to the host's immune cells[11] or are based on genetically engineered virus or antigen which can be obtained inexpensively in very large amounts.

The same strategies are being adopted for a vaccine against AIDS. A major obstacle is that there is not an entirely suitable animal host in which to test candidate vaccines. Current studies aim to induce a demonstrable humoral or cellular immune response to HIV.

That there might be distinct serotypes of HIV has been suggested by analysis of the amino acid sequence of several virus isolates that showed differences within the appropriate antigen. Such fears have, to some extent, been allayed by the finding that antibody to any one isolate neutralises other isolates.[12] Thus there is optimism that an effective vaccine will be available in the near future.

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