Viruses and Cancer

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The relative role that viruses play in causing human cancer remains ambiguous, but a number of studies have established their involvement in a few types of tumours. The viruses that have been strongly associated epidemiologically with human cancers are the human papillomaviruses(HPV), hepatitis B virus(HBV), hepatitis C virus(HCV), Epstein-Barr virus(EBV) and human T cell leukaemia viruses(HTLV-1 and HTLV-2). Other viruses which may have a possible role as a co-factor include herpes simplex virus(HSV), and human immunodeficiency virus-1(HIV-1). Now there are several reports on the possible association of human herpesvirus 8(HHV-8) with Kaposi's sarcoma.

The linkage between infection with HPV types 16 and 18 and the development of cervical, vulval, penile and rectal cancers has been made quite clear[1,2]. HPV types 6 and 11 cause cervical lesions as well but have a lower risk of progression to malignancy. Factors which may be implicated include the integration of the viral genome with the host genome and the activation of viral E6 and E7 genes which are required to maintain the transformed state of the human cells[3]. It should be remembered that many viruses can transform human cells but fortunately only a few are able to maintain the transformation. Even so with HPV, the presence of the specific strain of virus alone is not enough to maintain the transformation. With cervical cancer, cocarcinogens like cigarette smoke and concomitant HSV infection[4] are implicated as well. This is why cervical cancer is still an uncommon sequelae to those infected with these strains of HPV.

As for skin cancers, there is still no evidence that HPV is associated with it in normal individuals. On the other hand, 30% of immunosuppressed patients with the rare autosomal recessive disease epidermodysplasia verruciformis (due to HPV5 or HPV8) will develop multiple squamous cell carcinoma of the skin with ultraviolet light acting as a cocarcinogen.

The role of Hepatitis B virus(HBV) as a major aetiologic agent of hepatocellular carcinoma(HCC) has been firmly established, and the increased risk of developing HCC has been estimated to be 100-fold for chronic HBV carriers as compared with non-infected populations[5]. It has been postulated that HBV-associated HCC in humans could actually be a sequel to the continuous hepatocyte regeneration that occurs during persistent carriage of this virus. This is why cirrhosis of the liver itself carries a high risk for HCC development[6]. Recently integrated sequences have been found present in the tumour cells and these inserted sequences are thought to activate cellular oncogenes, or alter cell growth control.The fact that HCC has been reported to arise in a non-cirrhotic liver of a young chronic hepatitis B carrier confirms the presence of the virus-driven oncogenic event[7]. This dual pathogenesis is also seen with hepatitis C virus infection but the direct oncogenic effect appears to have a greater role[8].

Epstein-Barr virus(EBV) is closely linked with the development of nasopharyngeal carcinoma(NPC), which is common in Southern China and other parts of Asia, including Malaysia. The reason for the restricted geographical distribution is unknown but it has been postulated that genetic predisposition between racial groups or the presence of local cocarcinogens (e.g. nitrosamines in salted fish) could play a role[9]. EBV DNA has been demonstrated in the cancer cells but the precise mechanism for tumorigenicity is unknown. Cellular oncogenes have not been implicated. Those at risk of developing NPC have been shown to present with high levels of anti-VCA IgA a year or more before clinical symptoms appear. In 1995 Pathmanathan *et al* actually established the multistep involvement of EBV in the development of nasopharyngeal carcinoma[10].

Burkitt's lymphoma, a tumour of immature B cells, is

seen in Uganda and Papua New Guinea, occuring among 6-14 year old male children. EBV DNA is present in the tumour cells, but most of the EBV genes are not integrated into the host cell DNA. Here cellular oncogenes may be implicated. The fact that Burkitt's lymphoma is also localized geographically indicates that local cofactors like malaria may be involved. More recent evidence, principally the detection of EBV DNA, has suggested that EBV may be implicated in the pathogenesis of other tumours, notably HIV-associated lymphoma[11].

Human T cell leukaemia viruses(HTLV-1 and HTLV-2) are retroviruses with no oncogenes. HTLV-1 is known to cause adult T cell leukaemia[12] and lymphoma, particularly in Southern Japan, the Caribbean and West Africa. The carcinogenic nature of HTLV-1 is the result of a viral gene product that enhances host cell division. Less is known about HTLV-2 except that it can be isolated from a hairy T cell leukaemia.

Herpes simplex virus type 2 (HSV-2) was once thought to be a possible cause of cervical carcinoma. HSV-2 DNA and proteins are detectable in cancer cells and HSV-2 can transform certain cells *in vitro*. However, HSV-2 has now been relegated to a cocarcinogenic role[13]. Women with cervical cancer do have a higher incidence of antibody to HSV-2 but this merely reflects the association of cervical cancer with multiple sex partners.

Kaposi's sarcoma(KS) is 300-times as common in AIDS patients as in other immunosuppressed groups. This high incidence is actually probably due to the chronic immunosuppression which occurs in the disease, and not the result of any direct oncogenic activity of HIV even though it is a retrovirus. Since Kaposi's sarcoma is seen almost entirely in those who acquired HIV by sexual contact, it is probably due to an unidentified sexually transmitted infectious agent. This is where the newly described Kaposi's sarcoma associated herpesvirus (KSHV) or human herpesvirus 8 (HHV-8) comes into the picture. This herpesvirus occurs in both AIDS-related and unrelated forms of the disease, strongly supporting an aetiological role[14,15] and it has been successfully propagated in culture using a special cell line[16]. Whether this agent is oncogenic, however, requires further evaluation since it is absent in many Kaposi's sarcoma lesions.

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