Session 6: Human Herpes Virus 8 (Biomed-1 Concerted Action)

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HHV8 (KSHV) in lymphoproliferative disorders

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Recently, a novel γ-2 herpes virus HHV-8 or KSHV has been associated with various forms of Kaposi's sarcoma (KS). Subsequently it was also found in so called body cavity based lymphomas (BCBL) or primary effusion lymphomas (PEL) of AIDS patients and some cell lines derived from such lymphomas. Most PEL cases have been found in AIDS cases, but a few also in HIV negative patients.

These lymphomas are usually of anaplastic or immunoblastic morphology, show clonal Ig-gene rearrangements, but usually lack other B-cell markers. HHV-8 has also been shown to associate with cases of Castleman's disease. Preliminary results show a broader association of HHV8 with various types of malignant lymphoma in Tanzania. The apparent cell pleotropism and the possible pathogenic role of HHV8 will be discussed.

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Cell-homologous genes in the Kaposi's sarcoma-associated rhadinovirus HHV-8-Determinants of its pathogenicity?

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Kaposi's sarcoma associated herpesvirus, also termed human herpesvirus 8 (HHV-8), is the first known human member of the genus Rhadinovirus. It is regularly found by PCR in all forms of Kaposi's sarcoma, in certain types of Castleman's disease, and in body cavity based B-cell lymphoma. Other members of this virus group occur in non-human primates, ungulates, rabbits, and in mice, causing in part fulminant lymphomas and other neoplastic disorders of the haematopoietic system. Rhadinoviruses share a typical genome structure: most characteristically, they contain numerous sequences that appear to be sequestered from cellular DNA, including the coding sequences for enzymes of the nucleotide metabolism, for antagonists of the complement system, and for proteins that may be involved in growth stimulation of persistently infected cells, such as interleukins and interleukin receptor analogues. A genomic library from a KS biopsy was completely sequenced. It revealed collinear organization and extensive homologies with the open reading frames of H. saimiri. We found, in addition, the reading frames for homologues of cellular interleukin-6, the CC chemokines MIP1 and MIP1, and an interferon responsive factor. This lends support to a pathogenesis model according to which virus-encoded cytokine analogues contribute to autocrine and or paracrine growth stimulation of KS spindle and lymphoma cells. It complements recent serology and PCR based epidemiology, rendering it likely that HHV-8 is the essential factor, besides preexisting immunosuppression, that determines lymphoma genesis and the multifocal generation of Kaposi's sarcoma.

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HHV 8 and Kaposi's sarcoma: Cause or coincidence?

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Human herpesvirus 8 (HHV 8) is consistently found in Kaposi's sarcoma (KS) tissue, and its detection in peripheral blood correlates with, or predicts, the presence of KS lesions. Whether these observations indicate that HHV 8 is the cause of KS has been the subject of intensive investigation. In the UK and USA antibodies to both a latent nuclear HHV 8 antigen and a recombinant structural ('lytic cycle') protein, encoded by open reading frame (orf) 65, are largely confined to KS patients, those known to be at increased risk for KS (HIV-infected homosexual men), whereas other HIV risk groups (haemophilia patients, intravenous drug users) and blood donors have a low antibody prevalence. As measured by these two antigens, the prevalence of HHV8 infection is slightly higher in some Mediterranean countries, and much higher in several parts of Africa. HHV 8 can be sexually transmitted. The risk of infection increases with the number and geographic origin of partners, receptive anal intercourse, but is not linked to other behavioural variables such as 'rimming' and use of nitrite stimulants. These epidemiological data support a causative role of HHV 8 in the pathogenesis of KS, but co-factors other than immunosuppression may also play a role. In KS tissue HHV 8 is present in endothelial and spindle cells where it persists in a latent form. At least six HHV 8 encoded genes (orfs K12, K13, 72, 73, 74 and an unexpressed nuclear RNA) are expressed in these cells. The nuclear antigen, which is found in HHV 8 positive B-lymphoma cells and used for diagnostic immunofluorescence, is encoded by orf 73 and also expressed in KS spindle cells, but not endothelial cells. The function, and oncogenic potential, of these (and possibly other) latent proteins is presently under intensive investigation.

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Human herpes virus 8 and lymphoproliferative disorders

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HHV8 DNA sequences were searched for in a series of 250 B or T cell lymphoproliferative malignancies, as seen in France, including 126 leukemias and 124 lymphomas (232 non AIDS associated and 18 AIDS associated tumors). HHV8 sequences were detected in only 3 patients: the first two were HIV infected homosexual males, suffering from a BCBL. A high level of HHV8 copies was detected in the tumoral cells of these two BCBL, also carrying EBV genomes. In the third patient who had an AIDS associated immunoblatic lymphoma, the HHV8 sequences level was quite low. A semiquantitative PCR analysis revealed that HHV8 sequences were much more abundant in the effusion tumor cells of one patient than in his cutaneous Kaposi's tumor, while non HHV8 sequence was detectable in the peripheral blood lymphocytes. HHV8 was not found associated with any other T or B malignant lymphoid neoplasias studied so far. This study stresses the necessity of quantificative PCR for HHV8 sequences, especially in patients at risk for HIV infection of Kaposi's sarcoma.

We are developing 3 projects on HHV8: 1) Serological and viromolecular studies of the geographical distribution and of the epidemiological determinants of HHV8 including the modes of transmission in Africa, South America and the Far East. 2) Molecular studies on the genetic variability and molecular epidemiology of this virus. 3) Detection and molecular characterization of HHV8 in the different forms of Castleman's disease and in reactive or tumoral lymphoproliferative disorders of different geographical origins.

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ABSTRACT WITHDRAWN