molecular basis of disease
Haematologica 1996; 81:265-281

THE NEW LYMPHOTROPIC HERPESVIRUSES (HHV-6, HHV-7, HHV-8) AND HEPATITIS C VIRUS (HCV) IN HUMAN LYMPHOPROLIFERATIVE DISEASES: AN OVERVIEW

Mario Luppi, Giuseppe Torelli

Department of Medical Sciences, Section of Hematology, University of Modena, Italy

ABSTRACT

Considerable evidence has been accumulating in favor of a possible involvement of viral agents in the pathogenesis of human lymphomas. The most recent proposal for a lymphoma classification, the Revised European-American Classification, emphasized for the first time the pathogenetic importance of two viruses, namely Epstein-Barr virus (EBV) and human T lymphotropic virus I (HTLV-I) in the development of certain lymphoid neoplasias. However, in the last ten years new viral agents possibly related to lymphoproliferative activity have been discovered: three herpesviruses [human herpesvirus-6 (HHV-6), -7 (HHV-7) and -8 (HHV-8)] and a flavivirus, HCV. HHV-6 was isolated from the peripheral blood of patients with lymphomas and a possible role for this β-herpesvirus in Hodgkin's disease and in angioimmunoblastic lymphadenopathy (AILD) has emerged from serological and molecular studies. HHV-7, a β-herpesvirus genetically close to HHV-6, has not yet been found in a human disease but it utilizes CD4 as a receptor on the lymphocyte surface. Only partial HHV-8 genomic sequences have been identified so far, suggesting a genetic homology with members of the γ-herpesvirus family, including EBV. HHV-8 sequences have been identified for the first time in all forms of Kaposi's sarcoma as well as in a variety of lymphoid disorders, including body-cavity-based non Hodgkin's lymphomas, Castleman's disease, AILD and a type of HIV-negative reactive lymphadenopathy with peculiar histologic features. Finally, after its identification as the major cause of post-transfusion and sporadic non-A, non-B hepatitis, HCV has revealed a lymphotropism both *in vitro* and *in vivo*. A strong association between HCV infection and a benign lymphoproliferative disease, essential mixed cryoglobulinemia type II, has clearly emerged both from serological and molecular studies. A possible role for this viral infection in B-cell non Hodgkin's lymphomas not associated with cryoglobulinemia has also been proposed recently. The present work offers an overview of the huge amount of experimental and clinical observations supporting the possible involvement of these new lymphotropic viruses in human lymphoproliferative diseases.

key words: herpesviruses, HCV, lymphoproliferative diseases

Burkitt's description of an endemic malignancy in Africa raised the question of a possible infectious etiology for lymphoma,[1] a question that was strengthened by the isolation of Epstein-Barr virus (EBV) from Burkitt's lymphoma (BL) lymphocytes.[2] Although EBV was first associated with BL and undifferentiated nasopharyngeal carcinoma (NPC),[3] more recent evidence, mainly based on the detection of EBV-DNA/RNA sequences, has suggested that this virus may be involved in the pathogenesis of a wider spectrum of lymphoproliferative diseases. In the immunocompetent host these diseases include: Hodgkin's disease

Correspondence: Prof. Giuseppe Torelli, Dipartimento di Scienze Mediche, Cattedra di Ematologia, Policlinico, via del Pozzo 71, 41100 Modena, Italy. Tel. international +39.59.422329.
Acknowledgements: this work was funded by grants from Associazione Italiana per la Ricerca sul Cancro (AIRC), Italy, and from Consiglio Nazionale delle Ricerche (CNR).
Received March 6, 1996; accepted April 1, 1996.

(in approximately 50% of cases, predominantly the mixed cell type),[4-6] various T-cell lymphomas including angioimmunoblastic lymphoma,[7,8] angiocentric lymphoma[9] and nasal lymphoma,[10,11] and large granular lymphocyte leukemias from Asian countries;[12] in the immunocompromized host: malignant lymphomas in boys with the X-linked lymphoproliferative syndrome,[13] primary cerebral high-grade B-cell non Hodgkin's lymphomas (NHL),[14] some systemic lymphomas of the immunoblastic or large cell type in HIV-1-infected patients,[15] and lymphoproliferative disorders in patients who have undergone organ transplantation and subsequent immunosuppressive therapy.[16] Besides EBV, another virus known to be implicated in human lymphoid neoplasias is human T-lymphotropic virus type I (HTLV-I). HTLV-I infection was established by serological and molecular studies as the major etiologic factor in adult T-cell leukemia (ATL) and of a form of cutaneous T-cell leukemia/lymphoma (CTCL) in endemic areas.[17,18] Very recently, there have also been suggestions that in certain nonendemic areas HTLV-I may be associated with a number of CTCLs other than ATL, namely $CD30^+$ anaplastic large cell CTCLs, mycosis fungoides and its leukemic variant, the Sézary syndrome (SS).[19-21] Both EBV and HTLV-I have been studied extensively and although many aspects of their biology and interaction with the host are still obscure, a huge amount of reproducible evidence has been collected in support of a pathogenetic association between these viruses and specific subsets of lymphoid neoplasias. The list of lymphoproliferative diseases demonstrated to be associated with EBV and HTLV/I is now perhaps complete and although the mechanisms of viral lymphomagenesis are far from being understood, the importance of both these viral agents in the pathogenesis of human lymphomas was also emphasized in the *Revised European-American Classification of Lymphoid Neoplasms*, recently proposed by the *International Lymphoma Study Group*.[22]

The aim of the present work is to offer an overview of the latest evidence from the literature that indicates a possible pathogenetic association between lymphoproliferative diseases in humans and infection with other, less known, lymphotropic viruses, most of which have only been discovered in the last few years (like human herpesvirus-6 and human herpesvirus-7) or just one year ago (like human herpesvirus-8). Furthermore, although we are aware of the fact that hepatitis C virus cannot be strictly classified among the classical lymphotropic viruses, we cannot avoid discussing extensively its possible association with certain lymphoproliferative disorders.

HHV-6

HHV-6 was isolated in 1986 from the peripheral blood mononuclear cells (PBMC) of six patients affected with various lymphoproliferative disorders, some of whom were also infected with HIV-1.[23] HHV-6 is an enveloped virion containing about 160 kb of linear double-stranded DNA[24] and it is now classified as a β-herpesvirus.[25] This virus has been shown to be tropic *in vitro* for cells of the immune system, namely $CD4^+$ T cells, B cells, NK cells and monocytes-macrophages; it is also infectious, although at a lower level, for glial cells and megakaryocytes.[26-28] HHV-6 is ubiquitous in the human adult population throughout the world, with seroconversion occurring early in life.[29] Primary infection with HHV-6 may cause *exanthem subitum*[30] and acute febrile illness in young children,[31] while in adults infection may cause hepatitis[32] and a mononucleosis-like syndrome.[33] Like all other human herpesviruses, HHV-6 is probably capable of remaining latent in host cells subsequent to primary infection and then may reactivate in an immunocompromized state, as reported in cases of kidney, liver and bone marrow transplantation.[28] Recently, a consensus was reached on the classification of all HHV-6 isolates into two groups, called A and B.[25] This distinction is based not only on genetic and antigenic characteristics but also on the fact that the isolates from *exanthem subitum* were mainly of the B type, while those from immunocompromized patients were mainly of the A type.[28] The virus persists in PBMCs, although only rare cells are infected in healthy individu-

als, as demonstrated by studies using polymerase chain reaction (PCR).[34-36] The idea has also emerged that the amount of viral copies harbored in PBMC, is invariably low, not only in latent conditions but also in conditions of symptomatic primary infection in children (*exanthem subitum*) and of viral reactivation in post-transplant and HIV immunosuppressed patients, in whom HHV-6 sequences can never be detected by Southern blot analysis but only by the sensitive PCR technique. The level of viral genomes in PBMC does not correlate with anti-HHV-6 antibody titers, and these cells are certainly not the only site of viral latency/persistence. In fact, the oropharynx and/or salivary glands,[37] the epithelial mucosa of the female genital tract[28] and brain tissue[38-40] may harbor viral genomes and represent a reservoir of the virus in the healthy population. The state of the viral genome in infected host cells has not been fully investigated. The entire HHV-6 genome was found to be integrated in the short arm of chromosome 17 (17p13.3) in the PBMCs of three patients (one each with NHL, HD, and multiple sclerosis) harboring extraordinarily high levels of the viral genome.[41,42] In particular, the order of the HHV-6 viral integration site relative to two known genes, ABR and CRK,[43] was recently mapped in the PBMCs of the NHL patient, and the results place the HHV-6 integration site very close to, if not within, the telomeric sequences on 17p (manuscript in preparation). However, given the abnormally abundant HHV-6 DNA and the altered immune status of the hosts, it is still unclear whether this phenomenon of targeted chromosomal integration is also common to other clinical conditions and/or to the healthy population, possibly representing a usual mechanism of HHV-6 latency *in vivo*.

A possible pathogenetic role for HHV-6 in lymphoproliferative diseases was first suggested by the ability of its DNA, either as a complete genome or as specific cloned fragments, to transform established NIH 3T3 cells and human epidermal keratinocytes *in vitro*, causing them to form rapidly growing and metastasizing tumors when injected into nude mice.[44-46] In addition, a gene homologous to the so-called rep gene of human adeno-associated virus type 2 (AAV-2) has recently been identified in the HHV-6 genome.[47] The HHV-6 expression of a gene acting as a modulator of heterologous gene expression and cellular transformation is likely to have important consequences for infected host cells.[48] Thus, HHV-6 was considered an oncogenic virus candidate from the very beginning because of its presence in cases of human lymphomas and its *in vitro* transforming potential. Seroepidemiology has proven to be an important tool for linking viruses with cancer and other disorders. A role for HHV-6 infection in HD was first suggested by serological studies showing that anti-HHV-6 antibody titers were higher in HD than in normal blood donors[49,50] (Table 1) and that they were related to the evolution of the disease, rising during HD relapse and falling in non relapsing patients.[51] By contrast, the levels of anti-HHV-6 antibodies in NHL patients have been found to be similar to those documented in the healthy population[50,52] (Table 1). On the other hand, serological features alone are a suggestive, but certainly not a conclusive argument for the causal role of a virus in human pathology, and identification of the viral genome in pathologic specimens is considered crucial for determining the viral etiology of a disease. This caveat is likely to hold especially true for HHV-6,

Table 1. HHV-6 infection in lymphoproliferative diseases and in the normal population.

	References	*Anti-HHV-6 antibodies by IFA at 1:40 dilution*	*HHV-6 sequences by PCR and Southern blot*
		(% positive cases)	
HD	Torelli et al. (50)	80	12
	Di Luca et al. (53)	n.d.	29
NHL	Josephs et al. (57)	n.d.	6
	Jarrett et al. (58)	n.d.	2
	Torelli et al. (50)	62	0
	Di Luca et al. (53)	n.d.	0
AILD	Luppi et al. (59)	n.d.	58
Blood donors	Di Luca et al. (53)	n.d.	17
	Torelli et al. (50)	54	n.d.
	Luppi et al. (36)	54	20

HD: Hodgkin's disease; NHL: non Hodgkin's lymphoma; AILD: angioimmunoblastic lymphadenopathy; IFA: indirect immunofluorescence assay; n.d.: not done.

since unusual cases of herpesvirus latency have been described in which the absence of anti-HHV-6 IgM and IgG antibodies was matched by an unexpectedly high number of viral sequences in the PBMC of patients with lymphoproliferative disorders.[41] This is the reason for combining molecular methods with serologic studies to search for HHV-6 genomes, in order to avoid the risk of missing patients with a latent infection but negative serology. With the aid of PCR, HHV-6 specific sequences have been detected in the pathologic tissues of about 30% of the HD patients examined so far, and variant B has been more frequent than variant A[53] (Table 1). The majority of HD biopsies positive for HHV-6 belonged to the nodular sclerosis type, although a significant fraction of mixed cellularity and lymphocyte prevalence types also harbored HHV-6 sequences. Thus the frequency of HHV-6 sequences in HD tissues is slightly higher than in the PBMCs of the healthy population, evaluated to be about 17% under the same PCR conditions, supporting the idea that this virus might be associated with a subset of this disorder[53] (Table 1). Of interest, the only three cases found to be positive for HHV-6 DNA in a well-characterized series of twenty-five HD cases presented remarkable similarities.[50] In particular, the three patients, all young women, showed mesothelial effusions (pleuropericardial in two cases and pleuroperitoneal in the third). Two of them featured a predominant bulky mediastinal involvement, while the third patient showed mediastinal involvement as part of a generalized disease. All three cases belonged to the same histologic subgroup, nodular sclerosis-lymphocyte depletion, which generally accounts for a small proportion of HD cases and is associated with poor prognosis.[50] Although a relationship between the presence of HHV-6 and a particular subset of patients has not been solidly established, the possibility has been raised that HHV-6 infection may play a role in determining some basic clinical aspects of a limited number of cases. In two of these patients the level of viral sequences was extraordinarily high, so as to be easily detected not only by PCR but also, unexpectedly, by Southern blot analysis, which also revealed the presence of the B variant of HHV-6 with the same restriction fragment length polymorphisms in both cases. Of interest, Southern blot analysis also detected the presence of the entire viral genome in the pathologic lymph nodes and PBMCs of one patient, while documenting the deletion of the viral region containing the rep gene localized at the 3' end of the HHV-6 genome in the lymphomatous tissue of the other HD patient.[42,54] Although rep gene products have been shown to regulate the promoter/enhancer elements of a variety of cellular genes and to exert anti-proliferative activity *in vitro*, it is not possible at present to determine the biological consequences, if any, of either the presence or the absence of this gene in the HHV-6 infected cells of the HD patients examined. Of interest, while the patient infected with the complete HHV-6 genome achieved a complete remission that has lasted for 7 years, the other HD patient with a defective virus had an unfavorable clinical course and died 11 months after diagnosis, despite an initial response. The possibility that the presence of the rep gene may be related to a favorable clinical disease course is intriguing, but is still only a matter of speculation because of the small number of cases studied.[54] In any event, HHV-6 genomes that show variations in the genomic structure with respect to the A and B prototypes, although infrequent, do exist and must be kept in mind. In fact, another HD case of the mixed cellularity type, found positive for HHV-6 by Southern blot, showed abnormal cleavage patterns after digestion with various restriction enzymes, indicating gross alterations and/or rearrangement within the viral region homologous to the probes used.[55] The relevance of these abnormal HHV-6 variants in terms of pathogenicity deserves further investigation. Finally, we have examined HD lymph nodes by immunohistochemistry in our laboratory (in collaboration with R. Garber, PathoGenesis Corporation, Seattle, USA) using the monoclonal antibody p41/38, which recognizes a DNA replication factor, a protein whose function is still unknown but that is likely to be expressed in the early phase of the HHV-6 replicative cycle. This viral protein has clearly been shown to be expressed only in a significant number of Reed-Sternberg cells and in plasma cells, but not in the

reactive cellular population of HD lymph node tissues, representing the first unequivocal demonstration of HHV-6 in the putative neoplastic element of HD (manuscript in preparation). However, the assessment of HHV-6 involvement in HD will require defining the exact functions of this viral protein found in Reed-Sternberg cells, as well as identifying which HHV-6 proteins, if any, have transforming properties, analogously to the detection of the oncogenic latent membrane protein of EBV in the Reed-Sternberg cells of most cases of mixed cellularity type HD.

HHV-6 sequences have rarely been detected in pathologic tissues from NHL cases of B and T cell lineage[50,52,53] (Table 1). With sensitive PCR, the frequency of HHV-6 sequences in malignant lymphoma tissues was similar to that found in the PBMCs of the general population and increased only in patients with AIDS, probably due to reactivation of HHV-6 infection as a result of immunosuppression.[56] Only six out of the hundreds of NHL cases examined so far throughout the world (one of T and five of B cell lineage) have been found to harbor such a high viral load as to be detectable by Southern blot.[41,57,58] The entire viral genome was found to be integrated in the pathologic lymph node of one of these B cell NHL, but *in situ* hybridization studies were not performed to identify the cellular elements, either neoplastic or reactive, harboring the HHV-6 DNA.[42] On the other hand, integration of the HHV-6 genome was also demonstrated in PBMCs from the lymphoma patient in complete remission, i.e. in cells probably not involved in the neoplastic process, suggesting that in HHV-6 infection the integration process *per se* is not a direct cause of lymphoid neoplasia.[42] However, based on the direct oncogenic potential as well as on the putative, positive and/or negative regulatory functions of some viral genes, the presence of an integrated HHV-6 genome in the neoplastic lesion may suggest a pathogenetic role for this lymphotropic virus, at least as a modulating element, in the lymphoproliferative process of this patient. Among NHL, angioimmunoblastic lymphoma represents an exception. In fact, using PCR, HHV-6 DNA sequences were detected in three out of four angioimmunoblastic lymphadenopathy-like (AILD-like) lymphoma and in four out of eight angioimmunoblastic lymphadenopathy biopsies, with an approximately equal distribution between the A and B variants and one case of coinfection[59] (Table 1). Three of the seven HHV-6-positive specimens were simultaneously positive for EBV sequences, suggesting the possibility of an interaction between these two viruses in these tissues, especially given the ability of HHV-6 to activate EBV replication *in vitro*.[60] Although the cause of AILD is unknown and is likely to vary in different subjects, one common feature is excessive immunity, which leads to characteristic lymph node histology and clonal expansion of B and T lymphocytes. Therefore HHV-6 may be involved in the pathogenetic mechanisms of AILD by acting as a trigger, mainly through swithing on T cell activity, at least in the initial phase of the disease, which is characterized by the presence of activated T cells in the lymph nodes as well as in the peripheral blood, where most T cells express HLA-DR antigens. On the other hand, it is not possible to rule out the hypothesis that the presence of HHV-6, as well as of other viruses like EBV and HHV-8 (see below) may be a reflection rather than a cause of a disease process that is strictly related to the abnormal immunoregulation typical of this condition. In this view, HHV-6 itself may contribute to the immune impairment, given its proven ability to interfere with the cells of the immune system, mainly T cells, as well as with various cytokine networks.[61,62] At present, the mechanisms of HHV-6 infection involvement in the pathogenesis of AILD are obviously only a matter of speculation; however, the frequent detection of the HHV-6 genome in AILD and AILD-like lymphoma cases remains a very peculiar and distinctive phenomenon not found in other lymphoproliferative diseases, even though they are also associated with a marked impairment of the immune response.

Other instances of HHV-6 being found in lymphoid disorders include one case of S100 chronic lymphoproliferative disease showing variant B HHV-6 genome and HHV-6 RNA in tumor cells,[63] and one case of large granular

lymphocytic leukemia transformation during the course of a reactivated HHV-6 infection.[64] An association has also been proposed between HHV-6 infection and sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), a condition characterized by an accumulation of histiocytes in lymph node sinuses that leads to a painless cervical lymphadenopathy. HHV-6 sequences were found by *in situ* hybridization in pathologic tissues from seven out of nine cases of Rosai-Dorfman disease.[65] These findings suggest HHV-6 tropism for histiocytes *in vivo*, a fact confirmed by the detection of HHV-6 DNA in histiocytes but not in T cells in all the forms of lymphadenitis studied so far.[28] The role of HHV-6 in acute lymphoblastic leukemia (ALL) is controversial, with only one study on a small group of ALL patients documenting higher levels of anti-HHV-6 antibodies than in normal subjects;[66] another study on a larger number of ALL patients and normal blood donors did not observe any significant differences in the anti-HHV-6 antibody titers of the two groups.[67] Moreover, HHV-6 sequences were first detected by PCR and in situ hybridization in the bone marrow cells of the majority of children with T-ALL,[68] but a subsequent study showed that the presence of HHV-6 DNA is no more frequent in patients with ALL than in normal subjects.[69] Moreover, in ALL cases as in healthy individuals, HHV-6 infection is invariably characterized by a very low copy number of viral sequences detectable only by highly sensitive PCR, arguing against a major role for HHV-6 in this disease.

It is difficult to put all these observations into a coherent sequence of events to explain the clinical relationship between HHV-6 and lymphomagenesis. It is also difficult to differentiate between a virus that is a passenger in tumor tissue and one that plays a role in the etiology of the neoplasm, and the observations reported above regarding the presence of the HHV-6 genome in various lymphoma tissues should not be taken as proof of etiology. It should be kept in mind for HHV-6 as well as for other viruses like EBV and HTLV-I in endemic areas that the prevalence of viral infection is always much higher than the incidence of the associated disease. HHV-6 is a ubiquitous infectious agent with a long evolutionary relationship with its human host. Primary infections in adults are rare and although they appear to have more severe consequences than normal childhood acquisition, they are commonly associated with non neoplastic diseases, i.e. prolonged benign lymphadenopathy or mononucleosis-like illness. Thus, it is unlikely that HHV-6 has a major oncogenic effect, and it is conceivable that this herpesvirus may contribute to lymphomagenesis only under particular conditions of host immunosuppression or when specific viral proteins are expressed in an unusual cell type, as in the case of Reed-Sternberg cells in some HD cases. The effect of an oncogenic virus is generally to initiate a multistage process of lymphomagenesis by expressing proteins able to interact with host cell-encoded tumor-suppressor proteins and to abrogate the cell cycle checkpoint functions, thereby predisposing the cell to genetic instability. In the case of EBV for example, the lytic cycle protein BZLF1, rather than a latent protein, has been shown to abrogate p53 function.[70] However, specific HHV-6 oncoproteins able to bind to and functionally inactivate tumor suppressor proteins have not yet been identified, and the mechanisms through which this herpesvirus might affect the growth control of infected cells are far from being elucidated. Furthermore, in order to participate in cancer development DNA tumor viruses have to remain in infected cells for long periods without reproducing infectious viral particles.[71] It is still unclear whether HHV-6, which is cytopathic *in vitro*, has the ability to establish long-term latency in the host *in vivo*, a condition necessary for the accumulation of the additional genetic changes that mediate malignant progression in a virally infected cell. Targeted integration of the HHV-6 genome into the chromosomal DNA of the host cell may represent one important mechanism by which HHV-6 is capable of remaining in the latent state, but this type of latency seems rather infrequent since it has only been described in the PBMCs of a few patients with lymphoproliferative and immune disorders. Thus more information on HHV-6 latency/persistence and on viral interaction with

infected cells *in vivo* is needed to ascertain the role of this herpesvirus in the etiopathogenesis of human lymphoid neoplasias.

HHV-7

HHV-7, like HHV-6, is a member of the β subgroup of herpesviruses. The first two viral isolates of HHV-7 were obtained from the peripheral blood of a healthy individual[72] and of a patient with the so-called chronic fatigue syndrome.[73] Subsequently, HHV-7 was isolated from saliva in a high proportion of healthy adults,[74] suggesting that it can replicate *in vivo*, at least in selected sites, without clinically appreciable consequences. HHV-7 has a selective tropism for $CD4^+$ T lymphocytes, and the glycoprotein CD4 is an essential component of the cellular membrane receptor for HHV-7.[75] In fact, marked reciprocal interference between HHV-7 and HIV, which also uses CD4 as a receptor, has been observed in *in vitro* experiments.[75] Furthermore, it appears that HHV-7 reactivates latent HHV-6 genomes, an *in vitro* observation which might have clinical relevance. At this time, HHV-7 has not been linked to any human disease. Of interest, HHV-7 has been isolated from the PBMCs of a Japanese child suffering from recurrent fever, hepatosplenomegaly and pancytopenia, an illness clinically indistinguishable from chronic active EBV infection.[76] This finding raises the possibility that HHV-7 might play a role in lymphoid disorders, although further studies are needed to confirm the pathogenic potential of this herpesvirus *in vivo*.

HHV-8

Evidence for the most recent putative human herpesvirus was obtained using molecular techniques. Novel specific DNA sequences were first identified in Kaposi's sarcoma (KS) tissues from patients with AIDS, using the *representational difference analysis* (RDA) technique.[77] The reported sequences of the apparently KS-specific DNA segments showed partial similarity to two capsid protein-coding genes of known γ-herpesviruses, namely EBV and herpesvirus saimiri (HVS).[77] The presence of these sequences argued in favor of the existence of a new human herpesvirus called KS virus (KSHV)[77] or, more recently, HHV-8.[78] These herpesvirus-like sequences could be amplified by PCR in the vast majority of KS biopsies, not only the AIDS-associated[79] but also the endemic[80-82] and classic types,[83,84] suggesting that this putative new human herpesvirus might not be solely an opportunistic infectious agent but possibly an essential agent involved in all the different forms of KS. KS-associated herpesvirus sequences have been found in all the different stages of KS[84,85] and have been unequivocally identified by PCR in situ hybridization both in the endothelial and in the typical KS spindle cells, thought to represent the neoplastic elements in these lesions.[86]

The presence of HHV-8 is not, however, exclusive to KS lesions and evidence has been accumulating to indicate that these putative new herpesvirus sequences are associated with specific lymphoid disorders (Table 2). In fact, HHV-8 sequences have been documented in the vast majority of AIDS-related, body cavity-based B cell NHL cases examined so far in the USA[87] and in Europe.[88] These lymphomas are characterized by pleural, pericardial or peritoneal lymphomatous effusions in the absence of a contiguous tumor mass and probably represent a distinct category of AIDS-related lymphomas because of their unusual clinical, morphological and immunophenotypic features. Rearrangement of the immunoglobulin genes, the presence of a clonal EBV genome, the absence of myc rearrangement and immunophenotypic characteristics associated with the late stages of B cell differentiation are constant features of these lymphomas.[87] Few cases of body cavity-based B cell lymphomas occurring in HIV-negative subjects have been also described with the same characteristics.[89,90] Two cell lines derived from AIDS-related, body cavity-based B cell lymphomas have been established that show viral sequences in episomal structures.[91] The HHV-8 association seems to be almost exclusive for this unusual type of lymphoma, since hundreds of HIV-positive and negative cases of HD and B- and T cell NHL examined so far have invariably been nega-

Table 2. HHV-8 sequences in lymphoproliferative disorders.

Diagnosis	*No. of cases*	*No. of positive cases*	*Ref.*
Non-AIDS			
HD and NHL	382	2	(87,88,89, 92,94,104)
MCD	28	8	(93,94)
AILD	15	3	(92)
Reactive lymphadenopathies	55	5	(92,93)
AIDS			
HD and NHL	99	15	(87,88, 92,94,95)
MCD	20	19	(93,94,95)
PGL	31	8	(77,92,93,94)

HD: Hodgkin's disease; NHL: non Hodgkin's lymphoma; MCD: multicentric Castleman's disease; AILD: angioimmunoblastic lymphadenopathy; PGL: persistent generalized lymphadenopathy.

tive.[87,88,92] This finding apparently suggests a selective lymphomagenetic role for HHV-8 *in vivo*.

HHV-8 sequences have also been identified in pathologic lymph node tissues from a significant number of cases of HIV-positive and negative multicentric Castleman's disease (MCD),[93-95] which is an atypical lymphoproliferation with a known increased risk of developing KS,[96] but the pathogenetic role, if any, of the virus in this particular disease is merely speculative.[93] MCD lymph nodes may be asymptomatically infected by HHV-8, which would then be only a passenger in this lesion.[93] Alternatively, the cellular proliferation seen in MCD may be related to this herpesvirus acting as a cofactor, perhaps as a stimulus for cytokines, in a context of immune dysregulation.[93]

Furthermore, three patients with another atypical lymphoproliferation, namely AILD, were shown to harbor HHV-8 sequences in pathologic tissues, but again a pathogenetic link with the virus can only be hypothesized.[92] Excessive immunity is a typical feature of AILD, and much speculation has centered around the possibility that a viral infection could directly or indirectly trigger this disorder. In particular, human herpesviruses like EBV and HHV-6 have already been found to be associated with AILD, so it is not totally unexpected that this new putative herpesvirus, which belongs to the family of lymphotropic γ-herpesviruses, should be found in at least some cases of AILD.[92] On the other hand, the disease etiologically related to the presence of HHV-8 sequences, i.e. KS, is itself characterized by chronic immune activation and release of inflammatory cytokines, so that common immune dysfunctions underlying both disorders could be hypothesized.[92] Furthermore, at least 9 well-documented cases of KS have been reported in patients with AILD,[97] and vascular hyperplasia is characteristically observed in both pathologic lesions.

Of interest, HHV-8 sequences were identified in 4 out of 5 cases of HIV-negative reactive lymphadenopathies, all showing the same histologic features characterized by florid germinal center hyperplasia associated with varying degrees of condensation and regression of germinal centers in the presence of increased vascularity and monocytoid B cell hyperplasia.[92] Examination of the clinical records of the 4 HIV-negative patients with HHV-8-positive lymphadenopathies revealed that in all cases lymph node enlargement was localized and not accompanied by hepatosplenomegaly. Fever and constitutional symptoms were absent, and no laboratory abnormalities indicative of viral or other infections were documented. Marked thrombocytopenia was also present in two of them at the time of lymph node enlargement.[92] The histologic features of the florid germinal center hyperplasia recognized in the 4 HHV-8-positive, HIV-negative benign lymphadenopathies can be observed in a number of other clinical conditions like autoimmune disorders (especially rheumatoid arthritis and Sjögren's syndrome), MCD and HIV infection.[98] In fact, some cases of persistent generalized lymphadenopathy have also been found to harbor these viral sequences.[77] In addition, vascular hyperplasia is a common feature of all the HHV-8-positive lesions identified so far, including KS, MCD, AILD and the above described lymphadenopathies. In other words, the histologic features recognized in these HHV-8-positive cases of reactive lymphadenopathies represent a defined pattern of lymph node response, possibly induced by a wide range of antigenic stimuli,

and HHV-8 should now be considered in the differential diagnosis of the possible causes for this response. This peculiar histologic pattern of lymphoid response induced by HHV-8 is likely to reflect the original pathogenic potential of this herpesvirus in HIV-negative subjects.[92] Therefore these lymphadenopathy cases may represent the possible clinicopathologic condition, benign in nature, which might develop during primary HHV-8 infection in normal subjects, just as infectious mononucleosis represents the most common clinical manifestation of EBV infection in the general population. The possibility still remains that HHV-8 may exhibit indirect transforming ability in conjunction with other factors, like EBV, as has been proposed for the subgroup of body cavity-based lymphomas.[87] However, three of the four HHV-8-positive lymphadenopathies also harbored EBV sequences, suggesting that the presence of EBV together with HHV-8 is not necessarily associated with the full neoplastic phenotype.[92]

Like other herpesviruses, HHV-8 could be a benign agent responsible for the reactive lymphadenopathies described above, or it could be associated with malignant conditions like KS or body cavity-based lymphomas. At present, it is not known whether HHV-8 is an oncogenic virus or if it simply infects a subset of B lymphocytes which tend to proliferate in response to a developing cancer.[78] Alternatively, analogously to EBV, this virus might play a role in promoting malignancy by enhancing the proliferation of infected B cells and thus the rate of spontaneous or induced mutational events.[78] Finally, there is even the possibility that HHV-8-infected B cells are capable of producing cytokines that may in turn stimulate the growth of other B cell populations, leading to a malignant proliferation.[78,99] Isolation of this herpesvirus and study of its possible oncogenic properties *in vitro*, together with an analysis of the cytokine profiles released by HHV-8-infected cells, will give insights into the effective role of HHV-8 in human lymphomagenesis.[78]

HHV-8 is a widespread virus but, like EBV, it is probably undetectable in many individuals.[78] HHV-8 might be harbored in latently infected cells/tissues, such as circulating B cells,[100] tonsils[84] or semen,[101] and be sometimes reactivated by AIDS-related and/or therapeutic immunosuppression. In fact, these viral sequences have been found in various proliferative non KS skin lesions in immunocompromized organ transplant patients,[102] as well as in the PBMCs of a patient who developed KS after allogenic bone marrow transplantation.[103] A case of HHV-8-associated primary cerebral B cell lymphoma was recently described in an HIV-negative patient treated for years with prednisone because of an idiopathic uveitis.[104] It is conceivable that this particular clinical situation, characterized by prolonged steroid therapy, combined with subtle immunological defects associated with the uveitis might have contributed to the reactivation of HHV-8 in this patient with cerebral lymphoma. It should also be noted that a few cases of EBV-associated B cell lymphomas have already been reported in patients treated with cyclosporine and methotrexate for rheumatoid arthritis and dermatomyositis.[105,106] Analogously to EBV and its proposed role in promoting human lymphomagenesis, it is also possible to speculate on the involvement of HHV-8 in the multistep development of some B cell lymphomas that occur in certain immunosuppressed patients.

HCV

The cloning of HCV was achieved in 1989 in the absence of an observed viral particle from cDNA of infectious chimpanzee plasma,[107] and within one year the entire viral genome was sequenced and many of its structural and functional properties were defined.[108,109] HCV is a small single-stranded, positive-sense RNA virus of about 9,500 bases coding for about 3,000 amino acids, and is now considered a new member of the *Flaviviridae*.[110] HCV has no DNA intermediate and therefore cannot integrate into the host genome, but it does use negative-strand RNA in its replicative cycle in the liver.[110] Sequence analysis of specific regions of the viral genome has allowed classification of HCV variants into six major groups.[111] Distinction of HCV genotypes is important since the outcome of HCV disease and the response to antiviral

therapy with interferon correlates with the HCV type. In fact, genotype 1 (in particular subtype 1b) has been associated with more severe chronic liver disease and poor response to interferon therapy.[112-114] HCV has a high spontaneous mutation rate and as a result it exists as a heterogeneous group of viruses that show about 70% homology overall, similar to that of other flaviviruses.[109] This coexistence of multiple mutants has been termed *quasi-species* and it provides a very efficient and rapid mechanism for the virus to elude the immune response and persist in the host. HCV infection persists in about 80% of cases.[115] During persistent HCV infection anti-HCV antibodies with different specificities can be detected, but these antibodies do not lead to clearance of, or immunity to, the virus. The main route of transmission is parenteral.[116] Recent data showed an unexpectedly frequent patient-to-patient transmission of HCV in a hematology ward despite strict hygienic control, raising concern about spread through previously unsuspected contaminated sources.[117] HCV has been identified as the causative agent of different chronic liver diseases, including post-transfusion and sporadic non-A, non-B hepatitis,[118] as well as autoimmune chronic hepatitis.[119,120] Chronic infection with HCV is considered a risk factor for hepatocellular cancer, mostly in patients with liver cirrhosis, although very recently it has been suggested that HCV infection, mostly genotype 1b, is directly associated with the development of hepatocellular cancer without the intermediate step of cirrhosis.[121]

It should be noted that HCV is not only hepatotropic but it is also a lymphotropic virus able to replicate *in vitro* in a human T cell line.[122] Furthermore, viral genomic sequences have been found in both peripheral T and B cell populations as well as in the monocyte-macrophage fraction of HCV-related chronic hepatitis.[123] Recently, HCV infection has been documented in the vast majority of patients with essential mixed cryoglobulinemia (MC) type two[124,125] (Table 3). This is a benign lymphoproliferative disorder characterized by the presence of temperature sensitive protein complexes formed by polyclonal IgG and monoclonal IgM rheumatoid factors. Clonal expansion of IgMk-bearing B cells in peripheral blood, lymphoid aggregates in bone marrow biopsies and lymphocytic infiltration of liver, spleen or kidneys have been reported in MC patients, confirming the lymphoproliferative nature of the disease, which, however, evolves into a frank B cell NHL only in a minority of cases and generally after a long follow-up.[126] Anti-HCV antibodies were first documented in 42% of 19 patients with type II cryoglobulinemia and HCV RNA was detected in 84%, while controls with type I cryoglobulinemia proved to be negative for these markers.[127] Furthermore, anti-HCV antibodies and HCV RNA were found to be concentrated 10- and 1,000 fold, respectively, in the isolated cryoprecipitate.[127] The striking association of HCV infection with MC was also supported by a subsequent study documenting the presence of anti-HCV antibodies in 100% of 16 patients with type II (IgMk) MC studied by ELISA and confirmed by RIBA.[128] Moreover, HCV RNA was

Table 3. HCV infection in lymphoproliferative diseases.

	References	*Anti-HCV antibodies (% positive cases) by ELISA and RIBA*	*HCV RNA sequences (% positive cases) by RT-PCR*
EMC	Agnello et al. (127)	42	84
	Ferri et al. (128)	100	81
	Pozzato et al. (129)	84	96
	Luppi et al. (139)	84	n.d.
B-NHL in EMC			
	Ferri et al. (130)	100	100
B-NHL	Ferri et al. (137)	30	32
	Luppi et al. (139)	42	30
	Cavanna et al. (138)	25	n.d.
B-CLL	Cavanna et al. (138)	5	n.d.
	Luppi et al. (139)	n.d.	0
PCD	Luppi et al. (139)	12	n.d.
	Cavanna et al. (138)	16	n.d.
HD	Ferri et al. (137)	4	0
	Cavanna et al. (138)	10	n.d.
	Luppi et al. (139)	1	8

EMC: essential mixed cryoglobulinemia; B-NHL: B cell non Hodgkin's lymphoma; B-CLL: B-cell chronic lymphocytic leukemia; PCD: plasma cell dyscrasia; HD: Hodgkin's disease; n.d.: not done.

documented in the sera of 50% of the same patients by RT-PCR, and its frequency markedly increased to 81% when genomic sequences were detected in peripheral lymphocytes, suggesting that these cells could represent the viral reservoir of HCV infection.[128] On the other hand, the fact that HCV infection has been found in several MC cases in the absence of any clinical, biochemical or pathological evidence of liver damage indicates that in these cases MC cannot be considered as a mere extrahepatic manifestation of HCV-related chronic hepatitis. HCV genotyping has also demonstrated the occurrence of multiple genotypes and coinfections with different variants in MC patients.[129] Of interest, both serological and molecular markers of HCV infection have also been documented in 100% of 10 patients with B cell NHL complicating MC[130] (Table 3). Although various independent studies have now unequivocally confirmed the close relationship between HCV infection and MC, and although it appears that immune complexes involving HCV are intimately involved in cryoprecipitate formation, the pathogenetic pathways of this interaction are still unknown. Nonetheless, it has been proposed that the antigenic stimulus represented by HCV may induce complex cellular and humoral autoreactivity through different mechanisms, such as molecular mimicry or altered auto-antigens. As a consequence, the persistence of HCV in the immune system could greatly expand clones of Ig (cryoglobulin)-secreting lymphocytes by a direct or indirect mechanism, and a mutational event could eventually lead to activation of oncogenes, resulting in a B cell neoplasia.[124] One patient with MC and HCV infection was reported to develop a monoclonal multistep lymphoproliferative disorder that was first associated with bcl-2 translocation in the *benign* phase of the disease, and then with a second genetic alteration, the translocation of the myc oncogene, in the accelerated phase of the clinical course of the disease.[131]

It should also be considered that α-interferon (IFN) currently seems to be the drug of choice for treating MC, since it reduces symptoms and cryoglobulin production.[126] IFN shows antiproliferative action as well as antiviral effects, which are useful in HCV-related MC.[132,133] Long-term IFN therapy might be useful for controlling HCV replication and thus for preventing low-grade NHL, which is documented in the bone marrow in a significant percentage of MC cases.[129] Recently, the number of nucleotide mutations in the nonstructural protein NS5A was reported to correlate with the response to IFN in patients with chronic HCV 1b infection.[134] The possible clinical relevance of this phenomenon in the treatment of HCV-related MC has not yet been ascertained.

It was also recently reported that in a population of 500 patients with HCV hepatitis, 14 developed diffuse B cell NHL (8 low, 5 intermediate and 1 high-grade), supporting the notion that B cell NHL can be a harmful complication of chronic hepatitis type C able to change the prognosis of the disease.[135] The finding of serologic and molecular markers of HCV infection in a small series of patients with Waldenström's macroglobulinemia (WM), a rare B lymphocytic neoplasia characterized by monoclonal production of IgM, also argues in favor of a possible role for this viral infection not only in benign but also in neoplastic IgM gammopathies.[136] Antibodies against HCV and HCV genomic sequences have been documented in the sera of over one third of a series of unselected Italian B cell NHL cases not associated with MC, thus suggesting the involvement of this virus in a wider spectrum of B cell clonal lymphoproliferations.[137] This unexpectedly high prevalence of anti-HCV antibodies in Italian patients with B cell NHL not associated with MC (ranging from 25% to 42% in different studies) was independently confirmed[138,139] (Table 3), and is particularly significant when compared with the prevalence of HCV seropositivity in the healthy Italian population (1-3%).[138,140] Moreover, the prevalence of anti-HCV antibodies is invariably low in the group of patients affected with monoclonal gammopathies without cryoglobulinemic activity, namely multiple myeloma (MM), WM and monoclonal gammopathy of undetermined significance (MGUS),[139] as well as in the group of patients with chronic lymphocytic leukemia (CLL)[138] (Table 3). This suggests that the activation of an immune response against

HCV infection is not a general phenomenon in all B cell lymphoproliferative disorders, but is likely to be restricted to certain histologic subtypes. Furthermore, HCV-specific genomic sequences have been identified by RT-PCR directly in pathologic lymph node tissues from 13 out of 34 B cell NHL cases, and in particular in 6 out of 8 low-grade MALT type lymphomas and in five out of eight centroblastic-centrocytic follicular lymphomas.[139] This finding is unexpected and in contrast with the absence of viral RNA in T cell NHL samples and the majority of HD cases analyzed by RT-PCR in the same study. More importantly, neither peripheral blood samples nor pathologic lymph nodes from 14 patients with B-CLL/small lymphocytic lymphoma harbored HCV sequences.[139] Such marked differences in the prevalence of HCV RNA in neoplastic tissues between some B cell NHL (MALT and centroblastic-centrocytic follicular types) and other B neoplastic proliferations like CLL, or T cell NHL or HD clearly suggest that events like exposure to blood products or prolonged hospitalization are unlikely to account for the higher prevalence of this viral infection in certain types of B-NHL. Similarly, the immune impairment common to all these patients and in particular to CLL patients does not seem to be responsible for the observed differences in the distribution of HCV sequences among various subsets of neoplastic lymphoproliferations.[139] An association between HCV infection and low-grade MALT type lymphoma has also been suggested by the detection of anti-HCV antibodies by ELISA and RIBA, as well as of HCV sequences by RT-PCR in the sera of 8 out of 16 patients with MALT lymphoma (Luppi *et al.* submitted). Several chronic inflammatory conditions, most of which have shown an autoimmune component, including *Helicobacter pylori (HP)*-induced chronic gastritis, Sjögren's syndrome and Hashimoto's thyroiditis, result in the acquisition of MALT-like lymphoid tissue and have been identified as precursors in the development of MALT lymphoma. The possibility now arises that HCV is a potential infectious cofactor, along with HP, in the multistep transformation of low-grade MALT type lymphoma.

In conclusion, the detection of both serologic and molecular markers of HCV infection in a relevant percentage of B cell NHL not associated with cryoglobulinemia extends the spectrum of lymphoproliferative diseases associated with HCV infection and adds further evidence to the strengthening hypothesis of at least an indirect influence of this viral infection on the neoplastic transformation of some B lymphoid subsets. On the other hand, further evidence for the ability of HCV to directly infect and possibly deregulate specific populations of B lymphocytes is provided by the recent demonstration of clonal expansions of IgM-producing B cells, not only in all patients with MC type II but also in about one third of HCV-infected patients without cryoglobulinemia.[141] The increased serum levels of rheumatoid factor in all patients with a clonal expansion suggest that the expanded B cell clones belong to the rheumatoid factor-producing B cell subset. It is widely accepted that HCV RNA sequences cannot be integrated in the host genome, so that a direct transforming role for the virus in the lymphoproliferative process is unlikely,[109] although at least one nonstructural protein, NS3, has been shown to have oncogenic activity *in vitro*.[142] Thus, the pathogenetic role of HCV might be represented by the indirect effects of chronic infection of lymphocytes, possibly representing the viral reservoir. One may hypothesize that the virus, alone or in combination with other factors, i.e. genetic, infectious and/or environmental, may produce (among variable host responses) a proliferative response of lymphoid elements to HCV antigens. On the other hand, HCV may contribute to lymphomagenesis through alternative mechanisms by taking advantage of its tropism for salivary epithelial cells *in vivo*. In fact, the localization of HCV within a parotid NHL lesion in the course of MC was recently described, and the residual parotid epithelial cells were identified as the site of viral infection and replication in the NHL lesion.[143] Furthermore, these cells may abnormally express HLA class II antigens under inflammatory conditions, and then act as true antigen-presenting cells.[143,144] In this lymphoma case, HCV may have exerted its effect as an exogenous stimulus able to sustain B cell lym-

phoproliferation in either a T cell-independent or -dependent process.[143] Functional studies are needed to gain insights into the possible pathogenetic role of HCV in specific lymphoid neoplasias that is now suggested prevalently on the basis of epidemiologic studies.

Conclusions

The recent increase in knowledge about virally-associated lymphoproliferative diseases will offer many advantages both for the use of molecular techniques in diagnostics and for the development of therapeutic strategies. For example, PCR for EBV DNA in cerebrospinal fluid from patients with AIDS is proposed to be a sensitive and specific diagnostic tumor marker for the presence of an AIDS-related primary lymphoma of the central nervous system.[145] Viral oncoproteins able to associate with cell-encoded proteins may be exploited as a target for synthetic molecules which can inhibit these complexes, with possible therapeutic potential.[70,146] Similarly, the specific expression of virally-encoded proteins in tumors may be exploited for cancer cell-specific gene therapy.[70] Knowledge about the biology of EBV-induced lymphomas has led to the cure of devastating immunoblastic lymphomas occurring in recipients of allogeneic T-cell depleted bone marrow by the simple infusion of mononuclear cells from the EBV-seropositive marrow donor, which supply EBV-specific precursor cytotoxic T lymphocytes able to recognize EBV-infected lymphoma cells.[147-149] The ability of HHV-6 to integrate into chromosomal DNA at a targeted site *in vivo*[41,42] might be exploited for the development of new viral vectors for gene therapy, analogously to adeno-associated virus (AAV), which is the only other known DNA virus with the ability to integrate into a targeted site (19q13)[150,151] and to be used as a vector for delivering genes into human hemopoietic cells.[152-154] The demonstration of an antagonistic effect between HHV-7 and HIV could be exploited to develop new effective therapeutic approaches to AIDS.[75] The association of particular subsets of NHL with HCV infection is an important new acquisition that should be carefully considered in clinical follow-up because of the possible effects of chemotherapy on the course of the HCV infection, as was recently emphasized by the occurrence of fuminant hepatitis upon withdrawal of chemotherapy in two carriers of HCV infection also affected with lymphoma.[155]

Furthermore, the use of IFN may also represent a promising therapeutic option in patients with HCV-associated lymphomas without cryoglobulinemia. Since it has been reported that the presence of HHV-8 sequences in the circulating PBMCs of HIV-infected individuals might reflect a propensity for developing KS,[156] it is possible that the presence of circulating HHV-8 sequences might also predict the development of B cell lymphomas,[78] or at least represent a new indicator of immune dysregulation and propensity for developing proliferations. The role that HIV plays in the pathogenesis of B-cell lymphomas in HIV-infected individuals has always been thought to be indirect, as a result of the effect of HIV on immunoregulation.[70] However, the recent identification of a common clonal HIV integration site, upstream from the *c-fes/fps* proto-oncogene, in a few AIDS-associated T cell and mixed immunophenotype lymphomas suggested that HIV may contribute directly to lymphomagenesis.[157] The possible interaction between HHV-8 and HIV in the setting of AIDS-related lymphomagenesis might be an important field of interest.

The years ahead will tell us whether the vast amount of basic research on the biology of these new lymphotropic viruses, namely HHV-6, HHV-7, HHV-8 and HCV, may have an impact on the clinical management of their associated diseases.

Note added in proof

During revision of the manuscipt, Renne and colleagues reported the development of a system for the lytic growth of a latently HHV-8 infected B cell line and presented the first ultrastructural visualization of the virus.[158]

References

1. Burkitt D. A sarcoma involving the jaws in African children. Br J Surg 1958; 46:218-33.

2. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet 1964; 1:702-3.
3. Zur Hausen H, Schulte-Holthausen H, Klein E, et al. EBV DNA in biopsies of Burkitt tumours and anaplastic carcinomas of the nasopharynx. Nature 1970; 228:1056-8.
4. Weiss LM, Movahed LA, Warnke RA, et al. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. N Engl J Med 1989; 320:502-6.
5. Herbst H, Dallenbach F, Hummel M, et al. Epstein-Barr virus latent membrane expression in Hodgkin and Reed-Sternberg cells. Proc Natl Acad Sci USA 1991; 88:4766-70.
6. Klein G. Epstein-Barr virus-carrying cells in Hodgkin's disease. Blood 1992; 80:299-301.
7. Knecht H, Sahli R, Shaw P, et al. Detection of Epstein-Barr virus DNA by polymerase chain reaction in lymph node biopsies from patients with angioimmunoblastic lymphadenopathy. Br J Haematol 1990; 75:610-4.
8. Weiss L, Jaffe E, Liu X, et al. Detection and localization of Epstein-Barr viral genomes in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. Blood 1992; 79: 1789-95.
9. Peiper S. Angiocentric lymphoproliferative disorders of the respiratory system: incrimination of Epstein-barr virus in pathogenesis. Blood 1993: 82: 687-90.
10. Harabuchi Y, Yamanaka N, Kataura A, et al. Epstein-Barr virus in nasal T-cell lymphoma in patients with lethal midline granuloma. Lancet 1990; 335:128-30.
11. de Bruin PC, Jiwa M, Oudejans JJ, et al. Presence of Epstein-Barr virus in extranodal T cell lymphomas: differences in relation to site. Blood 1994; 83:1612-8.
12. Kawa-Ha K, Ishihara S, Ninomiya T, et al. CD3-negative lymphoproliferative disease of granular lymphocytes containing Epstein-Barr viral DNA. J Clin Invest 1989; 84:51-5.
13. Grierson H, Purtilo DT. Epstein-Barr virus infection in males with the X-linked lymphoproliferative syndrome. Ann Intern Med 1987; 106:538-45.
14. Mac Mahon EM, Glass JD, Hayward SD, et al. Epstein-Barr virus in AIDS-related primary central nervous system lymphoma. Lancet 1991; 338:969-73.
15. Shibata D, Weiss LM, Hernandez AM, et al. Epstein-Barr virus-associated non-Hodgkin's lymphoma in patients infected with the human immunodeficiency virus. Blood 1993; 91: 2101-9.
16. Riddler SA, Breinig MC, McKnight JL. Increased levels of circulating Epstein-Barr virus (EBV)-infected lymphocytes and decreased EBV nuclear antigen antibody responses are associated with the development of posttransplant lymphoproliferative disease in solid-organ transplant recipients. Blood 1994; 84:972-84.
17. Poiesz BJ, Ruscetti FW, Gazdar AF, et al. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T cell lymphoma. Proc Natl Acad Sci USA 1980; 77:7415-9.
18. Yoshida M, Seiki M, Yamaguchi K, et al. Monoclonal integration of human T-cell leukemia provirus in all primary tumors of adult T cell leukemia suggests causative role of human T-cell leukemia virus in the disease. Proc Natl Acad Sci USA 1984; 81:2534-7.
19. Hall WW. Human T cell lymphotropic virus type I and cutaneous T cell leukemia/lymphoma. J Exp Med 1994; 180: 1581-5.
20. Manca N, Piacentini E, Gelmi M, et al. Persistence of human T cell lymphotropic virus type 1 (HTLV-1) sequences in peripheral blood mononuclear cells from patients with mycosis fungoides. J Exp Med 1994; 180:1973-8.
21. Pancake BA, Zucker-Franklin D, Coutavas EE. The cutaneous T cell lymphoma, mycosis fungoides, is a human T cell lymphotropic virus-associated disease. J Clin Invest 1995; 95: 547-54.
22. Harris NL, Jaffe ES, Stein H, et al. A Revised European-American Classification of Lymphoid Neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361-92.
23. Salahuddin SZ, Ablashi DV, Markham PD, et al. Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. Science 1986; 234:596-600.
24. Josephs SF, Salahuddin SZ, Ablashi DV, et al. Genomic analysis of the human B-lymphotropic virus (HBLV). Science 1986; 234:601-3.
25. Ablashi D, Agut H, Berneman Z, et al. Human herpesvirus-6 strain groups: a nomenclature. Arch Virol 1993; 129:363-6.
26. Lusso P, Markham PD, Tschachler E, et al. In vitro cellular tropism of human B-lymphotropic virus (human herpesvirus 6). J Exp Med 1988; 167:1659-70.
27. Lusso P, Malnati MS, Garzino-Demo, et al. Infection of natural killer cells by human herpesvirus-6. Nature 1993; 337: 370-3.
28. Pellett PE, Black JB, Yamamoto M. Human herpesvirus 6: the virus and the search for its role as a human pathogen. Adv Virus Res 1992; 41:1-52.
29. Okuno T, Takahashi K, Balachandran K, et al. Seroepidemiology of human herpesvirus 6 infection in normal children and adults. J Clin Microbiol 1989; 27:651-3.
30. Yamanishi K, Okuno T, Shiraki T, et al. Identification of human herpesvirus-6 as a causal agent for exanthem subitum. Lancet 1988; i:1065-7.
31. Pruksananonda P, Breese-Hall C, Insel RA, et al. Primary human herpesvirus 6 infection in young children. N Engl J Med 1992; 326:1445-50.
32. Irving WL, Cunnigham AL. Serological diagnosis of infection with human herpesvirus type 6. Br Med J 1990; 300:156-9.
33. Steeper TA, Horwitz CA, Ablashi DV, et al. The spectrum of clinical and laboratory findings resulting from human herpesvirus 6 (HHV-6) in patients with mononucleosis-like illness not resulting from Epstein-Barr virus or cytomegalovirus. Am J Clin Pathol 1990; 93:776-83.
34. Gopal MR, Thomson BJ, Fox J, et al. Detection by PCR of HHV-6 and EBV DNA in blood and in oropharynx of healthy adults and HIV seropositives. Lancet 1990; 335:1598-9.
35. Jarrett RF, Clark DA, Josephs SF, et al. Detection of human herpesvirus-6 DNA in peripheral blood and saliva. J Med Virol 1990; 32:73-6.
36. Luppi M, Barozzi P, Marasca R, et al. Human herpesvirus-6 (HHV-6) in blood donors. Br J Haematol 1995; 89:943-5.
37. Fox JD, Briggs M, Ward PA, et al. Human herpesvirus 6 in salivary glands. Lancet 1990; 336:590-3.
38. Luppi M, Barozzi P, Maiorana A, et al. Human herpesvirus 6 infection in normal human brain tissue. J Infect Dis 1994; 169: 943-4.
39. Luppi M, Barozzi P, Maiorana A, et al. Human herpesvirus-6: a survey of presence and distribution of genomic sequences in normal brain and neuroglial tumors. J Med Virol 1995; 47: 105-11.
40. Challoner PB, Smith KT, Parker JD, et al. Plaque-associated expression of human herpesvirus 6 in multiple scerosis. Proc Natl Acad Sci USA 1995; 92: 7440-4.
41. Luppi M, Marasca R, Barozzi P, et al. Three cases of human herpesvirus-6 latent infection: integration of viral genome in peripheral blood mononuclear cell DNA. J Med Virol 1993; 40:44-52.
42. Torelli G, Barozzi P, Marasca R, et al. Targeted integration of human herpesvirus 6 in the p arm of chromosome 17 of human peripheral blood mononuclear cells in vivo. J Med Virol 1995; 46:178-88.

43. Fioretos T, Heisterkamp N, Groffen J, et al. CRK proto-oncogene maps to human chromosome band 17p13. Oncogene 1993; 8: 2853-5.
44. Razzaque A. Oncogenic potential of human herpesvirus-6 DNA. Oncogene 1990; 5: 1365-70.
45. Razzaque A, Williams O, Wang J, et al. Neoplastic transformation of immortalized human epidermal keratinocytes by two HHV-6 DNA clones. Virology 1993; 195:113-20.
46. Thompson J, Choudhury S, Kashanchi F, et al. A transforming fragment within the direct repeat region of human herpesvirus type 6 that transactivates HIV-1. Oncogene 1994; 9 167-75.
47. Thomson BJ, Efsathiou S, Honess RW. Acquisition of the human adeno-associated virus type-2 rep gene by human herpesvirus type-6. Nature 1991; 351:78-80.
48. Araujo JC, Doniger J, Kashanchi F, et al. Human herpesvirus 6A ts suppresses both transformation by H-ras and transcription by the H-ras and human immunodeficiency virus type 1 promoters. J Virol 1995; 69: 4933-40.
49. Clark DA, Alexander FE, McKinney PA, et al. The seroepidemiology of human herpesvirus-6 (HHV-6) from a case-control study of leukaemia and lymphoma. Int J Cancer 1990; 45: 829-33.
50. Torelli G, Marasca R, Luppi M, et al. Human herpesvirus-6 in human lymphomas: identification of specific sequences in Hodgkin's lymphomas by polymerase chain reaction. Blood 1991; 77:2251-8.
51. Levine PH, Ebbesen P, Ablashi DV, et al. Antibodies to human herpes virus-6 and clinical course in patients with Hodgkin's disease. Int J Cancer 1992; 51: 53-7.
52. Torelli G, Marasca R, Montorsi M, et al. Human herpesvirus 6 in non-AIDS related Hodgkin's and non Hodgkin's lymphomas. Leukemia 1992; 6:46S-8S.
53. Di Luca D, Dolcetti R, Mirandola P, et al. Human herpesvirus 6: a survey of presence and variant distribution in normal peripheral lymphocytes and lymphoproliferative disorders. J Infect Dis 1994; 170:211-5.
54. Luppi M, Barozzi P, Marasca R, et al. Integration of human herpesvirus-6 genome in chromosome 17 in two lymphoma patients. Leukemia 1994; 8:41S-5S.
55. Luppi M, Barozzi P, Marasca R, et al. Characterization of human herpesvirus-6 genomes from cases of latent infection in human lymphomas and immune disorders. J Infect Dis 1993; 168:1074-5.
56. Trovato R, Luppi M, Vago L, et al. Frequency of human herpesvirus type 6 (HHV-6) genome detection in AIDS-related lymphoproliferative disorders. J Acq Immune Def Synd 1995; 9:311-2.
57. Josephs SF, Buchbinder A, Streicher HZ, et al. Detection of human B-lymphotropic virus (human herpesvirus 6) sequences in B cell lymphoma tissues of three patients. Leukemia 1988; 2:132-5.
58. Jarrett RF, Glehill S, Qureshi F, et al. Identification of human herpesvirus 6-specific DNA sequences in two patients with non-Hodgkin's lymphoma. Leukemia 1988; 2:496-502.
59. Luppi M, Marasca R, Barozzi P, et al. Frequent detection of human herpesvirus-6 sequences by polymerase chain reaction in paraffin-embedded lymph nodes from patients with angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. Leu Res 1993; 17:1003-11.
60. Flamand l, Stefanescu I, Ablashi DV, et al. Activation of the Epstein-Barr virus replicative cycle by human herpesvirus 6. J Virol 1993; 67:6768-77.
61. Flamand L, Gosselin J, D'Addario M, et al. Human herpesvirus 6 induces interleukin-1 and tumor necrosis factor alpha, but not interleukin-6 in peripheral blood mononuclear cell cultures. J Virol 1991; 65: 5105-10.
62. Flamand L, Gosselin J, Stefanescu I, Ablashi D, Menezes J. Immunosuppressive effect of human herpesvirus 6 on T-cell functions: suppression of interleukin-2 synthesis and cell proliferation. Blood 1995; 85:1263-71.
63. Braun DK, Pellett PE, Hanson CA. Presence and expression of human herpesvirus 6 in peripheral blood mononuclear cells of S100-positive, T-cell chronic lymphoproliferative disease. J Infect Dis 1995; 171:1351-5.
64. Tagawa S, Mizuki M, Onoi U, et al. Transformation of large granular lymphocytic leukemia during the course of a reactivated human herpesvirus-6 infection. Leukemia 1992; 6:465-9.
65. Levine PH, Jahan N, Murari P, et al. Detection of human herpesvirus 6 in tissues involved by sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). J Infect Dis 1992; 166:291-5.
66. Ablashi DV, Josephs SF, Buchbinder A, et al. Human B lymphotropic virus (human herpesvirus-6). J Virol Meth 1988; 21: 29-48.
67. Levine PH, Ablashi DV, Saxinger WC, et al. Antibodies to human herpesvirus-6 in patients with acute lymphocytic leukemia. Leukemia 1992; 6: 1229-31.
68. Luka J, Pirruccello SJ, Kersey JH. HHV-6 genome in T-cell acute lymphoblastic leukaemia. Lancet 1991; 338:1277-8.
69. Barozzi P, Luppi M, Marasca R, et al. Human herpesvirus-6 (HHV-6) genome in acute lymphoblastic leukemia: evidence against an etiologic role. Acta Haematol 1995; 94:169-72.
70. Morris JDH, Eddleston ALWF, Crook T. Viral infection and cancer. Lancet 1995; 346:754-8.
71. Marx JL. How DNA viruses may cause cancer. Science 1989; 243:1012-3.
72. Frenkel N, Schirmer EC, Katsafanas G, et al. Isolation of a new herpesvirus from human CD4+ T cells. Proc Natl Acad Sci USA 1990; 87:748-52.
73. Berneman Z, Gallo RC, Ablashi DV, et al. Human herpesvirus 7 (HHV-7) strain JI: independent confirmation of HHV-7. J Infect Dis 1992; 166:690-1.
74. Wyatt LS, Frenkel N. Human herpesvirus 7 is a constitutive inhabitant of adult human saliva. J Virol 1992; 66:3206-9.
75. Lusso P, Secchiero P, Crowley RW, et al. CD4 is a critical component of the receptor for human herpesvirus 7: inteference with human immunodeficiency virus. Proc Natl Acad Sci USA 1994; 91:3872-6.
76. Kawa-Ha K, Tanaka K, Inoue M, et al. Isolation of human herpesvirus 7 from a child with symptoms mimicking chronic Epstein-Barr virus infection. Br J Haematol 1993; 84:545-8.
77. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994; 266:1865-9.
78. Levy JA, A new human herpesvirus: KSHV or HHV-8? Lancet 1995; 346:786.
79. Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and those without HIV infection. N Engl J Med 1995; 332:1181-5.
80. Huang YQ, Li JJ, Kaplan MH, et al. Human herpesvirus-like nucleic acid in various forms of Kaposi's sarcoma. Lancet 1995; 345:759-61.
81. Schalling M, Ekman M, Kaaya EE, et al. A role for a new herpesvirus (KSHV) in different forms of Kaposi's sarcoma. Nature Medicine 1995; 1:707-8.
82. Chang Y, Ziegler J, Wabinga H, et al. Kaposi's sarcoma-associated herpesvirus and Kaposi's sarcoma in Africa. Arch Intern Med 1996; 156:202-4.
83. Boshoff C, Whitby D, Hatziioannou T, et al. Kaposi's sarcoma-associated herpesvirus in HIV-negative Kaposi's sarcoma. Lancet 1995; 345:1043-4.
84. Luppi M, Barozzi P, Maiorana A, et al. Frequency and distribution of herpesvirus-like DNA sequences (KSHV) in differ-

ent stages of classic Kaposi's sarcoma and in normal tissues from Italian population. Int J Cancer 1996; in press.
85. Noel JC. Kaposi's sarcoma and KSHV. Lancet 1995; 346: 1359.
86. Boshoff C, Schulz TF, Kennedy MM, et al. Kaposi's sarcoma-associated herpesvirus infects endothelial and spindle cells. Nature Medicine 1995; 1:1274-8.
87. Cesarman E, Chang Y, Moore P, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med 1995; 332: 1186-91.
88. Pastore C, Gloghini A, Volpe G, et al. Distribution of Kaposi's sarcoma herpesvirus sequences among lymphoid malignancies in Italy and Spain. Br J Haematol 1995; 91:918-20.
89. Nador RG, Cesarman E, Knowles DM, et al. Herpes-like DNA sequences in a body-cavity-based lymphoma in an HIV-negative patient.(letter). N Engl J Med 1995; 333:943.
90. Cesarman E, Nador R, Knowles DM (reply). Body-cavity-based lymphoma in an HIV-seronegative patient without Kaposi's sarcoma-associated herpesvirus-like DNA sequences. N Engl J Med 1996; 334:272-3.
91. Cesarman E, Moore PS, Rao PH, et al. In vitro establishment and characterization of two acquired immunodeficiency syndrome-related lymphoma cell lines (BC-1 and BC-2) containing Kaposi's sarcoma-associated herpesvirus-like (KSHV) DNA sequences. Blood 1995; 86:2708-14.
92. Luppi M, Barozzi P, Maiorana A, et al. Human herpesvirus-8 (HHV-8) DNA sequences in HIV negative angioimmunoblastic lymphadenopathy and benign lymphadenopathy with giant germinal center hyperplasia and increased vascularity. Blood 1996; 87:3903-9.
93. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 1995; 86:1276-80.
94. Gessain A, Sudaka A, Brière J, et al. Kaposi's sarcoma-associated herpes-like virus (human herpesvirus type 8) DNA sequences in multicentric Castleman's disease: is there any relevant association in non-human immunodeficiency virus-infected patients? Blood 1996; 87:414-6.
95. Karcher DS, Alkan S, Dupin N, et al. Herpes-like DNA sequences, AIDS-related tumors, and Castleman's disease. N Engl J Med 1995; 333: 797-9.
96. Peterson BA, Frizzera G. Multicentric Castleman's disease. Semin Oncol 1993; 20:636-47.
97. Steinberg AD, Seldin MF, Jaffe ES, et al. NIH Conference. Angioimmunoblastic lymphadenopathy with dysproteinemia. Ann Intern Med 1988; 108:575-84.
98. Krishnan J, Danon AD, Frizzera G. Reactive lymphadenopathies and atypical lymphoproliferative disorders. Am J Clin Pathol 1993; 99:385-96.
99. Ford R, Tamayo A, Martin B, et al. Identification of B-cell growth factors (interleukin-14; high molecular weight B-cell growth factors) in effusion fluids from patients with aggressive B-cell lymphomas. Blood 1995; 86:283-93.
100. Ambroziak JA, Blackbourn DJ, Herndier B, et al. Herpesvirus-like sequences in HIV-infected and uninfected Kaposi's sarcoma patients. Science 1995; 268:582-3.
101. Lin J-C, Lin S-C, Mar E-C, et al. Is Kaposi's-sarcoma-associated herpesvirus detectable in semen of HIV-infected homosexual men? Lancet 1995; 346:1601-2.
102. Rady PL, Yen A, Rollefson JL, et al. Herpesvirus-like DNA sequences in non-Kaposi's sarcoma skin lesions of transplant patients. Lancet 1995; 345:1339-40.
103. Gluckman E, Parquet N, Scieux C, et al. KS-associated herpesvirus-like DNA sequences after allogenic bone-marrow transplantation. Lancet 1995; 346:1588-9.
104. Luppi M, Barozzi P, Marasca R, et al.HHV-8-associated primary cerebral B-cell lymphoma in an HIV-negative patient after long-term steroids. Lancet 1996; 347:980.
105. Zijlmans JMJM, van Rijthoven AWAM, Kluin PM, et al. Epstein-Barr virus-associated lymphoma in a patient with rheumatoid arthritis treated with cyclosporine. N Engl J Med 1992; 326:1363.
106. Kamel OW, van de Rijin M, Weiss LM, et al. Reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med 1993; 328:1317-21.
107. Choo Q-L, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244:359-62.
108. van der Poel C, Cuypers HT, Reesnik HW. Hepatitis C virus six years on. Lancet 1994; 344:1475-9.
109. Alter HJ. To C or not to C: these are the questions. Blood 1995; 85:1681-95.
110. Houghton M, Weiner AJ, Han J, et al. Molecular biology of the hepatitis C viruses: implication for diagnosis, development and control of viral disease. Hepatology 1991; 14:382-8.
111. Simmonds P, Alberti A, Alter HJ, et al. A proposed system for the nomenclature of hepatitis C viral genomes. Hepatology 1994; 19:1321-4.
112. Nousbaum J-P, Pol S, Nalpas B, et al. Hepatitis C virus type 1b (II) infection in France and Italy. Ann Intern Med 1995; 122; 161-8.
113. Martin P. Hepatitis C genotypes: the key to pathogenicity?. Ann Intern Med 1995; 122:227-8.
114. Shindo M, Arai K, Sokawa Y, et al. Hepatic hepatitis C virus RNA as a predictor of a long-term response to interferon-therapy. Ann Intern Med 1995; 122:586-91.
115. van der Poel CL, Cuypers HTM, Reesnik HW, et al. Confirmation of hepatitis C virus infection by second generation four-antigen recombinant immunoblot assay and polymerase chain reaction. Lancet 1991; 337:317-9.
116. van der Poel CL, Cuypers HTM, Reesnik HW, et al. Risk factors in HCV infected blood donors. Transfusion 1991; 31:777-9.
117. Allander T, Gruber A, Naghavi M, et al. Frequent patient-to-patient transmission of hepatitis C virus in a hematology ward. Lancet 1995; 345:603-7.
118. Alter HJ, Purcell RH, Shih JW. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med 1989; 321:1494-500.
119. Lenzi M, Johnson PJ, McFarlane IG, et al. Antibodies to hepatitis C virus in autoimmune liver disease: evidence for geographical heterogeneity. Lancet 1991; 338:277-80.
120. Magrin S, Craxi A, Fabiano C, et al. Hepatitis C viral replication in "autoimmune" chronic hepatitis. J Hepatol 1991; 13: 364-7.
121. De Mitri MS, Poussin K, Baccarini P, et al. HCV-associated liver cancer without cirrhosis. Lancet 1995; 345:413-5.
122. Shimizu Y-K, Iwamoto A, Hijikata M, et al. Evidence for in vitro replication of hepatitis C virus genome in a human T-cell line Proc Natl Acad Sci USA 1992; 89:5477-81.
123. Zignego AL, Macchia D, Monti M, et al. Infection of peripheral mononuclear blood cells by hepatitis C virus. J Hepatol 1992; 15:382-6.
124. Ferri C, La Civita L, Longobardo G, et al. Hepatitis C virus and mixed cryoglobulinaemia. Eur J Clin Invest 1993; 23: 399-405.
125. Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. Ann Intern Med 1995; 123:615-20.
126. Miescher PA, Huang Y-P, Izui S. Type II cryoglobulinemia. Semin Hematol 1995; 32:80-5.
127. Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med

1992; 327:1490-5.
128. Ferri C, Monti M, La Civita L, et al. Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia. Blood 1993; 82:3701-4.
129. Pozzato G, Mazzaro C, Crovatto M, et al. Low-grade malignant lymphoma hepatitis C virus infection and mixed cryoglobulinemia. Blood 1994; 84:3047-53.
130. Ferri C, Monti M, La Civita, et al. Hepatitis C virus infection in non-Hodgkin's B cell lymphoma complicating mixed cryoglobulinemia. Eur J Clin Invest 1994; 24:781-4.
131. Ellis M, Rathaus M, Amiel A, et al. Monoclonal lymphocyte proliferation and bcl-2 rearrangement in essential mixed cryoglobulinemia. Eur J Clin Invest 1995; 25:833-7.
132. Casato M, Lagana B, Antonelli G, et al. Long-term results of therapy with interferon-alpha for type II essential mixed cryoglobulinemia. Blood 1991; 78:3142-7.
133. Ferri C, Marzo E, Longobardo G, et al. α-interferon in mixed cryoglobulinemia patients: a randomized crossover controlled trial. Blood 1993; 81:1132-6.
134. Enomoto N, Sakuma I, Asahina Y, et al. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med 1996; 334:77-81.
135. Ferri C, La Civita L, Monti M, et al. Can type C hepatitis infection be complicated by malignant lymphoma? Lancet 1995; 346:1426-7.
136. Santini GF, Crovatto M, Modolo ML, et al. Waldenström macroglobulinemia: a role of HCV infection? Blood 1993; 82: 2932.
137. Ferri C, Caracciolo F, Zignego AL, et al. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Br J Haematol 1994; 88:392-4.
138. Cavanna L, Sbolli G, Tanzi E, et al. High prevalence of antibodies to hepatitis C virus in patients with lymphoproliferative disorders. Haematologica 1995; 80:486-7.
139. Luppi M, Ferrari MG, Bonaccorsi G, et al. Hepatitis C virus infection in subsets of neoplastic lymphoproliferations not associated with cryoglobulinemia. Leukemia 1996; 10:351-5.
140. Bellentani S, Tiribelli C, Saccoccio G, et al. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. Hepatology 1994; 20:1442-9.
141. Franzin F, Efremov DG, Pozzato G, et al. Clonal B-cell expansions in peripheral blood of HCV-infected patients. Br J Haematol 1995; 90:548-52.
142. Sakamuro D, Furukawa T, Takegami T. Hepatitis C virus nonstructural protein NS3 transforms NIH 3T3 cells. J Virol 1995; 69:3893-6.
143. De Vita S, Sansonno D, Dolcetti R, et al. Hepatitis C virus within a malignant lymphoma lesion in the course of type II mixed cryoglobulinemia. Blood 1995; 86:1887-92.
144. Fox RI, Luppi M, Kang HI, et al. Reactivation of Epstein-Barr virus in Sjögren's syndrome. Springer Semin Immunopathol 1991; 13:217-31.
145. Cinque P, Brytting M, Vago L, et al. Epstein-barr virus DNA in cerebrospinal fluid from patients with AIDS-related primary lymphoma of the cerebral central nervous system. Lancet 1993; 342:398-401.
146. Roth G, Curiel T, Lacy J. Epstein-Barr viral nuclear antigen 1 antisense oligodeoxynucleotide inhibits proliferation of Epstein-Barr virus-immortalized B cells. Blood 1994; 84:582-7.
147. Papadopoulos EB, Ladanyl M, Emanuel D, et al. Infusions of donor leukocytes to treat Epstein-Barr virus-associated lymphoproliferative disorders after allogeneic bone marrow transplantation. N Engl J Med 1994; 330:1185-91.
148. Lieberman J, Buchsbaum RJ. Using T cells to treat B-cell cancers. N Engl J Med 1994; 330:1231-3.
149. Rooney CM, Smith CA, Ng CYC, et al. Use of gene-modified virus-specific T lymphocytes to control Epstein-Barr virus-related lymphoproliferation. Lancet 1995; 345:9-13.
150. Kotin RM, Siniscalco M, Samulski RJ, et al. Site-specific integration by adeno-associated virus. Proc Natl Acad Sci USA 1990; 87:2211-5.
151. Samulski RJ, Zhu X, Xiao X, et al. Targeted integration of adeno-associated virus (AAV) into human chromosome 19. EMBO J 1991; 10:3941-50.
152. Goodman S, Xiao X, Donahue RE, et al. Recombinant adeno-associated virus-mediated gene transfer into hematopoietic progenitor cells. Blood 1994; 84:1492-500.
153. Walsh CE, Nienhuis AW, Samulski RJ, et al. Phenotypic correction of Fanconi anemia in human hematopoietic cells with a recombinant adeno-associated virus vector. J Clin Invest 1994; 94:1440-8.
154. Luo F, Zhou SZ, Cooper S, et al. Adeno-associated virus 2-mediated gene transfer and functional expression of the human granulocyte-macrophage colony-stimulating factor. Exp Hematol 1995; 23:1261-7.
155. Vento S, Cainelli F, Mirandola F, et al. Fulminant hepatitis on withdrawal of chemotherapy in carriers of hepatitis C virus. Lancet 1996; 347:92-3.
156. Whitby D, Howard MR, Tenant-Flowers M, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet 1995; 346:799-802.
157. Shiramizu B, Herndier BG, Mc Grath MS. Identification of a common clonal human immunodeficiency virus integration site in human immunodeficiency virus-associated lymphomas. Cancer Res 1995; 54:2069-72.
158. Renne R, Zhong W, Herndier B, et al. Lytic growth of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in culture. Nature Medicine 1996; 2:342-6.