HIV-1 related lymphoid proliferations
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HIV-1 infection is associated with a range of lymphoid alterations from generalized lymphadenopathy to malignant lymphomas. Persistent generalized lymphadenopathy is a chronic disease characterized by enlargement of two or more noncontiguous lymph nodes for at least 3 months. Associated symptoms are malaise, fever, night sweats, weight loss, hepatosplenomegaly, anemia, leukopenia and hypergammaglobulinemia. The enlarged lymph nodes are histologically characterized by prominent follicular hyperplasia with expanded germinal centers, which are surrounded by extremely reduced or absent mantle zones (1).

Immunohistochemical studies have shown that the major- ity of germinal centers are immunostained for p24 HIV-1 core protein and the immunostaining is associated with the follicular dendritic reticulum cells (EDOs), whose function is the antigen presentation to the B lymphocytes (2). Moreover, using in situ hybridization for HIV-1 RNA, it has been demonstrated that HIV-1 virions are trapped extracellularly on the FOGs of germinal centers (3).

The pathogenic processes involved in the earliest phases of HIV-1 infection include the balance in virus burden among blood and lymph nodes. Following primary infection, a burst of viremia is well documented, the virus is disseminated throughout the body and reaches the lymphoid tissue where its replication is only incompletely suppressed and where a reservoir of virus is established. The major source of the burst is the large number of cells in active viral replication present in the lymphoid tissues (4). Within several weeks, the high levels of plasma viremia are down-regulated and the decrease is associated with immune activation, germinal center formation and a partially effective HIV-specific immune response. In this phase, the chronic persistent infection is established and the HIV-1 virions are trapped on the FDCs of the yin-phoid tissue germinal centers; such trapping might interfere with release of HIV-1 virions into the circulation and thus result in lower levels of plasma viremia (5).

Similar results have been obtained in experimental models, in which inoculation of simian immunodeficiency virus (SIV) is followed by SIV detection in the regional lymph nodes within a few hours. Active Sly replication has been observed in the lymph nodes as early as 5 days after inoculation, where numerous cells expressing Sly are consistently detected. Within a week, a rapid down-regulation in the number of virus-expressing cells is associated with a progressive accumulation of virions trapped in the follicular dendritic cell network (6, 7).

Lymphadenopathy usually appears as an early manifestation of HIV-1 infection, whereas lymphomas arise at a relatively late stage of infection. The finding that a significant proportion of HIV-1 infected patients with lymphoma have a previous history of lymphadenopathy, together with the presence of monoclonal or oligoclonal Ig gene rearrangements in some of these lesions, suggests that yin- phadenopathy might represent a lymphomatous precursor lesion (8).

Between 3% and 10% of AIDS patients develop non-Hodgkin’s lymphoma (NHL) at some stage of their disease. AIDS-associated NHL is usually widespread at presentation and may involve multiple extranodal sites such as the central nervous system, gastrointestinal tract, bone marrow and liver or unusual sites such as the myocardium, soft tissues and oral cavity. There may be extensive organ infiltration, leading to organ failure, particularly in the bone marrow and liver. In HIV-infected patients, a rare form of lymphoma has been identified, characterized by involvement of the pericardial space, pleura or peritoneal cavity (primary effusion lymphoma) and associated with KSHV/HHV8 (9).

Most (60%) of the systemic lymphomas are diffuse large B-cell lymphomas (DLCL) and about 3000 are Burkitt’s (BL) lymphomas; the rest are T-cell or non-B-, non-T-cell origin. The pathogenesis of AIDS-associated non-Hodgkin’s lymphoma is probably related to chronic antigenic stimulation by HIV-1 and to Epstein-Barr virus (EBV) infection in association with impaired immunosurveillance, although AIDS-BL in contrast with AIDS-OLOL, tend to develop also in the presence of relatively sustained peripheral blood CD4 levels (10). EBV sequences and/or gene products are present in up to 80% of the large cell lymphomas and in about 40% of Burkitt-like lymphomas, suggesting that EBV does play a pathogenetic role in the development of AIDS-DLCL (11). Based on the high frequency of EBV infection, AIDS-DLCL have been regarded as EBV-driven lymphoproliferations arising in the context of highly disrupted T lymphocyte cytotoxic control directed against EBV. In support of this multistep hypothesis, emergence of EBV-infected B-cell clones in patients with persistent generalized lymphadenopathy has been correlated with the subsequent development of lymphoma.

The relationship between Hodgkin’s disease and HIV-1 infection remains controversial. Hodgkin’s disease in HIV-infected individuals usually pursues an aggressive clinical course with poor response to therapy. Extranodal disease with involvement of the bone marrow is common at presentation; mediastinal involvement is less frequent than in the general population. HIV-infected patients with Hodgkin’s disease have relatively high CD4 counts, suggesting that the development of this disease may depend on the presence of at least a partially intact immune response. Unlike Hodgkin’s disease in non-immunosuppressed individuals, CD8 rather than CD4 T-cells predominate in the background proliferation. An as yet undefined relationship between Hodgkin’s disease and EBV infection exists in patients with HIV infection. EBV RNA and EBV-encoded latent membrane protein can be found in Hodgkin’s and Reed Steinberg cells in almost every case of HIV-related Hodgkin’s disease (12).
JC virus and glial cells: Viral strategies for cell cycle deregulation in progressive multifocal leukoencephalopathy

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Progressive multifocal leukoencephalopathy (PML), a demyelinating opportunistic infection of the central nervous system that was extremely rare before the advent of AIDS, has become a relatively familiar condition in the AIDS era. The disease, caused by infection with the JC virus (JCV), is associated with inclusion bearing, large-sized oligodendrocytes and strikingly bizarre astrocytes. In fact, the atypical changes of astrocytes are of such magnitude that they have occasionally prompted an erroneous diagnosis of high-grade glioma. The conspicuousness of these histological changes renders PML an inviting scenario for the study of viral interactions with host glial cells.

When pondering over the mechanisms of JCV onslaught on glial cells, interplay with p53 emerges as a plausible viral strategy. Specifically, since some JOy T-proteins are known to bind cellular p53 in vitro, it seems reasonable to assume that p53 protein also interacts with a JOV product in the setting of PML. This binding, by stabilizing p53 and prolonging its half-life, would allow its immunohistochemical detection.

In agreement with this, JOy-infected oligodendrocytes and bizarre-looking astrocytes strongly immunostain for p53. Moreover, dual (p53/EBV) flow cytometry analysis of PML frozen tissue samples reveals that their p53 content is above that of isotypic controls. Thus, p53 build-up in JOy-harboring glial cells suggests a connection between the JOy-induced stabilization and inactivation of p53 and the striking tumor-like changes shown by these cells. In other words, the abnormal glial phenotypes seen in PML may well be linked to a loss of normal p53 function, allowing unrestrained entry into the DNA synthesis phase of the cell cycle.

The question then arises as to whether p53 protein accumulation in PML is really the result of its sequestration by JCV or whether it is the outcome of a p53 gene mutation which would also prolong p53 protein half life. A DNA sequencing study has demonstrated that the p53 gene harbors no mutations in PML and, therefore, that the p53 protein build-up in JOV-infected cells is not the consequence of a mutagenic interaction between JOV and the cell genome. Thus, it can be proposed instead that p53 accumulation results from its binding and stabilization by JOV T-protein.

Taking into account that stabilization and inactivation of p53 is associated with the development of genomic instability, abnormal cell DNA contents are to be expected in JOV-infected cells. Accordingly, image analysis of DNA content performed on PML tissues has shown that inclusion-bearing oligodendrocytes exhibit near tetraploid DNA indices, whereas atypical astrocytes are often polyploid. These disparate DNA contents can be construed as a consequence of the greater JOV permissiveness shown by oligodendrocytes, whose early lysis would prevent their reaching ploidy levels as high as those of the far more permissive astrocytes.

The aforesaid evidence of DNA amplification in PML glial cells is congruent with the occurrence of a functional abolation of p53 protein in association with JOV infection, since p53 roles include those of keeper of diploid status and guardian of genomic stability. Additionally, the overexpression of proliferating cell nuclear antigen (PCNA) and Ki-67 also observed in JOV-injected cells would reflect the proliferative status to be expected in cells undergoing viral sequestration and inactivation of their p53 protein.

How this JOV-induced cell cycle deregulation influences cyclin expression poses another intriguing question. As is often the case in JOV research, the answer can be anticipated from known effects of the much better studied simian virus 40 (SV40), another papovavirus that also makes use of its large T-antigen to subvert the host cell replicative machinery in order to serve its own reproductive needs.

It is known that SV40 large T-antigen is able to induce the expression of cyclins A, B, and E (but not of cyclin D1) in transfected diploid cells. In accordance with this, JOV infection has recently been shown to induce immunohistochemical positivity for cyclins A and B in inclusion-bearing oligodendrocytes and pleomorphic astrocytes. This recapitulation of SV40 T-antigen-associated cyclin changes suggests that JOV T-antigen shares some of the previously described capabilities of SV40 T-antigen to alter cyclin expression for the sake of viral replication.

References


