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Epstein-Barr Virus Associated Polymorphic Lymphoproliferative Disorders Occurring in Nontransplant Settings

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Epstein-Barr virus (EBV) is associated with a spectrum of lymphoproliferative disorders that are frequently found in patients with either acquired, iatrogenic, or congenital immunodeficiencies (Gaidano et al, 1998; Knowles, 1999). The longer survival of AIDS patients receiving multidrug antiretroviral therapy, an increased number of organ transplantations performed worldwide, and the widening usage of chemotherapeutic agents such as fludarabine in cancer patients seem to be factors in the increasing frequency of the EBV-related lymphoproliferative disorders (Demario and Liebowitz, 1998; Shields et al, 1997; Swinnen, 2000). The vast majority of these lymphoproliferative disorders are of B-cell derivation with a predilection for extranodal sites and an aggressive clinical course (Knowles, 1999). Despite many similarities, the EBV-associated lymphoproliferative disorders exhibit clinical, histologic, molecular, and cellular heterogeneity and vary in the expression patterns of the EBV-encoded genes, the stage of cell differentiation of the EBV-transformed cells, and virus-host interactions (Gaidano et al, 1998, 2000). In this review, we concentrate on the subset of the EBV-associated lymphoproliferations arising in nontransplantation patients. Clinically, the majority of such polymorphic lymphoproliferative disorders (PLDs) present with "B" symptoms, cytopenias, elevated serum lactate dehydrogenase (LDH) levels, and hepatosplenomegaly. A whole range of underlying immune defects seems to foster the development of PLDs. Morphologically, PLDs represent a spectrum of lymphoproliferations ranging from an atypical hyperplasia to overt malignant lymphomas. In addition to the pathologic and clinical features of PLDs, we discuss the putative role of EBV in the pathogenesis of these disorders, mechanisms of EBV-mediated cell transformation, and aberrant cytokine production.

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PLDs Represent a Spectrum of EBV-Associated Lymphoproliferative Disorders

Although PLDs are well recognized in transplant patients (Hanto et al, 1983), those occurring in patients with congenital, acquired, and nontransplant iatrogenic immunodeficiencies are not as well characterized (Table 1). Nador et al (1998) reviewed a large series of AIDS-related lymphomas and identified a small but distinct subset of lymphoproliferative disorders that closely resemble posttransplant lymphoproliferative disorders morphologically and molecularly. A monoclonal B-cell population was detected in 7 of 10 cases and a monoclonal EBV in 4 of 10 cases, supporting the notion that such AIDS-related cases represent a spectrum of immunodeficiency-related, EBV-associated PLDs. Cases displaying similar pleomorphic morphologic features were also identified in patients with rheumatoid arthritis treated with methotrexate and other immunosuppressive agents and in cancer patients who received chemotherapy or allogenic bone marrow transplant (Kamel, 1997, Thomason et al 1996). At least some cases of the pulmonary lymphomatoid granulomatosis (Guinee at al, 1994; Medeiros et al, 1991) seem also to represent the EBV-associated PLDs (Tao and Kahn, 2000; Tao and Valderrama, 1999; Tinguely et al 1998).

Some of the PLDs resemble more Hodgkin's lymphoma (HL) (Kamel et al, 1996; Kamel, 1997). Atypical cells in such PLD cases usually express B-cell lineage markers and the CD30 antigen. Tinguely et al (1998) reported six cases of lymphoproliferative disorders in patients with a spectrum of immunodeficiency disorders, some of which had distinct HL-like features. EBV genome was detected in all cases in the atypical pleomorphic cells, including the identified Reed-Sternberg-like cells. The distinction between HL and

Table 1. EBV-Associated Polymorphous Lymphoproliferative Disorders (PLDs) in Nontransplant Patients: Literature Summary

Reference	Disease
Zijlmans et al, 1992	EBV-associated lymphoma in a patient with rheumatoid arthritis treated with cyclosporine
Guinee et al, 1994	Pulmonary lymphomatoid granulomatosis
Kamel et al, 1996	HL and lymphoproliferations resembling HL in patients receiving long-term low-dose methotrexate therapy
Shields et al, 1997	HL-like transformation from low-grade B-cell lymphomas after fludarabine treatment
Nador et al, 1998	AIDS-related polymorphic lymphoproliferative disorders
Tinguely et al, 1998	HL-like lymphoproliferative disorders in patients with different underlying immunodeficiency states
Kingma et al, 1999	Low-grade monoclonal EBV-associated lymphoproliferative disorder of the brain in an AIDS patient
Tao and Valderrama, 1999	EBV-associated polymorphic B-cell lymphoproliferative disorders in children with AIDS
Tao and Kahn, 2000	EBV-associated high-grade mucosa-associated lymphoid tissue lymphoma in a congenital immunodeficiency patient

EBV, Epstein-Barr virus; HL, Hodgkin's lymphoma.

HL-like PLD is often challenging and perhaps arbitrary. In the immunocompromised patients, both disorders tend to have an aggressive course with poor therapeutic response and often present with disseminated extranodal disease. These cases are highly associated with EBV infection (Herndier et al, 1993; Rubio, 1994; Spina et al, 2000). Furthermore, frequent expression of B-cell markers and the EBV genome by Reed-Sternberg cells in the classic type of HL has been known for some time, even in patients without any known immune deficiency (Jaffe et al 1992; Zukerberg et al, 1991). More recent studies have demonstrated that the Reed-Sternberg cells typically represent a clonal population of germinal-center-cell–derived B lymphocytes (Hummel et al, 1996; Kanzler et al, 1996; Kuppers and Rajewsky, 1998). HL may follow non-Hodgkin's lymphoma (NHL), particularly in patients receiving immunosuppressive therapy (Shields et al, 1997), suggesting an evolutionary progression rather than the occurrence of a second malignancy. Finally, malignant cells from NHL and HL, both of which occurred in the same patients, have been shown to be clonally related (Kanzler et al, 1996). These findings indicate the rather close relationship between HL and NHL in at least some cases. PLDs in which the atypical cells almost universally express B-cell markers and carry EBV genome, regardless of their NHL or HL morphology, support this conclusion.

In Table 2 we summarized our own experience with nontransplant PLD cases (Tao and Kahn, 2000; Tao and Valderrama, 1999; Tao et al 2000a, 2000b). All 12 PLD patients displayed a form of an underlying immunodeficiency such as HIV-infection, congenital immunodeficiency, or treatment-induced immunosuppression. All lesions displayed the presence of EBV as demonstrated by in situ hybridization, Southern blotting, and polymerase chain reaction (PCR). Clinically, most of these cases presented with chronic fever, weight loss, night sweats, and wasting ("B" symptoms) during the early course of the disease, and pancytopenias, liver dysfunction, elevated LDH levels, and hepatosplenomegaly as the disease progressed. These disorders frequently involved extranodal sites and had an aggressive, fatal clinical course (Table 2A). Histologically (Table 2B), they encompass a spectrum of lymphoproliferations ranging from an atypical hyperplastic (Figure 1A), sometimes "infectious mononucleosis-like" morphology to a picture indistinguishable from an immunoblastic (plasmacytoid) lymphoma (Gaidano et al, 1998, 2000) or HL, classic type, particularly in the more advanced cases. Such HL-like cases displayed heterogeneous infiltrates of lymphocytes, epithelioid histiocytes, plasma cells, atypical immunoblasts, and Reed-Sternberg-like cells (Figure 1B), and they often showed prominent necrosis. Finally, the cases with scattered reactive lymphocytes and a large proportion of highly atypical cells present in the background of fibrohistiocytic stroma were also encountered (Figure 1C). Progression to such morphology resembling HL of nodular sclerosis grade II or lymphocyte-depletion type was seen in two patients (Cases 4 and 5) who underwent a second, follow-up biopsy. The atypical cells were B cells expressing CD20, CD30, CD45, and the EBV antigens, the latent membrane protein (LMP-1), and/or the Epstein-Barr virus encoded RNA 1 (EBER-1). The lesions, particularly the ones with the advanced lymphoma morphology, showed evidence of B-cell clonality. Our findings confirm that PLDs represent a spectrum of EBV-associated lymphoproliferative disorders ranging from atypical hyperplasia to overt malignant lymphomas with a characteristic constellation of clinical and histopathologic features.

Patterns of Latent Viral Gene Expression in EBV-Associated Malignancies

Beside PLDs, EBV has been associated with a variety of malignant tumors including nasopharyngeal carcinoma, Burkitt's lymphoma, a spectrum of overt

Table 2. Data for 12 Patients with EBV-Associated PLDs

	Case No.											
	1	2	3	4	5	6	7	8	9	10	11	12
A. Clinical and Laboratory Data												
Sex/Age (yr)	M/52	F/2	M/14	F/56	M/9	M/43	M/79	M/14	M/23	M/41	M/19	M/66
Cytopenia	−	+	+	+	+	+	+	+	+	+	+	−
LDH	H	H	H	−	H	H	H	H	H	NA	H	−
"B" symptom	+	+	+	+	+	+	+	+	+	+	+	+
Hepatosplenomagaly	±	+	−	−	+	+	+	+	+	NA	+	−
Base for immunodeficiency	AIDS	AIDS	AIDS	Metho	CID	low CD4	Chemo	AIDS	CID	Flu	?	Metho
Location	LN	Lung	Lung	LN	Lung	Lung	Sigmoid	Oral	Lung	Naso	Lung	LN
Outcome	DOD	DOD	AWD	AWD	DOD	DOD	AWD	DOD	NA	AWD	AWD	AWD
Diagnosis	APH	PL	APH	HL-like	MALToma	LG	HL-like	PL	DLBL	APH	LG	HL-Like

				4		5								
	1	2	3	E	L	E	L	6	7	8	9	10	11	12
B. Histopathologic Features														
Pattern of growth	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Zonal necrosis	−	+	−	+	++	−	+	++	++	++	++	+	+	+
Cell type	P	P	P	P	P	P	P	P	P	+	P	P	P	P
RS-like cells	1	1	1	1	1–2	1	1–2	1	2–3	P	1–2	1	2	2
Immunoblasts	3	2	2	2	1–2	2	2	2	2	1	2	2	2	2
Plasmacytic cells	2	2	2	2	1	3	1	2	2	3	2	3	2	1
Histiocytes	2	2	3	1	3	1	2	2	2	4	3	3	3	2
T-cells	2	3	2	3	1	3	1	4	3	3	3	4	3	3
Fibrohistiocytic Stroma	+	+	−	+	++	+	++	++	++	2	++	+	++	+
Clonality	Py	M	Py	NA	NA	M	M	M	M	M	M	NA	M	Py

NA, not available; H, high; Metho, history of long-term methotrate treatment; CID, congenital immunodeficiency or combined immunodeficiency; Chemo, patients with history of lymphoma receiving chemotherapy treatment or radiation, or fludarabin (Flu); DOD, died of the disease; AWD, alive with disease; APH, atypical polymorphic hyperplasia; PL, polymorphic lymphoma; HL-like, Hodgkin lymphoma-like lymphoproliferative disorders; LG, lymphomatoid granulomatosis; DLBL, diffuse large cell lymphoma; LDH, lactate dehydrogenase; E, early stage; L, late stage; D, diffuse; P, polymorphous; Py, polyclonal; M, monoclonal; 0, none; 1+, <5%; 2+, 5–25%; 3+, 25–50%; 4, >50%; −, absence; +, presence; ++, strong.

immunodeficiency-related lymphomas, Hodgkin's lymphoma, and nasal-type T/NK cell lymphomas (Shibata et al, 1993, Tao and Valderrama, 1999; Weiss et al, 1987, 1992). Latent EBV infection of malignant cells results in viral persistence and the expression of a restricted group of viral genes (Cohen 2000; Kawa, 2000). The viral genes include those for six EBV nuclear antigens (EBNA-1, -2, -3A, -3B, -3C, and LP) and three latent membrane proteins (LMP-1, -2A, and -2B). In addition, two small nonpolyadenylated RNA molecules, the EBV-encoded RNAs, EBER-1 and -2, are expressed in large quantities (Ambinder and Weiss, 1999; Kieff, 1996). The expression of EBNA-1, a sequence-specific DNA-binding protein, is required to maintain the viral genome in an episomal form nonintegrated into the DNA of the host cell. EBNA-2 up-regulates the expression of LMP-1, LMP-2, and cellular proteins that are involved in the transformation of B-cells (Cohen et al, 1989; Henkel et al, 1994). The EBNA-3A, -3B, and -3C proteins regulate expression of some B-cell activation proteins, whereas EBNA LP (ladder protein) augments the ability of EBNA-2 to up-regulate LMP-1.

LMP-1 has a direct oncogenic activity and prevents cell apoptosis (Cohen, 1997). LMP-1 binds to several of the tumor necrosis factor receptor-associated factors (TRAFs), both in vitro (Mosialos et al, 1995) and in vivo (Liebowitz, 1998). These activities result in activation of the nuclear factor-κB (NF-κB), which in turn stimulates expression of cellular adhesion molecules, production of cytokines, and B-cell proliferation. Although the function of EBERs remains unclear (Anagnostopoulos and Hummel, 1996), detection of their expression is widely used to identify latent EBV infection (Chang et al, 1992).

It is well established that the pattern of expression of the latent genes from the EBNA and LMP families varies among the EBV-associated malignancies. Endemic Burkitt's lymphoma displays the most restricted pattern (latency type I), in which only EBNA-1 is expressed. In contrast, posttransplant and AIDS-related lymphoproliferative disorders express the full set of EBNAs and LMPs (latency type III). Hodgkin's lymphoma and nasopharyngeal carcinoma have an intermediate (latency type II) pattern of gene expression in which EBNA-1 and LMP-1, -2A, and -2B are expressed (Kieff, 1996; Rickinson and Kieff, 1996). Both direct and indirect evidence indicate that nontransplant PLDs express the broad type III latency (Kawa, 2000).

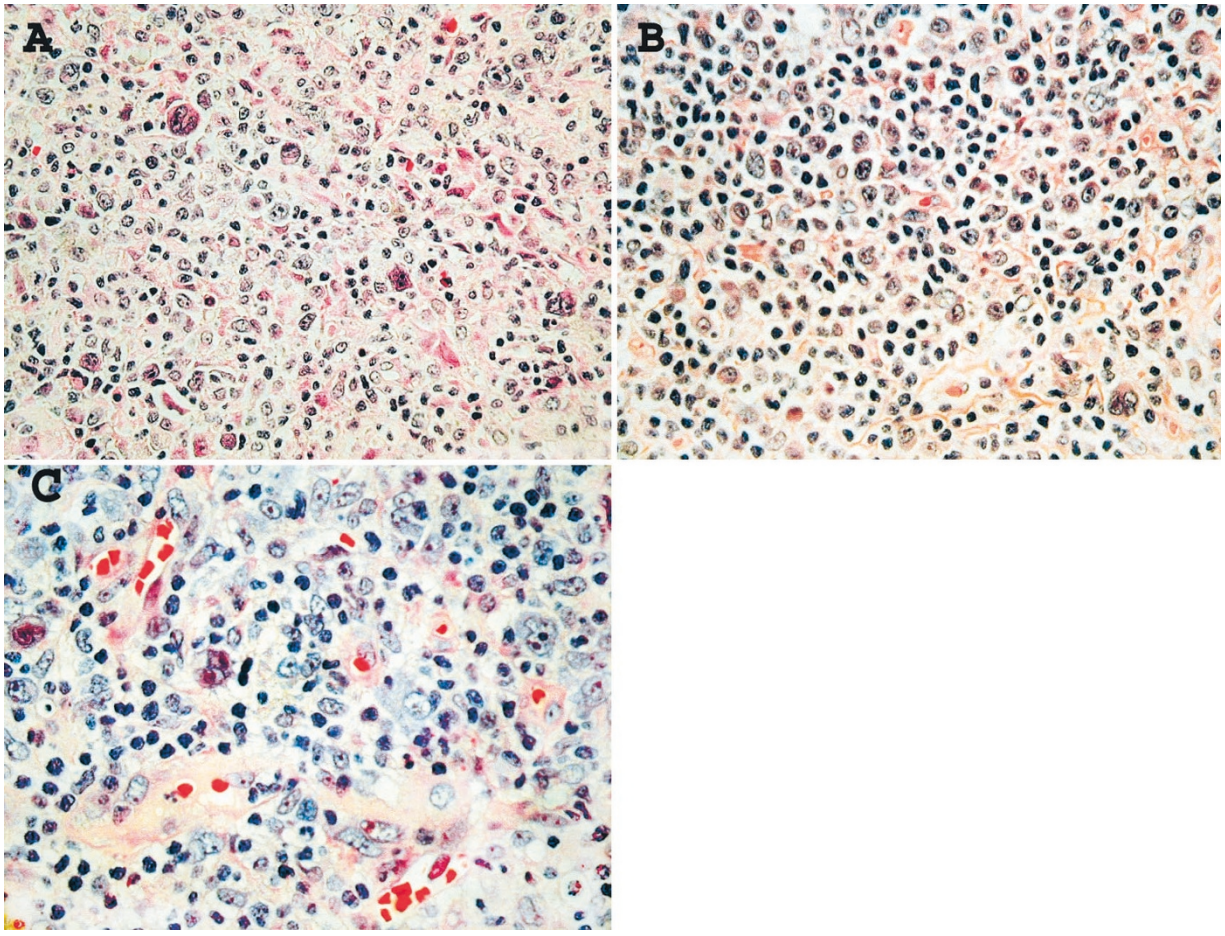

Figure 1.

A, Atypical polymorphic hyperplasia from the lung of an HIV-infected child showing polymorphic lymphoid infiltrate of small and medium-sized lymphocytes, immunoblasts, and plasmacytoid cells and mitosis. Multinucleated cells, some resembling Reed-Sternberg cells, are scattered throughout the lesion. B, Polymorphic lymphoma from a biopsy of a lung lesion of a child with congenital immunodeficiency. Polymorphous infiltrate is composed predominantly of atypical intermediate large cells, plasmacytoid cells, transformed immunoblasts, and Reed-Sternberg-like cells. C, Lymphoproliferative disorder resembling Hodgkin's lymphoma from a subsequent biopsy of an axiliary lymph node from a patient receiving methotrexate showing admixture of scarce amounts of reactive lymphocytes with a relatively large number of large immunoblasts and Reed-Sternberg-like cells in the background of fibrohistiocytic stroma.

Interestingly, among the EBV-positive AIDS-related NHL, expression of LMP-1 seems to cluster with the immunoblastic morphology and BCL-6-/CD138+ phenotype, suggesting the postgerminal center cell maturation stage of the LMP-1–expressing B cells (Gaidano et al, 1998, 2000). Posttransplant lymphoproliferative disorders, which usually also express LMP-1 and the other type III latency EBV genes, also seem to be derived from postgerminal B-cells (Paessler et al, 2001), as are the AIDS-related Hodgkin's lymphomas (Carbone et al, 1998). Whether the nontransplant PLDs, which display a number of similarities with the above-mentioned disorders, represent postgerminal center B-cells remains to be determined (Carbone et al, 1998, 1999).

Mechanisms of EBV-Mediated Cell Transformation

The exact role of EBV in cell transformation is still poorly understood, and both viral and host factors may play a role in the process. EBV-associated lymphomas usually occur many years after the primary EBV infection, which indicates the need for secondary transforming events. Reactivation and proliferation of EBV-infected B-cells, as frequently seen in immunocompromised patients, may result in the accumulation of genetic lesions that lead to a neoplastic transformation of the affected clones (Bessudo et al, 1996; Jain et al, 1994; Kuppers et al, 1994). Although the oncogenic role of LMP-1 is well documented (Wang et al, 1985; Wang et al 1990), the exact functions of this and the other EBV-encoded proteins are only now being elucidated. As depicted in Figure 2, several signaling molecules, such as TNF-receptor-associated factors (TRAF-1–3, and 5), Rel/nuclear factor κB (NF-κB), c-Jun N-terminal kinase (JNK)-AP-1 tandem, mitogen activated protein kinase (p38/MAPK), and Janus kinase 3 (JAK 3) and the Jak-3–activated signal transducers and activators of transcription (STATs) are implicated in the function of LMP-1. The Rel/NF-κB family is a group of transcription factors that regulate the expression of various cellular and viral genes, including those that control the immune response, acute phase reactions, and

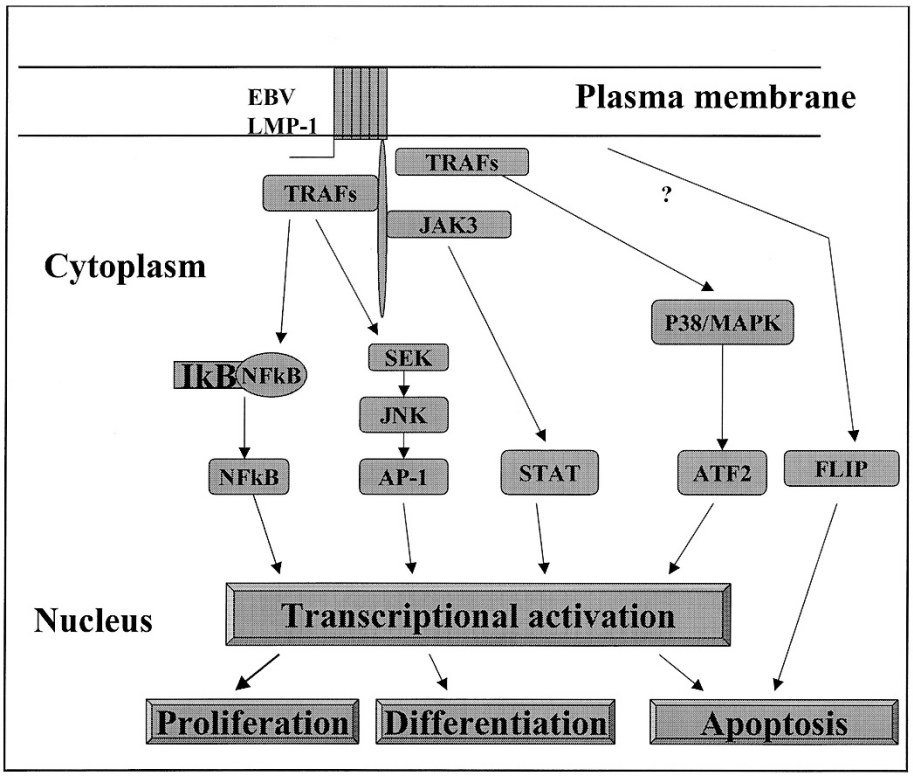

Figure 2.

Molecular signaling pathways activated by Epstein-Barr virus (EBV)-encoded latent membrane protein (LMP)-1. The cytoplasmic domain of LMP-1 interacts with tumor necrosis factor (TNF)-receptor-associated factors (TRAFs)-1,-2, -3, and –5, resulting in activation of transcriptional factor κB (NF-κB), p38/MAPK (mitogen activated protein kinase), and C-Jun amino-terminal kinase (JNK)/ATF2; activating transcription factor 2, JAK/STAT (Janus kinase and signal transducers and activators of transcription), and FLIP (FLICE inhibitory protein) signaling pathways. This leads to cell proliferation, differentiation, and apoptosis as well as elaboration of cytokines.

replication of the virus (Ghosh et al, 1998). In unstimulated cells, the ankyrin-containing IκB proteins interact with Rel/NF-κB complexes and sequester them in the cytoplasm by masking the nuclear localization signal. Upon cell stimulation, IκB is phosphorylated, ubiquitinated, and degraded. This allows NF-κB to translocate to the nucleus and bind to specific cis-acting consensus sequences (κB sites) located in the regulatory regions of the target genes. NF-κB induces gene expression for cytokines and adhesion molecules (Ewenstein and Tao, 1996; Tao and Ewenstein, 1999) and activates genes involved in apoptosis (TRAF1/2) and those involved in cell-cycle regulation and proliferation (ie, cyclin D1, myc, p53, Rb) (Barkett and Gillmore, 1999; Kopp and Ghosh, 1995). Therefore, activation of NF- κB appears to be a key event in the LMP-1–mediated cell signaling.

LMP-1 also activates the JNK cascade (Eliopoulos and Young, 1998). The JNK pathway ultimately leads to the activation of another transcription factor, AP-1, involved in cell proliferation (Eliopoulos et al, 1999a). LMP-1 was shown to interact with JAK3, which activates STAT proteins (Leonard and O'Shea, 1998) and may be responsible for many of the pleiotropic effects of LMP-1. p38/MAPK and the activating transcription factor 2 (ATF2) signaling pathway, which is also activated by LMP-1, are involved in the regulation of IL-6 and IL-8 production (Eliopoulos et al, 1999b).

A new mechanism linking cell transformation and immune evasion by tumor cells and virus has been recently described (Djerbi et al, 1999). Genes encoding inhibitors of death receptor-induced apoptosis, named vFLIPs, have been found in several herpes viruses. Although FLIP sequences have not been detected in the EBV genome, a recent study indicates that EBV-infected lymphoma cells escape Fas/CD95-mediated apoptosis by inducing up-regulation of cellular FLIPs (Tepper and Seldin, 1999).

Although important, these signaling mechanisms may represent only a part of the complex cell signaling network that probably exists in the EBV-infected cells in LPDs and other EBV-associated lymphoproliferative disorders. The type of the EBV latency (I to III) defining the spectrum of the expressed viral genes may be particularly important in this context. The pathologic outcome of the EBV-mediated cell transformation may, therefore, be attributable to a net effect of several signaling pathways activated by the virus-encoded proteins.

Dysregulation of Cytokine Secretion in EBV-Associated PLDs

Abundant cytokine secretion by the EBV-infected cells and surrounding reactive cells may be at least in part responsible for the distinctive clinical and histopatho-

logic features that characterize PLDs (Fig. 2). As stated above, EBV infection leads to the expression of a range of viral proteins including LMP-1 and activation of TRAFs, NF-κB, and the other signaling molecules (Liebowitz, 1998; Su et al, 1995). NF-κB is known to activate the expression of multiple viral and cellular genes through binding to the promoter elements of these genes and appears central to LMP-1 effects on B-cell lymphocyte differentiation and activation (Huen et al, 1995; Kaye et al, 1993). Genes of many cytokines, including TNFα, interferon-γ, IL-1, IL-5, IL-6, IL-10, and some adhesion molecules, such as E-selectin, vascular cell adhesion molecule, and intercellular adhesion molecule-1, have NF-κB binding site(s) in their respective promoter regions (Collins et al, 1995, Thanos and Maniatis, 1995). The release of TNF-α may lead to the observed necrosis, karyorrhexis, and proliferation and maturation of lymphoid cells, all of which occur in PLDs. In combination with interferon-γ and other cytokines, TNF-α promotes histocytic infiltrates and cytophagocytosis (Fujiwara et al, 1993). Furthermore, EBV induces production of IL-6 (Yokoi et al, 1990), the cytokine that enhances B-cell proliferation and differentiation into immunoglobulin-secreting plasma cells (Hilbert et al, 1995). Bone marrow suppression, pancytopenia, and renal failure, which can be seen in advanced cases of PLD, have been attributed in part to the effects of IL-2 derived from activated T cells. IL-2 can further enhance the secretion of TNF-α and interferon-γ (Fujiwara et al, 1993) (Fig. 3). Liver dysfunction and hepatosplemagaly are also known to result from the toxic effects of these two cytokines. Fever has been attributed to both the release of pyrogenic substances from activated histiocytes and the cytokine-mediated direct stimulation of prostaglandin E synthesis by the hypothalamus (Cotran et al, 1999).

Abnormally high levels of several cytokines, such as IL-6 and IL-10, have been demonstrated in AIDS-related lymphomas, posttransplant patients, and EBV-infected cell lines (Emilie et al, 1992, 1997; McGrath et al, 1993; Tosado et al, 1993). IL-10 promotes B-cell proliferation through the inhibition of IL-2 and IFN-γ and up-regulation of IL-4, a stimulatory cytokine for B-cell growth. In addition, it may contribute to the escape from virus specific immune surveillance (Demario and Liebowitz, 1998). IL-10 not only exerts an autocrine growth effect on AIDS lymphoma (Masood et al 1995) but also may down-regulate a cytotoxic T-lymphocyte response against EBV-infected cells (Herbst et al, 1996). Although the above evidence strongly suggests that these and similar cytokines may be involved in the pathogenesis of PLDs, further studies are required to elucidate the putative role of cytokines in such disorders.

Perspective and Conclusion

PLDs represent a spectrum of EBV lymphoproliferative disorders, ranging from atypical hyperplasia to overt malignant lymphoma, with a distinctive constellation of clinical and histopathologic characteristics. Geographic necrosis, cell heterogeneity, atypical immunoblasts, plasmacytoid differentiation, and Reed-Sternberg-like cells are typically found in such disorders. The pathogenesis of PLDs seems to be multifactorial and complex, with the EBV-mediated B-cell proliferation and transformation being at the heart of the disease process. EBV-triggered cytokine secretion by the EBV-infected and reactive cells may be, at least in part, responsible for the distinctive clinical and histopathologic features seen in PLDs. EBV-encoded LMP-1 protein is believed to play a central role in the pathogenesis of the EBV-associated lymphoproliferations by activating several intracellular signaling pathways such as TRAF, Rel/NF-κB, JNK-AP-1, p38/MAPK, and JAK-STAT.

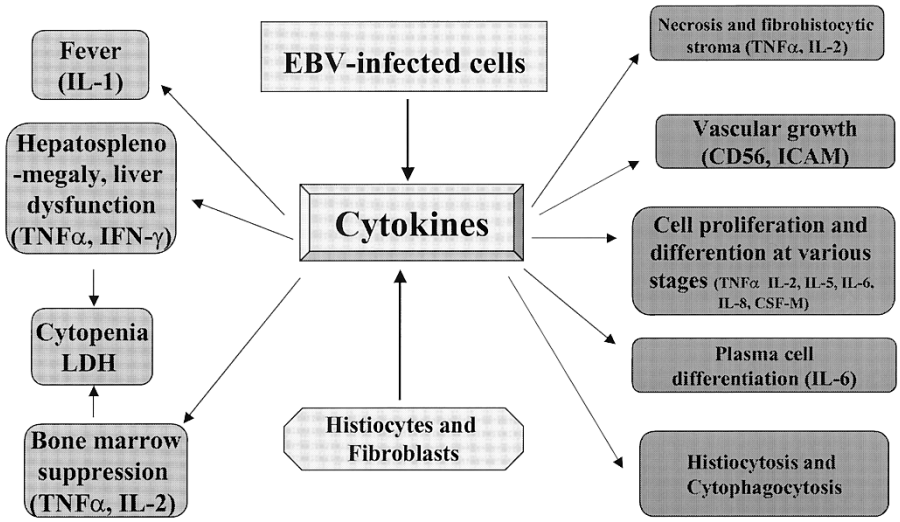

Figure 3.

Schematic model of EBV-driven cytokine dysregulation in polymorphic lymphoproliferative disorders (PLDs). EBV-infected cells secrete numerous cytokines that account for some histopathologic features and clinical manifestations. IFN-γ, interferon-γ; LDH, lactate dehydrogenase; IL-2, interleukin-2; ICAM, intercellular adhesion molecule; CSF-M, macrophage colony-stimulating factor.

As a consequence of their unusual clinical and morphologic presentation, PLDs often pose diagnostic and terminological problems. The distinction from other reactive and neoplastic disorders can be difficult, as can the classification of these lesions as NHL or HL. Molecular analysis for B-cell clonality and expression of EBV-encoded genes is crucial in some cases. The proper diagnosis of an EBV-associated PLD has important clinical implications because a subset of these neoplasms will resolve completely with discontinuation of inducing drugs such as methotrexate, thereby obviating the need for chemotherapy or radiation therapy. In other cases of PLDs, future treatment efforts may need to focus on elimination of EBV and/or EBV-infected cells and reduction of the cytokine-rich inflammatory milieu. Recent findings showing that anti-EBV therapy appears effective in posttransplant lymphoproliferative disorders (Oertel et al, 1999) and AIDS-related lymphomas (Schmidt et al, 2000), that in vitro expanded cytotoxic T cells reactive against autologous EBV-transformed cells are effective in transplant patients at risk of or with overt posttransplant lymphoproliferative disorders (Gustafsson et al, 2000; Khanna et al, 1999), and that EBV-transformed cells are highly sensitive to a novel class of drugs, macrocyclic lactons, which act via inhibition of cytokine signaling and cell-cycle progression (Majewski et al, 2000) suggest that such novel therapeutic approaches may prove effective in the EBV-associated PLDs.

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