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Genetic pathways and histogenetic models of AIDS-related lymphomas

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Abstract

Acquired immunodeficiency syndrome (AIDS)-related lymphomas consistently display a B-cell phenotype and are histogenetically related to germinal centre or post-germinal centre B cells in the overwhelming majority of cases. The pathogenesis of AIDS-related lymphoma is a multistep process involving factors provided by the host as well as alterations intrinsic to the tumour clone. The molecular pathways of viral infection and lesions of cancer-related genes associated with AIDS-related lymphomas vary substantially in different clinicopathological categories of the disease and highlight the marked degree of biological heterogeneity of these lymphomas.

Keywords: AIDS; Lymphomas; Pathogenesis; Histogenesis

1. Introduction

Acquired immunodeficiency syndrome (AIDS)-related lymphomas are predominantly represented by the non-Hodgkin lymphomas (NHL) sharing a number of similarities [1,2]. All AIDS-related NHL (AIDS-NHL) derive from B-cells, are characterised by extreme clinical aggressiveness, and display a predilection for extranodal sites.

Despite these similarities, however, AIDS-NHL are markedly heterogeneous. The pathological spectrum of AIDS-NHL includes systemic AIDS-NHL, primary central nervous system lymphomas (AIDS-PCNSLs), primary effusion lymphoma (AIDS-PEL) and plasmablastic lymphoma (AIDS-PBL) of the oral cavity. Systemic AIDS-NHL are histologically classified into AIDS-related Burkitt lymphoma (AIDS-BL) and AIDS-related diffuse large cell lymphoma (AIDS-DLCL). Hodgkin's lymphoma (HL) has also been reported in HIV-infected individuals, although this disease does not confer a diagnosis of AIDS in these patients ([1–5] and Knowles and Pirog in this issue). Clinically, AIDS-NHL vary substantially in terms of the host's residual CD4 levels and the time of incubation since HIV infection [1–5]. Genetically, AIDS-NHL can be separated into distinct categories based on the profile of the genetic lesions harboured by the tumour clone [1–5]. Histogenetically, the AIDS-NHL correspond to distinct stages of physiological B-cell development, i.e. germinal centre (GC) or post-GC B-cells, in the overwhelming majority of cases [6].

This review will summarise the major pathogenetic pathways of AIDS-related lymphoma with particular emphasis on the genetic alterations involved. Novel histogenetic subsets of AIDS-NHL will also be described.

2. Molecular pathways in AIDS-related lymphomas

The genetic alterations of AIDS-NHL predominantly involve activation of proto-oncogenes by chromosomal translocations [7]. Overall, the genetic lesions of AIDS NHL are targeted to very specific regions of the genome, which is otherwise relatively stable in these tumours.

2.1. AIDS-related Burkitt's lymphoma

AIDS-BL may be the first manifestation of AIDS in a significant fraction of cases since it may develop also in

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the presence of relatively sustained peripheral blood CD4 levels [8–14]. These epidemiological features of AIDS-BL are in contrast with those proper of AIDS-DLCL, which tend to develop in the presence of low CD4 counts and are frequently a late manifestation of HIV infection [8–14]. The molecular pathogenesis of AIDS-BL is complex and involves antigen stimulation and selection as well as the accumulation of genetic lesions. The role of genetic lesions in AIDS-BL has been studied in depth, and it is now well established that the molecular pathway associated with AIDS-BL involves activation of *c-MYC*, inactivation of *TP53* and infection by Epstein–Barr virus (EBV).

2.1.1. *Activation of* c-MYC

In common with all BL variants, 100% of AIDS-BL harbour a reciprocal chromosomal translocation between band 8q24 and one of the Ig gene loci [7,15–18] (Table 1). The pathogenetic relevance of *c-MYC* alterations is well described, since translocated *c-MYC* alleles are able to transform B-cells *in vitro* and cause lymphomas *in vivo*, whereas antisense oligonucleotides targeted against *c-MYC* translocated alleles are able to suppress lymphoma growth [19–21].

2.1.2. *EBV infection*

Infection by EBV occurs in 30% of AIDS-BL [16]. EBV infection in AIDS-BL (Table 1) is generally monoclonal, consistent with the hypothesis that the virus has been present in the tumour progenitor cell since the early phases of its clonal expansion and thus putatively contributed to lymphoma development [16,17,22]. The precise role of EBV in AIDS-BL pathogenesis, however, has remained controversial.

2.1.3. *Inactivation of* TP53

Inactivating mutations and deletions of the *TP53* tumour supressor gene occur in 60% of AIDS-BL, a rate which is substantially higher than that detected in sporadic and endemic BL (30%) [16] (Table 1).

2.2. *AIDS-related diffuse large cell lymphoma*

Systemic AIDS-DLCL are distinguished into AIDS-related large non-cleaved cell lymphoma (AIDS-LNCCL) and AIDS-related immunoblastic lymphoma plasmacytoid (AIDS-IBLP) [3]. The risk for AIDS-DLCL increases substantially as the immune function decreases, and AIDS-DLCL patients display a more severe immunodeficiency than AIDS-BL cases [8–14]. The molecular pathogenesis of systemic AIDS-DLCL is complex and more heterogeneous than that of AIDS-BL. A unifying genetic lesion, such as *c-MYC* activation in AIDS-BL, has not yet been found. At present, the molecular alterations most frequently associated with AIDS-DLCL involve EBV infection and deregulation of the *BCL-6* proto-oncogene (Table 1).

2.2.1. *EBV infection*

EBV infection occurs in approximately 70–80% of cases [16,23,24]. EBV-positive AIDS-DLCL frequently, although not always, express the EBV-encoded transforming antigen latent membrane protein-1 (LMP-1) and, in some cases, also Epstein–Barr Virus Nuclear Antigen-2 (EBNA-2), suggesting that the virus does play a pathogenetic role in the lymphoma development [23,24].

Based on the high frequency of EBV infection, AIDS-DLCL have been regarded as EBV-driven lymphoproliferations arising in the context of highly disrupted cytotoxic control directed against EBV.

2.2.2. *Deregulation of* BCL-6

Molecular alterations of the *BCL-6* proto-oncogene associate with a significant fraction of AIDS-DLCL [25,26]. Expression of *BCL-6* is physiologically restricted to GC B-cells and mouse 'knock out' experiments

Table 1
Molecular lesions of AIDS-NHL

Histology	*c-MYC* (%)	p53 (%)	*BCL-6* (%)		EBV (%)		HHV-8 (%)
			Rearrangement	Mutation	Infection	*LMP-1* status	
AIDS-BL	100	60	–	70	30	–	–
AIDS-DLCL							
AIDS-LNCCL	–	Rare	20	70	40	–	–
AIDS-IBLP	–	Rare	–	70	90	+	–
AIDS-PCNSL							
AIDS-LNCCL	–	nd	–	70	100	–	–
AIDS-IBLP	–	nd	–	70	100	+	–
AIDS-PEL	–	–	–	70	90	–	100

EBV, Epstein–Barr Virus; HHV-8, Human Herpes Virus-8; NHL, Non-Hodgkin's lymphoma; LMP-1, latent membrane protein-1; –, absence of genetic lesion/expression; +, positive expression; nd, not done; AIDS-BL, AIDS-related Burkitt's lymphoma; AIDS-DLCL, AIDS-related systemic diffuse large cell lymphoma; AIDS-PCNSL, AIDS-related primary central nervous system lymphoma; LNCCL, large non-cleaved cell lymphoma; IBLP, immunoblastic lymphoma plasmacytoid; AIDS-PEL, AIDS-related primary effusion lymphoma.

indicate that it is an essential requirement for GC formation [27–29]. Rearrangements of *BCL-6* are detected in 20% AIDS-DLCL and approximately 40% of DLCL of the immunocompetent host [25,30].

Mutations of the 5′ regulatory sequences of the gene represent an additional mechanism of genetic alteration of *BCL*-6 occurring in 70% AIDS-DLCL and other AIDS-NHL types as well as in a similar proportion of DLCL of the immunocompetent host [26,31,32].

Whereas the BCL-6 protein is expressed by all DLCL of the immunocompetent host [27], AIDS-DLCL can be distinguished into *BCL*-6 expressing and BCL-6 non-expressing cases [6,33]. BCL-6 expressing AIDS-DLCL include rearranged and non-rearranged cases and belong to the LNCCL morphological variant [6,33]. If EBV infected, BCL-6 expressing AIDS-DLCL fail to express the LMP-1 antigen [6,33]. Conversely, it is possible to identify a subset of AIDS-DLCL characterised by the absence of BCL-6 expression, absence of *BCL-6* rearrangements, and frequent expression of LMP-1 [6,33]. This subset of AIDS-DLCL tends to display an IBPL morphology [6,33]. The potential histogenetic relevance of these phenotypic distinctions of AIDS-DLCL will be discussed below.

2.3. AIDS-related primary central nervous system lymphoma

AIDS-PCNSL are predominantly, if not exclusively, represented by AIDS-DLCL and associate with advanced stages of HIV infection with profoundly disrupted immune function and very low levels of peripheral blood CD4 cells [3,5,8–14]. Virtually all AIDS-PCNSL harbour EBV [34,35]. Infection by EBV among AIDS-PCNSL is associated with the expression of the EBV-encoded transforming antigen LMP-1 in approximately 50% of cases, suggesting a direct oncogenic role of the virus in the pathogenesis of these disorders [35] (Table 1). Mutations of *BCL-6* 5′ regulatory regions are relatively frequent among AIDS-PCNSL, suggesting that AIDS-PCNSL may derive from the GC-related B-cells [35]. Overall, although EBV is a major player in AIDS-PCNSL development, the consistent monoclonality of these tumours suggests that additional, presently unknown, genetic alterations are involved.

2.4. AIDS-related primary effusion lymphoma

Infection by HHV-8 is the genetic hallmark of AIDS-PEL and is a *sine qua non* for AIDS-PEL diagnosis [4,36–38] (Table 1). Although the precise pathogenetic contribution of HHV-8 to AIDS-PEL is still under investigation, several pieces of evidence suggest that HHV-8 may be required for AIDS-PEL pathogenesis.

3. Histogenesis of AIDS-related lymphoma

Evidence from biological studies of AIDS-NHL suggests a putative model for the histogenetic derivation of these lymphomas (Fig. 1). This model is based on both genotypic and phenotypic markers which allow the distinction of mature B-cells into different compartments, including virgin B-cells, GC B-cells and post-GC B-cells. Genotypic markers of B-cell histogenesis are represented by mutations of *IgV* genes and of *BCL-6*, which are somatically acquired by B-cells at the time of transit through the GC [32,39,40]. Positivity for *IgV* and/or *BCL-6* mutations indicates that a given lymphoma derives from GC or post-GC B-cells. Phenotypic markers are represented by the BCL-6 and CD138/syndecan-1 proteins and allow the distinction between GC and post-GC B-cells. In fact, expression of BCL-6 clusters with the GC stage of differentiation [27], whereas CD138/syndecan-1, a member of the family of syndecans, is a marker of pre-terminal B-cell differentiation [6]. On this basis, lymphomas may be histogenetically distinguished into: (1) lymphomas devoid of somatic *IgV* and *BCL-6* hypermutation, which derive from pre-GC B-cells; (2) lymphomas associated with somatic *IgV* and/or *BCL-6* hypermutation and BCL-6 expression, which closely reflect GC B cells; and (3) lymphomas associated with somatic *IgV* and/or *BCL-6* hypermutation, as well as CD138/syndecan-1 positivity, representing lymphomas of post-GC B cells.

Recently, MUM1/IRF4 (for Multiple Myeloma-1/Interferon Regulatory Factor-4) has been added to the panel of phenotypic markers available for the characterisation of B-cell lymphoma histogenesis [41]. MUM1 was discovered because of its involvement in the t(6;14)(p25;q32) translocation of multiple myeloma, which causes the juxtaposition of the *MUM1* gene, mapping at 6p25, to the Ig_H locus on 14q32 [42]. MUM1 is a lymphocyte-specific member of the interferon regulatory factor (IRF) family of transcription factors which is also known as ICSAT (for Interferon Consensus Sequence binding protein for Activated T cells) and Pip (for PU.1 Interaction Partner) [43]. Recent studies have shown that MUM1 expression may denote the final step of intra-GC B-cell differentiation, as well as subsequent steps of B-cell maturation toward plasma cells [43–46].

In reactive lymphoid tissues, the phenotypic patterns identified by MUM1, BCL-6 and syn-1 map to lymph node areas which are populated by B-cells at different stages of differentiation [47]. Comparison of the topography of MUM1 and BCL-6 within the GC reveals that expression of BCL-6 occurs immediately after a B-cell enters the GC and is maintained until GC exit (Fig. 1), whereas MUM1 positivity begins only at the centrocyte stage and is maintained during post-GC maturation (Fig. 1) [41,44,45]. In this respect, most B-cells

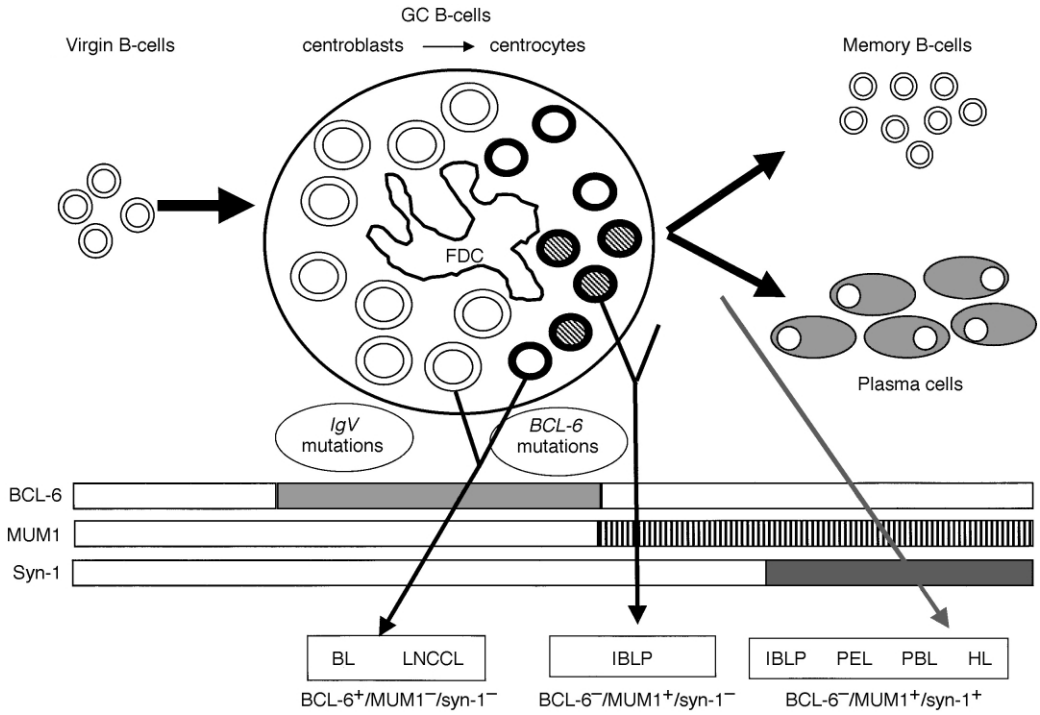

Fig. 1. A proposed model for the histogenesis of HIV-related lymphomas. The model is based on the physiological stages of mature B-cell development identified by histogenetic markers, such as mutation pattern of immunoglobulin variable region genes (*IgV*) and *BCL-6* gene and expression profile of BCL-6, MUM1 and CD138/syndecan-1 (syn-1) proteins (rectangles). Virgin B-cells do not display Ig and *BCL-6* mutations, and lack protein expression of BCL-6, MUM1 and syn-1. At the time of B-cell transit through the germinal centre (GC), B-cells acquire *IgV* and *BCL-6* mutations which are maintained during further differentiation, thus constituting genotypic markers of the GC transit. B-cells within the GC (i.e. centroblasts and centrocytes) express BCL-6 but not syn-1. Post-GC B-cells undergoing maturation towards the plasma cell stage switch off BCL-6 expression and stain positive for syn-1. The histogenetic model presented in the figure has been enriched by the addition of the MUM1 marker, which is expressed at late stages of intra-GC differentiation (centrocytes), and by post-GC B-cells undergoing plasma cell maturation. GC B-cells are identified as follows: centroblasts, large open circles; MUM1− centrocytes, small open circles; MUM1+ centrocytes, small striped circles; FDC, follicular dendritic reticulum cell. The major HIV-lymphoma categories are indicated as BL (for Burkitt's lymphoma), LNCCL (for diffuse large cell lymphoma with a large non-cleaved cell morphology), IBLP (for immunoblastic lymphoma plasmacytoid), PEL (for primary effusion lymphoma), PBL (for plasmablastic lymphoma) and HL (for Hodgkin's lymphoma). The putative histogenetic derivation of each lymphoma category is indicated by an arrow originating from the relevant B-cell compartment. The common phenotypic patterns exhibited by the different categories of HIV-lymphomas are indicated in the lower part of the figure. Some lymphoma categories, namely IBLP, are characterised by histogenetic heterogeneity.

within the GC, including all centroblasts and almost all centrocytes express the BCL-6+/MUM1−/syn-1− phenotype. A small fraction of GC B-cells, located in the light zone of the GC and morphologically identifiable as a subset of centrocytes, express the BCL-6−/MUM1+/syn-1− phenotype. As such, MUM1 expression by GC cells may denote the final step of intra-GC B-cell differentiation, i.e. late centrocytes (Fig. 1). On GC exit, B-cells retain MUM1 expression and start to express syn-1, as documented by the observation that post-GC B-cells undergoing maturation towards the plasma cell stage predominantly display the BCL-6−/MUM1+/syn-1+ phenotype (Fig. 1). Because many MUM1-positive cells in the GC are negative for syn-1, MUM1 expression most likely precedes syn-1. Consequently, MUM1 provides a novel histogenetic marker denoting B-cell transition from BCL-6 positivity (GC B-cells) to syn-1 expression (immunoblasts and plasma cells).

The phenotypic profiles displayed by AIDS-NHL, combined with the distribution of MUM1, BCL-6 and syn-1 among the normal B-cell subsets, point to a histogenetic model of these neoplasms [47]. According to this model (Fig. 1), AIDS-BL and systemic AIDS-DLCL belonging to the LNCCL morphological variant express the BCL-6+/MUM1−/syn-1− phenotypic pattern and closely reflect B-cells residing in the GC, namely centroblasts and early (i.e. MUM1-negative) centrocytes. AIDS-IBLP, either systemic or primarily localised to the central nervous system (AIDS-PCNSL), appear to be characterised by a certain degree of histogenetic heterogeneity since these lymphomas may reflect either classical post-GC B-cells (BCL-6−/MUM1+/syn-1+) or late centrocytes/early post-GC B-cells (BCL-6−/MUM1+/syn-1−). Finally, AIDS-PEL, AIDS-PBL and HIV-HL consistently display the BCL-6−/MUM1+/syn-1+ phenotype and therefore reflect post-GC B-cells in all cases.

4. Conclusions

After more than 10 years of biological research on AIDS-NHL, the emerging picture substantiates two facts. First, different clinicopathological categories of AIDS-related lymphoma derive from distinct B-cell subsets and associate with different pathogenetic pathways. Second, the host's background selects which type of AIDS-related lymphoma will develop in a given patient.

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