

## REVIEW

## Burkitt's lymphoma: new insights into molecular pathogenesis

C Bellan, S Lazzi, G De Falco, A Nyongo, A Giordano, L Leoncini

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The World Health Organisation classification reports three subcategories of Burkitt's lymphoma (BL)—endemic, non-endemic, and immunodeficiency associated—proposed to reflect the major clinical and genetic subtypes of this disease. These different types of BL have been reviewed and studied by immunohistochemistry and molecular methods. The results point out the heterogeneity of BL and suggest that AIDS related BL may have a different pathogenesis from that of classic BL.

In 1958, Dennis Burkitt first described a disorder associated with jaw tumours in African children.<sup>1</sup> In 1961, the neoplasm was identified as a form of malignant lymphoma, and what had initially emerged as a clinical syndrome became a pathological entity called Burkitt's lymphoma (BL).<sup>2</sup> Histologically, Burkitt's tumours are composed of monomorphic, medium sized cells with round nuclei, multiple nucleoli, and relatively abundant basophilic cytoplasm, which may give the cells a "cohesive appearance" (fig 1). These tumours have an extremely high rate of proliferation, in addition to a high rate of cell death (apoptosis). A "starry sky" pattern is usually present, imparted by numerous benign macrophages that have ingested apoptotic tumour cells. The cell of origin of BL is currently thought to be a germinal centre B cell,<sup>3</sup> although several studies of IgHV genes in BLs suggest that they may derive from memory B cells rather than germinal centre B cells.<sup>4</sup>

"Most AIDS related Burkitt's lymphomas in Western countries are Epstein-Barr virus (EBV) negative, whereas in Africa they are strongly associated with EBV"

BL occurs as an Epstein-Barr virus (EBV) associated malignancy among children in the malaria belt of equatorial Africa (endemic BL),<sup>5</sup> and sporadically in other geographical areas, where it also occurs among adults (sporadic BL).<sup>6,7</sup> The most common site of involvement of endemic BL is the kidneys. Jaw tumours are age related with an overall incidence in Uganda of 50%.<sup>7</sup> In contrast, the terminal ileum and lymph nodes are the more commonly involved sites in sporadic BL.<sup>8,9</sup> A common translocation t(8;14) and the consequent c-myc rearrangement and overexpression have been identified in endemic and sporadic BL. However, some not very strict associations be-

tween JH and DH recombination have been identified at 14q32, with distant 5' c-myc recombination in endemic cases of BL, whereas in sporadic cases S $\mu$  and S $\alpha$  recombination was identified<sup>10</sup> at 14q32, with near 5' or intronic c-myc recombination at 8q24. These differences between endemic and sporadic BL do not mean that each of these subtypes of lymphoma represents a perfectly homogeneous entity.<sup>5</sup> Instead, it seems probable that BL is composed of a mixture of molecular types and that the incidence of each subtype might depend upon environmental factors.<sup>8,11</sup> Yet, the sporadic form of BL can also occur in endemic areas,<sup>12</sup> as reported in table 1, which summarises the distribution of BL collected from endemic areas of Kenya according to the age of patients, the clinical pathological characteristics, and the EBV and human immunodeficiency virus (HIV) status. These observations emphasise the importance of precise disease definition for biological and epidemiological studies. In particular, it is interesting that eight cases stand out from BL occurring in young adults as being HIV positive.

In fact, BL has frequently been reported as a common neoplasm in HIV infected patients,<sup>13</sup> although it is not known why BL is so common in HIV and not in other forms of immunodepression. These lymphomas, which are now better listed as "AIDS related BL",<sup>14</sup> usually display an activation of c-myc by chromosome translocations that show structural similarities to those found in patients with sporadic BL.<sup>15</sup> Nonetheless, most AIDS related BLs in Western countries are EBV negative,<sup>15</sup> whereas in Africa they are strongly associated with EBV.<sup>12</sup>

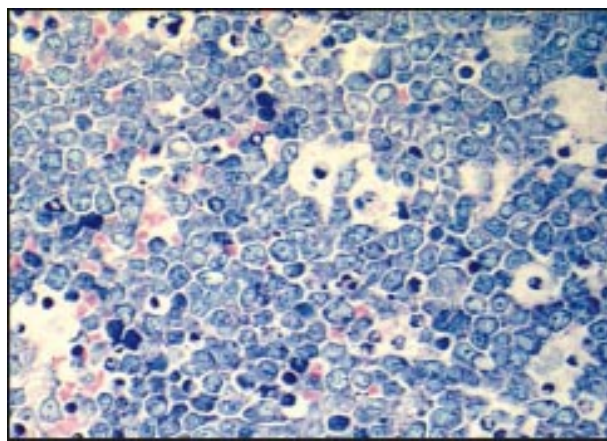
The term Burkitt-like (BL-like) lymphoma has been commonly applied to those tumours that have morphological features intermediate between large cell lymphoma with centroblastic or immunoblastic features and typical BL. The revised European-American lymphoma classification gives BL-like lymphoma provisional status, leaving the differential diagnosis between BL and diffuse large B cell lymphoma (DLBCL) unresolved.<sup>16</sup> The oncologists recommended that the category of BL-like lymphoma be reserved for tumours to be treated "like Burkitt lymphoma". A recent study by the southwest oncology group concluded that BL-like lymphoma can be recognised by its combined morphology and phenotypical features and that it represents a high

**Abbreviations:** BL, Burkitt's lymphoma; DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; Rb, retinoblastoma; WHO, World Health Organisation

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**Figure 1** Typical morphological pattern of Burkitt's lymphoma (Giemsa stained; original magnification,  $\times 375$ ).

grade lymphoma much closer to BL than DLBCL.<sup>17</sup> In the World Health Organisation (WHO) classification, BL-like lymphoma is listed as a morphological variant of BL (atypical BL), in addition to the three subcategories—endemic, sporadic, and immunodeficiency associated—proposed to reflect the major clinical and genetic subtypes of this disease.<sup>14</sup> In the WHO classification, the definition of atypical BL is a lymphoma that morphologically resembles BL, but has more pleiomorphism or larger cells than classic BL, and has a proliferation fraction of  $> 90\%$ . The necessary cytogenetics for the diagnosis of BL should be the presence of the t(8;14) (q24;q32) translocation and its variants, or c-myc rearrangement. If cytogenetic or Southern blot cannot be applied to solid tumours the most reasonable surrogate for c-myc rearrangement is probably the proliferation fraction. Therefore, cases in which cytogenetic analysis is not available should not be diagnosed as BL or BL-like without a Ki-67 fraction close to 100%.<sup>14</sup>

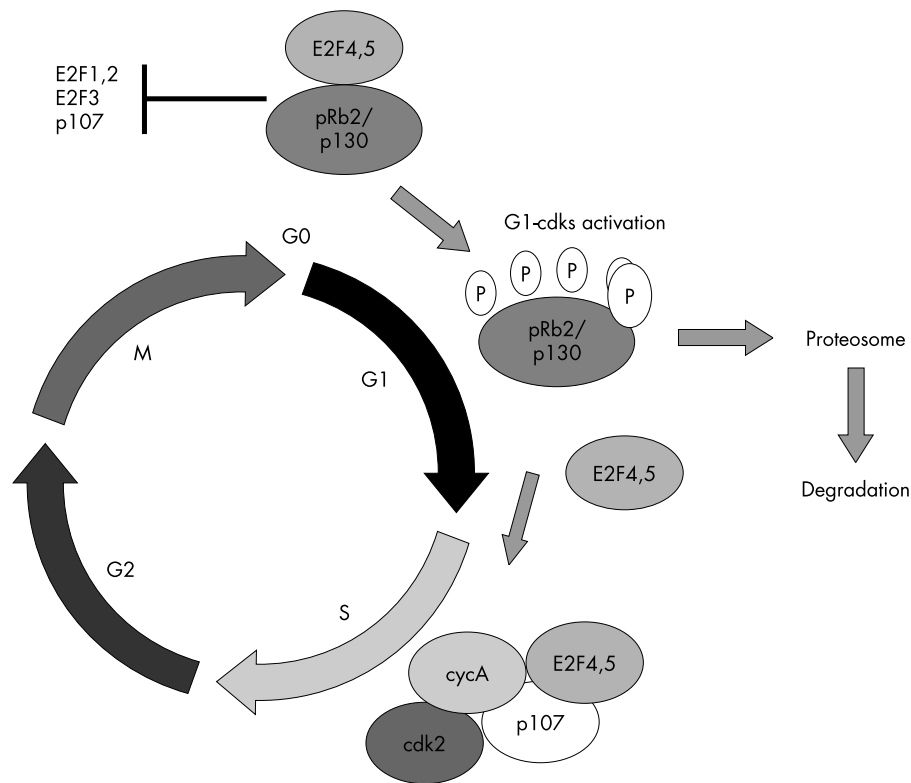
**Table 1** Distribution of BL collected from endemic areas according to the age of patients, the clinicopathological characteristics, and EBV and HIV status

	BL age under 16 years (range 2–16; median 6)	BL age over 16 years (range, 17–58; median 29)
Total cases	23	16
Male/Female	14/9	10/6
Site		
Jaw	16	2
Nodal	3	7
Ileum	2	5
Other	2	2
HIV	0	8
EBV	21	12

BL, Burkitt's lymphoma; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.

The morphological similarity between BLs probably results from the fact that they all have a common translocation, t(8;14), and consequent c-myc rearrangement and overexpression. However, it is also true that BLs account for only 30% of lymphomas bearing a c-myc translocation at presentation.<sup>18</sup> Furthermore, the c-myc translocation is not the only genetic lesion found in BL,<sup>8</sup> and myc transformed cells are usually characterised by the loss of expression of several genes.<sup>19</sup> Cooperating alterations of cell cycle associated genes probably contribute to the pathogenesis of BL.<sup>8, 20</sup> p53 mutations have been found in 30–40% of BL samples,<sup>21</sup> and most lymphomas with wild-type p53 might have lesions in other growth suppressor genes.<sup>22</sup>

“The necessary cytogenetics for the diagnosis of Burkitt's lymphoma should be the presence of the t(8;14) (q24;q32) translocation and its variants, or c-myc rearrangement”



**Figure 2** In quiescent G0 cells, the nuclear E2F-pRb2/p130 complex is responsible for the active repression of several cellular promoters. After its release into the cell cycle, pRb2/p130 is phosphorylated by G1 cyclin dependent kinases (cdks) and subsequently degraded through a proteasome dependent mechanism, resulting in the derepression of a variety of genes, including p107. The accumulated p107 protein is then able to interact with E2F4 and E2F5, which have been released from pRb2/p130, and associate with cyclin A (cyc A)/cdk2.

**Table 2** Distribution of Rb2/p130 gene mutations according to endemic, sporadic, and AIDS related Burkitt's lymphoma

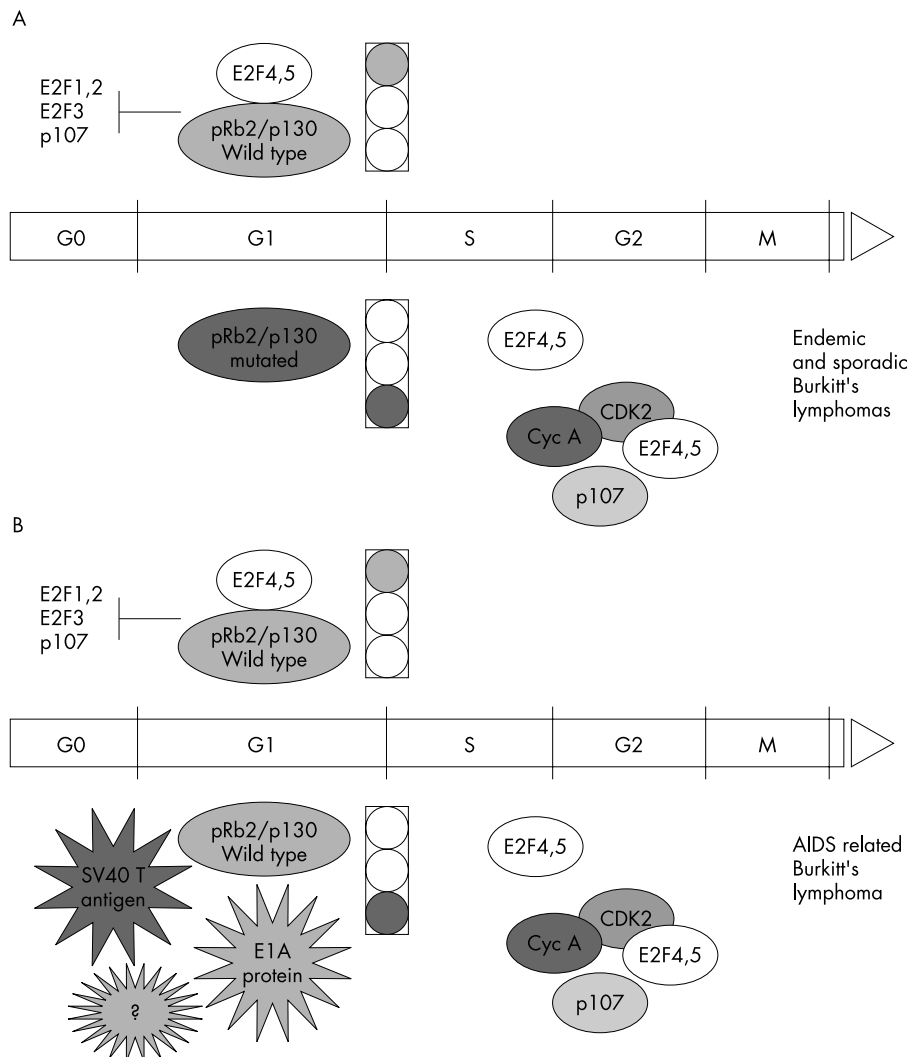
	Rb2/p130 mutated	Rb2/p130 wild type
Endemic Burkitt's lymphoma	16/19	3/19
Sporadic Burkitt's lymphoma	6/13	7/13
AIDS related Burkitt's lymphoma	0/11	11/11

Recently, mutations of the nuclear localisation signal of the Rb2/p130 tumour suppressor gene have also been detected in BL cell lines and primary tumours.<sup>23</sup> The pRb2/p130 tumour suppressor gene belongs to the retinoblastoma (Rb) gene family, along with Rb and p107. Although they have similar functional properties, Rb family members are not functionally redundant and each protein has a different temporal profile of interaction with different E2F members.<sup>23-25</sup> Whereas Rb is found in both quiescent and proliferating cells, the expression of Rb2/p130 and p107 is related to the cell cycle.<sup>26</sup> In an ideally controlled proliferating cell population with identical cell cycle and cycle phase times, during which a given protein can be detected in the nucleus by the corresponding antibody, the percentages of cells expressing pRb2/p130 and p107 should be inversely correlated (fig 2).<sup>27</sup> Although such a pattern of Rb2/

p130 and p107 expression has been demonstrated in different types of non-Hodgkin's lymphomas, this is not the case in BLs.<sup>28</sup>

The Rb2/p130 gene is mutated in most cases of endemic BL and to a lesser extent in sporadic BL. In contrast, in AIDS related BL, the wild-type pRb2/p130 gene is highly expressed (table 2).<sup>28, 29</sup> In those tumours in which the Rb2/p130 gene is mutated, the interaction between individual proteins and E2F family members and the timing of formation of particular protein-E2F complexes during the cell cycle can be deregulated (fig 3A).<sup>25</sup> In addition to mutations of the gene, interaction with viral oncoproteins is another important mechanism of pRb2/p130 inactivation.<sup>30-31</sup> pRb2/p130 shares, with all members of the retinoblastoma gene family, the ability to interact physically with certain DNA virus oncoproteins (fig 3B); by this mechanism, pRb2/p130 is inactivated yet maintained in its underphosphorylated form.<sup>30-34</sup> Thus, the absence of mutations in the Rb2/p130 gene and the unusually high expression of pRb2/p130 in tumours with high proliferative activity, such as AIDS related BL, may suggest a physical interaction of pRb2/p130 with viral products.

Although HIV-1 has long been recognised as the aetiological agent of AIDS, the role of HIV-1 as an oncogenic virus has not yet been well established. Data exist that clearly suggest that the HIV gene product Tat can contribute to the growth and oncogenesis of human and animal cells.<sup>35</sup> Soluble Tat can function as a biologically active extracellular protein released by infected cells and readily taken up by uninfected cells.<sup>36, 37</sup>



**Figure 3** (A) In the tumours where the Rb2/p130 gene is mutated, the interaction between individual proteins and E2F family members and the timing of formation of particular protein-E2F complexes during the cell cycle can be deregulated. (B) pRb2/p130 shares, with all members of the retinoblastoma gene family, the ability to interact physically with certain DNA virus oncoproteins, including simian virus 40 large T antigen and adenovirus E1A protein; by this mechanism, pRb2/p130 is inactivated. CDK, cyclin dependent kinase; Cyc A, cyclin A.

**Take home message**

- It is possible that different pathogenetic mechanisms exist among Burkitt's lymphoma subtypes
- The Rb2/p130 oncosuppressor protein may be one of the targets in the interaction between human immunodeficiency virus (HIV) type 1 and host proteins
- The study of HIV associated lymphomas may provide a rich opportunity to explore aetiological interactions between HIV gene products and host cell cycle related proteins

This has also been shown to occur in AIDS related B cell lymphomas, by the diffuse and nuclear staining seen in tissue sections immunostained with anti-Tat monoclonal antibody.<sup>29</sup> In addition, there is experimental evidence that extracellular Tat acts directly on B cells.<sup>38</sup> In particular, germinal centre B cell proliferation was enhanced by the addition of Tat at the initiation of the culture, suggesting that Tat acts on the early stage of B cell activation, probably before the G1 to S phase transition.<sup>39</sup> This is in line with new data indicating that the well established function of Rb2/p130 in the control of the G0/G1 transition can be inactivated by physical interaction with the Tat protein of HIV-1. In fact, the results of an in vitro and in vivo binding assay suggest that the Tat protein of HIV-1 is one of those viral oncoproteins that interact with the Rb family. In particular, they revealed that the Tat protein of HIV-1 interacts specifically with the pocket region of the Rb2/p130 protein.<sup>29</sup> This can result in the inactivation of Rb2/p130 oncosuppressive properties and the induction of genes needed to proceed through the cell cycle including p107, cyclin A, and cyclin B.<sup>28</sup> Consequently, some B cell clones among a virus induced B cell proliferation might have an uninterrupted cell cycle and a growth advantage, thus favouring the incidence of B cell malignancies in lymphoid organs of HIV-1 positive patients. Increased cell proliferation has been shown to account almost entirely for tumour prevalence in immunocompromised patients.<sup>40</sup> Spontaneous regression of HIV-1 associated lymphoproliferative disorders has been reported after highly active antiretroviral therapy.<sup>41-43</sup>

"New data indicate that the well established function of Rb2/p130 in the control of the G0/G1 transition can be inactivated by physical interaction with the Tat protein of human immunodeficiency virus 1"

In conclusion, our data provide evidence that different pathogenetic mechanisms may occur among BL subtypes and that the Rb2/p130 oncosuppressor protein may be one of the targets in the interaction between the HIV-1 and host proteins. The study of HIV associated lymphomas may provide a rich opportunity to explore the aetiological interactions between HIV gene products and host cell cycle related proteins.

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Some of the results contained in this paper have already been presented at the XI Meeting of the European Association of Haematopathology, held in Siena on 26-30 May 2002.

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## ECHO

### Troponin T better than standard enzymes for estimating extent of myocardial infarct



Please visit the Journal of Clinical Pathology website [[www.jclinpath.com](http://www.jclinpath.com)] for link to this full article.

One measurement of the protein troponin T 72 hours after the start of chest pain is better than using standard enzyme tests to estimate the extent of tissue damage following heart attack, concludes German research.

Creatine kinase, CK-MB, and lactate dehydrogenase require serial sampling to identify peak or cumulative serum concentrations and depend on coronary reperfusion. Furthermore, these enzymes are not exclusive to the myocardium and increases could indicate causes other than myocardial cell damage.

Enzyme activities and serum troponin T were measured after the start of chest pain in 37 patients with a first time heart attack. Blood samples were drawn every four hours on day 1, every eight hours on days 2 and 3, and then once daily until day 10. All but 14 (group 1) had early coronary reperfusion (group 2). Quantitative single photon emission computed tomography thallium-201 scintigraphy was performed at rest two to three weeks after symptoms had begun.

Troponin T concentrations peaked briefly within the first 24 hours, and then again on days 3 to 4 in both groups. The extent of irreversible myocardial damage, indicated by scintigraphy, was accurately reflected in troponin T concentrations taken 72 hours after the start of symptoms in both groups.

The authors conclude that a single measurement of troponin T, taken 72 hours after the start of chest pain, is simple, reliable, and better than enzyme methods.

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