PERGAMON

European Journal of Cancer 37 (2001) 1184–1187

European Journal of Cancer

www.ejconline.com

Acquired immunodeficiency syndrome-related cancer. A study model for the mechanisms contributing to the genesis of cancer

A. Carbone [a,*], G. Gaidano [b]

[a] *Division of Pathology and Scientific Direction, Centro di Riferimento Oncologico, IRCCS, Istituto Nazionale Tumori, Via Pedemontana Occidentale, Aviano I-33081, Italy*

[b] *Division of Internal Medicine, Department of Medical Sciences, "Amedeo Avogadro" University of Eastern Piedmont, Novara, Italy*

Received 5 February 2001; accepted 5 March 2001

Abstract

The study of AIDS and cancer has resulted in an important convergence of clinical–epidemiological investigations, molecular research and virological studies. This shared effort has led to significant discoveries in the field of human carcinogenesis. In a relatively short time, several topics have been clarified, namely:

- The spectrum of AIDS-related tumours has been identified;
- The role of HIV in lymphomagenesis and in the development of Kaposi's sarcoma (KS) has been defined;
- AIDS-related cancers have allowed the discovery and extensive biological characterisation of the novel virus human herpes virus type 8 (HHV8), also called KS-associated herpesvirus;
- Genetic, molecular and phenotypic studies of AIDS-related lymphomas have contributed to the formulation of a pathogenetic and histogenetic model of B-cell non-Hodgkin's lymphomas (NHL). © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: AIDS; Cancer; Lymphomagenesis; Human carcinogenesis

1. Introduction

Soon after the beginning of the AIDS epidemic in the early 1980s, AIDS resulted in the development of many different diseases, many of them fatal, that had never before been observed in a single person. This association of concomitant infectious and neoplastic diseases has placed a great burden on patients, many of whom are young, and has confronted physicians with unknown and unexpected medical problems.

Because of the effects of HIV infection on human society, an intense convergence of clinical–epidemiological investigations, molecular research and virological studies has occurred. This joint effort has led to significant discoveries in the field of human carcinogenesis. In a relatively short time, several topics have been clarified, in particular those identified below.

1.1. The spectrum of AIDS-related tumours has been identified [1–3]

The cancers currently considered as AIDS-defining include Kaposi's sarcoma (KS), high-grade non-Hodgkin's lymphomas (NHL) and uterine cervical carcinomas. Interestingly, each of these distinct neoplasms has been associated with a specific viral infection in addition to HIV: KS with human herpesvirus type 8 (HHV8); a subset of NHL with Epstein–Barr virus (EBV) and/or HHV8; cervical carcinoma with human papilloma virus (HPV).

The interaction of HHV8, EBV and HPV with the disrupted immunological and cytokine milieu induced by HIV has allowed the understanding of the pathogenetic mechanisms involved in the development of AIDS-related cancers.

1.2. The role of HIV in lymphomagenesis and in the development of KS has been defined [4]

Regarding NHL, the consistent failure to unequivocally detect HIV sequences within the tumour clone

* Corresponding author. Tel.: +39-434-659292; fax: +39-434-659370.

E-mail address: acarbone@cro.it (A. Carbone).

0959-8049/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0959-8049(01)00102-2

suggests that HIV is not directly implicated in the transformation of B-cells *in vivo*. Rather, the role of HIV in lymphomagenesis appears to be predominantly indirect and related to the disrupting effects of the virus on host's immune regulation. Immunological alterations induced by HIV include reduced immunosurveillance, chronic antigen stimulation and cytokine dysregulation, which have all been shown to play a role in lymphomagenesis of HIV-infected persons. These alterations induced by HIV result in B-cell oligoclonal expansion and proliferation, which commonly occur in the early phases of HIV infection. In clinical and pathological terms, the phase of oligoclonal B-cell expansion and proliferation corresponds to persistent generalised lymphadenopathy. In subsequent phases, the neoplastic transformation of a B-cell clone is due to the accumulation of genetic lesions which eventually transform the clone into a true NHL. This model of lymphomagenesis, initially developed for NHL associated with HIV, may be applicable also to other examples of virus-associated lymphomagenesis (Fig. 1).

KS lesions are composed of various cellular lineages, conceivably represented in great part by endothelial cells and fibroblastoid cells, which proliferate in response to several growth factors. The Tat protein of HIV has been shown to harbour angiogenic properties in animal models and to stimulate the growth of KS spindle cells *in vitro*, and may therefore be a factor for the development of KS lesions. The effects of HIV Tat combine and synergise with the immunosuppression induced by HIV and with the inflammatory state created by HHV8 infection, which are additional major factors implicated in the development of KS.

1.3. AIDS-related cancers have allowed the discovery and extensive biological characterisation of the novel virus HHV8, also called Kaposi's sarcoma-associated herpesvirus [5,6]

HHV8 was initially discovered in AIDS-related KS tissues, a tumour that was subsequently found to be consistently infected by this novel virus. Beside KS, HHV8 has also been also associated with several lymphoproliferative disorders. The virus is consistently found in primary effusion lymphomas (PEL), also known as body cavity-based lymphomas, as well as in all HIV-associated and in a proportion of HIV-unrelated multicentric Castleman's disease tissues.

PEL has been instrumental in determining the genomic sequence of HHV8, as well as in establishing the expression pattern and function of several of the genes harboured by the virus. In this respect, a major tool toward the understanding of HHV8 biology has been obtained with the establishment and detailed

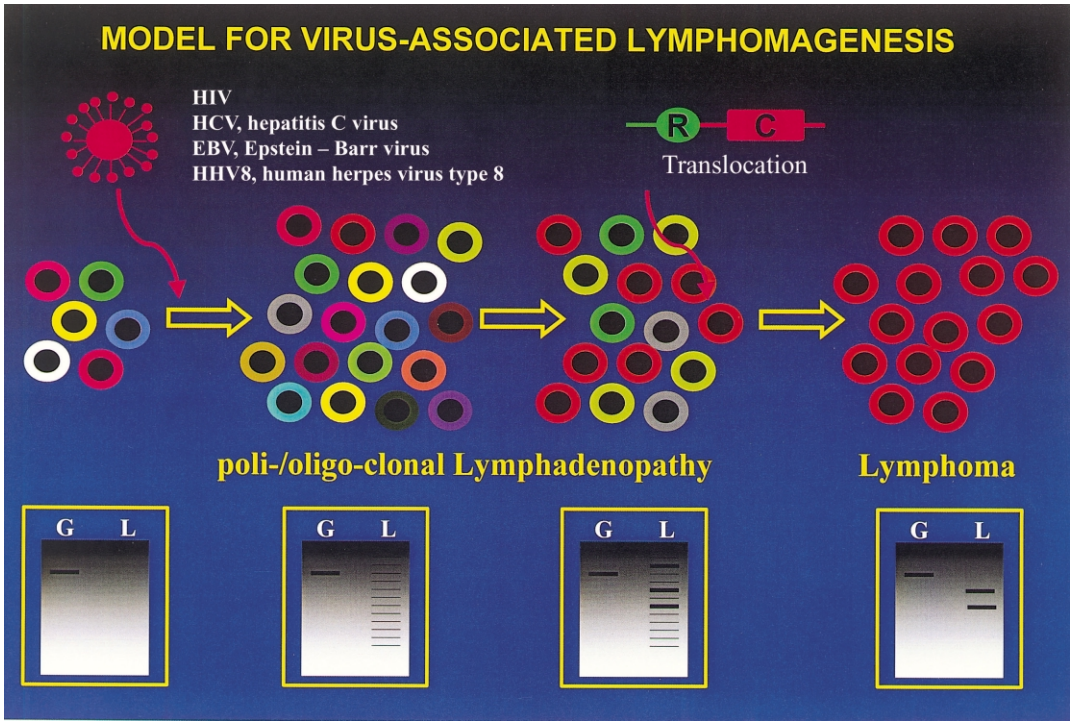

Fig. 1. A proposed model for the pathogenesis of virus-associated non-Hodgkin's lymphomas (NHL). In the initial stages, host predisposing conditions (B-cell chronic stimulation, HIV-induced cytokine deregulated production, immunosurveillance alterations) favour the development of a polyclonal to oligoclonal B-cell hyperplasia. On this basis, multiple genetic lesions accumulate within one single clone inducing its neoplastic transformation. The progression from poly-oligoclonality to monoclonality is depicted by schematic profiles of immunoglobulin gene rearrangement analysis (G, germ line; L, lymphoid lesion).

characterisation of a number of PEL cell lines representative of EBV-positive and negative PEL. In particular, the use of PEL cell lines has been instrumental for the first serodiagnostic assays of HHV8 infection. In addition, manipulation of PEL cell lines by the induction of lytic phase infection has allowed the grouping of HHV8 genes into different classes depending on whether they are expressed in the latent or lytic phases.

1.4. Genetic, molecular and phenotypic studies of AIDS-related lymphomas have contributed to the formulation of a pathogenetic and histogenetic model of B-cell non-Hodgkin's lymphomas [7–11]

Research performed during the last decade has led to the notion that AIDS-NHL are heterogeneous in terms of (i) target cell derivation, (ii) pathogenetic pathway, and (iii) immunological status of the tumour host. As molecular alterations similar to those harboured by AIDS-NHL are already present in HIV-infected individuals before lymphoma development, it is conceivable that host factors select which genetic pathways will be activated in a given patient.

At present, four major molecular pathways can be identified. Each of these molecular pathways associates with peculiar clinical features and is restricted to a given AIDS-NHL histological type. The first pathway associates with AIDS-Burkitt lymphoma (BL) and is characterised by relatively mild immunodeficiency of the host and multiple genetic lesions of the tumour, including activation of *c-MYC*, disruption of *TP53*, and, less frequently, infection by EBV. Typically, EBV-infected AIDS-BL fail to express the viral transforming antigens Latent Membrane Protein-1 (LMP-1) and Epstein–Barr Virus nuclear antigen-2 (EBNA-2). Histogenetic studies have shown that AIDS-BL derives from germinal centre (GC) B-cells, of which the lymphoma closely mimics the phenotype.

Two distinct pathways associate with AIDS-diffuse large cell lymphomas (DLCL), a type of AIDS-NHL frequently characterised by a marked disruption of immune function. Whereas the majority of AIDS-DLCL are EBV-positive, only a fraction of cases express the viral antigen LMP-1. Expression of LMP-1 and BCL-6 segregate the two pathways associated with AIDS-DLCL. On the one hand, LMP-1-positive AIDS-DLCL fail to express the BCL-6 protein and display

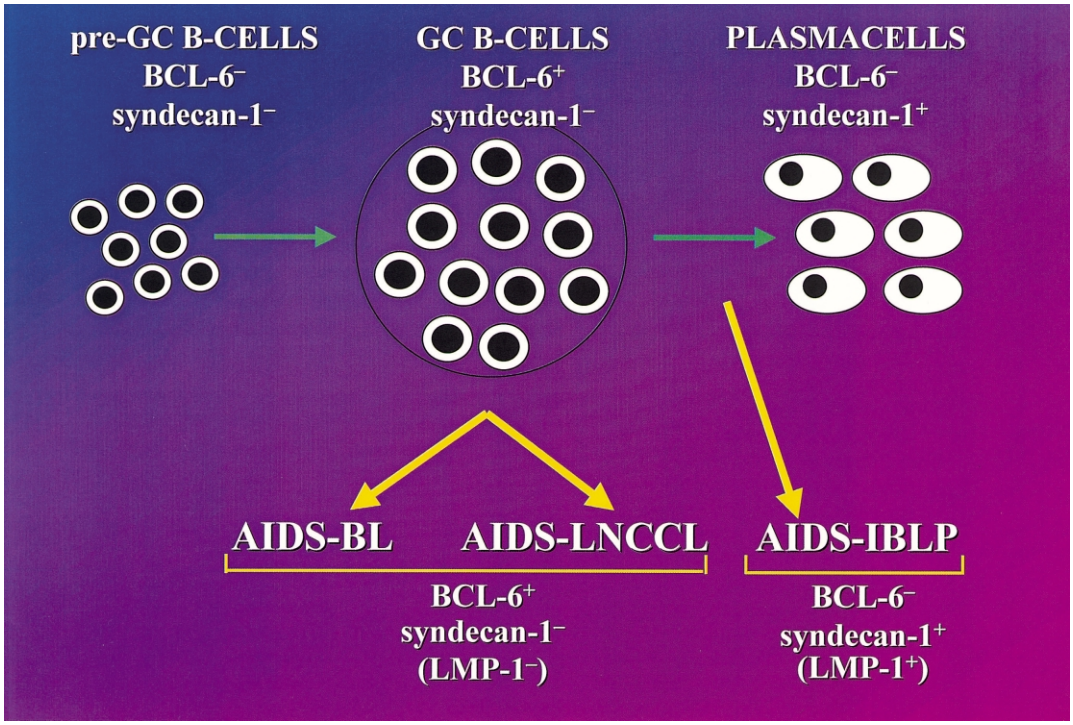

Fig. 2. A proposed model for the histogenesis of systemic AIDS-related non-Hodgkin's lymphomas (AIDS-NHL). The model is derived from the expression profile of BCL-6 and CD138/syndecan-1 (syn-1) throughout physiological B cell maturation. B cells within the germinal center (GC) display the BCL-6$^+$/syn-1$^-$ phenotype, whereas B cells that have exited the GC and have undergone further maturation toward the plasma cell stage exhibit the BCL-6$^-$/syn-1$^+$ phenotype. Systemic AIDS-NHL displaying the BCL-6$^+$/syn-1$^-$ phenotype, i.e., AIDS-Burkitt lymphoma (AIDS-BL) and AIDS-diffuse large cell lymphomas which display a large non-cleaved cell morphology (AIDS-LNCCL), are postulated to originate from GC B cells. Conversely, systemic AIDS-NHL displaying the BCL-6$^-$/syn-1$^+$ phenotype, i.e., AIDS-immunoblastic-plasmacytoid lymphoma (AIDS-IBLP), are postulated to derive from post-GC, preterminally differentiated B cells. In the case of systemic AIDS-NHL infected by Epstein–Barr virus (EBV), only the BCL-6$^-$/syn-1$^+$ phenotype is permissive for expression of the EBV-encoded antigen LMP1. Conversely, expression of LMP1 is consistently absent among AIDS-NHLs displaying the BCL-6$^+$/syn-1$^-$ phenotype.

features consistent with immunoblastic-plasmacytoid differentiation, suggesting a derivation from post-GC cells. On the other hand, LMP-1-negative AIDS-DLCL express BCL-6 and display a large non-cleaved cell morphology, suggesting an origin from the GC (Fig. 2).

Finally, the fourth pathway associates with AIDS-PEL. This rare lymphoma type consistently harbours infection by HHV8 and, frequently, also by EBV. All other genetic lesions commonly detected among AIDS-NHL are consistently negative in AIDS-PEL. Histogenetic studies have shown that PEL reflects a post-GC stage of differentiation close to plasma cells.

The identification of the molecular and histogenetic heterogeneity of AIDS-NHL is of potential clinical value, because the molecular and histogenetic features of the tumour have been shown to influence the prognosis of several B-cell disorders of immunocompetent hosts.

2. Conclusions

New information on the molecular and virological pathogenesis of AIDS-related cancers is uncovering many potential targets for therapy. Eventually, it is conceivable that the biological features specific of each type of AIDS-related cancer may be exploited for therapeutic strategies targeted at the genetic alteration of the tumour. As in general for human neoplasias, however, the clinical application of gene therapy will have to overcome several obstacles which now prevent its widespread use. At present, several ongoing clinical trials exploit the biological knowledge of AIDS-related cancers for stratification of patients according to prognosis and for immunological and/or cytokine treatment of these tumours. Ongoing trials of AIDS-NHL with anti-CD20 antibodies represent an example of 'intelligent' therapy which is based on knowledge of the biological features of the tumour.

As this work progresses, an additional primary focus of therapy is to sustain a high level of cellular immunity with effective antiretroviral therapy, since clinical, epidemiological and biological studies have clearly shown that immune suppression is a major player in the development of cancer in HIV-infected patients.

Acknowledgements

Work by the authors described in this review has been supported by Istituto Superiore di Sanità, III Programma Nazionale di Ricerca sull'AIDS 1999 — Progetto Patologia, Clinica e Terapia dell'AIDS, Rome, Italy; Progetto di ricerca finalizzata ''Nuovi marcatori molecolari e sierologici nella linfomagenesi virus-associata'', Ministero della Sanita', Rome, Italy.

References

1. Gaidano G, Carbone A. AIDS-related lymphomas: from pathogenesis to pathology. *Br J Haematol* 1995, **90**, 235–243.
2. Goedert JJ, Coté TR, Virgo P, *et al*. Spectrum of AIDS-associated malignant disorders. *Lancet* 1998, **351**, 1833–1839.
3. Levine AM. Acquired immunodeficiency syndrome-related lymphoma: clinical aspects. *Semin Oncol* 2000, **27**, 442–453.
4. *Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 67. Lyon, International Agency for Research on Cancer/World Health Organization, 1996.
5. Sarid R, Flore O, Boehenzky RA, Chang Y, Moore PS. Transcription mapping of the Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) genome in a body cavity-based lymphoma cell line (BC-1). *J Virol* 1998, **75**, 1005–1012.
6. Gaidano G, Carbone A. Primary effusion lymphoma. A liquid phase lymphoma of fluid-filled body cavities. *Adv Cancer Res* 2001, **80**, 116–146.
7. Ballerini P, Gaidano G, Gong JZ, *et al*. Multiple genetic lesions in acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma. *Blood* 1993, **81**, 166–176.
8. Gaidano G, Carbone A, Dalla-Favera R. Pathogenesis of AIDS-related lymphomas: molecular and histogenetic heterogeneity. *Am J Pathol* 1998, **152**, 623–630.
9. Carbone A, Gloghini A, Gaidano G, *et al*. Expression status of BCL-6 and syndecan-1 identifies distinct histogenetic subtypes of Hodgkin's disease. *Blood* 1998, **92**, 2220–2222.
10. Gaidano G, Capello A, Carbone A. The molecular basis of acquired immunodeficiency syndrome-related lymphomagenesis. *Semin Oncol* 2000, **27**, 431–441.
11. Carbone A, Gloghini A, Larocca LM, *et al*. Expression profile of MUM1/IRF4, BCL-6, and CD138/syndecan-1 defines novel histogenetic subsets of human immunodeficiency virus-related lymphomas. *Blood* 2001, **97**, 744–751.