Acknowledgments: This work was supported by the Swedish Council for Working Life and Social Research and Deutsche Krebshilfe.

Contribution: K.H. conceived the study and wrote the paper; A.F. commented on the results; X.L. carried out statistical analysis; and J.S. and K.S. provided the database. All authors read and approved the final manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Kari Hemminki, German Cancer Research Center, Im Neuenheimer Feld 280, Heidelberg, 69120 Germany; e-mail: k.hemminki@dkfz.de.

References

1. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. *Amyloid.* 2010;17(3-4):101-104.
2. Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. *J Clin Oncol.* 2011;29(14):1924-1933.
3. Telio D, Bailey D, Chen C, Crump M, Reece D, Kukreti V. Two distinct syndromes of lymphoma-associated AL amyloidosis: a case series and review of the literature. *Am J Hematol.* 2010;85(10):805-808.
4. Benson MD. The hereditary amyloidoses. *Best Pract Res Clin Rheumatol.* 2003;17(6):909-927.
5. Suhr OB, Svendsen IH, Andersson R, Danielsson A, Holmgren G, Ranløv PJ. Hereditary transthyretin amyloidosis from a Scandinavian perspective. *J Intern Med.* 2003;254(3):225-235.
6. Hemminki K, Li X, Försti A, Sundquist J, Sundquist K. Incidence and survival in non-hereditary amyloidosis in Sweden. *BMC Public Health.* 2012;12:974.
7. Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med.* 2008;40(3):232-239.
8. Westermark P. Systemic amyloidoses—new treatment methods make early and exact diagnosis more and more important. *Lakartidningen.* 2007;104(19):1517-1521.

To the editor:

The microenvironment of AIDS-related diffuse large B-cell lymphoma provides insight into the pathophysiology and indicates possible therapeutic strategies

We read with great interest the article by Liapis and Colleagues[1] that was published in *Blood* on May 7, 2013 (online ahead of print). The authors investigated the tumor, microenvironment, and viral components in AIDS-related diffuse large B-cell lymphoma (DLBCL). The results of the study showed that AIDS-related DLBCL is highly angiogenic, with markedly higher blood-vessel density than sporadic DLBCL cases. Importantly, the investigation also highlighted the role of Epstein-Barr virus (EBV) in angiogenesis.[1] In a previous work,[2] we used gene expression profile (GEP) analysis (~12 000 genes) to further define the phenotype of AIDS-related non-Hodgkin lymphoma (AIDS-NHL).[2] The AIDS-NHL cases selected for the study included several subtypes displaying distinct histologic appearance. Indeed, the spectrum of AIDS-NHL ranged from DLBCL of the centroblastic or immunoblastic type to primary effusion lymphoma and Burkitt lymphoma. In agreement with their distinct morphologic appearance, the results indicated that EBV-positive AIDS-DLBCL of the immunoblastic type (AIDS-DLBCL-IB) represented a separate entity relative to AIDS-NHL. Among the various subtypes of AIDS-NHL, EBV-positive AIDS-DLBCL-IB seemed to be more similar to primary effusion lymphoma.[2]

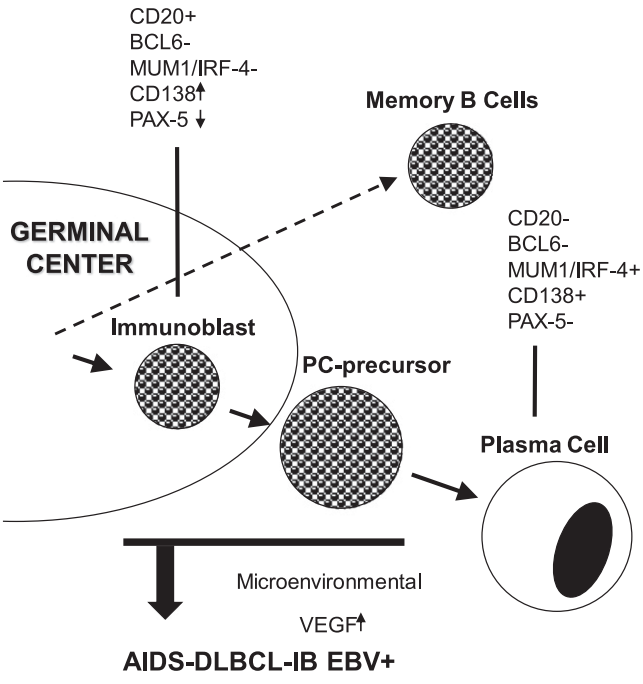

Figure 1. EBV-positive AIDS-related DLBCLs of the immunoblastic type display a phenotype related to plasma cells. The tumor cells display immunoblast-associated antigens together with plasma-cell–associated markers. The figure also shows the putative role of EBV in the microenvironmental angiogenesis by inducing vascular endothelial growth factor (VEGF) upregulation.

Since an additional aim of the original work[2] was to investigate the relationship of AIDS-NHL to normal B cells and to AIDS-unrelated NHL, we would like to raise 2 more questions about EBV-positive AIDS-DLBCL-IB: (1) what is the relationship with the supposed lymphoma counterpart in immunocompetent hosts?, and (2) where do tumor cells derive from? To determine the relationship with the lymphoma counterpart in the immunocompetent hosts, we compared GEPs by unsupervised and supervised analyses. The results of the comparative analysis revealed that AIDS/Burkitt lymphoma and AIDS-DLBCL of the centroblastic type, but not EBV-positive AIDS-DLBCL-IB, were indistinguishable from their counterparts in immunocompetent hosts. To define the cellular origin, we compared the GEPs of the individual AIDS-NHL cases with the specific gene expression signatures of normal B-cell subsets. We included in the comparative analysis EBV-immortalized B-cell lines as representative of immunoblasts and multiple myeloma cell lines as representative of the terminally differentiated plasma cell stage. We found relatedness of the GEP of the EBV-positive AIDS-DLBCL-IB cases to the multiple myeloma cell lines. In summary, EBV-positive AIDS-DLBCL-IB represented a distinct entity when compared with the other AIDS-NHL subtypes and its supposed counterpart in immunocompetent hosts. Moreover, by GEP analysis, EBV-positive AIDS-DLBCL-IB displayed a phenotype related to plasma cells (Figure 1).[3] This finding was not surprising, since it is known that

EBV infection in AIDS-DLBCL is consistently linked to plasmacytoid/plasmablastic differentiation.[4]

Although latency programs predominate in EBV-driven tumors, lytic EBV replication may also be of pathogenic relevance, at least in the early phases of cell transformation.[5,6] This finding is particularly relevant for AIDS-related lymphomagenesis, since the underlying impairment of immune responses may favor uncontrolled activation of EBV lytic replication in latently infected B lymphocytes. Importantly, regarding tumor microenvironment, EBV infection is implicated in angiogenic mechanisms.[5-7] In conclusion, the results reported by Liapis and colleagues[1] are consistent with genetic and virological data suggesting that in AIDS-DLBCL, neovascularization is linked to EBV status of tumor and to immunoblastic features.

Antonino Carbone
Department of Pathology, Centro di Riferimento Oncologico Aviano, Istituto Nazionale Tumori, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Aviano, Italy

Annunziata Gloghini
Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Contribution: A.C. designed the paper; and A.C. and A.G. wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Antonino Carbone, Centro di Riferimento Oncologico Aviano, Istituto Nazionale Tumori, IRCCS, Via F. Gallini 2, 33081 Aviano, Italy; e-mail: acarbone@cro.it.

References

1. Liapis K, Clear A, Owen A, et al. The microenvironment of AIDS-related diffuse large-B-cell lymphoma provides insight into the pathophysiology and indicates possible therapeutic strategies. *Blood.* 2013;122(3):424-433.
2. Klein U, Gloghini A, Gaidano G, Chadburn A, Cesarman E, Dalla-Favera R, Carbone A. Gene expression profile analysis of AIDS-related primary effusion lymphoma (PEL) suggests a plasmablastic derivation and identifies PEL-specific transcripts. *Blood.* 2003;101(10):4115-4121.
3. Carbone A. HIV-associated lymphomas - Focus on unusual lymphomas occurring specifically in HIV-infected patients. In: Proceedings from the 11th Annual International Meeting of the Institute of Human Virology. September 11-13, 2008; Baltimore, MD. Abstract 152.
4. Carbone A, Cesarman E, Spina M, Gloghini A, Schulz TF. HIV-associated lymphomas and gamma-herpesviruses. *Blood.* 2009;113(6):1213-1224.
5. Hong GK, Kumar P, Wang L, et al. Epstein-Barr virus lytic infection is required for efficient production of the angiogenesis factor vascular endothelial growth factor in lymphoblastoid cell lines. *J Virol.* 2005;79(22):13984-13992.
6. Ma SD, Hegde S, Young KH, et al. A new model of Epstein-Barr virus infection reveals an important role for early lytic viral protein expression in the development of lymphomas. *J Virol.* 2011;85(1):165-177.
7. Wang Z, Luo F, Li L, et al. STAT3 activation induced by Epstein-Barr virus latent membrane protein1 causes vascular endothelial growth factor expression and cellular invasiveness via JAK3 And ERK signaling. *Eur J Cancer.* 2010;46(16):2996-3006.

To the editor:

No familial aggregation in chronic myeloid leukemia

There is a fivefold to sevenfold elevated risk of myeloproliferative neoplasms (MPNs) among first-degree relatives of MPN patients.[1,2] In contrast, aside from early-onset patients, there is no significant familial aggregation in acute myeloid leukemia (AML).[3]

The molecular underpinnings of the development of chronic myeloid leukemia (CML) are unclear. Ionizing radiation in high doses is the only known risk factor.[4] Benzene and benzene-containing products have been reported to be significantly related to morbidity and mortality from CML,[5] although recent case-control literature indicates the opposite.[6] Apart from extremely rare pedigrees with multiple cases of CML/myeloproliferative disorders,[7] there is essentially no data on familial aggregation of CML in the population. According to The National CML Society, "Occasionally, there are families that may have other members living with leukemia, however, there is no conclusive evidence that family members are predisposed to develop leukemia."[8]

Taking advantage of high-quality registry data from Sweden, we conducted a population-based registry study to evaluate risk of CML, MPN, AML, and other malignancies among 9491 first-degree relatives of 4619 patients (45% females) with CML compared with 42 474 first-degree relatives of matched controls. Our methods have been previously described.[3] In brief, using the Swedish Cancer Registry, we identified all patients with a primary diagnosis of CML diagnosed between 1958 and 2004. For each CML patient, 4 population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish population database. All control individuals had to be alive at the time of CML diagnosis for their corresponding case patient and without a hematologic malignancy at the date of CML diagnosis for their corresponding case patient. We obtained information on all first-degree relatives of cases and controls from the Swedish Multigenerational Registry, which includes data on parent-sibling-offspring relations for all Swedish citizens born in 1932 or later. We used a marginal survival model to calculate familial aggregation.

We found that neither CML (relative risk, 1.62; 95% confidence interval, 0.52-5.11), AML (0.94; 0.44-2.0), nor MPN (1.11; 0.58-2.17) aggregated significantly in relatives of patients with CML (vs relatives of controls) (Table 1). In addition, the relative risks for any lymphoproliferative, hematologic, or solid tumor were not significantly increased. We also analyzed the risks in relatives by gender and age at diagnosis of proband ($\leq$60 vs $>$60 years) and could not reveal any significant associations (data not shown).

CML patients may worry about their family members having a potentially increased risk of developing CML or other cancer. In this population-based study, including all age groups of patients with CML, we found no significant familial aggregation for CML, AML, MPN, lymphoproliferative neoplasm, or any other cancer among relatives of CML patients (vs relatives of matched controls). Our findings are in sharp contrast to those observed in MPNs where an increased familial aggregation supports the notion that genetic susceptibility genes may play a strong role in these patients.

Magnus Björkholm
Department of Medicine, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden