Elevated Serum Levels of Soluble CD23 (sCD23) Precede the Appearance of Acquired Immunodeficiency Syndrome–Associated Non-Hodgkin’s Lymphoma

By Sigal Yawetz, William G. Cumberland, Meta van der Meyden, and Otoniel Martinez-Maza

Human immunodeficiency virus (HIV) infection-associated B-cell hyperstimulation, in particular, the chronic stimulation of B cells to undergo isotype switching, may play an important role in the pathogenesis of acquired immunodeficiency syndrome–associated lymphoma (AIDS lymphoma). Isotype switching can be induced by various immune system factors, including cytokines, cell-surface stimulatory molecule interactions, and CD23. CD23 is a B-cell differentiation and activation marker expressed on mature B cells that is lost after isotype switching; soluble CD23 (sCD23) also is a B-cell—stimulatory factor. Because sCD23 is associated with Ig isotype switching, and because an enhancement of isotype switching may contribute to the genesis of AIDS lymphoma, we examined serum sCD23 levels in a retrospective study of HIV-seropositive subjects who had gone on to develop lymphomas. Subjects were participants in the Multicenter AIDS Cohort Study at UCLA, a study of the natural history of AIDS. Greatly elevated sCD23 serum levels were seen in subjects who developed AIDS lymphoma, when compared with others with AIDS (without lymphoma) or to HIV-seronegative or HIV-seropositive subjects who did not have AIDS. Because the induction of IgE has been tied to the activity of CD23, serum IgE levels were also examined in this study, and found to be significantly elevated in those who developed AIDS lymphoma. These findings suggest that serum sCD23 levels potentially may serve as a clinical tool for early detection of lymphomas in people who have HIV infection. Also, these observations provide clues on possible pathogenetic mechanisms that result in lymphomagenesis in the context of HIV infection and AIDS.

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levels of sCD23 were seen to correlate with clinical stage.\textsuperscript{69} In two recent studies, sCD23 levels were measured in the serum of HIV-infected individuals. In both of these studies, serum sCD23 appeared to be slightly, but not significantly, elevated in the HIV-infected group.\textsuperscript{50,51}

Several studies have reported that IgE levels, and the percentage of individuals with high IgE levels, increase in HIV infection and in AIDS.\textsuperscript{52-55} This increase is correlated with the severity of the disease (both CD4 number and clinical manifestations),\textsuperscript{53,54} but does not appear to be related to allergic manifestations or opportunistic infections.\textsuperscript{55} Therefore, the elevated IgE levels seen in HIV infection may represent dysregulation of the regulatory mechanism for IgE production and B-cell activation.

In this study, sCD23 and IgE levels were examined in the sera of HIV-infected people, including those who went on to develop AIDS lymphoma. Much higher levels of serum sCD23, and significantly elevated levels of serum IgE, were seen before the clinical diagnosis of lymphoma in people who developed AIDS-NHL, when compared with others with AIDS, but without lymphoma, or to healthy, HIV-seropositive or seronegative subjects. This finding suggests that serum sCD23 may serve as a clinical tool for early detection of the presence of AIDS-NHL and may also shed light on possible pathogenetic mechanisms that result in lymphoma genesis in the context of HIV infection and AIDS.

**MATERIALS AND METHODS**

**Study subjects.** Serum samples were obtained from subjects participating in the UCLA Multicenter AIDS Cohort Study (UCLA-MACS). The UCLA-MACS cohort is composed of adult homosexual men and was established in 1984, with 1,637 original participants. Subjects in the UCLA-MACS are seen at 3 to 6 months intervals, at which time serum is collected and stored frozen in \(-70^\circ C\). Information on the clinical status of subjects is also collected. Four groups of patients were examined in this study. Group I—people with AIDS-associated non-Hodgkin’s lymphoma (AIDS-NHL) group; Group II—those with AIDS but without detectable AIDS-related cancers, matched on CD4 T cell number to subjects in Group I (AIDS—no-cancer group); Group III—HIV-positive, asymptomatic individuals without AIDS-defining illness; and Group IV—HIV-seronegative individuals. Subjects in the control groups (Groups II, III, and IV) were selected to exclude any subjects who had NHL or KS. Subjects were staged according to the Centers for Disease Control (CDC) classification of 1992, and determination of HIV infection was made using enzyme-linked immunosorbent assay (ELISA) and Western blotting. In the AIDS-NHL group, representing all available AIDS-NHL cases in the UCLA MACS at the time specimens were examined, sCD23 and/or IgE levels were measured in all available sera from visits in the 18 months before the diagnosis of AIDS-NHL. Sera from all other subjects represent a serum sample collected at a single MACS visit. All sera tested were frozen and thawed before measurement of sCD23 and/or IgE levels.

**Determination of the number of CD4-positive T cells in peripheral blood.** CD4 (T helper/inducer cell) T-cell percentage was determined by flow cytometry. Briefly, red blood cells in a whole blood sample were lysed by combining 50 \(\mu L\) of blood with ammonium-chloride based lysing solution. Samples were then washed two times in a phosphate-buffered saline (PBS)-2% fetal calf serum (FCS) buffer, containing 0.1% sodium azide. Purified anti-CD4/Leu 3\' (Becton-Dickinson Immunocytometry Systems, Mountain View, CA) was then added to cells, which were incubated for 30 minutes at 4°C, washed, and analyzed immediately by flow cytometry. The absolute number of CD4-positive cells was then obtained by multiplying the percentage of CD4-positive cells, determined by flow cytometry, by the lymphocyte count, determined by standard microscopic analysis.

**Determination of serum sCD23 levels.** Serum levels of sCD23 were measured by enzyme immunoassay (C-axis Test Kit, CEL-TREE, T Cell Diagnostic, Inc, Cambridge, MA), a sandwich-type immunoassay, which can be used for the quantitative determination of sCD23 in serum. Briefly, anti-CD23 monoclonal antibody has been precoated onto polystyrene microtiter wells. Samples or standards are then introduced into the wells, followed immediately by horseradish peroxidase-conjugated anti-CD23 monoclonal antibody preparation. After this, unreacted components are removed by washing. Next, a chromogen solution is added to the wells, resulting in the formation of a colored product, the amount of which is proportional to the amount of CD23 present in the samples; the reaction is stopped by the addition of stop solution, and absorbance at 490 nm is measured to quantify the amount of color development. Levels of CD23 in samples are determined by comparison with standard curve prepared from six CD23 standards, ranging from 0 to 800 units CD23/mL. CD23 levels are expressed in U/mL. The lower level of detection of this assay is approximately 15 U/mL, with no prozone effect seen up to levels of CD23 of 10,000 U/mL, according to information provided by the manufacturer.

**Determination of serum IgE levels.** Serum IgE levels were measured by enzyme immunoassay (Bindazyme Human IgE EIA Normal Level Kit, The Binding Site Ltd, Birmingham, UK), a capture-type immunoassay that can be used for the quantitation of human IgE in serum. Briefly, samples, control sera, or standards are added to anti-IgE monoclonal antibody precoated microwells. After washing to remove unbound proteins, antihuman IgE peroxidase conjugate is added to wells. After this, unreacted components are removed by washing. Next, a substrate solution is added to the wells, resulting in the formation of a colored reaction product, the amount of which is proportional to the amount of IgE present in the samples; optical density was read at 450 nm using a Titertek ELISA plate reader (Flow Laboratories, McLean, VA). Levels of IgE in samples are determined by comparison with standard curve prepared from five IgE standards, ranging from 5 to 400 kU IgE/L. CD23 levels are expressed in U/mL. The range of detection of this assay is approximately 5 to 400 kU IgE/L, with no high-dose hook effect seen at extremely high IgE levels (18,000 kU/L), according to information provided by the manufacturer. IgE Levels are reported as the calculated amount, from the IgE concentration range of 5 to 400 kU/L. Levels higher than 400 kU/L are reported as more than 400 kU/mL.

**Statistical methods.** The AIDS-NHL group of individuals had between one and six repeated measurements taken over the 18 months before diagnosis. The other three groups had single measurements taken. Thus, the data consist of unbalanced repeated longitudinal measurements on four groups, and statistical procedures were chosen that allow for the correlations that exist among the repeated measurements on any single subject, because it is misleading to assume these represent independent observations. Means for Group I were calculated as the average of the means for each subject, and standard errors were estimated using a components of variance model, which automatically incorporates constant correlation among the repeated measurements. For the other groups, means and standard errors were calculated directly.

Comparisons of group means were done using the BMDP5V program (BMDP Statistical Software, Los Angeles, CA) which adjusts for missing observations and/or unbalanced data in a repeated measures analysis with structured covariance matrices. This procedure made efficient use of all the available data on each subject, while allowing for the correlations between repeated measurements on the
Table 1. Lymphoma Classification for Group I

<table>
<thead>
<tr>
<th>Lymphoma Classification*</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large cell</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>High grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large cell, immunoblastic</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Small noncleaved cell Burkitt's</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Non-Burkitt's</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary of brain</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Other†</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>100</td>
</tr>
</tbody>
</table>

* Based on the working formulation for classification of NHL.
† Several hospital pathologists reporting to the Los Angeles MACS have not used the working formulation terminology for classifying the lymphomas. These cases were treated in this study as AIDS-associated lymphoma, not otherwise specified.

Table 2. AIDS-Defining Conditions for Subjects in Groups I and II

<table>
<thead>
<tr>
<th>AIDS Defining Condition*</th>
<th>Group I (AIDS NHL)</th>
<th>Group II (AIDS non-malignancy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Candididal esophagitis</td>
<td>3</td>
<td>9.1</td>
</tr>
<tr>
<td>Candida (other, AIDS-defining)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coccidiomycosis (AIDS-defining)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococciosis (extrapulmonary)</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>Cryptosporidiosis (chronic, intestinal)</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>Cytomegalovirus (AIDS-defining)</td>
<td>2</td>
<td>6.1</td>
</tr>
<tr>
<td>Cytomegalovirus (retinitis)</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>Encephalopathy (HIV-related)</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Herpes-Simplex (AIDS-defining)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histoplasmosis (AIDS-defining)</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>Isosporiasis (chronic intestinal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi's sarcoma</td>
<td>4</td>
<td>12.1</td>
</tr>
<tr>
<td>Lymphoma, non-Hodgkin's</td>
<td>12</td>
<td>36.4</td>
</tr>
<tr>
<td>Lymphoma, primary of brain</td>
<td>2</td>
<td>6.1</td>
</tr>
<tr>
<td>Mycobacterium avium complex or M. Kansasii</td>
<td>3</td>
<td>10.7</td>
</tr>
<tr>
<td>M. tuberculosis, any site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium species, other (AIDS-defining)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis Carinii pneumonia</td>
<td>6</td>
<td>18.2</td>
</tr>
<tr>
<td>Pneumonia, recurrent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>Salmonella septicemia, recurrent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis of brain</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>Wasting syndrome due to HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 &lt;200 cells/μL, or &lt;14%</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>Total</td>
<td>334</td>
<td>100</td>
</tr>
</tbody>
</table>

* Based on the conditions included in the 1993 expansion of the AIDS surveillance case definition.
† Not used as an AIDS-defining condition in this study.
‡ Of the 27 patients in group I, four had two AIDS-defining illnesses (diagnosed at the first AIDS visit) and one had three; therefore, the total is 33.

RESULTS

Study subjects. Group I included 27 individuals with AIDS-NHL (Table 1). The mean age in this group was 39 years (range, 24 to 52 years). Among the 27 subjects in this group, three had diffuse large cell lymphoma, seven had large cell immunoblastic lymphoma, six had primary lymphoma of the central nervous system (CNS) (of which two were specified as large cell), five had SNCCL of Burkitt's type, and two had a non-Burkitt's SNNCL. In five cases the pathologic diagnosis was high-grade lymphoma not otherwise specified. The pathologic diagnoses were made in several medical centers and clinics in the Los Angeles area. The mean CD4 cell number for this group was 212 ± 18 CD4 cells/mm³.

Group II included 28 individuals with an AIDS-defining illness, but with no history of an AIDS-related malignancy. The mean age was 38 years (range, 29 to 48 years). The mean CD4 count for this group was 200 ± 38 CD4 cells/mm³. Table 2 summarizes the AIDS-defining conditions for groups I and II.

Group III included 15 HIV-seropositive individuals with no AIDS-defining conditions. The mean age for this group was 37 years (range, 32 to 43 years) and the mean CD4 cell number was 631 ± 64 CD4 cells/mm³. Group IV included 16 HIV-seronegative individuals. The mean age was 36 years (range, 29 to 48 years), and the mean CD4 count was 933 ± 67 CD4 cells/mm³. All subjects in all four groups were homosexual males participating in the Los Angeles center of the MACS study.

Elevated levels of serum sCD23 were seen in people who went on to develop AIDS-NHL. The mean level of serum sCD23 in those with AIDS-NHL (group I) was 73.9 ± 17.6 U/mL, with serum sCD23 levels ranging from undetectable to 377 U/mL. Two subjects in group I (AIDS-NHL) had no detectable serum sCD23, one individual had CNS lymphoma and the other AIDS-associated lymphoma—not otherwise specified.
Subjects with AIDS, but without a clinically apparent malignancy (group II), had a mean serum sCD23 value of 3.6 ± 3.0 U/mL, with individual subjects' sCD23 levels ranging from not detectable to 82.9 U/mL. Only one individual in this group had a serum sCD23 level more than 10 units/mL, with 21 of 28 subjects having no detectable serum sCD23.

Asymptomatic HIV-seropositive individuals (group III) had a mean serum sCD23 value of 2.7 ± 1.3 U/mL, with individual levels ranging from not detectable to 16 U/mL. Only one person in this group had a serum sCD23 level more than 10 U/mL. The mean serum sCD23 level in HIV-seronegative subjects (group IV) was 5.5 ± 2.8 U/mL, with individual levels ranging from not detectable to 41 U/mL, and with three subjects in this group having serum sCD23 levels more than 10 U/mL. Figure 1 depicts the mean values of serum sCD23 for each group, along with an indication of the standard error.

A comparison of serum sCD23 levels with the BMDP5V repeated measures program showed that subjects with AIDS-NHL (group I) had dramatically higher values than did other groups (P < 10⁻⁵). Individual comparisons between groups showed that group I had uniformly higher serum sCD23 levels than those with AIDS (group II), HIV infection without AIDS-defining illness (group III), and those who were HIV-seronegative (group IV). A comparison of groups II, III, and IV showed no significant differences in serum sCD23 levels between them. Therefore, significantly elevated levels of serum sCD23 were not seen in people with AIDS (with no malignancies), or in HIV-infected subjects without an AIDS-defining condition, when compared with HIV-seronegative control donors, as has been reported previously by others. The conservative (and much less powerful) nonparametric procedure confirmed the difference among these groups (P < .00001).

Serum sCD23 levels did not appear to correlate with the number of CD4 cells in any of the four subject groups studied. Also, serum sCD23 levels within group I did not appear to correlate to type or distribution of lymphoma.

Serum IgE levels were preferentially elevated in subjects with AIDS-NHL. Serum IgE levels were measured in selected subjects' sera from the four groups examined in the studies on serum sCD23 described earlier. Serum IgE levels were truncated at 450 kIU/L (the highest standardized point on the IgE immunoassay standard curve), and means were calculated using the value of 450 kIU/L, for all values corresponding to or exceeding this level.

Serum IgE levels were determined for 18 patients with AIDS-NHL (group I). The mean level of IgE in this group was 294 ± 41.4 kIU/L (Fig 2), with individual subjects' serum IgE levels ranging from 3.9 kIU/L to more than 450 kIU/L. In this group, 10 subjects (45%) had serum IgE values more than 450 kIU/L.

In subjects with AIDS (no malignancies) (group II), serum IgE levels were determined on 21 subjects. In this group, the mean serum IgE level of 122 ± 35 kIU/L (Fig 2), with individual levels ranging from 2.9 kIU/L to 450 kIU/L, and with three individuals (14%) having serum IgE levels more than 450 kIU/L.

Levels of serum IgE were determined in 13 subjects in each of groups III (HIV-seropositive, no AIDS) and IV (HIV-seronegative subjects). The mean level of serum IgE for HIV-infected subjects who did not have AIDS (group III) was 20 ± 6 kIU/L (Fig 2), with serum IgE levels for
individuals in this group ranging from not detectable to 64 kIU/L. None of the subjects in this group had a serum IgE level more than 450 kIU/L. The mean serum IgE level for individuals in group IV (HIV-seronegative) was 50 ± 34 kIU/L (Fig 2), with one subject showing a serum IgE level equal to 450 kIU/L. Figure 2 depicts the mean values of serum IgE for each group, along with an indication of the standard error.

A comparison of IgE levels among groups with the repeated measures program showed highly significant differences (P < 10⁻⁶). Further analysis indicated that serum IgE levels in group I were significantly elevated over those in each of the other three groups. A simple nonparametric comparison of serum IgE levels among groups II, III, and IV with the Kruskal-Wallis ANOVA showed no significant difference (P = .283) between these groups. Therefore, higher serum IgE levels were seen in people with AIDS-NHL (group I), when compared with others, but without malignancies (group II), or to HIV-seropositive or seronegative control subjects without AIDS (groups III and IV). Elevated levels of serum IgE were seen in subjects with an AIDS-defining condition in previous studies by other workers.⁵²⁻⁵⁵

Because both IgE and sCD23 serum levels are strongly associated with the development of AIDS-NHL, a repeated measures analysis of covariance using BMDP5V was done to investigate their association and value together as indicative of lymphoma development. In a model with both diagnosis group and IgE, only the group proved important in differentiating sCD23 levels. The coefficient for IgE was not statistically significant in the model (P = .238), indicating that within groups there is weak correlation between IgE and sCD23. A plot by group of sCD23 against IgE showed no relationship between the two measurements (not shown).

**DISCUSSION**

An elevated frequency of non-Hodgkin’s lymphoma is seen in HIV infection.¹⁴ It is generally believed that HIV infection-associated immune dysfunction, in particular chronic B-cell hyperstimulation,¹⁵⁻¹⁸ may contribute to the genesis of AIDS-associated lymphoma by increasing the size of the pool of B cells at risk for a genetic error (chromosomal translocation) that results in the generation of a lymphoma clone. More specifically, the nature of the translocation (c-myc/switch-μ region of the Ig gene) seen in a significant fraction of AIDS-associated lymphomas suggests that the genetic error resulting in this chromosomal translocation occurs during isotype switching. Therefore, even though little is known about the aspects of HIV-associated immune dysfunction that contribute to lymphomagenesis, the chronic stimulation of B cells to undergo isotype switching may be of great pathogenetic importance in lymphomagenesis. Isotype switching can be induced by various immune system factors, including cytokines (IL-4 and IL-13),⁴⁻¹⁸ as well as noncognate, cell surface stimulatory molecule interactions (CD40 - CD40 ligand),³⁵⁻³⁶ and, in the case of isotype switching to IgE, soluble CD23.³¹,⁴⁰ CD23 is a B-cell differentiation and early activation marker expressed on mature B cells that is lost after isotype switching.³¹,³³⁻³⁶ the expression of which is upregulated by the same factors that can promote isotype switching, such as exposure of B cells to IL-4 or IL-13,²³⁻³¹,³⁷,⁴² and interaction with T cells expressing the CD40 ligand.²⁹⁻³⁰ The soluble form of CD23 (sCD23) is produced by the cleavage of cell surface CD23.³¹,⁴⁴

Because sCD23 is associated with Ig isotype switching, and because the enhancement of immune mechanisms that induce isotype switching may contribute to the genesis of AIDS-NHL, we examined serum sCD23 levels in a retrospective study of sera collected from individuals with HIV infection that went on to get AIDS-associated lymphoma. As controls, we examined serum sCD23 levels in other groups of subjects, specifically, in people with AIDS who did not have clinically-detected malignancies, in HIV-infected subjects who did not have AIDS, and in HIV-seronegative subjects. All subjects were homosexual men who participated in the UCLA-MACS.

A dramatic, and very significant, elevation in sCD23 was seen in sera collected from people who went on to develop AIDS-related lymphoma (group I), when compared with others with AIDS, but without lymphoma or other AIDS-associated cancers (group II), as well as those who did not have AIDS (HIV-seronegative and seropositive, groups III and IV). Elevated levels of serum IgE were seen in subjects with an AIDS-defining condition in previous studies by other workers.⁵²⁻⁵⁵

Because the induction of IgE has been closely tied to the activity of CD23, IgE levels also were examined in this study and found to be significantly elevated in people with AIDS-associated lymphoma (Fig 2). Several previous studies have reported that IgE levels, and the percentage of individuals with high IgE levels, increase in HIV infection and in AIDS.⁵²⁻⁵⁵ and that this increase is correlated with the severity of the disease,⁵²⁻⁵⁴ but does not appear to be related to allergic manifestations or opportunistic infections.⁵⁵ The elevation in serum IgE levels in HIV infection has not been seen to be related to atopy or the presence of opportunistic infections, but has been observed to be related to increased immune cell loss, a poor clinical prognosis, and in this study, related to the appearance of AIDS-NHL. This suggests that the observed increase in serum IgE in HIV infection may reflect immune dysregulation, in particular, the enhancement of immune factors that result in excessive Ig isotype switching activity.

The presence of elevated levels of serum sCD23 before the clinical recognition of AIDS-NHL suggests that the determination of serum sCD23 levels in HIV-infected subjects has the potential to serve as a clinical tool for early detection of the presence of AIDS-NHL. While a few subjects in each of the nonlymphoma control groups did show elevated levels of serum sCD23, a markedly higher fraction of those in the
group that went on to develop AIDS-NHL showed elevated serum sCD23 levels. Certainly, the establishment of the value of serum sCD23 as a useful marker to assist in determining which HIV-infected individuals are at greatest risk for developing AIDS-NHL will require confirmation of this finding, as well as the completion of appropriately-designed prospective studies. Also, prospective studies, using fresh sera that have not been frozen, are needed to establish appropriate healthy control ranges for serum sCD23 levels, because the sCD23 values obtained using archival, frozen serum specimens may not be directly comparable, numerically, with values obtained using freshly obtained serum specimens (unpublished observations).

Perhaps more importantly, the observation that elevated serum sCD23 is seen in those who developed AIDS-NHL may shed light on possible pathogenetic mechanisms that result in lymphomagenesis in the context of HIV infection and AIDS. This finding could result from the overproduction and shedding of sCD23 by emerging prelymphoma or lymphoma B cells, or alternatively, might reflect a profound difference in the nature of the HIV-associated immune dysfunction seen in those individuals who develop AIDS-NHL. Perhaps, these elevated sCD23 levels reflect the loss of immune regulation of Epstein-Barr virus (EBV)-activated B cells, or result from the overproduction of immune stimulatory factors that result in enhanced polyclonal B-cell hyperstimulation. Further studies are needed to resolve this question, by determining the origin of the elevated levels of sCD23 seen in the circulation of those individuals who develop AIDS-NHL. Perhaps, these elevated sCD23 levels reflect the loss of immune regulation of Epstein-Barr virus (EBV)-activated B cells, or result from the overproduction of immune stimulatory factors that result in enhanced polyclonal B-cell hyperstimulation. Further studies are needed to resolve this question, by determining the origin of the elevated levels of sCD23 seen in the circulation of those individuals who develop AIDS-NHL, and defining the immune system factors (cytokines and cell-surface stimulatory molecules) involved in the induction of sCD23 production in HIV infection. It is important to note that sCD23 is not only a marker for B-cell differentiation, and perhaps a marker for the emergence of AIDS-NHL in people with HIV infection, but also is a biologically active B-cell growth factor. Therefore, studies to determine the effects of sCD23 as a direct, stimulatory factor for B cells in HIV infection and/or as a direct growth-promoting factor for AIDS-NHL cells should be performed in the future.

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REFERENCES

21. Pelicci PG, Knowles DM, Arlin ZA, Wieczorek R, Luciw P, Dina D, Basilico C, Dalla-Favera R: Multiple monoclonal B cell expansions and c-myc rearrangements in acquired immunodeficiency...
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35. Waldschmidt TJ, Conard DH, Lynch RJ: The expression of B cell surface receptors. II. IL-4 can accelerate the developmental expression of the murine B cell IgE Fc receptor. J Immunol 143:2820, 1989.


43. Nakajima T, Sarafati M, Delespesse G: Relationship between human IgE-binding factors (IgE-BF) and lymphocyte receptors for IgE. J Immunol 139:848, 1987.


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