CORRESPONDENCE

Seroprevalence of Kaposi's Sarcoma-Associated Herpes Virus Antibody in Young Adult Hodgkin's Disease

To the Editor:

Epidemiologic evidence strongly suggests that young adult Hodgkin's disease (YAHD) is a rare sequelum of a late (adolescence or young adulthood) infection with a common childhood virus, analogous to the appearance of paralysis after natural infection with poliovirus.[1] Although Epstein-Barr virus (EBV) is considered the leading candidate as the putative causal virus, current evidence is inconclusive. EBV DNA has been demonstrated in Hodgkin's tumors, but is much less prevalent in tumors from young adult cases or cases of the nodular sclerosis type.[2] If EBV does play an etiologic role, there is likely to be a cofactor, possibly another virus.

KSHV (Kaposi's Sarcoma Associated Herpes Virus or Human Herpes Virus 8), like EBV, is a gamma Herpes virus, with sequence homology to EBV. It was first isolated from Kaposi's sarcoma tumor tissue[3] and subsequently from tumor tissue and peripheral blood mononuclear cells from patients with body cavity lymphomas,[4] Castleman's disease,[4] and multiple myeloma (in bone marrow stromal cells only).[5] Ninety percent of Kaposi's sarcoma patients and 11% of human immunodeficiency virus-negative adult blood donors are positive for KSVH antibody.[6] Although a few cases of Hodgkin's disease have been evaluated for evidence of this virus (with negative results), neither age at diagnosis nor histologic type was specified.[4,5]

We examined serum from 39 twin pairs with Hodgkin's disease diagnosed before age 50, plus 46 controls, to assess the seroprevalence of KSHV antibody in YAHD patients. Subjects were recruited from the International Twin Study, a large registry developed by advertising for twins with chronic disease. Three twin pairs were concordant for YAHD and 36 were discordant, totaling 42 YAHD cases (60% nodular sclerosis, 12% mixed cellularity, 5% lymphocyte predominant, 2% lymphocyte depleted, 7% not otherwise specified, and 14% unknown histology). Thirty-six healthy twins of cases were also tested. Controls comprised spouses or friends of either member of the twin pair (38), two healthy identical twin pairs (4), and laboratory staff (2). Forty-six percent of the twin pairs were male and 54% were female; 48% of controls were male and 52% were female. Laboratory investigators were blinded with respect to the identity of the case, cotwin, and control.

KSHV-IgG antibody was measured from thawed frozen serum using whole viral lysate containing the majority of the KSHV structural proteins in an enzyme-linked immunosorbent assay. Serum from 92 Kaposi's sarcoma patients gathered in a population-based case-control study were analyzed simultaneously as an internal control for the assay. One YAHD case and one control were each positive for KSVH antibody, at the lowest detectable concentration (0.05 to 0.20), giving a prevalence in cases and controls of 2%. Both the case and the control were male. None of the 36 healthy twins of YAHD cases was positive. In contrast, 40 of the 92 KS sera were positive for KSVH antibody (44%).

KSHV antibody was not detectable in any substantial number of YAHD cases. Thus, it appears that KSHV does not play a role in the etiology of YAHD, and the search to identify the etiologic agent of YAHD must continue.

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A Retinoic Acid Receptor-α (RARα) Selective Agonist Modulates Procoagulant Activity of Acute Promyelocytic Cells and Induces Their Differentiation Into Neutrophils

To the Editor:

We recently found that a subtype of retinoic acid receptors (RARs), RARα, mediates upregulation of TM gene expression in human promyelocytic leukemia cells (NB4), acute monocytic leukemia cells, and human umbilical vein endothelial cells and that the cooperation of RARα and RARβ exerts downregulation of TF gene expression in NB4 cells.[1] We introduce here new data to support our previous findings

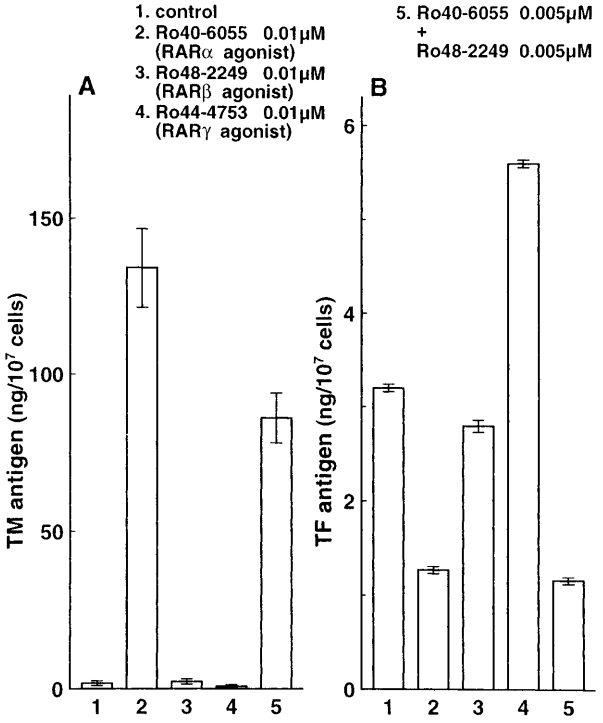

Fig 1. Effects of RARα, RARβ, and RARγ selective retinoids on the expression of the toal TM an TF antigens in NB4 cells. NB4 cells were incubated with 0.01 μmol/L of Ro40-6055 (lane 2), Ro48-2249 (lane 3), Ro44-4753 (lane 4), or a combination of 0.005 μmol/L each of Ro40-6055 and Ro48-2249 (lane 5) for 24 hours. Total TM (A) and TF (B) antigen levels in cell lysates were measured by enzyme-linked immunosorbent assay, as previously reported.[1] Results are shown as the means ± SD of three different experiments.

using RARα, RARβ, and RARγ selective agonists, Ro40-6055, Ro48-2249, and Ro44-4753, respectively. These synthetic retinoids were kindly provided by F. Hoffman-La Roche, Ltd (Basel, Switzerland). Our experiments also showed that the incubation of NB4 cells with the RARα selective agonist, Ro40-6055, induced cell differentiation into neutrophils and apoptosis. These effects were not exerted by Ro48-2249 and Ro44-4753.

When NB4 cells were incubated with 0.01 μmol/L of Ro40-6055, Ro48-2249, or Ro44-4753 for 24 hours, Ro40-6055 caused induction of TM antigen and reduction of TF antigen (Fig 1A and B), which was similar to the results induced by a synthetic retinoid Am80, which is an agonist to RARα and RARβ.[1] The TM upregulation by the incubation with Ro40-6055 was more effective than that by the stimulation of the combination with Ro40-6055 and Ro48-2249 (Fig 1A). Ro40-6055 and Ro48-2249 showed downregulation of TF in NB4 cells, and the TF downregulation by the combined incubation of Ro40-6055 and Ro48-2249 was more significant than that by each retinoid (Fig 1B). Interestingly, the incubation of NB4 cells with Ro44-4753 induced upregulation of TF antigen level, although its mechanism is not yet known.

NB4 cells were further incubated with 0.01 μmol/L of Ro40-6055 for 7 days and were evaluated for changes in the morphology and surface markers of the leukemic cells. NB4 cells with frequent mitotic figures and morphologic features characteristic of acute promyelocytic leukemia cells were shown to have significant morphologic changes, such as condensed chromatin, smaller nuclei, decreased nuclei/cytoplasm ratio, and appearance of neutrophilic granules in the cytoplasm when treated with Ro40-6055. Differentiation of NB4 cells was also assessed by flow cytometric analysis for several membrane-bound differentiation markers. Expression of the cell surface antigens CD11b (a marker of β-integrin subunit expressed by both granulocytes and monocytes), CD11c (granulocytic lineage), and CD14 (late monocytic cell) is gradually detected during the normal development of mature monocytes from hematopoietic stem cells.[2] The expression levels of CD11b and CD11c antigens (19.1% and 43.2%, respectively) were significantly increased after incubation with 0.01 μmol/L of Ro40-6055 to 91.6% and 90.8%, respectively. CD14 expression level was only slightly increased from 6.5% to 8.4%. DNA fragmentation assay of NB4 cells showed the occurrence of apoptosis by Ro40-6055 stimulation (0.01 μmol/L for 7 days).

These results support the idea that RARα mediates TM gene expression and that RARα and also RARβ are relevant to the retinoid-induced TF downregulation. A selective RARα agonist, Ro40-6055, is a potent inducer of differentiation and apoptosis with anticoagulant effect on acute promyelocytic leukemia cells.

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Plasma Levels of Endothelial Cell Protein C Receptor Are Elevated in Patients With Sepsis and Systemic Lupus Erythematosus: Lack of Correlation With Thrombomodulin Suggests Involvement of Different Pathological Processes

To the Editor:

The endothelial protein C receptor (EPCR) is a recently described member of the protein C anticoagulant pathway.[1,2] The membrane form of EPCR works in concert with thrombomodulin (TM) to augment protein C activation on endothelial cells,[3] whereas a soluble form of EPCR from normal human plasma inhibits the generation and function of activated protein C.[4] The protein C pathway plays a critical role in both anticoagulant processes and in the host response to inflammation, especially bacterial sepsis.[5] TM is a well-known endothelial receptor of