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Susceptibility Genes for AIDS and AIDS-Related Lymphoma

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HIV-1-infected individuals are at greatly increased risk of Burkitt's and other high-grade non-Hodgkin's lymphomas, which arise as a late complication in the setting of advanced immunodeficiency [1]. Heterogeneous acquired lesions are present in varying subsets of these B-cell tumors, including activation of the c-*myc* (especially in Burkitt's lymphoma), *bcl*-6, and *ras* protooncogenes, inactivation of the p53 tumor suppressor gene, and latent infection with the Epstein-Barr virus (EBV) [2,3]. The mechanisms by which immune dysregulation leads to B-cell lymphoma are poorly understood, but may be related to disruption of cytokine control and chronic B-cell hyperactivation. Lymphomagenesis may be a multistage process progressing from polyclonal B-cell proliferation to oligoclonal expansion of antigen-selected clones to subsequent outgrowth of a monoclonal tumor [4].

Chemokines (chemotactic cytokines) are important regulators of normal B-lymphocyte maturation and proliferation [5]. In addition, chemokine receptors are coreceptors with CD4 for entry of HIV-1 into host cells, and several genetic polymorphisms in chemokine and chemokine receptor genes have been shown to modify progression of HIV-1 infection. A 32 base-pair deletion in the coding region of the CCR5 chemokine receptor gene, termed CCR5-Δ32, is protective against progression to AIDS in heterozygotes and against HIV-1 infection in homozygotes [6]. A valine to isoleucine substitution at position 64 in the transmembrane domain of the chemokine receptor gene CCR2, termed CCR2-64I, is protective against AIDS in heterozygotes but has not been shown to affect risk of infection [7]. A variant of the SDF-1 (stromal cell-derived factor 1) chemokine gene, with a G-to-A transition at position 801 of the 3' untranslated region of the SDF-1ß gene transcript (designated SDF1-3'UTR-801G-A, and abbreviated as SDF1-3'A) has been variably associated in homozygotes with slower [8] or faster [9] progression of HIV-1 infection to AIDS and death.

The variation in lymphoma occurrence in the course of HIV infection suggests host and/or environmental factors influence lymphoma risk. The chemokine and chemokine receptor genes are logical candidates, given their significance in normal B-cell development. We have therefore examined the effects of the previously reported SDF1-3'A, CCR5-Δ32, and CCR2-64I gene variants as risk factors for HIV-associated non-Hodgkin's lymphoma in three HIV-infected cohorts: 146 HIV-infected children followed at the NIH Clinical Center; 120 subjects from a cohort study of homosexual men, and 480 from a prospective cohort study of HIV-infected hemophilia patients.

Although SDF1-3'A had been initially reported to prevent progression of HIV

disease [8], we found that it increased risk of HIV-associated non-Hodgkin's lymphoma (but not other AIDS-defining conditions), with homozygotes at higher risk than heterozygotes. After a median 12 years of follow-up, 19% of homozygous and 10% of heterozygous SDF1-3'A carriers developed lymphoma, compared to 5% of wild-type subjects (p<.01 for both comparisons) [10]. Overall risk of lymphoma was significantly lower in the hemophilic patients, half of whom became infected in childhood, corresponding to the slower course of HIV-1 disease in children (excluding those neonatally infected) compared to adults. Nevertheless, cumulative incidence of non-Hodgkin's lymphoma was consistently higher in SDF1-3'A carriers (heterozygous plus homozygous) compared to homozygous wildtype for all three cohorts (Fig.).

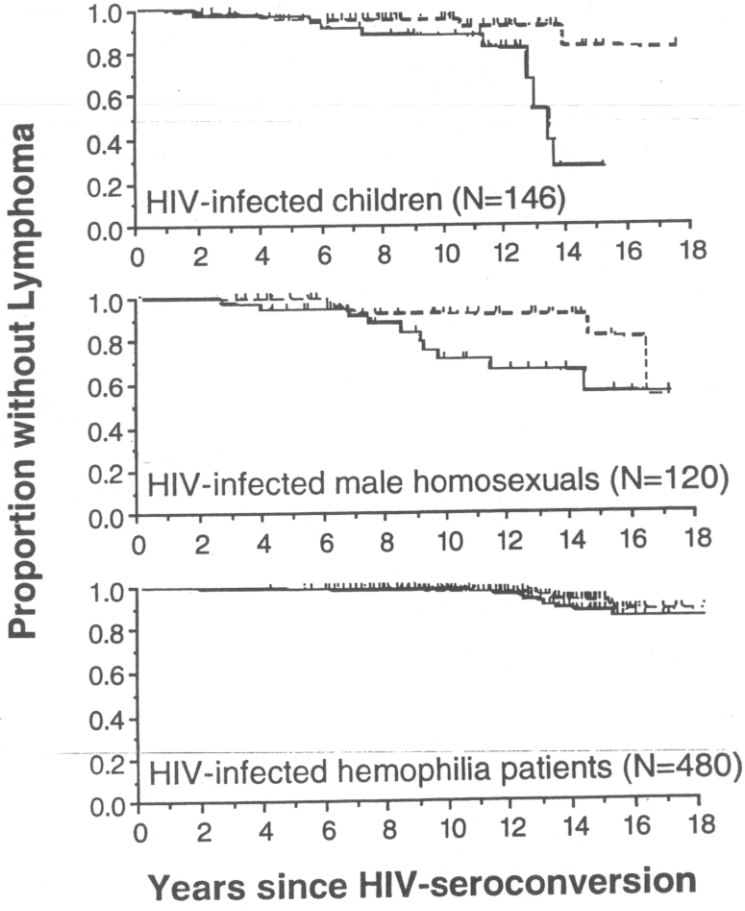

Fig. Non-Hodgkin's lymphoma risk in carriers (heterozygous plus homozygous) of SDF1-3'A (solid lines) compared to homozygous wildtype (dashed lines).

In Cox proportional hazards models (stratified by cohort to account for variation in lymphoma risk), SDF1-3'A was associated with approximate doubling of the non-Hodgkin's lymphoma hazard in heterozygotes as compared to the wildtype, and roughly a four-fold increase in homozygotes. The adjusted relative hazard of non-Hodgkin's lymphoma per copy of the SDF1-3'A allele was 2.0 (95% CI=1.3-3.1). The increased risk was particularly pronounced for Burkitt's and Burkitt-like tumors, although other high-grade systemic tumors and primary brain lymphomas were also increased.

In marked contrast, SDF1-3'A carriers were not overrepresented among 24 cases of HIV-1-negative Burkitt's and other non-Hodgkin's lymphoma that were tested for comparison [10]. This polymorphism thus appears to increase risk of non-Hodgkin's lymphoma only in the setting of HIV infection, but more cases of HIV-negative lymphoma will need to be tested to confirm this specificity.

We also found a protective association of CCR5-Δ32 against HIV-1-associated lymphoma. In the three cohorts combined, non-Hodgkin's lymphoma developed in 2% of CCR5-Δ32 carriers compared to 8% of wild-type subjects (odds ratio=0.2, p=0.03). Conversely, the protective effect of CCR2-64I against AIDS appeared to be restricted to an effect on opportunistic infection, because 6% of CCR2-64I carriers developed lymphoma compared to 5% of wild-type subjects (odds ratio=1.3, p=0.6) [10].

Burkitt's and Burkitt-like tumors uniformly have a c-myc activating chromosomal translocation [11]. We have investigated these mutations in HIV-infected individuals without lymphoma from the homosexual cohort, and previously reported that 13 (12%) of 110 subjects had detectable c-myc translocations in circulating peripheral blood mononuclear cells[12]. However, the frequency of these translocations in subjects with chemokine and chemokine receptor polymorphisms was similar to that of the overall cohort [10].

Our data seemingly explain the previous observation [13] that non-Hodgkin's lymphoma is approximately one-half as common among blacks than in whites among U.S. AIDS cases. The prevalence of SDF1-3'A varies by race, with allele frequencies of 21% in whites and 6% of blacks [8]; based on the adjusted relative hazards from the Cox model, we estimated the etiologic fraction of HIV-associated lymphoma attributable to SDF1-3'A as 36% for whites and 10% for blacks. Thus, racial differences in incidence of HIV-associated non-Hodgkin's lymphoma may in part be due to an excess of SDF1-3'A-associated cases in whites.

In summary, SDF1-3'A increases susceptibility to AIDS-related lymphoma, whereas CCR5-Δ32 is strongly protective. Lymphoma risk is greater in SDF1-3'A homozygotes than heterozygotes, indicating a co-dominant effect of this allele on AIDS-related lymphoma, in contrast to its recessive effect on overall AIDS. The adjusted hazard per copy is 2, so each copy of the variant allele doubles the risk of non-Hodgkin's lymphoma. SDF1-3'A carrier distribution may also underlie the racial difference in risk of this disorder. SDF1-3'A has a much stronger association with Burkitt's lymphoma than with other AIDS-related lymphomas. Nevertheless, SDF1-3'A does not appear to be associated with the characteristic Burkitt's lymphoma translocation in HIV-infected subjects without lymphoma, nor with Burkitt's lymphoma in the absence of HIV infection. Deciphering the genetic control of AIDS-related lymphoma may further the understanding of B-cell neoplasia and provide fundamental insights into carcinogenesis.

References

1. Biggar RJ, Rabkin CS (1996) The epidemiology of AIDS--related neoplasms. Hematol Oncol Clin North Am 10:997-1010
2. Ballerini P, Gaidano G, Gong JZ, et al (1993) Multiple genetic lesions in acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma. Blood 81:166-176
3. Shibata D, Weiss LM, Hernandez AM, Nathwani BN, Bernstein L, Levine AM (1993) Epstein-Barr virus-associated non-Hodgkin's lymphoma in patients infected with the human immunodeficiency virus [see comments]. Blood 81:2102-2109
4. Przybylski GK, Goldman J, Ng VL, et al (1996) Evidence for early B-cell activation preceding the development of Epstein-Barr virus-negative acquired immunodeficiency syndrome-related lymphoma. Blood 88:4620-4629
5. Baggiolini M (1998) Chemokines and leukocyte traffic. Nature 392:565-568
6. Liu R, Paxton WA, Choe S, et al (1996) Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 86:367-377
7. Smith MW, Dean M, Carrington M, et al (1997) Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), ALIVE Study. Science 277:959-965
8. Winkler C, Modi W, Smith MW, et al (1998) Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. ALIVE Study, Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC) [see comments]. Science 279:389-393
9. Mummidi S, Ahuja SS, Gonzalez E, et al (1998) Genealogy of the CCR5 locus and chemokine system gene variants associated with altered rates of HIV-1 disease progression. Nat Med 4:786-793
10. Rabkin CS, Yang Q, Goedert JJ, Nguyen G, Mitsuya H, Sei S (1999) Chemokine and chemokine receptor gene variants and risk of non-Hodgkin's lymphoma in HIV-1 infected individuals. Blood (in press)
11. Magrath IT, Bhatia K Pathogenesis of small noncleaved cell lymphomas (Burkitt's lymphoma). In: The Non-Hodgkin's Lymphomas. Magrath IT (ed)(1997) Arnold, London. 2nd ed. pp 385-409
12. Muller JR, Janz S, Goedert JJ, Potter M, Rabkin CS (1995) Persistence of immunoglobulin heavy chain/c-myc recombination-positive lymphocyte clones in the blood of human immunodeficiency virus-infected homosexual men. Proc Natl Acad Sci U S A 92:6577-6581
13. Beral V, Peterman TA, Berkelman R, Jaffe H (1991) AIDS-associated non-Hodgkin lymphoma. Lancet 337:805-809

Discussion

Martin Lipp: Does the 3' mutation in the SDF-1 gene result in any functional consequences? In the publication, it was not reported whether the mutation affects the stability of the mRNA or the level of protein expression. Do you have further information on that?
Charles Rabkin: No, it is in a non-translated region so it is unknown. Our speculation is that it would result in increased levels of the SDF1 product. We proposed a model that would be a stimulating factor that might be both protective against HIV infection but also perhaps be a driving force for lymphomagenesis, but that is pure speculation.
Richard Scheuermann: The polymorphisms in these receptors came about from resistance to HIV infection, and now you are seeing these associations in Burkitt's lymphoma, so I wonder if there is any evidence that these things might be coreceptors for EBV, or is this some type of secondary effect on activation of B cells?
Charles Rabkin: That is an excellent suggestion. I am not aware that they have been examined as a coreceptor for EBV, but they are coreceptors for HIV, and it would be a very good thing to follow up.
Katherine Siminovitch: How many of those receptor polymorphisms detected in patients with immunodeficiency diseases have been examined in the general population? Do you find those polymorphisms generally among "healthy" individuals?
Charles Rabkin: It has not been looked at.
Martin Lipp: We looked for polymorphisms within the gene of the SDF-1 receptor, CXCR4, in about 150 leukemia and lymphoma patients as well as in about 50 healthy individuals. We found only one point mutation in several members of both groups indicating a very low genetic variation within CXCR4.
Charles Rabkin: That is also the case in a large group of lymphoma patients as well as in normals.