Susceptibility Alleles for Aberrant B-1 Cell Proliferation Involved in Spontaneously Occurring B-Cell Chronic Lymphocytic Leukemia in a Model of New Zealand White Mice

By Yoshitomo Hamano, Sachiko Hirose, Akinori Ida, Masaaki Abe, Danqing Zhang, Sanki Kodera, Yi Jiang, Jun Shirai, Yoko Miura, Hiroyuki Nishimura, and Toshikazu Shirai

B-cell chronic lymphocytic leukemia (B-CLL) and autoimmune disease are a related event, and genetic factors are linked to both diseases. As B-CLL is mainly of B-1 cell type that participates in autoantibody production, genetically-determined regulatory abnormalities in proliferation and/or differentiation of B-1 cells may determine their fate. We earlier found that, in H-2-congenic (NZB x NZW) F1 mice, while H-2\(^d\) heterozygosity predisposes to autoimmune disease, H-2\(^z\) homozygosity predisposes to B-CLL. Studies also suggested the involvement of non-H-2-linked NZW allele(s) in leukemogenesis. Using H-2-congenic NZW and B10 mouse strains, their F1 and backcross progeny, we have now identified three major NZW susceptibility loci for aberrant B-1 cell proliferation, which form the basis of leukemogenesis; one H-2-linked locus on chromosome 17 and the other two non-H-2-linked loci, each on chromosome 13 and chromosome 17. Each susceptibility allele functioned independently, in an incomplete dominant fashion, the sum of effects determining the extent of aberrant B-1 cell frequencies. The development of leukemia was associated with age-related increase in B-1 cell frequencies in the blood. Thus, these alleles probably predispose B-1 cells to accumulate genetic alterations, giving rise to B-CLL. Potentially important candidate genes and correlation of the findings with autoimmune disease are discussed.

© 1998 by The American Society of Hematology.
clonal expansion, giving rise to B- CLL.\textsuperscript{37} B- CLL also developed in H-2\textsuperscript{d/d} homozygous NZB and NZW, hence a gene or a cluster of genes located in the vicinity of NZW H-2\textsuperscript{d} was suggested to play a critical role in the process of leukemogenesis.

In these studies, we also noted that the H-2-congenic B10.NZW strain carrying homozygous H-2\textsuperscript{d} haplotype\textsuperscript{38} did not manifest as much increase in peripheral B-1 cell frequencies as that seen in H-2\textsuperscript{d/-} homozygous NZW and NZB, and B- CLL did not occur. Thus, it is clear that, in addition to the H-2\textsuperscript{d/-}-linked gene, non–H-2\textsuperscript{d/-}-linked gene(s) also controls abnormal proliferation and subsequent leukemogenesis of B-1 cells in New Zealand mouse strains. Taking advantage of H-2-congenic strains and their crosses and of analyses using microsatellite markers as tools for genome-wide linkage studies,\textsuperscript{39} we did chromosomal mapping of susceptibility alleles and analyzed their patterns of inheritance.

**MATERIALS AND METHODS**

**Mice.** NZW and B10.D2 mice were originally obtained from the Shizuoka Laboratory Animal Center (Shizuoka, Japan). NZW.H-2\textsuperscript{d} strain was established by selective backcrossing of the (NZB x NZW) F1 hybrid to NZW for 12 generations.\textsuperscript{35} B10.NZW mice were kindly donated by Dr J. Klein, Max-Planck-Institute for Biology, Tubingen, Germany.\textsuperscript{38} The F1 hybrid mice between strains NZW, B10.D2, and B10.NZW and the (NZW x B10.NZW) x B10.NZW backcross progeny were bred and maintained in our animal facility. Genotyping of backcross progeny was performed as described below. Only female mice were used in the present studies.

**Cell counts and cytologic examination.** Peripheral blood was taken from the periorbital sinus. White blood cell counts were performed using a MEK-6158 Automatic Blood Cell Counter (Nihon Koden, Tokyo, Japan) according to the manufacturer’s instructions. White blood cell-rich populations were separated from 40 µL of heparinized blood using a MEK-6158 Automatic Blood Cell Counter (Nihon Koden, Tokyo, Japan) according to the manufacturer’s instructions. White blood cell counts were performed from the periorbital sinus. Peripheral blood was taken from the periorbital sinus, followed by lysis of red blood cells with ammonium chloride. For Flow cytometry. Peripheral blood was taken from the periorbital sinus, followed by lysis of red blood cells with ammonium chloride. For flow cytometric analysis, aliquots of 5 to 10 × 10\textsuperscript{6} cells in 20 µL of phosphate-buffered saline (pH7.4) supplemented with 0.2% bovine serum albumin and 0.05% NaN\textsubscript{3} were incubated with fluorescein isothiocyanate (FITC)-labeled rat antinouse CD5 (clone 53-7.3) monoclonal antibodies and biotinylated rat antimouse CD45R (B220) (clone RA3-6B2) antibodies, followed by phycoerythrin (PE)-avidin (Becton-Dickinson, Mountain View, CA). All incubations were run for 30 minutes at 4°C. The stained cells were examined using FACStar Plus (Becton Dickinson), equipped with the FITC/PE filter system.

**Genotyping of mice.** Genomic DNA was extracted from murine tail skins using standard techniques. Chromosomal markers consisting of simple-sequence length polymorphisms were identified by polymerase chain reaction (PCR).\textsuperscript{39} The primers were purchased from Research Genetics (Huntsville, AL). PCRs were performed in the presence of radioactively-labeled primers with [γ\textsuperscript{32P}] adenosine triphosphate (ATP), using T4 kinase (Takara Shuzo, Kyoto, Japan) according to the manufacturer’s instruction. A 40-ng aliquot of genomic DNA was amplified in 10 µL of PCR solution containing Taq polymerase (Takara Shuzo). A three temperature PCR protocol (94°C, 35 cycles, and 2°C, 25 to 30 cycles or 94°C, 50°C, and 72°C, 35 cycles) was conducted in a Geneamp 9600 Thermal Cycler (Perkin Elmer Cetus, Norwalk, CT). PCR products were diluted twofold with loading buffer consisting of xylene cyanol and bromophenol blue dyes in 100% formamide and were run on 7% polyacrylamide gels. After electrophoreses, gels were dried and examined using a Bio-imaging analyzer BAS 2000 (Fuji Film, Tokyo, Japan).

**RESULTS**

**Involvement of both H-2\textsuperscript{d/-}-linked and nonlinked genes in aberrant B-1 cell proliferation in peripheral blood of New Zealand mice.** Table 1 compares age-associated changes in the proportion of peripheral blood CD5\textsuperscript{+} B (B-1) cells per total B cells in mouse strains with different genetic backgrounds, NZW (H-2\textsuperscript{d/-}), NZW.H-2\textsuperscript{d} (H-2\textsuperscript{d/-}), B10.NZW (H-2\textsuperscript{d/-}), B10.D2 (H-2\textsuperscript{d/-}), (NZW x B10.NZW) F1 (H-2\textsuperscript{d/-}), (NZW x B10.D2) F1 (H-2\textsuperscript{d/-}), and (NZW x B10.NZW) F1 x B10.NZW backcross mice at 8, 12, and 16 months of age. H-2\textsuperscript{d/-}-homoygous NZW mice at any given age showed much higher B-1 cell frequencies compared with NZW.H-2\textsuperscript{d/-} mice, a finding consistent with our earlier observation that the H-2\textsuperscript{d/-}-linked gene(s), provisionally designated Bpal-1 (B1 cell proliferation-associated locus), acts as one major predisposing genetic element for abnormal proliferation of B-1 cells.\textsuperscript{36,37} Because the H-2-congenic NZW.H-2\textsuperscript{d} strain was established by selective backcrossing of

<table>
<thead>
<tr>
<th>Strains</th>
<th>H-2 Haplotypes</th>
<th>Age (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B10.NZW</td>
<td>z/z</td>
<td>8 12 16</td>
</tr>
<tr>
<td>B10.D2</td>
<td>d/d</td>
<td>No. of mice</td>
</tr>
<tr>
<td>(NZW x B10.NZW) F1</td>
<td>z/z</td>
<td>No. of mice</td>
</tr>
<tr>
<td>(NZW x B10.D2) F1</td>
<td>z/d</td>
<td>No. of mice</td>
</tr>
</tbody>
</table>

*Frequencies of peripheral blood B-1 cells are expressed as mean percentage ± standard error of CD5\textsuperscript{+} B cells in total 6B2\textsuperscript{+} B cells.
(NZW x NZB) F1 to NZW for 12 generations, $^{35}$ Bpal-1 is estimated to be located within or in close proximity of the H-2 complex. Compared with findings in H-2$^d$-homozygous NZW, however, B-1 cell frequencies in H-2$^{d0}$-homozygous B10.NZW mice at any given age were much less, indicating that an additional non–H-2-linked NZW gene or genes are also involved.

Comparison of data shown in Table 1 indicate several inheritance patterns of the H-2$^z$-linked and nonlinked susceptibility alleles: (1) because B-1 cell frequencies were higher in strains bearing either one of the H-2$^z$-linked or nonlinked genes (B10.NZW and NZW.H-2$^{d0}$, respectively) than those found in the B10.D2 strain, which lacks both genes, each gene can act to propagate B1 cells in an independent manner; (2) because H-2$^{d0}$-heterozygous (NZW x B10.D2) F1 at any given age had lower B-1 cell frequencies than did H-2$^{d0}$ homozygous (NZW x B10.NZW) F1 mice and because H-2$^{d0}$ homozygous (NZW x B10.NZW) F1 had higher B-1 cell frequencies than did H-2$^{d0}$ homozygous B10.NZW, the H-2$^z$-linked and the non-H-2$^z$-linked genes both appeared to be inherited in an incomplete dominant fashion; and (3) because the NZW strain, which carries all susceptibility alleles, has the highest frequencies of B-1 cells compared with others bearing fewer or none such as (NZW x B10.NZW) F1, (NZW x B10.D2) F1 and B10.D2, the extent of B-1 cell frequencies in the progeny appeared to depend on additive effects of the sum of each H-2$^z$-linked and non-H-2$^z$-linked susceptibility allele.

Mapping of non–H-2$^z$-linked susceptibility alleles for aberrant B-1 cell proliferation. To map the non-H-2$^z$-linked NZW locus or loci for abnormal proliferation of B-1 cells, (NZW x B10.NZW) F1 x B10.NZW female backcross mice, all bearing homozygous H-2$^{d0}$, were generated and genotyped using microsatellite markers. Of a total of 504 markers screened, 192 markers were polymorphic between the two parental strains and 103 markers were selected for further studies (Fig 1). Figure 2 illustrates histograms of the distribution of blood B-1 cell frequencies in NZW, B10.NZW, the F1 hybrid and the F1 x B10.NZW backcross mice at 8 and 16 months of age. When cut-off points were determined based on criteria that B-1 cell frequencies of over 5% and 10% were regarded as abnormal levels at age 8 and 16 months, respectively, $\chi^2$ analyses using 127 to 140 backcross mice showed that NZW/B10.NZW (NB) genotype at loci on each chromosome 13 and 17 was significantly associated with abnormal proliferation of B-1 cells (Table 2).

Interval mapping of data from backcross mice at 8 and 16 months of age using MAPMAKER/QTL showed that the locus on chromosome 13, provisionally designated Bpal-2, is located on the centromeric portion and is either significantly or suggestively linked to D13Mit136, D13Mit61, and D13Mit13. However, second peaks were always identified within each MAPMAKER/QTL analysis. In mice aged 8 months, the locus was most closely linked to D13Mit136 and, in mice aged 16 months, it was closely linked to D13Mit13 (Table 2 and Fig 3). The existence of these two peaks and the large size of the one-log confidence support interval (29 centiMorgans) obtained by analysis in mice aged 8 months suggest the possible existence of two susceptibility loci in this region (Fig 3). As numbers of recombinants between D13Mit136 and D13Mit13 were few, we could not confirm this possibility.

On the other hand, the non–H-2$^z$-linked locus on chromosome 17 showed a suggestive association in lod scores with D17Mit222 in MAPMAKER/QTL analysis of 8 months old mice. Although the lod scores were not in the range of significant values, the existence of QTL close to this locus was suggested in ANOVA, as based on four groups of backcross progeny, classified according to combinations of genotypes for D13Mit136 (Bpal-2) and D17Mit222, ie, group A, B10.NZW/ B10.NZW (BB) genotype for both D13Mit136 and D17Mit222, groups B and C, either one of the two loci is NZW/B10.NZW (NB) and the other is BB; and group D, NB for both loci (Fig 4). Among these four groups, the extent of B-1 cell frequencies was in the order of group D, groups B and C, and group A, indicating that the frequencies are increased in a manner depending on the number of the corresponding NZW susceptibility alleles. The differences were statistically significant in mice at 8 and at 16 months of age ($P < .0001$ at 8 months, and $P < .01$ at 16 months) by ANOVA. Thus, in addition to the effects of Bpal-1 (H-2$^z$-linked) and Bpal-2, the third non–H-2$^z$-linked locus on NZW chromosome 17, tentatively designated Bpal-3, is also likely to play a role in the abnormal proliferation of B-1 cells.

Development of B-CLL in backcross progeny. At the age of 23 months, a time when 70% of NZW mice had developed B-CLL, as determined by blood smear samples, 12% of the (NZW x B10.NZW) x B10.NZW backcross mice developed leukemia, and this was associated with age-related abnormal increase in the frequency of B-1 cells in the blood. Figure 5 shows a representative result of age-associated changes in the frequency of B-1 cells in the blood, as determined by fluorescence-activated cell sorting (FACS) analysis in cytospinned leukocyte films in a (NZW x B10.NZW) x B10.NZW backcross mouse at ages 8, 16, and 23 months. FACS profiles showed that proportions of B-1 cells per total B cells were progressively increased in this mouse with aging (11%, 44%, and 97% at 8, 16, and 23 months of age, respectively). In the leukemic stage in the mouse 23 months of age, total leukocyte counts were markedly high (35,500/mm$^3$). Morphologically, most lymphocytes in the peripheral blood in the 8-month-old mouse were small and had condensed nuclear
chromatin and a scant cytoplasm. At 16 months of age, there occasionally appeared relatively larger lymphocytes with a basophilic cytoplasm, some of which had irregular nuclei with irregular networks of chromatin. The majority of blood lymphocytes at the leukemic stage were composed of lymphoid cells with a basophilic cytoplasm and nuclei with a coarse granular chromatin. Smudged cells and broken lymphocytes were frequent (data not shown). Surface markers of leukemic cells were positive for surface IgM, CD2, CD5, CD19, and MHC class II and negative for CD25 and CD38, with patterns similar to those seen in human B-CLL cells.

**DISCUSSION**

We identified three susceptibility loci responsible for abnormal proliferation of B-1 cells, an event that forms the basis of leukemogenesis in a B-CLL model of NZW strain. All three susceptibility alleles function independently and are inherited in an incomplete dominant fashion. The extent of B-1 cell frequencies in the peripheral blood depends on the sum of each susceptibility allele, indicating additive effects of these alleles. These features are consistent with the polygenic inheritance of the abnormality as a threshold liability. It is highly plausible that these susceptible alleles predispose B-1 cells to accumulate genetic alterations, thus giving rise to B-CLL.

As usual in studies of interval mapping of genes with incomplete penetrance, support intervals associated with B-CLL susceptibility alleles were long. Thus, further approaches for identification of the causative gene in each interval include the establishment of a congenic strain for support intervals, followed by exon-trapping. Another approach would be charac-

---

**Table 2. Linkage of Particular Loci With B-1 Cell Proliferation in the Backcross Progeny**

<table>
<thead>
<tr>
<th>Chr*</th>
<th>Locus</th>
<th>Distance†</th>
<th>Direction‡</th>
<th>8 Months§</th>
<th>16 Months§</th>
<th>8 Months</th>
<th>16 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>D13M1780</td>
<td>15.8</td>
<td>NB &gt; BB</td>
<td>9.48</td>
<td>0.0021</td>
<td>6.04</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>D13M1781</td>
<td>11.3</td>
<td>NB &gt; BB</td>
<td>8.38</td>
<td>0.0038</td>
<td>7.44</td>
<td>0.0064</td>
</tr>
<tr>
<td></td>
<td>D13M1782</td>
<td>19.0</td>
<td>NB &gt; BB</td>
<td>8.38</td>
<td>0.0038</td>
<td>14.42</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>D13M1783</td>
<td>15.1</td>
<td>NB &gt; BB</td>
<td></td>
<td></td>
<td>8.08</td>
<td>0.0045</td>
</tr>
<tr>
<td></td>
<td>D13M1784</td>
<td>11.4</td>
<td>NB &gt; BB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D13M1785</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>D17M1733</td>
<td>10.6</td>
<td>NB &gt; BB</td>
<td>6.02</td>
<td>0.014</td>
<td>8.44</td>
<td>0.0037</td>
</tr>
<tr>
<td></td>
<td>D17M1734</td>
<td>8.1</td>
<td>NB &gt; BB</td>
<td></td>
<td></td>
<td>3.41</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>D17M1735</td>
<td>6.6</td>
<td>NB &gt; BB</td>
<td></td>
<td></td>
<td>2.78</td>
<td>0.096</td>
</tr>
<tr>
<td></td>
<td>D17M1736</td>
<td>3.5</td>
<td>NB &gt; BB</td>
<td></td>
<td></td>
<td>6.79</td>
<td>0.0092</td>
</tr>
<tr>
<td></td>
<td>D17M1737</td>
<td>6.4</td>
<td>NB &gt; BB</td>
<td></td>
<td></td>
<td>6.79</td>
<td>0.0092</td>
</tr>
<tr>
<td></td>
<td>D17M1738</td>
<td>11.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D17M1739</td>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D17M1740</td>
<td>9.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Chromosome number.
†Distance in centiMorgans (Kosambi function) between two consecutive markers as calculated by MAPMAKER/EXP. Markers are arranged from centromeric to telomeric.
‡NB, heterozygous loci of NZW and B10.NZW; BB, homozygous loci of B10.NZW. An inequality NB > BB indicates that the phenotype is biased to progeny genotyped as NB.
§Peripheral B-1 cell frequencies are considered as increased if exceeding 5% in mice 8 months of age or 10% in mice 16 months of age.
∥Log of the likelihood ratio (lod) scores are analyzed by MAPMAKER/QTL. Lod scores only greater than 1 are indicated.
terization of relevant candidate genes potentially related to the
dysregulation of B-1 cell proliferation. In this context, because
Bpal-1, an H-2-linked susceptibility allele, retains the effect in
H-2-congenic B10.NZW mice that have been established by
selective backcrossing of mice for 12 generations, the candi-
date gene appears to be located within or in close proximity of
the H-2 complex. A potentially important polymorphic candidate
gene for Bpal-1 may be a structural gene of MHC class II antigens. Evidence is accumulating that B-CLL cells use
restricted repertoires of nonmutated Ig V genes.21,22 V H genes of
B-CLL are preferentially selected from relatively small V H
subgroups and the structure of the complementarity-determining
region (CDR) 3 is biased to be longer than that of the normal
counterpart,20 suggesting that an antigen-driven, strong selec-
tive force is operative on B-1 cells during leukemogenesis.
Considering that the majority of B-1 cells can cross-react with a
variety of self-antigens, which can be processed and presented
as an MHC class II-peptide complex, chronic stimulation via a
certain ubiquitous self-peptide plus class II may serve as a
selective force for the restricted repertoires, and the risk for
neoplastic transformation into B-CLL would increase. In this
regard, the H-2 d haplotype of NZW strain is unique. Our earlier
studies using H-2-congenic New Zealand mouse strains showed
that the major NZW contribution to severe SLE in (NZB x
NZW) F1 mice is the H-2d-linked locus that forms H-2dS
heterozygosity in the F1 hybrid mice.43,44 Importance of the H-2
d heterozygosity for SLE has been confirmed in F244 and
backcross45 analyses, except for one that showed a minor
influence.46 The most plausible hypothesis for the difference
between homozygous H-2dS for B-CLL and heterozygous H-2dS
for autoimmune disease in (NZW x NZB) F1 mice is that, in the
latter, the formation of mixed haplotype-class II molecules, ie,
Aeββ, Aeββ, Eαββ, and Eαββ allows selected B-1 cells to
undergo class switch and affinity selection, giving rise to plasma
cells producing pathogenic autoantibodies.47,48 In contrast, in the former
H-2dS homoyzogotes, because of the lack of genetic element
(mixed haplotype class II molecules) required for such B-1 cell
maturation, only signals for proliferation would be function-
ing.14

Another candidate for Bpal-1 may be the tumor necrosis factor (TNF) gene. Both structural and regulatory genes of
TNF-α and -β are mapped to the D subregion of the H-2
complex.49 It was reported that although TNF-α weakly triggers
the growth of B-CLL cells,50 it does exert a synergistic proliferative effect in combination with interleukin (IL)-2.51
Serum levels of TNF-α are increased in B-CLL patients
compared with findings in healthy age-matched individuals.52
Thus, it is possible that the polymorphic TNF-α gene in the H-2
complex controls the proliferation of B-1 cells in NZW mice.
However, this is less likely because production of TNF-α in the
NZW strain is downregulated, rather than upregulated, by the
unique polymorphic NZW TNF-α allele,53 and because this
NZW TNF-α allele upregulates SLE in (NZB x NZW) F1
mice.54 Our recent genetic studies suggested that both class II
and NZW TNF-α polymorphisms appear to be functioning as
H-2-linked predisposing genetic elements for SLE, and that the
TNF-α polymorphism functions to modulate an initial process
of the autoimmune disease in these mice.54

One-log confidence interval containing Bpal-2 on chromo-
some 13 covers potent candidate loci, ie, encoding T-cell receptor γ chain (Tcrγ), inhibin βA (Inhba), prolactin (Prl), and
Friend murine leukemia virus (MuLV) integration site-1 (Fim-
1). Among these, Inhba deserves attention. A homodimer of
inhibin βA is activin A produced in stromal cells in the bone
marrow and regulates differentiation and proliferation of cells, including hematopoietic cells and leukemic cells. We are now determining if Inhba is polymorphic and has the potential to proliferate B-1 cells. This segment of murine chromosome 13 is homologous to portions of human chromosomal regions 7p15 (as for Tcrg and Inhba) and 6p23 (as for Prl). Among genes on the centromeric portion of chromosome 17, Igf2r (insulin-like growth factor 2 receptor [IGF2R]) is a plausible candidate for Bpal-3. Evidence is accumulating that Igf2r acts as a tumor suppressor gene in both humans and mice. Loss of IGF2R function leads to an increased extracellular concentration of IGF2 and a decreased level of activated TGF-β, a condition under which human hepatocytes are susceptible to malignant transformation. In human breast cancers, loss of heterozygosity was found at the locus of IGF2R. Overexpression of IGF2 can increase frequencies of diverse malignancies, including lymphoma in mice. Thus, a potential genetic polymorphism of the NZW Igf2r gene may be involved in leukemogenesis. To examine all of these possibilities, we are now generating interval-specific congenic strains for Bpal-2 and Bpal-3. Such strains will also be useful for the analysis of epistatic effects between susceptibility alleles.

Raveché et al reported that aged NZB mice, a spontaneous model of autoimmune hemolytic anemia, exhibit a clonal expansion of hyperdiploid B-1 cells that resemble B-CLL. In our earlier studies, the frequencies of B-1 cells in the NZB strain (H-2k) were much lower than found in the homozygous H-2b-congenic NZB strain. However, considering the disparity in B-1 cell frequencies between the H-2b-congenic NZB and the H-2b-congenic B10.NZW (present study), it is highly plausible that the NZB strain also carries certain susceptibility alleles such as Bpal-2 and/or Bpal-3 for abnormal proliferation of B-1 cells. In concert with effects of the susceptibility alleles for aberrant B-1 cell differentiation, such Bpal-2 and/or Bpal-3 may possibly relate to the autoimmune disease seen in NZB and (NZB × NZW) F1.

In conclusion, New Zealand mouse models provide a valuable tool for determination of the genetic basis of not only B-CLL ontogeny, but also autoimmune disease, in which dysregulated proliferation of B-1 cells forms the basis of B-CLL and the associated aberrant maturational processes of these expanded populations of B-1 cells can lead to autoimmune disease.

ACKNOWLEDGMENT

We thank Dr T. Ushijima, National Institute for Cancer Research, Japan for helpful discussion and M. Ohara for comments on the manuscript.

REFERENCES


23. Tarlinton D, Stall AM, Herzenberg LA: Repetitive usage of immunoglobulin V_{H} and D gene segments in CD5+ Ly-1 B clones of (NZB x NZW) F1 mice. EMBO J 7:3705, 1988


44. Kono DH, Burlingame RS, Owens D, Kuramochi A, Balderas RS, Balomenos D, Theofilopoulos AN: Lupus susceptibility loci in New Zealand mice. Proc Natl Acad Sci USA 91:10168, 1994