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Influence of Maternal-Fetal Histocompatibility and MHC Zygosity on Maternal Microchimerism

Joseph Kaplan2* and Susan Land†

To investigate the relationship between maternal-fetal histocompatibility and maternal microchimerism, we developed a sensitive quantitative PCR assay for the neomycin resistance gene (neoR), and, in a mouse model system, used neoR as a noninherited maternal allele marker of maternal cells to detect and quantitate maternal microchimerism in tissues of neoR+/− N2 backcross progeny of (neoR+/−)F1 females mated with neoR−/− males. Using this approach, we obtained evidence for the presence of chimeric maternal cells in the brain, spleen, and thymus of all weanling and adult mice so tested. The numbers of chimeric maternal cells present in the spleen did not differ significantly from those in the thymus regardless of age or maternal-fetal histocompatibility. At all ages, brain tissue had higher level of maternal microchimerism than lymphoid tissue in mice MHC identical with their mothers, but the levels were similar in mice MHC disparate with their mothers. The levels of chimeric maternal cells in both brain and lymphoid tissue of mice with homozygous syngenicity and maternal allogenicity were similar, and tended to be higher than tissue-specific levels in mice with either combined maternal-fetal allogenicity or heterozygous syngenicity. Thus, MHC homozygous progeny had higher levels of maternal microchimerism than MHC heterozygous progeny. We conclude that normal mice possess small numbers of maternal cells in spleen, thymus, brain, and probably most other tissues, and that maternal-fetal histocompatibility influences the levels of these cells by mechanisms related to MHC zygosity of the progeny. The Journal of Immunology, 2005, 174: 7123–7128.

Maternal microchimerism, the presence of very small fractional concentrations of chimeric maternal cells, occurs in at least half of all humans from fetal life into adulthood (1–4). The factors that govern maternal microchimerism are poorly understood, but may be of considerable clinical relevance in view of the fact that maternal microchimerism has been associated with autoimmunity (5) and allograft tolerance (6), and may serve as a vehicle for vertical transmission of pathogenic microbes and allergens (7).

The notion that maternal-fetal histocompatibility plays a role in the regulation of persistent maternal microchimerism derives from the well-known importance of donor-host histocompatibility in regulating donor cell chimerism in allogeneic bone marrow transplant recipients (8). Much of the evidence for this has come from studies that have taken advantage of the ready availability of inbred mouse strains with well-defined MHC genes. There have been several previously reported investigations of maternal microchimerism in mouse model systems that, taken together, demonstrate the frequent occurrence in fetal, neonatal, and adult lymphoid and hematopoietic tissues of chimeric cells transferred in utero and/or through breastfeeding from allogeneic (9), semiallogeneic (10), and syngeneic (11, 12) mothers. However, mouse models have not been used to systematically investigate the possible influence of maternal-fetal histocompatibility on maternal microchimerism. To help fill this gap in knowledge, we have developed a sensitive and accurate quantitative PCR (QPCR)3 assay for the neomycin resistance gene (neoR), and have used neoR as a noninherited maternal allele (NIMA) in mice to quantitate chimeric maternal cells in neoR+/− N2 backcross progeny of (neoR+/−)F1 females mated with neoR−/− males. In the studies described in this work, we have used this approach to examine the relationship between maternal-fetal histocompatibility and the prevalence and levels of maternal microchimerism in lymphoid tissues and brains of weaning and adult mice. The results indicate that small amounts of NIMA-specific DNA probably representing maternal cells are present in lymphoid and nonlymphoid tissues of virtually all neonatal and adult mice regardless of their pattern of maternal-fetal histocompatibility, with a tendency for higher levels in MHC homozygous mice. Consistent with previously reported evidence of the normalcy of maternal cell transfer and long-term engraftment in immunocompetent progeny (9), the current findings lend support to the possibility that maternal cells have a normal physiological role.

Materials and Methods

Mice

Male BALB/cByJ, NZM2410/J, and C57BL/6J (B6) mice age 5 wk were obtained from The Jackson Laboratory. Adult male and female FVIII-knockout mice, homozygous for the neoR gene within the mouse FVIII gene and bred onto the B6 background, were kindly provided by H. Kazazian (University of Pennsylvania School of Medicine, Philadelphia, PA).

Generation of progeny and tissue harvesting

As described below, matings were conducted between various strains of male and female mice ranging in age from 2 to 5 mo. Each of the female mating partners in this study had produced one to two previous litters derived from matings with the same strains of males. All progeny were weaned at age 22 days. At 0–45 days of age, all progeny of a single litter were sacrificed, and specimens of spleen, thymus, brain, and bone marrow were individually quick frozen in liquid nitrogen for subsequent individual

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* Carmen and Ann Adams Department of Pediatrics, School of Medicine, and †Department of Genetics, Center of Molecular Medicine and Genetics, Wayne State University, Detroit, MI 48201

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2 Address correspondence and reprint requests to Dr. Joseph Kaplan at the current address: Children’s Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, MI 48201. E-mail address: jkaplan@med.wayne.edu

3 Abbreviations used in this paper: QPCR, quantitative PCR; NIMA, noninherited maternal allele.
from a single neoR the relative standard curve method. The amount of available from Applied Biosciences. Quantitation of the fractional amount Biosystems). As a reference control, a TaqMan QPCR assay for murine and 1 min at 60°C. The amplifications were performed on an ABI Prism; and H-2z consisted of DNA isolated from spleen cells obtained from B6, H-2 genotyping Mouse DNA samples were genotyped for H-2, as previously described (13), using PCR amplification of highly polymorphic microsatellites in the second intron of the H-2Eb gene. Positive controls for H-2b, H-2d, and H-2x consisted of DNA isolated from spleen cells obtained from B6, BALB/c, and NZM mice.

QPCR analysis
QPCR analysis was performed using the TaqMan PCR Core Reagent kit (Applied Biosystems). Reactions for neoR-genomic DNA quantification were performed in 30 μl with 0.5 μg of DNA; 3 μl of 10× TaqMan buffer A (500 mM KCl, 100 mM Tris-HCl, pH 8.3); 5 mM MgCl2, 200 μM each of dATP, dCTP, and dGTP; 400 μM dUTP; 0.3 U of uracil-N-glicosidase; 0.75 U of AmpliTaq Gold DNA polymerase; 50 nM probe; and 100 nM sense and antisense primers. neoR gene nucleotide sequence data obtained from the GenBank database (accession US2109) and Primer Express software (Applied Biosystems) were used to design the following neoR-specific oligonucleotide probe and forward and reverse PCR primers specific for an invariant section of the neoR transcript: neoR sense primer, 5′-TGA GCC TGG CGA ACA GTT C-3′; neoR antisense primer, 5′-CCG GTG TTG TCG ATC AGG AT-3′; and neoR probe, 5′-6FAM-ATG CTC TTC GTC CAG AT-MGBFQ-3′. All were purchased from Applied Biosystems. The QPCR program used an initial temperature of 50°C for 2 min and then 95°C for 10 min, followed by 40 amplification cycles run for 15 s at 95°C and 1 min at 60°C. The amplifications were performed on an ABI Prism 7700 sequence detector equipped with a 96-well thermal cycler. Data were collected and analyzed with Sequence Detector v1.6.3 software (Applied Biosystems). As a reference control, a TaqMan QPCR assay for murine GAPDH was run in parallel on each DNA sample using probes and primers available from Applied Biosciences. Quantitation of the fractional amount of neoR genomic DNA present in each DNA sample was calculated using the relative standard curve method. The amount of neoR present in DNA from a single neoR+/− cell was considered one genome equivalent of neoR, and the amount of GAPD in one diploid cell was considered one genome equivalent of GAPDH. The fractional concentration of neoR+/− cells represented in each sample of DNA was calculated as a ratio to the GAPD genome equivalents detected in the same DNA sample. All of the assays were done at two different concentrations in duplicate with probes labeled with FAM and TAMRA.

Statistical analysis
Differences in the means of the log-transformed fractional levels of NIMA-specific DNA were compared by ANOVA or by the Mann-Whitney U test. Fisher’s protected least significant difference test was used for multiple comparisons with significance set at p < 0.05. All statistical analyses were conducted using the StatView 4.5 software program for Macintosh computers.

Results
Development of a 5′ nuclease (TaqMan) QPCR assay for the neoR gene
Our overall strategy in these experiments was to use the neoR gene as a NIMA to quantitate the levels of chimeric maternal cells in neoR+/− N2 backcross progeny of neoR+/− females mated with neoR−/− wild-type males. As a first step, we sought to develop a sensitive and accurate QPCR method for detection of the neoR gene. We first generated obligatory neoR−/− heterozygotes by mating neoR−/− homozygous B6 FVIII-knockout females with wild-type B6 males. A known amount of genomic DNA isolated from tissue derived from a neoR−/− mouse was then serially diluted in a fixed known amount of genomic DNA from a wild-type neoR+/− mouse, and each dilution was used as genomic DNA in QPCR assays for the neoR gene. To standardize the assay for genomic DNA, a TaqMan assay for rodent GAPDH available from Applied Biosystems was run in parallel with the neoR TaqMan assays on each of the DNA samples. The results showed a tight fit to linearity (Fig. 1), sensitivity to the level of detection of one neoR genome equivalent, and neoR specificity because PCR product was only detected with DNA from neoR+ mice; none was detected after 40 cycles of real-time PCR using DNA from wild-type neoR− B6 mice. Based on these results, subsequent experiments used QPCR assays instead of standard PCR assays to determine the neoR genotype of backcross progeny of all neoR+/− × neoR−/− matings.

Generation of NIMA informative neoR+/− progeny differing in maternal-fetal histocompatibility
Four different backcross mating schemes were used to generate neoR+/− progeny of neoR− mothers with different maternal-fetal histocompatibility relationships across the entire H-2 complex (Table I). The terms used in this work to describe these maternal-fetal histocompatibility relationships, homozygous syngenicity, heterozygous syngenicity, fetal semiallogenicity, maternal semiallogenicity, and combined maternal and fetal semiallogenicity, are based on those described by Hoff et al. (14). All members of a given litter of N2 progeny were killed on the same day, and samples of their spleen, thymus, and brain were snap frozen and stored at −80°C. Aliquots of genomic DNA isolated from frozen tissues were used in H-2-specific PCR to determine the H-2 genotypes of the tissue donors, and in neoR-specific QPCR assays to determine their neoR genotypes, and to detect and quantitate NIMA-specific DNA in tissues of mice found to be neoR negative.

Effects of tissue source and donor age on prevalence and levels of maternal microchimerism
We detected at least some NIMA-specific DNA in the brain, spleen, and thymus of all weaning and adult mice so tested. The fractional levels of NIMA-specific DNA in each of these tissues

![Graph](https://example.com/graph.png)

**FIGURE 1.** Standard curve for QPCR assay for the neoR gene. The graph plots Ct, the threshold values of the PCR cycle number first detecting signal for amplified genomic DNA in the QPCR, against log (concentration of genomic DNA) of serially diluted samples of DNA from a neoR-positive mouse. The plot shows tight linearity and sensitivity of detection to one genome equivalent.
showed no relationship to age, nor were there any differences between the levels detected in spleen and thymus. Therefore, we pooled data from mice of all ages, and from spleen and thymus, and compared data from this pooled lymphoid tissue with that obtained from brain. As shown by regression analysis (Fig. 2), the levels of NIMA-specific DNA in brain correlated with those in lymphoid tissue.

Effects of maternal-fetal histocompatibility on levels of NIMA-specific DNA in brain and lymphoid tissue

The results presented in Table II and Figs. 3 and 4 compare the fractional levels of NIMA-specific DNA in brain and lymphoid tissue from mice generated by pregnancies with different types of maternal-fetal histocompatibility. The data for each maternal-fetal histocompatibility type represent pooled data from the different mating schemes generating each of these types because we detected no significant within-type differences. The fractional levels of NIMA-specific DNA in brain and lymphoid tissue of all adult mice so tested regardless of the presence and levels of maternal microchimerism. Our strategy was to use NIMA-specific DNA as a marker of chimeric maternal cells to assess the prevalence and fractional amount of maternal microchimerism in the brain and lymphoid tissue of informative homozygous neoR−/− backcross progeny of heterozygous neoR+/− female mice mated with male wild-type neoR−/− mice. The mating partners were chosen to be homozygous or heterozygous at the MHC locus for either shared or disparate alleles to create progeny with four possible patterns of maternal-fetal histocompatibility. Using this approach, we detected NIMA-specific DNA in the brain and lymphoid tissue of all adult mice so tested regardless of the presence or absence of maternal-fetal histocompatibility. However, comparison of the fractional levels of NIMA-specific DNA in mice derived from pregnancies with different types of maternal-fetal histocompatibility revealed a consistent pattern: regardless of their age at testing, the levels in mice derived from pregnancies with maternal-fetal homozygous syngenicity and maternal semiallogenicity were similar, and tended to be higher than in mice with either combined maternal-fetal semiallogenicity or heterozygous syngenicity. By ANOVA, the mean fractional level of NIMA-specific DNA in the brain was significantly higher in mice with homozygous syngenicity than in mice with either combined maternal-and-fetal semiallogenicity (p = 0.016) or heterozygous syngenicity (p = 0.05). In lymphoid tissue, as in the brain, the mean fractional level of NIMA-specific DNA in mice with maternal-fetal homozygous syngenicity was significantly higher than in mice with maternal-fetal heterozygous syngenicity (p = 0.02), and tended to be higher than in mice with combined maternal-and-fetal semiallogenicity (p = 0.08). Lymphoid tissue levels were also significantly higher in mice with maternal semiallogenicity than in mice with either combined maternal-and-fetal semiallogenicity (p = 0.02) or heterozygous syngenicity (p = 0.004). As pointed out above, across all mice tested, brain tissue had significantly higher fractional levels of NIMA-specific DNA than lymphoid tissue. However, when analyzed for the effect of maternal-fetal histocompatibility, this difference was only significant in the case of mice with histocompatible mothers, i.e., those with maternal-fetal homozygous syngenicity (p < 0.0001) or heterozygous syngenicity (p = 0.0013), and not in those with maternal semiallogenicity (p = 0.94) or maternal-fetal semiallogenicity (p = 0.69).

Discussion

In the studies described in this work, we developed a highly sensitive QPCR assay for quantitation of the neoR gene, and used the neoR gene as a NIMA in mouse model experiments designed to test for the effects of maternal-fetal histocompatibility on the presence and levels of maternal microchimerism. Our strategy was to test for the effects of maternal-fetal histocompatibility on the presence and levels of maternal microchimerism. Our strategy was to use NIMA-specific DNA as a marker of chimeric maternal cells to assess the prevalence and fractional amount of maternal microchimerism in the brain and lymphoid tissue of informative homozygous neoR−/− backcross progeny of heterozygous neoR+/− female mice mated with male wild-type neoR−/− mice. The mating partners were chosen to be homozygous or heterozygous at the MHC locus for either shared or disparate alleles to create progeny with four possible patterns of maternal-fetal histocompatibility. Using this approach, we detected NIMA-specific DNA in the brain and lymphoid tissue of all adult mice so tested regardless of the presence or absence of maternal-fetal histocompatibility. However, comparison of the fractional levels of NIMA-specific DNA in mice derived from pregnancies with different types of maternal-fetal histocompatibility revealed a consistent pattern: regardless of their age at testing, the levels in mice derived from pregnancies with maternal-fetal homozygous syngenicity and maternal semiallogenicity were similar, and tended to be higher than in mice derived from pregnancies with either combined maternal-fetal semiallogenicity or heterozygous syngenicity.

It seems likely that most, if not all, of the NIMA-specific DNA detected in these studies derives from intact chimeric cells, and thereby provides an accurate reflection of the presence and level of maternal microchimerism. However, in the absence of direct evidence for chimeric cells using such techniques as in situ immunohistochemistry and immunofluorescence, it remains possible that at least some of the NIMA-specific DNA represents cell-free DNA released from dead cells either in situ or in the circulation. This is a particularly important consideration with regard to the data obtained in this study with brain tissue, because, while direct evidence for chimeric maternal cells in lymphoid tissues of adult progeny has been previously reported (10), the current findings are the first evidence supporting the presence of chimeric maternal

### Table I. Mating schemes

<table>
<thead>
<tr>
<th>NeoR⁺/⁺ Mother</th>
<th>NeoR⁻/⁻ Father</th>
<th>H-2 Genotype(s)</th>
<th>Progeny</th>
<th>Maternal-Fetal Histocompatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>(B6neoR⁺⁺ × B6)F₁ (H-2b/b)</td>
<td>B6 (H-2b/b)</td>
<td>H-2b/b</td>
<td>Homozygous syngenicity</td>
<td></td>
</tr>
<tr>
<td>(B6neoR⁺⁺ × BALB/c)F₁ (H-2b/d)</td>
<td>BALB/c (H-2d/d)</td>
<td>H-2b/d</td>
<td>Heterozygous syngenicity</td>
<td></td>
</tr>
<tr>
<td>(B6neoR⁺⁺ × BALB/c)F₁ (H-2b/d)</td>
<td>B6 (H-2b/b)</td>
<td>H-2b/b</td>
<td>Maternal semiallogenicity</td>
<td></td>
</tr>
<tr>
<td>(B6neoR⁺⁺ × NZM)F₁ (H-2b/z)</td>
<td>CByB6F₁ (H-2b/d)</td>
<td>H-2b/z</td>
<td>Heterozygous syngenicity</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 2. Direct correlation between levels of maternal microchimerism in brain and lymphoid tissue. Data represent Ln (fractional levels of NIMA-specific DNA × 10E-5) detected by real-time PCR in brain and lymphoid tissue (spleen and/or thymus) in 16 mice.
cells in the brain. The existence of the blood barrier to large molecules and the extremely short $t_{1/2}$ of foreign DNA in the circulation (15) makes it unlikely that the NIMA-specific DNA detected in this study in brain represents circulating DNA released into the circulation by dead cells outside the brain. Moreover, even if the NIMA-specific DNA derives in part from DNA released in situ by chimeric cells, the data still support the presence of such cells in the brain. The only previously reported data bearing on this question is that of Piotrowski and Croy (11), who, using histochemical methods, failed to detect maternal cells in sections of fetal mouse brain tissue obtained from gestation day 8 to term. The discrepancy between the results of that previous study and the data obtained in this study could be due to a lower sensitivity of NIMA detection by histochemistry compared with PCR.

The current data do not permit estimation of the extent to which the NIMA-specific DNA detected in this study represents maternal cells derived from prenatal transplacental passage or maternal cells derived from postnatal lactational transfer. However, previously reported evidence that prenatally acquired maternal cells have a greater capacity for long-term postnatal persistence than those acquired postnatally (10, 16) taken together with the observation that chimeric maternal cells first appear and are most prevalent in the bone marrow (17) favors the notion that the NIMA-specific DNA detected in this study in adult lymphoid tissue and brain represents maternal cells that had originally seeded and successfully engrafted the fetal bone marrow in utero.

Our detection of NIMA-specific DNA in progeny with maternal semiallogenicity fits with findings previously reported by Zhang and Miller (10), who, using immunofluorescence assays, detected small numbers of maternal cells expressing the noninherited maternal H-2d allele in lymph nodes of many, but not all, 6-wk-old H-2b backcross offspring of H-2b$^{b0d}$ B6D2F1 females mated with H-2b$^{b0d}$ B6 males. The greater prevalence of maternal microchimerism suggested by our results is probably related to a higher sensitivity of detection of NIMA by PCR than by direct immunofluorescence.

The occurrence of maternal microchimerism in mice in the face of maternal-fetal histoincompatibility is also entirely consistent with similar findings in humans (18–20). In both species, this can be explained, in part, by the fact that partial tolerance to noninherited maternal alloantigens is a normal occurrence. Thus, both human and mouse studies indicate that in utero and neonatal exposure to NIMA-expressing cells frequently induces long-lasting NIMA-specific transplant tolerance in vivo (6, 10, 21, 22) and reductions in the frequency and functional activity of NIMA-specific T cells (22, 23). In the current study, support for a role for NIMA-specific T cells in regulating maternal microchimerism comes from the observation that brain tissue had significantly higher fractional levels of NIMA-specific DNA than lymphoid tissue in mice with histocompatible mothers, but not in mice with histoincompatible mothers. Consistent with the findings of Marleau et al. (9) that the prevalence and level of maternal microchimerism in extramedullary tissues are lower and more transient than in bone marrow in immunocompetent offspring of MHC disparate mothers, but not in immunodeficient or histocompatible offspring, this finding also suggests that NIMA-specific T cell regulation of chimeric maternal cells may play a more important regulatory role in some tissues than others.

Although classic T and B cell alloreactivity to noninherited maternal MHC Ags clearly plays a role in regulating chimeric maternal cells, the overall pattern of similarities and differences in the levels of maternal microchimerism detected in this study in mice derived from pregnancies with different types of maternal-fetal histocompatibility cannot be readily explained by any single mechanism involving unidirectional or bidirectional maternal-fetal T or B cell alloreactions. The expected T and B cell tolerance to self MHC Ags in adult mice derived from pregnancies with homozgyous syngenicity and the expected T and B cell alloreactivity to noninherited maternal MHC Ags of adult mice derived from pregnancies with combined maternal and fetal semiallogenicity could readily account for the higher levels of maternal microchimerism detected in the former than in the latter, but none of these mechanisms explains why progeny of homozgyous syngenic pregnancies have higher levels of persistent maternal microchimerism than progeny of heterozygous syngenic pregnancies in both brain and lymphoid tissue. Homozgyous syngenic progeny and heterozygous syngenic progeny should both be tolerant to maternal cells because such cells presumably express exactly the same complement of MHC Ags as cells from the progeny themselves. Differences in the presence or absence of T or B cell self-tolerance and alloreactivity also fail to explain why the level of maternal microchimerism is higher in mice with maternal allogenicity than in mice with either heterozygous syngenicity or combined maternal-fetal allogenicity.

Further analysis of the data suggests that zygosity at the MHC locus is the one histocompatibility characteristic that distinguished progeny with relatively high vs those with relatively low levels of maternal microchimerism. Thus, as shown in Fig. 4, compared with progeny with MHC heterozygosity (i.e., those with H-2$^{b0d}$, H-2$^{b0b}$, or H-2$^{b0d}$ genotypes), mice with MHC homozygosity (i.e., those with H-2$^{b0b}$ or H-2$^{b0d}$ genotypes) had significantly higher levels of maternal microchimerism in both brain (p = 0.05) and lymphoid tissue (p = 0.004). It can be argued that the zygosity effects on maternal microchimerism observed in this study are due
to zygosity effects of non-MHC genes rather than zygosity effects of MHC genes. However, this seems unlikely because identical MHC zygosity effects were observed in comparisons of several different types of MHC homozygous and heterozygous progeny even though the relative maternal and fetal zygosity of most of their non-MHC-linked genes should not necessarily correspond to the relative maternal and fetal zygosity of their MHC genes. Formal confirmation of a role for MHC zygosity in regulating maternal microchimerism could come from studies similar to those described in this work comparing the levels of chimeric maternal cells in MHC congenic mice with different genetic backgrounds.

The apparent importance of MHC zygosity in regulating in vivo levels of persistent maternal microchimerism highlights the likely importance of host NK cells in this phenomenon, because in contrast to T and B cell specificity, NK cell specificity is determined in many cases by the relative MHC zygosity of NK cells and their targets (24, 25). For example, transplanted fully allogeneic cells are rapidly removed by mouse and rat NK cells, whereas semiallogeneic cells usually are not (26–28). Based on such findings, Zhang and Miller (10) previously pointed out that this pattern of NK specificity favors survival of maternal cells in offspring because such cells are normally semiallogeneic rather than fully allogeneic, and presented evidence directly supporting that hypothesis.

All of the mice tested in this study resulted from pregnancies yielding NeoR-positive as well as NeoR-negative progeny, and derived from matings of mothers with at least two similar pregnancies. Therefore, while most of the NIMA-specific DNA detected in this study almost certainly represents intact chimeric maternal cells, at least some of the NIMA-specific DNA detected in this study could be one or more of three other possible chimeric cells: cells derived from NeoR-positive cohort embryos; cells present in the maternal circulation as a result of transfer from NeoR-positive embryos of previous pregnancies; and cells in the maternal circulation that derived perinatally from a neoR-positive maternal grandmother. The presence and levels, if any, of such alternative chimeric cells remain to be determined.

The recent report of myocardial cells bearing maternal markers in a human neonate with neonatal lupus syndrome (29) suggests that at least some chimeric maternal cells either develop or intrinsically possess properties of somatic tissue cells. Together with our demonstration of the ubiquity and widespread tissue distribution of chimeric maternal cells in both weanling and adult mice, this fits with the possibility that small numbers of chimeric maternal cells may have the beneficial effect throughout an offspring’s life of participating in tissue repair and regeneration.

If maternal microchimerism occurs throughout life, and has the potential for exerting both beneficial tissue reparative effects and deleterious autoimmune effects, what might determine the balance between the two? That scleroderma in women is associated with increased levels of fetal microchimerism, but not increased prevalence of fetal microchimerism (30), suggests that autoimmunity is associated with relatively high levels of normally occurring microchimerism. If so, the relatively lower levels of maternal microchimerism observed in this study in association with MHC heterozygosity may account in part for the recently described protective effect of MHC heterozygosity on autoimmunity (31). In light of this possibility, and the association of autoimmunity with both maternal and fetal microchimerism, it will be of interest to determine whether MHC zygosity affects fetal microchimerism in the same manner as it affects maternal microchimerism.

Disclosures

The authors have no financial conflict of interest.

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