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The Lupus-Susceptibility Locus, Sle3, Mediates Enhanced Resistance to Bacterial Infections

Borna Mehrad,2* Stacy J. Park,* Gangaram Akangire,* Theodore J. Standiford,‡ Tianfu Wu, ‡ Jiankun Zhu, † and Chandra Mohan2‡

The genetic predisposition to many autoimmune diseases is inherited as a polygenic trait. It is conceivable that some of the causative alleles in these diseases became prevalent in the population by conferring a survival benefit against environmental assaults, such as infections. We used mice congenic for genetic loci predisposing to systemic lupus erythematosus to test the hypothesis that some of these genetic loci protect the host from bacterial infections. Mice with the Sle3 lupus-susceptibility locus on a wild-type background were found to have enhanced antibacterial responses in the context of pneumonia and intra-abdominal sepsis than wild-type animals. This was associated with markedly augmented accumulation of neutrophils in infected tissues, and was bone marrow transferable and dependent on the presence of neutrophils, but not lymphocytes. There was no difference in in vitro leukocyte killing of bacteria nor influx of phagocytes between lupus-susceptible and wild-type animals, but neutrophils from lupus-susceptible mice displayed markedly reduced rate of apoptosis, associated with altered expression of Bcl-2 family proteins, contributing to their greater accumulation. Importantly, deliberately inhibition of apoptosis in wild-type animals significantly boosted the accumulation of neutrophils at the site of infection and resulted in an enhanced antimicrobial response. These observations support the concept that some of the genetic loci that mediate autoimmunity may also confer augmented antimicrobial innate immunity. The Journal of Immunology, 2006, 176: 3233–3239.

Systemic lupus erythematosus is a common autoimmune disease with a polygenic mode of inheritance (1). Like all polygenically inherited diseases, susceptibility to lupus depends not on any single gene, but on cumulative interaction of many genetic loci containing polymorphic variants, each of which may contribute only incrementally to pathogenesis. The individual genes that, in aggregate, cause lupus have yet to be identified, but the genetic basis of this illness has been greatly illuminated by studies of inbred mice that spontaneously develop the disease (2). Specifically, backcrossing the lupus-prone NZM2410 strain onto the normal C57BL/6 (B6) background has allowed the contribution of specific loci to the pathogenesis of lupus to be examined (3, 4). Thus, a locus on chromosome 1, Sle1, breaches immunologic tolerance to chromatin (5), and another locus on chromosome 4, Sle2, triggers generalized B cell hyperactivity (6). A third locus on chromosome 7, Sle3, is associated with several T cell aberrations that are mediated via myeloid cells (7–9).

It is conceivable that some of the genetic polymorphisms that, in combination, cause polygenic autoimmune diseases such as lupus are prevalent in the population because they individually confer resistance against environmental assaults. Such assaults would almost certainly include infections caused by endogenous bacteria that colonize the distal alimentary tract constitute the largest population of mammalian commensal microflora and cause some of the most common human infections, such as pneumonia, urinary tract infections, and peritonitis.

We reasoned that some of the genetic polymorphisms that render an individual susceptible to lupus may also confer enhanced host resistance against common infections caused by endogenous microflora. We therefore tested the hypothesis that mice congenic for the Sle1, Sle2, or Sle3 loci on B6 background are more resistant to bacterial infections than wild-type B6 mice.

Materials and Methods

Animals

The derivation and immunological phenotype of B6.Sle1NZM2410/NZM2410 (B6.Sle1), B6.Sle2NZM2410/NZM2410 (B6.Sle2), and B6.Sle3NZM2410/NZM2410 (B6.Sle3) have been reported (5–7, 9). Briefly, B6.Sle3 mice are B6 mice rendered congenic homozygotes for a 24 cM interval on mouse chromosome 7, with termini at D7mit158 and D7mit161. B6.Sle1 mice are B6 mice congenic homozygotes for a 37 cM interval on murine chromosome 1, spanning the 95% confidence interval flanking Sle1, derived from NZM2410, with termini at D1mit58 and D1mit60. B6.Sle2 mice are B6 mice congenic homozygotes for a 37 cM interval on murine chromosome 1, spanning the 95% confidence interval flanking Sle1, derived from NZM2410, with termini at D1mit101 and D1mit135. B6.Sle2 mice are congenic homozygotes for the 95% confidence interval flanking Sle2, derived from NZM2410, with termini at D1mit17 and D1mit12 on chromosome 4. C57BL/6 (B6), B6.RAG-1-/-, and NZM2410 mice were purchased from The Jackson Laboratory or Taconic Farms. New Zealand White (NZW)3 mice were originally purchased from The Jackson Laboratory and bred in our colony. B6.Sle3.RAG-1-/- mice were generated by breeding B6.Sle3 mice to B6.RAG-1-/- mice. All mice were bred and housed in a specific pathogen-free colony at University of Texas Southwestern Medical Center. Age- and gender-matched 2– to 5-mo-old mice were used in experiments. No age- or gender-dependent differences were noted in the experiments performed.

Infection models

Experimental Klebsiella pneumoniae pneumonia was induced, as described, using strain 43816 (American Type Culture Collection), with inocula ranging from 500 to 1500 CFU in various experiments (10). Cecal ligation and puncture was used as a model of polymicrobial intra-abdominal sepsis, as described (11).

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Abbreviation used in this paper: NZW, New Zealand White.
In vivo treatments
A mAb (RB6-8C5) was used for in vivo depletion of neutrophils, as described (12, 13). Administration of Ab to uninfected mice resulted in no detectable alteration in nonneutrophil leukocyte populations in blood or examined organs (data not shown). The nonselective caspase inhibitor, Z-VAD-fmk (R&D Systems), was administered i.v. (10 mg/kg) an hour before bacterial challenge, as described (14, 15). Bone marrow transplantations, performed according to described protocols (8), preceded experimental infections by 4–6 wk.

Morphometric analysis
H&E-stained lung sections were examined using a Leica Laborlux S photomicroscope, and 10–12 different fields of consolidated lung from three mice per condition were photographed at ×630 magnification with an Optronics VI-470 analog charge-coupled device color camera interfaced with a Macintosh G4 computer equipped with a Scion CG-7 frame digitizer. Images were captured and analyzed using Scion Image software (Scion). For each data point, the perimeter of an alveolus was defined and the alveolar area was calculated. The neutrophils, bacteria, and apoptotic neutrophils within the alveoli were counted, and the number of each per alveolar area was calculated.

Myeloperoxidase studies and ELISA
Lung samples were homogenized and myeloperoxidase activity was measured, as described (16). Lung slurry was pelleted and ELISA was performed on filtered supernatants, according to manufacturer’s instructions (R&D Systems; minimum detectable concentration 300 pg/ml for both CXCL-1/KC and CXCL-2/3/MIP-2).

Flow cytometry
Lung single cell suspensions were prepared, as described (17). The following Abs were used (from BD Pharmingen or Caltag Laboratories): 7/4-biotin, anti-CD3 allophycocyanin (clone 17A2), anti-CD4 biotin (GK1.5), anti-CD8 PE (53-5.8), anti-CD11b allophycocyanin (M17/0), anti-CD11c PE (HL3), anti-CD45 PerCP (clone 30-F11), anti-CD45R PE (RA3-6B2), anti-F4/80 PE (CL3-1), anti-VE-1 PE or biotin (PK136), and anti-Gr-1 FITC or biotin (RB6-8C5). For apoptosis detection, cells were labeled with Annexin V-FITC or biotin and propidium iodide, according to manufacturer’s instructions (TACS apoptosis detection kit; R&D Systems). Samples were analyzed on a FACSCalibur cytometer using CellQuest software (both from BD Biosciences).

In vitro leukocyte studies
Bone marrow-derived macrophages were generated by culturing bone marrow cells (3–5 × 10^7) in DMEM (HyClone) with 10% FCS (HyClone) and 30% L cell-conditioned medium at 37°C in 10% CO2. During the final 18 h, cells were incubated in DMEM, 10% FCS, and 100 U/ml murine IFN-γ (R&D Systems). Viability of recovered cells was >95% by trypan blue exclusion. Casein-elicted peritoneal neutrophils were obtained, as described (18). After enrichment over a Percoll gradient, obtained cells were >90% neutrophils by differential counts and >95% viable by trypan blue exclusion. Mature, resting bone marrow neutrophils were prepared using previously described protocols (19, 20). Obtained cells were 95% band forms or segmented polymorphonuclear cells by light microscopy and were >99% viable by trypan blue exclusion.

The capacity of leukocytes to kill bacteria in vitro was examined both in suspension and in fibrin gels, using modifications of previously described protocols (21, 22). In both assays, bacteria were first opsonized in fresh mouse serum for 60 min at 37°C. In suspension assays, various concentrations of leukocytes were incubated with bacteria in 400 μl of 75% fresh mouse serum in HBSS for 90 min at 37°C with shaking. Tubes were then centrifuged, leukocytes were lysed hypotically, and numbers of remaining viable bacteria were measured by serial dilution and culture. In fibrin gel assays, fresh mouse serum, mouse fibrinogen (Sigma-Aldrich; final concentration 1 mg/ml), various numbers of resting bone marrow neutrophils, opsonized bacteria, and mouse thrombin (Sigma-Aldrich; final concentration 1 U/ml) were sequentially mixed in 96-well plates. Plates were incubated for 5 min at room temperature for fibrin clots to form, and d-Phe-Pro-Arg-chloromethylketone (Calbiochem; final concentration 10 μM) was added to inhibit thrombin activity. After 90 min of incubation at 37°C, clots were dissolved and neutrophils were lysed by adding cytochalasin D and trypsin (both from Sigma-Aldrich; final concentrations 24 μg/ml and 0.6 mg/ml, respectively, in distilled water) and incubating the samples on ice for 20 min. Numbers of viable bacteria were then determined by serial dilution and culture on solid medium.

To examine in vitro neutrophil apoptosis, elicited peritoneal neutrophils were incubated at 1 × 10^6 cells/ml in RPMI 1640 (HyClone) with 10% FCS at 37°C in 5% CO2, with or without heat-killed K. pneumoniae (100:1 ratio of bacteria to neutrophils) or LPS (from Sigma-Aldrich; 1 μg/ml). Apoptosis rate was measured by flow cytometry and by morphologic criteria on cytospin samples.

Western blot analysis
Neutrophil whole cell extracts were denatured in lysis buffer (50 mM Tris-HCl, 1% Triton X-100, 1 mM EDTA, 1 mM EGTA, 50 mM NaF, 10 mM β-glycerophosphate, 5 mM Na2PO4, 1 mM Na3VO4, and 1 mM PMSF), and protein was quantified (bicinchoninic acid protein assay, Pierce). Equal amounts of samples were separated by SDS-PAGE and transferred to Immobilon-P membranes (Millipore). Membranes were blocked with 5% nonfat milk for 1 h at room temperature and incubated with primary Abs against Bax, Bcl-xL, Cell Signaling Technology), Bcl-2 (Santa Cruz Biotechnology), Bim (StressGen Biotechnologies), X-linked mammalian inhibitor of apoptosis protein (BD Pharmingen), and β-actin (Abcam). Protein bands were detected with ECL detection reagents (Amersham Biosciences), analyzed with imageJ software (National Institutes of Health), and normalized to actin content.

Statistical analysis
Data were analyzed using Prism statistics software (GraphPad) on a Macintosh G4 computer. Survival data were compared using Fisher’s exact test. To compare values between two groups over time, two-way ANOVA was used. All other data were expressed as mean ± SEM and compared using unpaired two-tail Mann-Whitney (nonparametric) test. Probability values were considered statistically significant if they were <0.05.

Results
Outcome of Klebsiella pneumoniae in lupus-susceptible mice
To assess the severity of Klebsiella pneumoniae in mice congenic for lupus-associated genetic loci, we compared the lung and blood bacterial content in B6, B6.Sle1, B6.Sle2, and B6.Sle3 mice on day 2 after intrapulmonary inoculation of bacteria (Fig. 1a). The bacterial burden did not differ significantly among B6, B6.Sle1, and B6.Sle2 mice, but was markedly reduced in B6.Sle3 lungs as compared with other groups. In comparing the lethality of the infection, the same bacterial inoculum resulted in >3-fold higher mortality in B6 than in B6.Sle3 animals (Fig. 1b). Lung histology on day 2 of infection also showed differences: there was dense infiltration of neutrophils in alveolar spaces in infected regions of both B6 and B6.Sle3 lungs, but B6.Sle3 lungs were more congested with evidence of focal hemorrhage (Fig. 1c). Morphometric analysis of high power histological images of consolidated areas showed greater numbers of neutrophils (1.84 ± 0.12 vs 1.18 ± 0.19 cells/100 μm2, p = 0.0137) and fewer visible bacteria (0.059 ± 0.033 vs 0.354 ± 0.048 bacteria/100 μm2, p = 0.0007) per alveolar surface area in B6.Sle3, as compared with B6, mice. In addition, apoptotic neutrophils were visible in wild-type, but not B6.Sle3, alveoli (Fig. 1c).

To assess the effect of the strain background on the protective role of lupus-associated loci in this infection, we also compared the severity of infection between NZM2410 (from which Sle1, Sle2, and Sle3 loci were originally derived) and B6 mice. On day 2 of infection, lungs and blood of NZM2410 mice had markedly more bacteria than B6 mice (2.14 ± 10^8 vs 2.69 ± 10^7 CFU/lung, and 3.42 ± 10^1 CFU/l blood; six mice per group, p < 0.03 for both comparisons). We have found similar increased susceptibility in the related NZW strain (which carry Sle1, Sle3, and part of the Sle2 locus) as compared with B6 mice (data not shown). These results indicate that, similar to their role in predisposing to autoimmunity, the protective effect of lupus-susceptibility loci in this infection is critically dependent on their interaction with other genes in the background strain.
To examine the mechanism of increased resistance to infection in B6.Sle3 animals, we examined the lungs for the presence of various leukocyte subsets at early time points after inoculation. Surprisingly, we found more than twice the number of neutrophils in B6.Sle3 as compared with B6 lungs on days 1 and 2 of the infection (Fig. 2a), although the number of neutrophils was similar in uninfected B6 and B6.Sle3 animals in the lungs (Fig. 2a, time point 0), peripheral blood (2.82 ± 9.96 × 10⁶ vs 4.13 ± 9.37 × 10⁵ cells/ml, n = 5/group, p = 0.37), and spleen (9). The larger number of neutrophils in the lungs of B6.Sle3 mice was particularly remarkable given that it coincided with ~30-fold lower lung bacterial burden in B6.Sle3 mice at that time point (Fig. 1a).

In keeping with described elevated CD4:CD8 T cell ratio in lymphatic organs of B6.Sle3 mice (7), we found fewer CD8⁺ T cells in uninfected lungs and more lung CD4⁺ T cells on day 2 of infection in B6.Sle3 animals (Fig. 2, e and f). The number of lung monocytes/macrophages, myeloid dendritic cells, and B cells did not differ between the two groups (Fig. 2, b–d). There were also no differences between the numbers of lung NK cells, Gr-1⁻ intermediates, and Gr-1⁻ negative monocyte subsets, and F4/80⁺ macrophages between the two groups (data not shown).

To determine the contribution of various leukocyte subsets to host defense against infection, we compared the resistance of bone marrow chimera animals to Klebsiella pneumonia (Fig. 3a). B6 recipients of B6.Sle3 bone marrow had a marked reduction in lung bacterial burden as compared with B6 recipients of B6 bone marrow, indicating that the resistant phenotype is bone marrow transferable. We next measured the lung bacterial content in B6 and B6.Sle3 animals with concomitant neutrophil depletion, or in mice bred onto the RAG-1⁻/⁻ background (Fig. 3b). Given the anticipated impairment of host defenses in these mice, we used a smaller bacterial inoculum (500 rather than 1500 CFU) than used in earlier experiments. In the setting of neutrophil depletion, lung bacterial burden did not differ significantly between B6 and B6.Sle3 animals. In contrast, lungs of B6.Sle3.RAG⁻/⁻ mice contained a smaller bacterial burden than B6.RAG⁻/⁻ lungs. There was also a substantially smaller lung bacterial burden in mice on RAG⁻/⁻ background as compared with neutrophil-depleted mice, consistent
with the well-described role of neutrophils as a critical line of defense against this infection (23). These data suggest that the enhanced host defense of B6.Sle3 animals is neutrophil dependent, but not dependent on the presence of mature lymphocytes.

We next asked whether the augmented host defense of B6.Sle3 mice is explained by better phagocyte antibacterial action, independent of their number in the lungs. We compared in vitro ability of neutrophils or macrophages from B6 and B6.Sle3 animals to kill K. pneumoniae (Fig. 3, c–e). As expected, increasing the concentration of both neutrophils and macrophages resulted in augmented bacterial killing, but there was no difference in bacterial killing by either cell type between wild-type and B.Sle3 mice.

Given that B6.Sle3 neutrophils appeared to be required for the augmented host defense observed in these mice, but did not have augmented bactericidal capacity, we next investigated possible mechanisms for their greater accumulation in the lungs. We reasoned that the number of lung neutrophils at any given time represents the balance between influx on the one hand, and apoptosis on the other. We thus compared the levels of the neutrophil chemotactic chemokines in B6 and B6.Sle3 animals, because these molecules have been shown previously to play a critical role in neutrophil influx in bacterial pneumonia (10, 24). There was no difference in lung levels of CXCL-1 (KC) or CXCL-2/3 (MIP-2) between B6 and B6.Sle3 lungs, while in the same samples, myeloperoxidase activity (a surrogate for the presence of neutrophils in vitro) was significantly higher in B6.Sle3 than B6 lungs (Fig. 3, f and g). This finding argues against chemokine-mediated influx as the mechanism for greater number of lung neutrophils in B6.Sle3 mice.
Role of delayed neutrophil apoptosis

We next sought to determine whether the observed difference in lung neutrophil numbers between wild-type and B6.Sle3 animals is explained by differences in the rate of neutrophil apoptosis. Elicited neutrophils from wild-type and B6.Sle3 animals were incubated in vitro, in the presence or absence of heat-killed K. pneumoniae, and examined at various time points for evidence of apoptosis. There was a lower rate of neutrophil apoptosis in B6.Sle3 than B6 mice in both conditions, as determined by annexin V staining and by microscopy (Fig. 4, a and b). We then assessed whether these in vitro findings were replicated in the lung in the setting of Klebsiella infection. We found the proportion of lung neutrophils that were apoptotic was 55% lower in infected B6.Sle3 as compared with infected B6 mice (Fig. 4c). In contrast, we found no differences in the apoptosis rate of lung monocytes/macrophages, or CD4 or CD8 T cells between B6 and B6.Sle3 mice on day 1 of infection (data not shown).

We also examined the role of this locus in another bacterial infection: in a model of intra-abdominal sepsis, we found greater number of i.p. neutrophils in B6.Sle3 as compared with B6 mice associated with fewer viable bacteria in the peritoneal cavity and bloodstream on day 1 of infection (supplemental data), suggesting that the microbicidal and neutrophil phenotype conferred by the Sle3 locus is not restricted to a single organ or pathogen. These findings did not result in improved survival in intra-abdominal infection, indicating that the locus is not sufficient to confer a survival benefit in all bacterial infections.

To probe the mechanism of reduced apoptosis in B6.Sle3 neutrophils, we measured intracellular levels of selected pro- and antiapoptotic proteins in freshly isolated and cultured neutrophils (Fig. 5). Freshly isolated B6.Sle3 neutrophils contained lower levels of Bax, a proapoptotic member of the Bcl-2 family. Conversely, B6.Sle3 neutrophils incubated with LPS expressed high levels of apoptosis inhibitors Bcl-2 and Bcl-xL. This indicates a potential role for Bcl-2 family proteins in altered apoptosis of B6.Sle3 neutrophils.

Our data show that B6.Sle3 neutrophils have a reduced apoptotic rate and enhanced accumulation in the lungs in the context of K. pneumoniae infection, and that the locus may influence neutrophil survival in other bacterial infections as well. These findings suggest that the Sle3 locus plays a role in regulating neutrophil apoptosis, which may contribute to the observed differences in lung neutrophil numbers between wild-type and B6.Sle3 animals.

FIGURE 5. Alterations of selected pro- and antiapoptotic molecules in B6.Sle3-elicited neutrophils. Band densities were measured on Western blot analysis and normalized to the density of actin bands for each sample. “Fresh,” cells that were processed immediately after isolation; “no LPS” and “+ LPS,” isolated neutrophils incubated in RPMI 1640/10% FBS for 4 h, with or without 1 μg/ml LPS. Data denote mean ± SEM of triplicate samples; representative from two experiments. *, p < 0.05 compared with B6 neutrophils.

FIGURE 6. Effect of inhibition of apoptosis on lung neutrophils in Klebsiella pneumonia. Proportion of apoptotic neutrophils (a), total number of lung neutrophils (b), and number of lung bacteria (c) in lungs of B6 mice 18 h after K. pneumoniae inoculation, with or without i.v. treatment with apoptosis inhibitor. Data show mean ± SEM (n = 5–7 mice/group); representative of two experiments. “Apoptosis inhibitor,” z-VAD-fmk in PBS; “vehicle,” equal volume of PBS; *, p < 0.05 compared with other two groups.
Bcl-xL, in neutrophils exposed to endotoxin. The critical role of increased levels of the proapoptotic molecule, Bax, in resting neutrophils displays reduced apoptosis rate and altered apoptotic pathways in response to bacterial products (36), whereas some microorganisms specifically modulate neutrophil apoptosis as a pathogenic mechanism in persisting infections (37–39). Our findings provide evidence for a pathway that mediates both delayed neutrophil apoptosis and enhanced resistance against bacterial infections (reviewed in Ref. 30).

To our knowledge, the present work represents the first recognition of a neutrophil-intrinsic determinant of host resistance to infection. Neutrophil apoptosis is known to be involved in non-inflammatory turnover of circulating cells (31) and clearance of cells from inflamed tissues (32–35). In the context of infection, neutrophils display reduced apoptosis rate and altered apoptotic pathways in response to bacterial products (36), whereas some microorganisms specifically modulate neutrophil apoptosis as a pathogenic mechanism in persisting infections (37–39). Our findings provide evidence for a pathway that mediates both delayed neutrophil apoptosis and enhanced resistance against bacterial pneumonia. In this context, we found evidence of altered expression of several key members of the Bcl-2 family, including increased levels of the proapoptotic molecule, Bax, in resting neutrophils, and reduced levels of antiapoptotic molecules, Bcl-2 and Bcl-xI, in neutrophils exposed to endotoxin. The critical role of Bcl-2 family members in neutrophil apoptosis and inflammatory accumulation has been documented (40, 41), and our data now implicate a pathway that controls levels of several members of this family in neutrophil-mediated host defense.

The present work also provides evidence that, on the B6 background, a genetic locus known to contribute to the lupus phenotype also mediates enhanced antibacterial host defenses. In this context, other genetic factors shown to mediate both autoimmunity and antimicrobial immunity include CD32b (42, 43) and Tyk2 tyrosine kinase (44). Although it is certainly possible that separate genes within the interval mediate the autoimmunity and resistance to infection, we propose that these phenotypes are related to the same genetic event because, first, both the autoimmune and host defense phenotypes appear to be causally linked to reduced leukocyte apoptosis, and second, both phenotypes are intrinsic to the myeloid lineage (8, 9). According to this hypothesis, a genetic event within the locus causes reduced apoptosis of myeloid leukocytes, resulting in enhanced accumulation of neutrophils (thus contributing to antimicrobial innate immunity), but also increased activation of dendritic cells (leading to an inappropriate T cell proliferation and contributing to autoimmunity). Ultimately, whether the enhanced antibacterial host defense and autoimmunity phenotypes mediated by the Sle3 locus are caused by the same genetic event awaits the identification of the genes mediating each phenotype. Definitive identification of the causative gene within the interval should also allow for comparison of the corresponding NZW-derived and B6-derived variants in the reciprocal strain, and help determine whether the genetic background modifies the observed phenotypes of autoimmunity and resistance to infection.

These data may have implications for the genetics of human lupus, particularly because a human locus with synteny to murine Sle3 has been implicated in lupus susceptibility (45). Most studies of infections in patients with lupus are confounded by concomitant use of immunosuppressive medications; it is nevertheless recognized that patients with lupus have altered immune response to some infections (46–48); intriguingly, this includes a lower than expected rate of infection with the Gram-negative bacterium, Helicobacter pylori (49). These data are consistent with the hypothesis that some of the genetic polymorphisms that mediate lupus may also influence the immune response against infecting pathogens.

Disclosures

The authors have no financial conflict of interest.

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