Sendai Virus Infection in Genetically Resistant and Susceptible Mice

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The pathogenesis of Sendai virus infection in genetically resistant (C57Bl/6) and susceptible (DBA/2) nonimmune adult mice was investigated. Rising serum complement-fixation (CF) antibody titers were delayed in DBA/2 mice as compared with C57Bl/6 mice. C57Bl/6 mice developed descending desquamative endobronchiolitis, and DBA/2 mice developed descending proliferative endobronchiolitis and bronchogenic alveolitis. Peribronchiolar lymphoid cuffs that formed in C57Bl/6 mice were thicker and more densely populated than those of DBA/2 mice. Immunofluorescence demonstrated viral antigens confined to the epithelial lining of conducting airways in C57Bl/6 mice but extending to alveolar corner cells in DBA/2 mice. Studies with a transmission electron microscope confirmed that Type II pneumocytes were infected only in DBA/2 mice. IgG-containing cells selectively accumulated along the airways of both strains, but fewer were recruited by DBA/2 mice. These results suggest that genetic resistance to Sendai virus is expressed through the immune system. (Am J Pathol 1981, 105:156-163)

SENDAI VIRUS, a parainfluenza 1 virus, is a natural respiratory pathogen of laboratory mice. Resistance to lethal Sendai virus infection varies among nonimmune adult mice of inbred strains,[1,2] but outbred or randombred adult mice are generally resistant.[1-7] The pathogenesis of Sendai virus infection has been studied primarily in mice with resistant genotypes.[3-7] In the lungs, virus replicates in bronchial and bronchiolar epithelium,[8,9] resulting in epithelial degeneration or proliferation accompanied by an inflammatory response of variable intensity.[1,3,5] Little is known about the pathogenesis of Sendai virus infection in genetically susceptible mice, but mortality has been correlated with widepread alveolitis.[1]

The immune response is critical to host survival in primary Sendai virus infection.[5-7, 10-12] Immunosuppression abrogates genetic resistance to this virus.[6,7,12] In this report, we compare the morphogenesis of virus-induced lung injury in mice genetically resistant (C57Bl/6) and susceptible (DBA/2) to Sendai virus and correlate this injury with the distribution of viral antigens. As an initial step in evaluating the role of the immune system in genetic resistance to Sendai virus infection, we compare the sequential distribution of immunoglobulin-containing cells in the lungs and the development of specific serum antibody titers in these two mouse strains after intranasal exposure.

Materials and Methods

Mice

Male DBA/2NCrlBR and C57Bl/6NCrlBR mice (Charles River Breeding Colonies, Kingston, NY), 4-6 weeks old, were shipped in filtered boxes and transferred immediately upon arrival to a Centers for Disease Control (CDC) Level 3 containment facility. Mice were housed in polystyrene cages (29 × 19 × 13 cm) with corn-cob bedding and filter caps within a negative pressure laminar flow cabinet. They were fed Purina Laboratory Chow and hyperchlorinated water (9 mg/l) *ad libitum*. Mice were free of Sendai virus, pneumonia virus, K virus, mouse hepatitis virus, ectromelia, reovirus 3, encephalomyelitis virus, lymphocytic choriomeningitis virus, mouse adenovirus, *Pasteurella pneumotropica, Corynebacterium kutscheri, Pseudomonas aeruginosa, Mycoplasma pulmonis*, and intestinal oxyurids as determined by microbiologic, serologic, and pathologic monitoring.

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Virus

Sendai virus (isolate 771076) was isolated from a case of spontaneous Sendai viral pneumonia in a 1-year-old male C3H mouse. A 10% (wt/vol) lung suspension was stored at −70 C and contained 10^7 median tissue culture infectious doses ($TCID_{50}$) per 0.1 g of tissue.

Mode of Infection

Mice were infected intranasally with 0.01 ml of undiluted or diluted 10% infected mouse lung suspension under light methoxyflurane (Metaphane, Pitman-Moore, Washington Crossing, NJ) anesthesia. Dilutions were made in phosphate-buffered saline (PBS) containing 3% heat-inactivated fetal bovine serum and penicillin (1000 U/nl) and streptomycin (100 μg/ml). Control mice were given 0.01 ml of diluent intranasally.

Necropsy

Mice were anesthetized and exsanguinated by cardiac puncture, and the serum was stored at −20 C for antibody assay. Lungs for virus assay were removed and separated from heart, mediastinum, esophagus, and trachea. They were weighed and stored at −70 C. Lungs for histologic and transmission electron-microscopic studies were removed intact, perfused through the trachea to the expanded state with paraformaldehyde-glutaraldehyde fixative (550 mOsm)[13] in 0.2 M cacodylate buffer, and immersed in fixative for 4 hours. The left lung was tied off, removed, and stored in phosphate-buffered formalin (pH 7.2) for histologic study. Lungs for immunohistochemical study were removed intact and perfused through the trachea with 95% cold ethanol (4 C). After 5 minutes, 0.5-cm frontal sections were cut, and these were dehydrated through graded ethanol as previously described.[14] Tissues were stored in cold xylene.

Virus Assay

Virus in the lung was quantitated by hemadsorption of guinea pig erythrocytes by infected monolayer tube cultures of BHK-21 cells. Cultures were inoculated with serial tenfold dilutions of a 10% lung suspension. Five days after inoculation, each tube was washed twice with PBS, and then 1 ml of a 0.5% suspension of guinea pig erythrocytes was added. Hemadsorption was scored as positive or negative after the tubes had incubated for 20 minutes at 4 C. Positive and negative controls were included in all assays. Titers were calculated by the method of Reed and Muench.[15]

Serum Antibody Assay

Serum antibody titers were determined by the complement-fixation (CF) test.[16] Titers were expressed as the reciprocal of the highest serum dilution fixing two units of complement in the presence of an optimal antigen concentration.

Histologic Studies

Formalin-fixed lungs were routinely processed, embedded in paraffin, cut at 4 μ, and stained with hematoxylin and eosin. Selected sections were stained with Brown and Brenn.

Immunofluorescence Reagents

Heavy-chain-specific goat antiserum to mouse IgG was kindly provided by C. A. Janeway, Department of Pathology, Yale University School of Medicine, New Haven, Conn. Heavy-chain-specific goat antiserum to mouse IgM was obtained from Cappel Laboratories (Cochranville, Pa). Heavy-chain-specific rabbit antiserum to mouse IgA, fluorescein-labeled goat antiserum to rabbit IgG, and fluorescein-labeled rabbit antiserum to goat IgG were obtained from Miles Laboratories (Elkhart, Ind). Goat antiserum to Sendai virus was obtained from M.A. Bioproducts (Walkersville, Md).

Immunohistochemical Studies

Lungs were embedded in paraffin, cut at 6 μ, and mounted on slides coated with gelatin. Slides were heated at 60 C for 2 hours, deparaffinized in xylene, and rehydrated through graded ethanol to distilled water. Indirect immunofluorescence was used to localize Sendai viral antigens and murine immunoglobulins in lung sections. Antiserum to viral antigens and murine immunoglobulins was diluted 1:15. Fluorescein-conjugated antiserum was diluted 1/20, and Evans blue was added to a final concentration of 3%. Sections were incubated in a moist chamber at 37 C for 30 minutes and washed 3 times in 0.05 M Tris-buffered saline (pH 7.6 at 25 C) after each stage. Antiserum dilutions were also made with Tris-buffered saline. Slides were viewed with a Zeiss IV Fl epifluorescence microscope fitted with BG-12 and UG5 exciter filters and an LP 478 barrier filter.

Transmission Electron-Microscopic Examination

Lungs were cut into 1-2-mm cubes, washed with 0.1 M phosphate buffer (pH 7.25), and postfixed in Millonig's phosphate-buffered osmium tetroxide for 1 hour. Tissues were dehydrated in graded ethanol and embedded in epoxy resin (Epon, Lab Research Industries, Inc., Burlington, Vt). Sections 2 μ thick were stained with toluidine blue. Selected specimens were sectioned at 80-90 nm with a diamond knife, stained with uranyl acetate and lead citrate, and viewed with a Philips 201 transmission electron microscope (N.U. Philips Co., Eindhoven, The Netherlands).

Design of Experiment

Mortality rates were determined by infecting 35 mice of each strain, housed 5 per cage, with virus at concentrations ranging from 4.0 to -2.0 $\log_{10}$ $TCID_{50}$. Deaths were recorded daily for 14 days, and the results were computed as previously described.[15]

Ninety-seven mice of each strain were housed 5 per cage and were inoculated with -2.0 $\log_{10}$ $TCID_{50}$ of Sendai virus. This dose of virus was determined to be infectious for all mice by seroconversion and to produce less than 2% and 20% mortality in C57Bl/6 and DBA/2 mice, respectively, over 30 days. On Days 2, 4, 6, 8, 10, necropsies were performed on 11 mice: 4 for virus assay, 4 for immunohistochemical study and 3 for histologic and transmission electron-microscopic studies. Antibody assays were performed on serum samples from all mice necropsied and from 3 to 8 mice that were bled by cardiac puncture on Days 12, 14, 16, 18, 20, and 30.

Eight control mice of each strain were housed separately, and 2 mice were necropsied on Days 0, 6, and 10 for histologic and transmission electron-microscopic studies, immunohistochemical study, and serum antibody assay.

Results

Mortality

Adult C57Bl/6 mice had lower mortality rates than adult DBA/2 mice after intranasal inoculation of 10^{-2}–10^{4} $TCID_{50}$ Sendai virus (Figure 1). About 40,000 times more virus was required to kill a C57Bl/6 mouse than to kill a DBA/2 mouse.

Patterns of Viral Replication

Sendai virus grew in the lungs of both strains of mice with peak titers achieved on or after Day 6. They were slightly higher in DBA/2 mice (Figure 2).

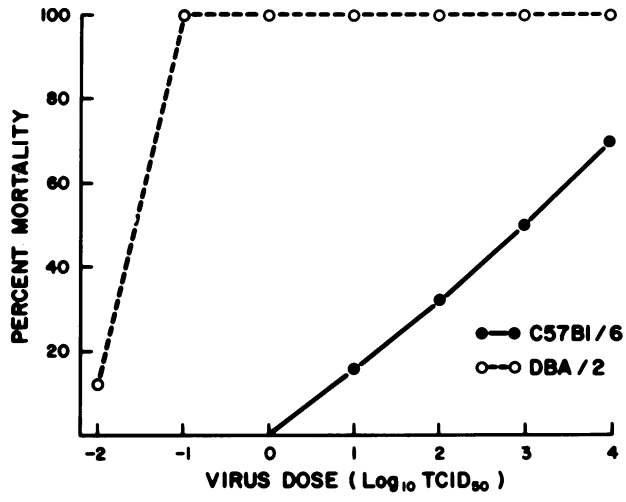

Figure 1—Fourteen-day mortality rates in C57Bl/6 and DBA/2 mice infected with varying doses of Sendai virus.

Antibody Responses

Serum CF antibody titers were first detected on Day 10 in both mouse strains (Figure 3). Titers increased rapidly after Day 10 in C57Bl/6 mice, but this result did not occur until after Day 16 in DBA/2 mice. Antibody titers were significantly higher in C57Bl/6 mice than in DBA/2 mice on Days 14 ($P < 0.01$, Student t test) and 30 ($P < 0.02$).

Histologic Studies

Murine lungs contain five orders of conducting airways. Because only primary bronchi have cartilaginous rings, the four distal arborizations were designated lobar, segmental, preterminal, and terminal bronchioles. Sendai virus produced descending endobronchitis and endobronchiolitis in both strains of mice. Initial evidence of infection appeared in the bronchi on Day 6. There was no detectable difference in the ultimate distribution of viral-induced changes in conducting divisions. Some distal airways were spared, while others were extensively altered.

C57Bl/6 Mice

On Day 6, there were single or multiple foci of disorganized bronchial epithelium that bulged slightly due to expansion of the lamina propria with small and medium-size lymphocytes. On Day 8, the epithelium of all conducting divisions was altered to some degree. The superficial bronchial epithelium was sloughing in sheets, leaving a layer of hypertrophied basal cells. The epithelium of lobar through terminal

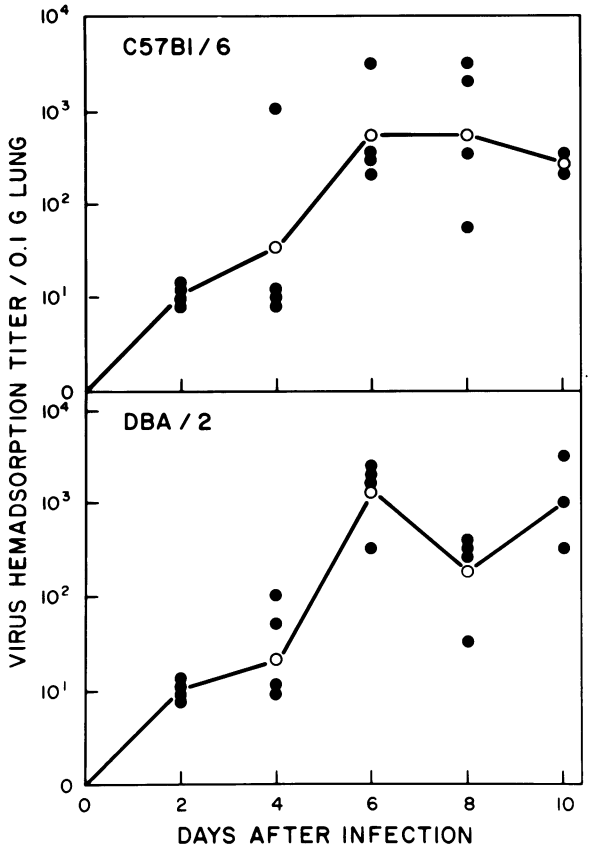

Figure 2—Virus titers in lungs of C57Bl/6 and DBA/2 mice infected with 10^{-2} $TCID_{50}$ of Sendai virus. *Closed circles*, titers of individual animals; *open circles*, geometric mean titers.

bronchioles was hypertrophied and hyperplastic with a papillary appearance. The lamina propria and adventitia of all affected airways were heavily infiltrated with reactive lymphoid cells similar to those seen earlier in the bronchi. Lymphoid cells were also marginating in adventitial blood vessels and were spilling into juxtabronchiolar alveoli. On Day 10, the exposed bronchial basal cells were proliferating in a disorderly fashion. The epithelium of lobar, segmental, and preterminal bronchioles was sloughing in sheets and undergoing necrosis (Figure 4). Epithelial cells were swollen and had intensely eosinophilic cytoplasm and pyknotic nuclei. The epithelium of terminal bronchioles was attached and appeared viable. Peribronchiolar lymphoid collars were enlarged and densely populated with reactive lymphocytes. Substantial numbers of immature plasma cells were also present. Lymphoid collars encircling bronchioles with necrotic, desquamative epithelium were expanded by edema and diffusely infiltered with macrophages and granulocytes.

DBA/2 Mice

On Day 6, superficial bronchial epithelium was diffusely hypertrophied and hyperplastic but lymphoid cells were not apparent in the underlying lamina propria. On Day 8, the epithelium of all conducting divisions was undergoing some degreee of papillary hyperplasia and hypertrophy. There was mild necrosis and desquamation of bronchial epithelium. The lamina propria and adventitia of affected airways were sparsely infiltrated with lymphoid cells. Radiating from altered terminal bronchioles were well circumscribed areas of alveolar inflammation in which alveolar septa were unevenly thickened by mononuclear cells, and alveolar spaces contained foamy macrophages, pleomorphic lymphoid cells, and neutrophils. On Day 10, epithelial necrosis and desquamation were still confined to the bronchi. Epithelial hyperplasia and hypertrophy were prominent in all bronchiolar divisions, peribronchiolar lymphoid collars remained attenuated or absent, and foci of alveolar inflammation had expanded and many had coalesced (Figure 5).

Immunohistochemical Studies

Control mouse lungs did not stain specifically for Sendai viral antigens or murine IgG. Cells that stained for cytoplasmic IgM or IgA were present in small numbers in the submucosa of large conducting airways.

C57 Bl/6 Mice

Sendai viral antigens were initially detected in the apical cytoplasm of bronchial epithelium on Day 6. Cells with cytoplasmic IgG were accumulating in the

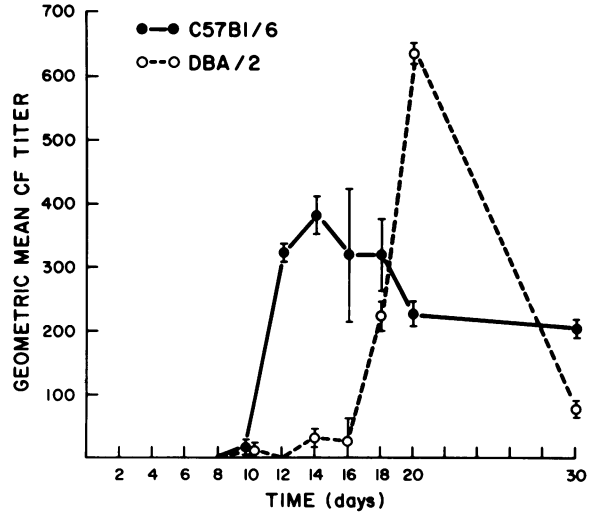

Figure 3—Complement-fixing serum antibody responses of C57Bl/6 and DBA/2 mice infected with 10^{-2} $TCID_{50}$ of Sendai virus. The values at each interval represent the geometric mean titers for 11 animals up to Day 10, 8 animals on Days 14 and 30, and 3 animals on Days 12, 16, 18, and 20.

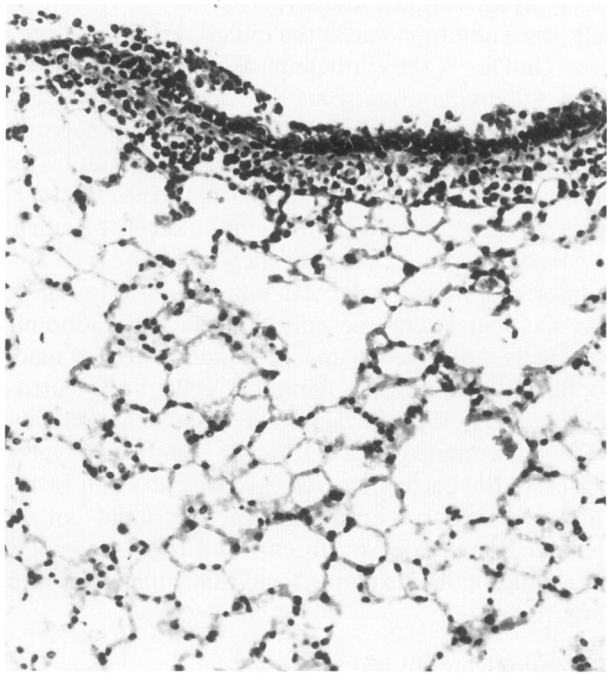

Figure 4—Lung from an adult C57Bl/6 mouse 10 days after infection with Sendai virus. The epithelium of the preterminal bronchiole is necrotic, and the adventitia is expanded primarily by mononuclear cells. There is minimal inflammation of surrounding alveoli. (H&E, ×170)

underlying lamina propria. On Day 8, viral antigens were found in the epithelium of all conducting divisions. The lamina propria and adventitia of infected bronchi and bronchioles were heavily infiltrated with IgG-containing cells. On Day 10, the intensity of immunofluorescent staining for viral antigens in lobar, segmental, and preterminal bronchioles had decreased, and most of the antigens were confined to detached epithelium. Immunofluorescent staining in terminal bronchioles remained intense and confined to the attached epithelium. IgG-containing cells continued to accumulate along infected airways, and desquamating epithelium also stained for IgG.

DBA/2 Mice

Sendai viral antigens were initially detected in bronchial epithelium on Day 6. Immunoglobulin-containing cells were not accumulating in the underlying lamina propria or elsewhere in the lung. On Day 8, viral antigens were found throughout the epithelium of all conducting divisions and in alveolar cells radiating from infected terminal bronchioles. These alveolar cells contained diffuse cytoplasmic viral antigens and were located in alveolar corners (Figure 6). The distribution of infected alveolar cells was similar to the distribution of alveolar injury seen histologically. There were small numbers of IgG-containing cells in the lamina propria and adventitia of infected airways and small numbers of IgM-, IgG-, and IgA-containing cells in injured alveoli. On Day 10, immunofluorescent staining for viral antigens remained intense in the epithelium of all conducting divisions except the bronchi, which were largely denuded. There were increased numbers of alveolar lining cells that contained viral antigens, and these radiated farther from infected bronchioles. Free alveolar cells also contained diffuse or granular cytoplasmic viral antigens. The number of IgG-containing cells accumulating along infected airways remained relatively sparse. There were increased numbers of immunoglobulin-containing cells in alveolar spaces. Most of these immunocytes contained IgG, although cells containing IgM of IgA were also prevalent.

Transmission Electron-Microscopic Examination

Both strains of mice had productively infected airway lining epithelium, beginning with the bronchi, on Day 6. There was no evidence of viral replication in the alveoli of C57Bl/6 mice during the course of the study.

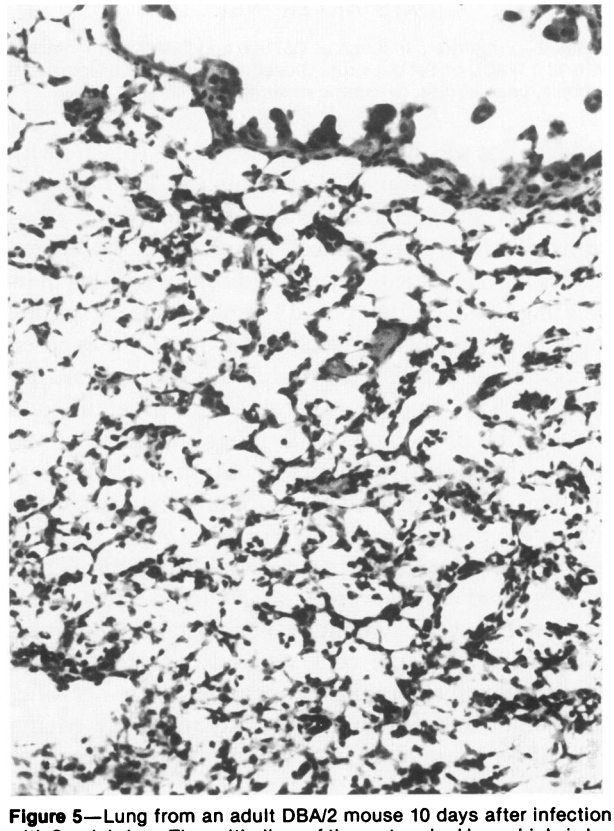

Figure 5—Lung from an adult DBA/2 mouse 10 days after infection with Sendai virus. The epithelium of the preterminal bronchiole is hyperplastic and adventitial infiltrates are sparse. Inflammatory exudates are present in surrounding alveoli. (H&E, ×170)

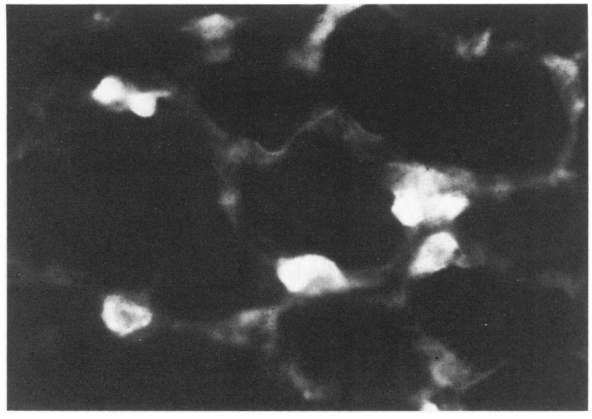

Figure 6—Lung from an adult DBA/2 mouse 8 days after infection with Sendai virus. Alveolar cells, located in alveolar corners, contain diffuse cytoplasmic Sendai viral antigens. (Immunofluorescence, ×675) (With a photographic reduction of 66%)

Evidence of viral replication was widespread in the alveoli of DBA/2 mice beginning on Day 8. Viral nucleocapsids, which appeared as hollow fibrils, formed aggregates in the cytoplasmic matrix of Type II pneumocytes (Figure 7A). Filamentous, spherical, and pleomorphic virions were budding from the plasma membranes of these cells (Figure 7B). Infected Type II pneumocytes were partially detached from their normal positions in alveolar corners, and many were free in alveolar spaces. Alveolar macrophages were the only other cells that contained viral components. Virions or remnants of virions were confined to heterophagosomes and secondary lysozomes and therefore did not represent replicative forms.

Discussion

Adult DBA/2 mice were more susceptible than adult C57Bl/6 mice to the lethal effects of Sendai virus infection, and they developed more diffuse pulmonary injury during a low-dose infection. The mechanisms contributing to the phenotypic expression of genetic resistance to Sendai virus have not been investigated, but results reported herein indicate that genetic resistance may be expressed through the immune system.

DBA/2 mice recruited fewer lymphoid cells, including IgG-containing cells, to infected airways than did C57Bl/6 mice. Current evidence favors the view that locally recruited immunocytes participate in the eradication of Sendai virus from infected airways[5-8,10,11] and that IgG-secreting cells may be the principal class of immunoglobulin-secreting cells involved.[11,17] IgG is the only class of specific immunoglobulin detected in lung lysates of Sendai-virus-infected mice[17] prior to or immediately after the disappearance of infectious virus,[2,3,5,6,12,18] although both IgA- and IgG-containing cells are reported to accumulate in bronchial submucosa during Sendai virus replication.[11] IgG- but not IgA-containing cells

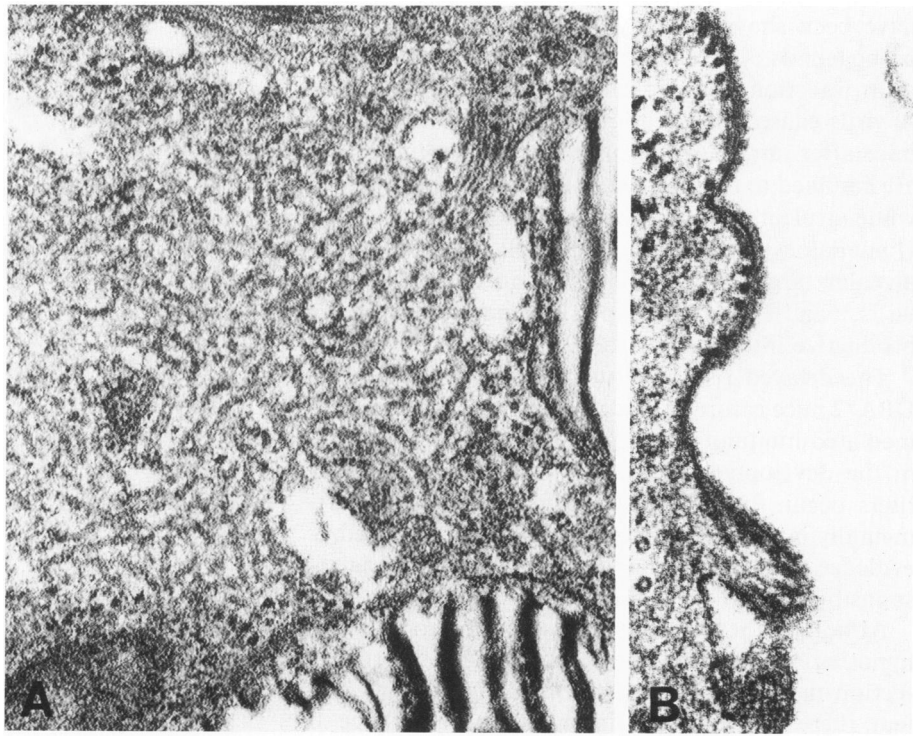

Figure 7—Type II pneumocyte from an adult DBA/2 mouse 10 days after infection with Sendai virus. **A**—Viral nucleocapsids are present in the cytoplasmic matrix adjacent to lamellar bodies. (×80,000) **B**—Virus particles are budding from the plasma membrane. (×90,000)

preferentially accumulated along infected airways of both mouse strains in the present study. The lack of IgA immunocyte recruitment by our mice may have reflected strain differences, microbial experience, or differences in the dose or virulence of virus used. The preinfection eminence of bronchial IgA-containing cells reported previously[11] was not seen in the present study.

DBA/2 mice lagged behind C57Bl/6 mice in the shift from airway epithelial proliferation to necrotic desquamative inflammation. A similar difference distinguishes the response of athymic nude (nu/nu) mice from the response of heterozygous (nu/+) mice naturally infected with Sendai virus.[19] Athymic nude mice fail to develop T-cell-dependent cellular and humoral immune responses to Sendai viral antigens, while heterozygotes do.[19] The failure to mount an effective immune response correlates with the failure to initiate necrotic desquamative inflammation, which is probably immunologically mediated.[11,19]

DBA/2 mice were less capable than C57Bl/6 mice of preventing the spread of Sendai viral antigens to air exchange tissues (alveolar ducts and alveoli). Similarly, resistant strains of mice lose the capacity to restrict Sendai viral antigens to conducting airway (bronchi and bronchioles) epithelium when they are immunosuppressed.[6,7,12] The cells that served as targets for viral extension in DBA/2 mice were Type II pneumocytes, which were productively infected.[20] These cells have not been previously reported to be sites of Sendai virus replication. Type II pneumocytes have been shown to play an important role in the pathogenesis of alveolar injury caused by influenza A virus infection in mice. Like Sendai virus, influenza A virus causes a descending respiratory infection in mice after intranasal inoculation.[21] Avirulent strains are confined to the epithelium of conducting airways, while virulent strains spread to alveolar cells.[21] Type II pneumocytes have been tentatively identified as the alveolar targets for the WSN strain of Influenza A virus,[22] and Type I and Type II pneumocytes support productive infections by the PR8 strain *in vivo*.[23,24]

The delayed rise in serum CF antibody titers of DBA/2 mice is further evidence of impaired antibody-mediated immunity to Sendai virus. A similar delay in the development of serum-neutralizing antibody titers occurs in genetically susceptible mice experimentally infected with mousepox virus and is used as evidence that reduced immune responsiveness is responsible for genetic susceptibility to this virus.[25]

Although these results provide support for the hypothesis that genetic resistance to Sendai virus infection may be expressed through the immune system, there is no evidence linking genetic resistance to Sendai virus infection with immune response genes in the major histocompatibility complex. Resistance among mouse strains of H-2^k and H-2^b haplotypes varies widely.[1] Genetic resistance to Sendai virus infection that is not abrogated by immunosuppression has been demonstrated in mice of the A2G strain.[26-30] These mice carry an autosomal dominant allele, Mx, that confers resistance to the lethal effects of several pneumotropic paramyxoviruses and myxoviruses.

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