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Neutrophil-Mediated Suppression of Virus Replication after Herpes Simplex Virus Type 1 Infection of the Murine Cornea

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Herpes simplex virus type 1 (HSV-1) infection of the murine cornea induces the rapid infiltration of neutrophils. We investigated whether these cells could influence virus replication. BALB/c mice treated with monoclonal antibody (MAb) RB6-8C5 experienced a profound depletion of neutrophils in the bloodstream, spleen, and cornea. In these animals, virus titers in the eye were significantly higher than those in the immunoglobulin G-treated controls at 3 days postinfection. By day 9, virus was no longer detectable in the controls, whereas titers of 10^3 to 10^6 PFU were still present in the neutrophil-depleted hosts. Furthermore, virus spread more readily to the skin and brains of MAb RB6-8C5-treated animals, rendering them significantly more susceptible to HSV-1-induced blepharitis and encephalitis. Only 25% of the treated animals survived, whereas all of the controls lived. Although MAb RB6-8C5 treatment did not alter the $CD4^+$ T-cell, B-cell, natural killer cell, or macrophage populations, the $CD8^+$ T-cell population was partially reduced. Therefore, the experiments were repeated in severe combined immunodeficiency mice, which lack $CD8^+$ T cells. Again virus growth was found to be significantly elevated in the eyes, trigeminal ganglia, and brains of the MAb RB6-8C5-treated hosts. These results strongly indicate that in both immunocompetent and immunodeficient mice, neutrophils play a significant role in helping to control the replication and spread of HSV-1 after corneal infection.

Lymphocytes and macrophages have long been considered to be the major cellular defense mediators against viral infections. Neutrophils, on the other hand, are usually viewed as being important in fighting bacterial infections, especially those mediated by extracellular pyogenic bacteria (33). However, there are a number of reasons for believing that neutrophils may also contribute to host defense against virus attack. It is known, for example, that certain virus infections can lead to an increase in blood neutrophil count (10). Indeed, brisk and predominant neutrophil responses have been reported to occur at sites of viral infection (11, 13, 49). Thus, viral infections can provide the necessary stimulus for neutrophil migration. In addition, neutrophils have been reported to specifically adhere to virus-infected cells (11, 32, 39), a phenomenon which may be enhanced by the presence of complement and/or virus-specific antibodies (11). More recently, it has become clear that mature neutrophils, although limited in their capacity to synthesize and secrete proteins, nevertheless do produce a variety of mediators, some of which may have antiviral activity (4, 31).

Herpes simplex virus type 1 (HSV-1) infection of the cornea elicits a diverse host response which is both nonspecific and specific. With respect to the former, macrophages (25, 58), natural killer (NK) cells (18), and cytokines such as the interferons (50, 57) are thought to be the early mediators of resistance. However, it is the neutrophil that initially infiltrates the cornea, and it is this cell that remains the predominant cell type during the development of herpes stromal keratitis (HSK) (36, 37, 56). Neutrophils have been shown in vitro to adhere to HSV-infected cells after complement activation (53) and to phagocytose antibody-coated (1, 47, 54) but not complement-coated (55) herpes virions. Currently, it is not known what effect, if any, neutrophils have in limiting HSV-1 growth in vivo. We have investigated this question in the present study. The experimental approach was to treat mice with monoclonal antibody (MAb) RB6-8C5, which recognizes a surface marker (Gr-1) on murine granulocytes (5, 6, 21, 22, 24, 41, 51). We used this antibody to deplete mice of neutrophils and then tested the effect of this treatment on virus replication in the eye and in the peripheral and central nervous systems. The data support the hypothesis that the neutrophil response is an important host defense in limiting HSV-1 replication in vivo.

MATERIALS AND METHODS

Virus infection. HSV-1 strain RE, a known HSK inducer (29), was used to initiate infection. Virus stocks were grown and titrated on Vero cells as previously described (28). Four-week-old female BALB/c mice or CB.17 severe combined immunodeficiency (SCID) mice (Charles River Breeding Laboratories, Wilmington, Mass.) were anesthetized with 1.0 mg of sodium pentobarbital in 0.2 ml of phosphate-buffered saline (PBS) injected intraperitoneally (i.p.). The right eye was lightly scarified by three twists of a 2-mm corneal trephine. A 2-μl volume containing 1×10^4 to 5×10^4 PFU of virus was then dropped onto the corneal surface and massaged in with the eyelids. Eyes were examined weekly, using a dissecting biomicroscope. Corneal opacity was graded on a scale of 0 to +5 as described elsewhere (35); a score of 0 indicates a clear cornea, whereas a score of +5 represents severe necrotizing HSK. Blepharitis was graded as previously described (30): 0, normal eyelids; +1, minimal swelling; +2, mild swelling; +3, moderate swelling; +4 severe swelling; and +5, severely swollen eyelids with tissue necrosis. Eyes and eyelids were examined in a coded fashion, with the reader unaware of the treatment given. The data were evaluated by using the Mann-Whitney *U* test.

Antibody treatment. The hybridoma RB6-8C5, which produces a rat (immunoglobulin G2b [IgG2b]) anti-mouse granulocyte MAb, was a gift from R. Coffman, DNAX Research Institute (Palo Alto, Calif.). The antibody was purified

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from hybridoma culture medium by affinity chromatography on protein G-Sepharose Fast Flow (Pharmacia, LKB Biotechnology, Piscataway, N.J.) and quantified with a radial immunodiffusion kit (ICN Immunobiologicals, Costa Mesa, Calif.). Mice received an i.p. injection of 0.5 mg of purified antibody 5 h before infection and again on day 3 postinfection. To maintain sufficient depletion of neutrophils, mice received 1 mg of antibody on days 5 and 7 and 2 mg on day 8. Control mice received the same treatment of rat IgG antibody (Sigma, St. Louis, Mo.).

Blood cell counts. To perform differential cell counts, peripheral blood was obtained from two or three mice via tail bleeds on the days indicated. Thin smears were prepared and stained with Leukostat (Fisher Diagnostics, Orangeburg, N.Y.). For each sample, at least 100 cells were counted at a magnification of ×1,000. Absolute numbers of leukocytes were determined following treatment with MAb RB6-8C5. Eight BALB/c mice from both the control and neutrophil-depleted groups were bled via branchial vessels on day 9. A 0.5- to 1-ml of sample of blood was collected from each animal, and the leukocytes were counted with a Coulter Counter.

Assay of tissues for infectious HSV-1. To test the effect of MAb RB6-8C5 treatment on HSV-1 replication in the cornea, individual whole eyes were excised and placed in 600 μl of 2% fetal bovine serum in Dulbecco modified Eagle medium with antibiotics. Individual trigeminal ganglia and brains were also collected and placed in 800 μl and 1 ml, respectively, of medium. Preparations were frozen at −70°C, thawed, and homogenized in a Ten Broeck homogenizer (Bellco, Vineland, N.J.). The homogenates were frozen and thawed again and sonicated for 20 s with a Sonic 300 Dismembrator (Artek Systems Corporation, Farmingdale, N.Y.). Following centrifugation, the supernatants were then titrated for infectious virus on Vero cell monolayers in a 48-h plaque assay (28).

Flow cytometry. Cells from the spleen (10^6), lymph nodes (10^6), and peripheral blood (200 μl) of individual mice (three per time point) were obtained at selected intervals postinfection and incubated on ice for 40 min with the following primary rat MAb or rabbit polyclonal antibody adjusted to 1 μg/ml; anti-Lyt-2 (clone 2.43; American Type Culture Collection [ATCC], Rockville, Md.), anti-L3T4 (GK1.5; ATCC), antigranulocyte (RB6-8C5), antimacrophage (F4/80; ATCC), or anti-NK cell (rabbit anti-asialo GM1; Wako Chemicals, Richmond, Va.). The cells were washed in fluorescence-activated cell sorting diluent (PBS with 0.1% sodium azide and 2.0% fetal bovine serum) and incubated with fluorescein-conjugated goat anti-rat antibody (Jackson ImmunoResearch, West Grove, Pa.) for 30 min over ice. Goat anti-mouse immunoglobulin directly labeled with fluorescein was used at a 1:50 dilution to stain B cells (Dako Corp., Carpinteria, Calif.). The cells were again washed twice and analyzed with a FACS 440 (Becton Dickinson, Mountain View, Calif.).

Immunohistochemistry. Immunohistochemical examination of infected corneas was performed as previously described (20). Four infected eyes from each experimental group on the days indicated were enucleated and embedded in OCT medium (Tissue Tek, Miles, Naperville, Ill.) and snap-frozen in an isopentane dry ice bath, and 6-μm sections were cut at −20°C. The sections were fixed in cold acetone for 10 min and then exposed to the primary antibodies overnight at 4°C. Rat MAbs to various leukocyte markers were used as primary antibodies as described above. The sections were then stained by using the streptavidin-biotin complex immunoperoxidase staining procedure (Zymed Laboratories, South San Francisco, Calif.). HSV-1 antigens were identified by exposing fixed sections to a polyclonal rabbit anti-HSV antiserum used at a 1:100 dilution. The sections were then washed for 10 min and incubated for 30 min with biotinylated rabbit anti-rat IgG (heavy and light chains) or biotinylated goat anti-rabbit IgG (heavy and light chains) which had been adsorbed with mouse serum protein and diluted in a mouse skin extract. Following two washes, the sections were exposed to 3% H_2O_2 in methanol and washed two times for 10 min each. The sections were then incubated for 10 min with the streptavidin-biotinylated peroxidase complex. Following two washes, sections were incubated for 5 min in 3-amino-9-ethyl-carbazole (Sigma Chemical Company) solution, which was made from 1 ml of 3-amino-9-ethyl-carbazole (4 mg/ml) in *N,N*-dimethylformamide, 14 ml of 0.1 M acetate buffer (pH 5.5), and 150 μl of 3% H_2O_2. The slides were then washed in distilled water and counterstained with Mayer's hematoxylin for 6 min.

RESULTS

Effect of MAb *RB6-8C5* administration on the blood leukocyte count. Initial studies showed that profound neutrophil depletion could be achieved transiently with a single dose of MAb RB6-8C5. However, to effectively maintain depletion for 9 days, the time frame of HSV-1 replication in the cornea, we found that the antibody dosage and the frequency of treatment had to be intensified over time. MAb RB6-8C5 was given i.p. repeatedly over an 8-day period starting 5 h before HSV-1 corneal infection. Blood samples from two or three animals were collected 1 h before each i.p. injection in order to monitor the neutrophil count. It was established that the protocol used produced and maintained ≥96% depletion of neutrophils (Fig. 1). On the other hand, lymphocyte and monocyte levels were not noticeably affected. Total leukocyte counts in BALB/c mice were reduced by approximately 29%, as the mean peripheral blood leukocyte population fell from 2.1×10^6 to 1.5×10^6 cells per ml after treatment with MAb RB6-8C5. Cessation of antibody treatment on day 8 was followed by rapid restoration of blood neutrophils to normal or above-normal levels by 48 h.

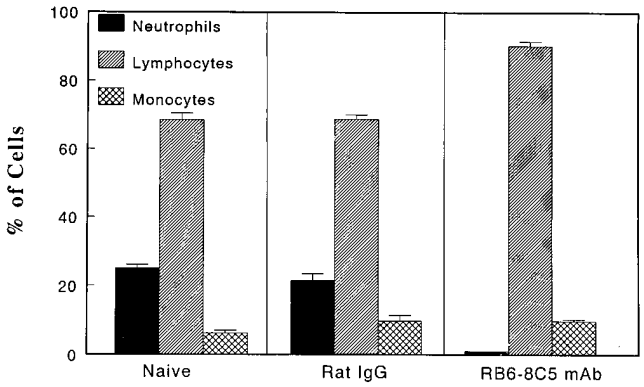

FIG. 1. Effect of MAb RB6-8C5 administration on blood leukocyte counts. BALB/c mice received repeated i.p. injections of antigranulocyte MAb RB6-8C5 beginning 5 h before HSV-1 corneal infection. The protocol was to give 0.5 mg of MAb on days 0 and 3, 1.0 mg on days 5 and 7, and 2.0 mg on day 8. Control mice were given rat IgG. Neutrophil depletion was monitored 1 h before each MAb injection by performing differential counts on tail vein blood smears. The results at day 9 postinfection are shown and are expressed as the mean ± standard error percentage of cells of each type. There were two to four mice per group.

Effect of MAb RB6-8C5 treatment on neutrophil infiltration into HSV-1-infected BALB/c corneas. Immunohistochemistry was performed to monitor inflammatory cell migration into the cornea and to determine whether MAb RB6-8C5 treatment could inhibit neutrophil infiltration. One day after infection, cells which reacted positively with MAb RB6-8C5 were observed in the perivascular regions of the limbus (Fig. 2A) and lightly scattered throughout the paracentral cornea (Fig. 2B) of the control animals. By day 2, the neutrophil influx was evident in the central cornea (Fig. 2C), with the greatest accumulation underlying the foci of HSV-1 infection seen in the corneal epithelial layer (Fig. 2D). The epithelial lesions overlying the central stroma had healed by day 4, and RB6-8C5-positive cells were not detectable in the central cornea. However, they continued to be observed at the corneal limbus. Staining reactions performed with antibodies specific for T-cell surface antigens (CD4 and CD8), B-cell surface antigen (IgG), NK cells (asialo GM1), and macrophages (F4/80) were uniformly negative during the first week postinfection. Therefore, neutrophils were the first and only readily detectable cell type to migrate into the cornea during the initial days after infection. Furthermore, their appearance correlated with the appearance of HSV-1 antigens. MAb RB6-8C5 treatment was effective at preventing neutrophil migration into the cornea because neutrophils were not detected at any time during the first week postinfection (Fig. 2E). Epithelial lesions containing HSV-1 antigen were readily detected in the corneas of the neutrophil-depleted animals (Fig. 2F) during the first 5 days of infection, whereas in the controls, no viral antigen could be detected after day 3 (not shown). Corneal scarification in the absence of HSV-1 infection did not induce neutrophil migration.

HSV-1 replication in the eyes and brains of MAb RB6-8C5-treated BALB/c mice. The histologic evidence of early neutrophil infiltration beneath the foci of HSV-1 infection seen in the epithelial layer raised the possibility that neutrophils suppress

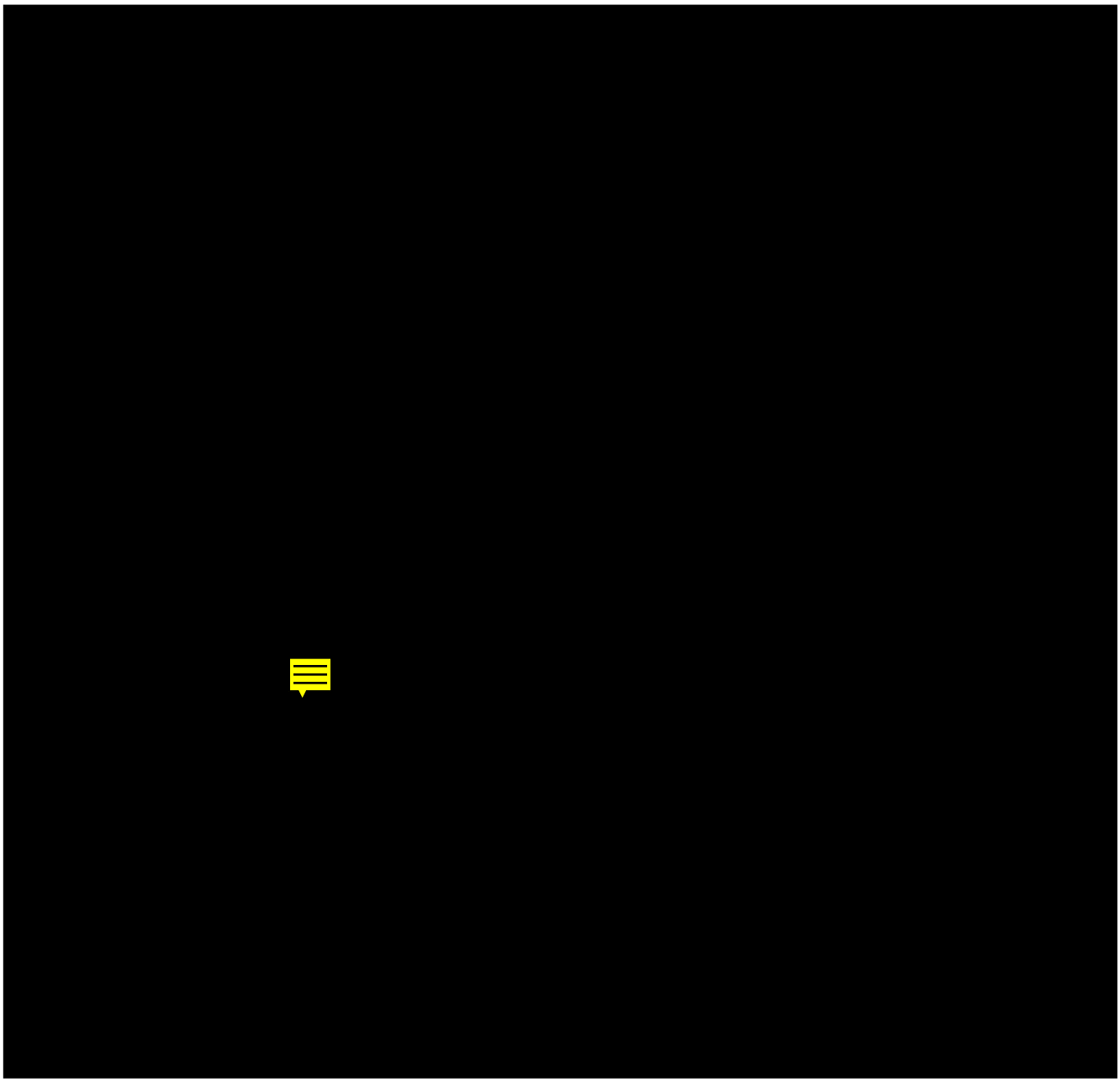

FIG. 2. Immunohistochemical staining of corneas from HSV-1-infected BALB/c mice obtained during the early course of infection. The reddish brown color denotes a positive reaction. On day 1 of infection, the corneas from control mice were positive for neutrophils (arrows point to positively stained cells) in the perivascular regions of the limbus (A) and the paracentral cornea (B). On day 2 of infection, a marked influx of neutrophils into the central corneas of the control mice was observed (C), and foci of HSV antigens could be seen in the epithelial layer (D). In contrast, corneas collected on day 2 from animals receiving MAb RB6-8C5 showed no staining for neutrophils (E), but an abundance of HSV antigens could readily be detected in the epithelium (F). Magnification, ×62.

HSV-1 growth in the cornea. This point was investigated by comparing virus titers in the eyes of RB6-8C5-treated mice with those in eyes of their IgG-treated counterparts. Figure 3A shows that the mean HSV-1 titer was significantly higher in the neutrophil-depleted hosts beginning 3 days after infection. Infectious virions began to be cleared from control eyes after day 5 and were not detected in any of the eight samples tested on day 9. By contrast, nine of nine eyes from RB6-8C5-treated hosts still had titers in excess of 10^3 PFU on day 9.

Following corneal infection, HSV-1 typically spreads via peripheral nerves to the trigeminal ganglia and then travels into the central nervous system. Figure 3B shows that the mean virus titer was also significantly higher in the brains of RB6-8C5-treated mice 7 and 9 days postinfection. At the infectious doses used (1×10^4 to 5×10^4 PFU), symptoms of encephalitis are infrequently seen and death is rare in HSV-1 strain RE-challenged BALB/c mice. However, we found that the majority of RB6-8C5-treated mice (17 of 20) showed signs of encephalitis manifested by hunched posture, lethargy, ataxia, and anorexia. Furthermore, 15 of 20 succumbed to infection by day 10. In contrast, no animals given rat IgG displayed signs of encephalitis or died over the 21-day observation period.

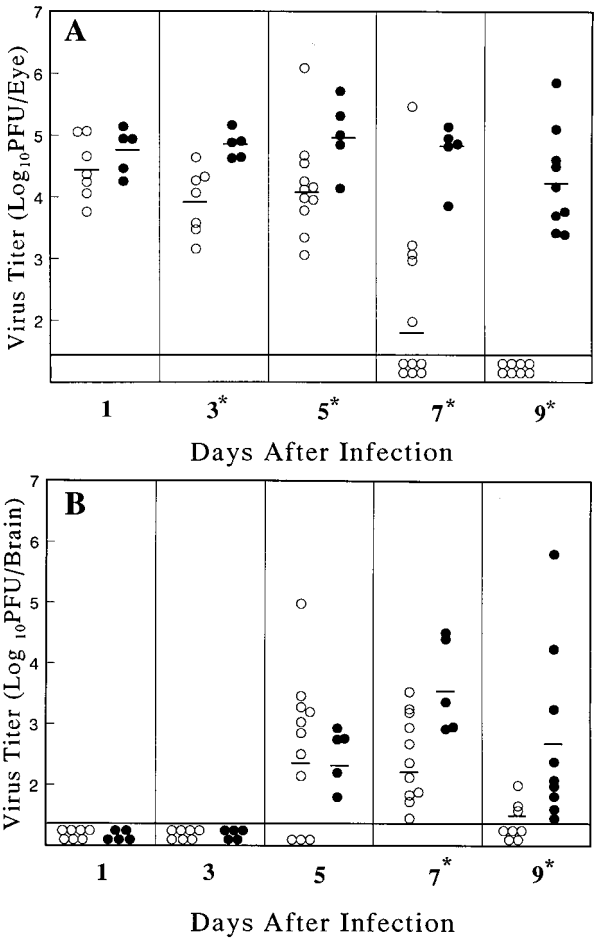

FIG. 3. Effect of neutrophil depletion on HSV-1 growth in the eyes and brains of BALB/c mice. Mice infected on the cornea with HSV-1 were treated with MAb RB6-8C5 (●) as described in the legend to Fig. 1 or given control immunoglobulin (○). On the days indicated, 5 to 11 animals in each group were killed, and the eyes (A) or brains (B) were excised and individually titrated for infectious virus content. *, significant difference ($P \leq 0.05$) in virus titer between the RB6-8C5-treated and rat IgG control groups, based on the Mann-Whitney *U* test.

HSV-1-induced blepharitis in MAb RB6-8C5-treated BALB/c mice. HSV-1 infection on the cornea is usually accompanied by eyelid disease (30). Blepharitis typically reaches maximum severity 8 to 12 days postinfection, after which healing begins. We found that treatment of HSV-1-infected mice with MAb RB6-8C5 significantly enhanced the severity of blepharitis (Fig. 4). In addition, periocular skin lesions were prominently displayed in the antibody-treated hosts but not the controls. The latter was especially prevalent in those animals in which MAb treatment was initiated 1 day before infection.

Effect of MAb RB6-8C5 treatment on the $CD8^+$ T-cell population. It has been reported that MAb RB6-8C5, in addition to binding to mature neutrophils, can cross-react with the Ly-6C allele found on some $CD8^+$ T cells and monocytes (6, 14). It was therefore important to determine whether MAb treatment affected $CD8^+$ T cells in our infection model. Accordingly, flow cytometry studies of blood cell subpopulations were carried out on day 9 following completion of RB6-8C5 treatment. The results are shown in Fig. 5. It was found that in vivo treatment with MAb RB6-8C5 consistently resulted in ≥96% reduction in neutrophils. No significant reduction in the $CD4^+$ T-cell, B-cell, NK cell, or $F4/80^+$ macrophage populations was observed. Analogous results were obtained when spleen cells were analyzed (data not shown). However, the $CD8^+$ T-cell population was reduced by 40 to 50% in both the peripheral blood and spleens of MAb RB6-8C5-treated mice. Thus, our results confirmed that in vivo RB6-8C5 treatment not only profoundly reduced the neutrophil count but also partially reduced the $CD8^+$ T-cell population.

Effect of MAb RB6-8C5 administration on HSV-1 replication in the eyes of SCID mice. Immune $CD8^+$ T cells have been reported to participate in HSV-1 clearance from infected tissue (2, 27, 48), and so a reduction in their number may have contributed to the uncontrolled growth of virus seen in MAb RB6-8C5-treated mice. SCID mice are known to be devoid of both functional T lymphocytes and functional B lymphocytes (3, 7, 8). Thus, experiments to test the effect of neutrophil depletion could be conducted in these animals while avoiding the confounding problem of simultaneous depletion of $CD8^+$ T cells. Preliminary studies established that MAb RB6-8C5 treatment was as efficient in depleting neutrophils as in BALB/c mice and that, as expected, no $CD4^+$ or $CD8^+$ T cells were detected in the SCID mice circulation. At various times following HSV-1 corneal infection, the eyes of RB6-8C5-treated and control SCID mice were collected, and the infectious virus titer in each eye was determined. Figure 6A shows that significantly higher (5- to 14-fold) virus titers were observed at each time period examined in MAb RB6-8C5-treated animals compared with the controls. Elevated virus replication was also observed in the peripheral nervous systems of MAb RB6-8C5-treated mice (Fig. 6B), and the mean HSV-1 titer in the brain was 10-fold higher than that of the controls on day 9 postinfection. These results establish that neutrophil depletion in SCID mice is correlated with elevated virus titers in three distinctly different tissues. Additional studies showed that 9 of 10 SCID mice depleted of neutrophils and challenged ocularly with 10^2 PFU of HSV-1 died, whereas none of the 10 controls succumbed to infection.

DISCUSSION

The results of this study indicate that neutrophils play an important role in inhibiting the uncontrolled growth of HSV-1 following ocular infection of mice. Treatment with MAb RB6-

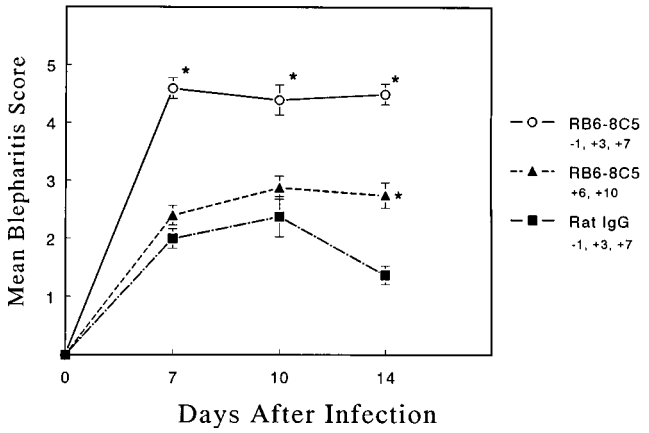

FIG. 4. Effect of MAb RB6-8C5 treatment on the severity of HSV-1-induced blepharitis. Mice (10 per group) were infected on the scarified cornea with HSV-1 and were given RB6-8C5 or control rat IgG on the days indicated. *, significant difference ($P \leq 0.05$) between the RB6-8C5-treated and rat IgG control groups, based on the Mann-Whitney *U* test.

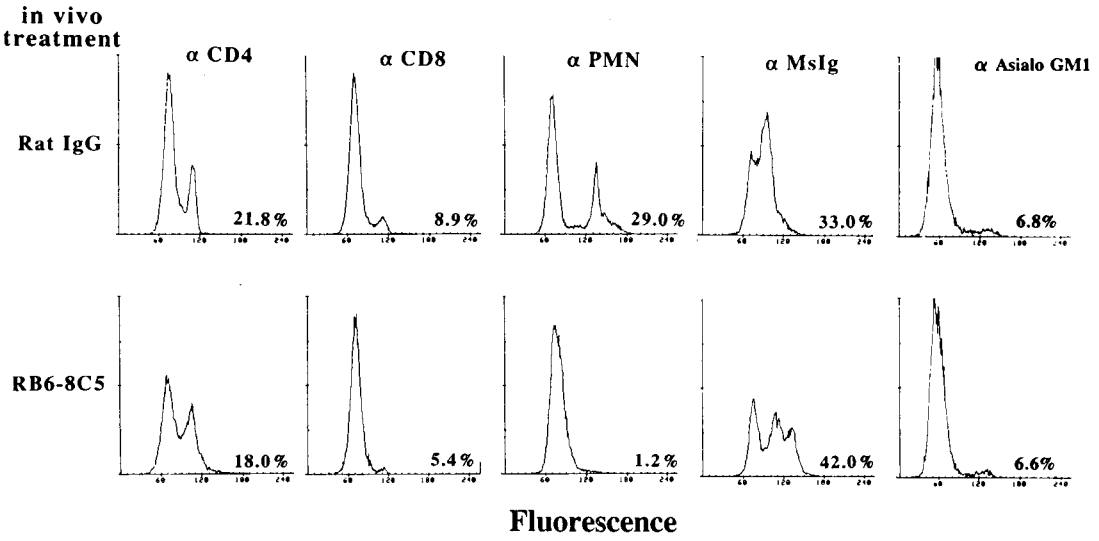

FIG. 5. Cytofluorimetric analysis of murine leukocyte populations from BALB/c mice. Mice were given MAb RB6-8C5 or rat IgG as described in the legend to Fig. 1. On day 9, cell suspensions from the peripheral blood were prepared, stained with the indicated antibody, washed, and then stained with an anti-immunoglobulin conjugated to fluorescein isothiocyanate.

8C5 caused profound depletion of neutrophils in the blood and tissues. In these animals, virus titers were significantly higher than in control hosts. As a consequence, virus-induced disease in the form of blepharitis and encephalitis was markedly more severe. Antibody treatment depleted the mouse of eosinophils as well as neutrophils. However, the former have not been associated with sites of HSV-1 infection, whereas the latter are present in abundance (36, 37, 56). Thus, we attribute our results to neutrophil depletion. A number of observations provide support for this conclusion. Neutrophils began migrating into the cornea within 24 h after infection, and their presence was correlated with suppressed virus replication evident on day 3. The observation that virus suppression was demonstrated in SCID mice as well as immunocompetent mice argues against the explanation that an early antibody or T-cell response accounted for our results. In fact, previous studies have shown that passive transfer of high-titer neutralizing antibody does not accelerate virus clearance from the eye (29). This conclusion is strengthened by the fact that we (Fig. 5) and others (5, 6, 41) have found that $CD4^+$ T-cell, B-cell, and NK cell levels are not significantly affected by MAb RB6-8C5 treatment. Others have shown that MAb RB6-8C5 does not affect NK (or macrophage) cell migration and/or function in immunocompetent or SCID mice (6, 41).

Flow cytometry evaluation showed that in vivo MAb RB6-8C5 treatment partially reduced the $CD8^+$ T-cell population. Curiously, this antibody was not observed to stain $CD8^+$ T cells in immunofluorescence tests. Likewise, MAb 2.43, which is specific for $CD8^+$ T cells (44), did not stain neutrophils. Interestingly, mice treated with MAb 2.43 in vivo, which depleted $CD8^+$ T cells by >99%, caused a 15 to 41% reduction in blood neutrophils (52a). Whether these results reflect the presence of a cross-reacting antigen which is difficult to detect, the mutual requirement of each cell type to support the replication of the other, or some other explanation is unclear. Nevertheless, the partial depletion of $CD8^+$ T cells is highly unlikely to account for our results because (i) $CD8^+$ T cells were not detected in the BALB/c cornea early in the course of infection and (ii) neutrophil-depleted SCID mice, which lack functional $CD8^+$ T cells, also were more susceptible to HSV-1 replication. The view that neutrophils participate in restricting HSV-1 growth is supported by the recent report (40) that activated adult human neutrophils but not neutrophils from newborns or patients with chronic granulomatous disease could inhibit HSV-1 replication in vitro. Tsuru and coworkers (15, 52) have reported that neutrophils can protect mice against influenza virus infection, indicating that neutrophils can also play a role in other virus infections.

It is not clear how neutrophils exert their antiviral effect, as their defense capabilities are quite diverse. They may directly inhibit HSV-1 growth by the synthesis and release of mediators such as defensins (16) or other factors (42). Virus-infected cells may be lysed via the production of reactive oxygen and/or nitrogen species (46). Neutrophils may also act indirectly by producing cytokines (4, 31), which in turn recruit other effector cells such as T cells and macrophages to the site of virus infection. Finally, neutrophils may collaborate with other defensive factors such as antibody (19, 23, 45) or complement (52, 53) to kill virus-infected cells via cellular cytotoxicity reactions.

HSK is believed to be at least in part a T-cell-mediated immunopathological disease because this disease is not seen in T-cell-deficient animals (34, 43). However, it is the neutrophil which is the predominant cell type in the cornea as HSK develops. Thus, it was initially thought that MAb RB6-8C5 treatment would be useful in evaluating whether neutrophils were a contributing factor in the progression of this disease. We found that the severity of HSK in the treated animals was not significantly different from that in the controls. This was also the case when mice were given RB6-8C5 starting on day 7 and continuing through day 13, i.e., the time frame during which corneal inflammation becomes clinically apparent (unpublished observations). However, interpretation of these results is obscured by three factors. First, neutrophil depletion could not be maintained until peak disease was reached (14 days) because the passive transfer of inordinate amounts of antibody would be required. Second, elevated virus growth in the neutrophil-depleted hosts could produce more tissue damage, thereby compensating for the loss of putative destructive neutrophil activity. Third, there was partial depletion of $CD8^+$

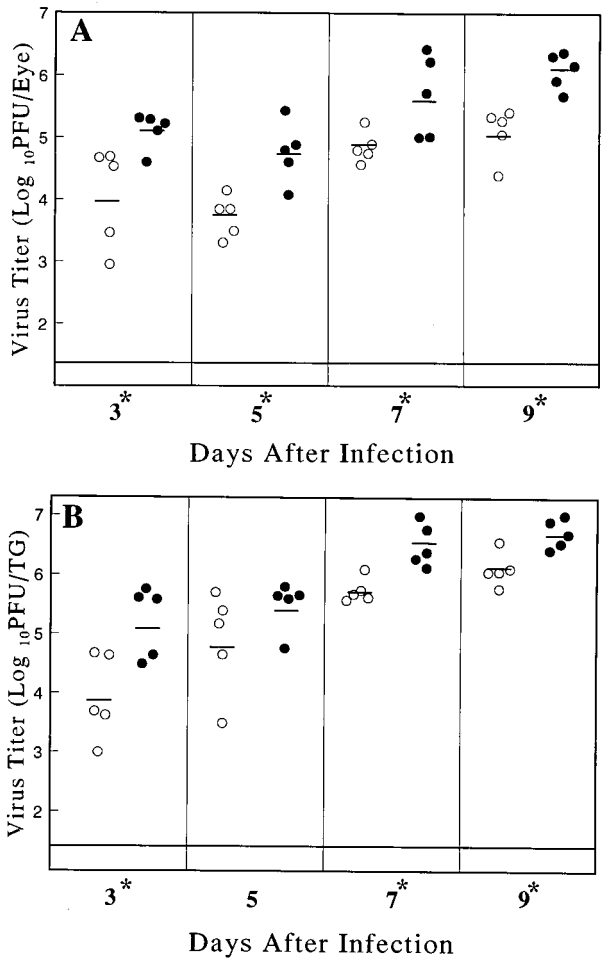

FIG. 6. Effect of neutrophil depletion on HSV-1 growth in SCID mice. Mice infected on the cornea with HSV-1 (10^4 PFU) were treated with MAb RB6-8C5 (●) as described in the legend to Fig. 1 or given control immunoglobulin (○). On the days indicated, five animals in each group were killed, and the right eyes (A) and trigeminal ganglia (B) were excised and individually titrated for infectious virus content. *, significant difference ($P \leq 0.05$) in virus titer between the MAb RB6-8C5-treated and rat IgG control groups, based on the Mann-Whitney *U* test.

T cells, and these cells have been suggested to play a protective role in HSK (38). Thus, the role that neutrophils play in HSK is still unclear.

In conclusion, our results indicate that neutrophils are a contributing element in the control of acute HSV-1 infection. Their ability to limit virus replication early in infection can be seen as buying time until specific immune responses can develop. Thus, this study does not dispute the importance of T cells and macrophages in resistance to HSV-1. Rather, it emphasizes how different cell types collaborate to control the growth and promote clearance of a common virus pathogen in immunocompetent and immunocompromised hosts.

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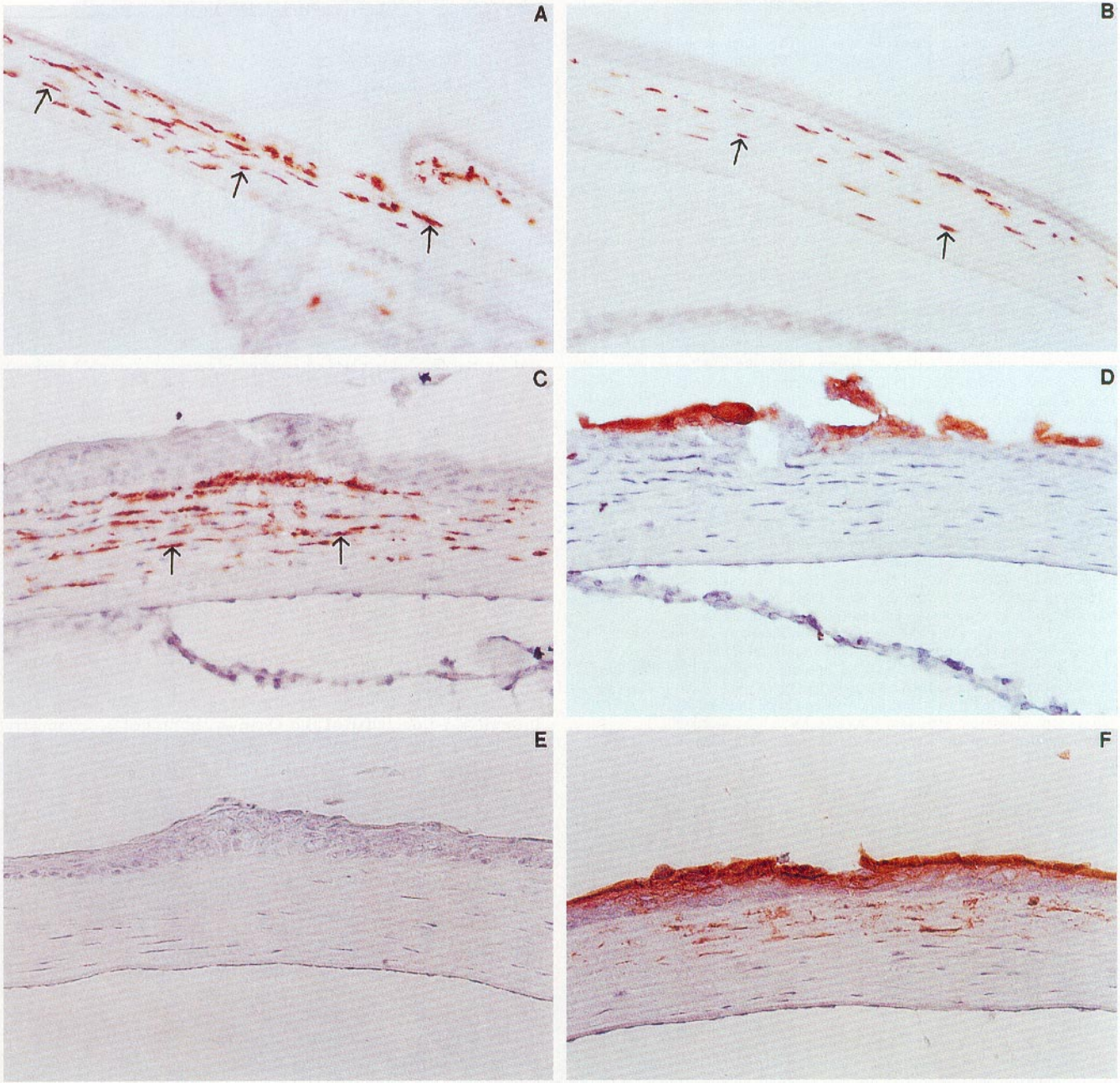
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